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Global Health & Medicine
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E-mail: office@globalhealthmedicine.com

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(The photo was taken by Dr. Shigeyuki Kano in front of the National Center for Global Health and Medicine, JIHS, during the cherry blossom season.)

In April 2025, the Japan Institute for Health Security (JIHS) is established through the merger of the National Institute of Infectious Diseases (NIID) and the National Center for Global Health and Medicine (NCGM). The vision of the JIHS is to become Japan's "Integrated Science Center for Infectious Diseases", leading the world in infectious disease countermeasures, with world-class capabilities in information collection, analysis, risk assessment, research and development, and clinical functions.

Norihiro Kokudo, President,
Japan Institute for Health Security

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The establishment of the Japan Institute for Health Security (JIHS): A new era in infectious disease response and research

Norihiro Kokudo[1,*,#], Koji Wada[1,#], Teiji Takei[1,#], Tetsuro Matano[2,#], Takaji Wakita[2,#]

[1] National Center for Global Health and Medicine, Tokyo, Japan;
[2] National Institute of Infectious Diseases, Tokyo, Japan.

Abstract: On April 1, 2025, the National Center for Global Health and Medicine (NCGM) and the National Institute of Infectious Diseases (NIID) will be merged to establish the Japan Institute for Health Security (JIHS). This merger strengthens Japan's capacity to address infectious diseases and health threats, aiming for a resilient and secure society. This paper highlights the establishment of JIHS, its alignment with government reforms, and its strategic priorities for the future. The initiative originated on October 6, 2020, when the Liberal Democratic Party's Policy Research Council proposed measures to address vulnerabilities exposed by COVID-19. In 2022, the Japanese government called for formulating a central control tower, the Cabinet Agency for Infectious Disease Crisis Management (CAICM), upgrading the divisions related to infectious diseases to the Department of Infectious Disease Prevention and Control in the Ministry of Health, Labour and Welfare (MHLW), and establishing the JIHS. JIHS will serve as a scientific advisory body during infectious disease crises, guiding the Prime Minister and the MHLW. It focuses on four key areas: *i*) Disease intelligence: risk assessment and data analysis; *ii*) Research, development, and innovation: advancing medical science; *iii*) Comprehensive medical services: strengthening clinical response capacity; and *iv*) Human resource development and international cooperation: building expertise and partnerships. Through integration, JIHS aims to improve existing systems and create synergy between basic and clinical research. As a hub for domestic and international collaboration, JIHS will consolidate critical information, catalyze innovative research, and deliver transformative solutions to address domestic and global infectious disease challenges.

***Keywords*:** JIHS, health security, infectious disease control, Japan

Introduction

The COVID-19 pandemic prompted a reassessment of governmental frameworks worldwide, leading to significant organizational reforms to improve crisis response preparedness and capabilities for future pandemics (*1*). In Japan, these reforms encompassed restructuring the frameworks for planning and implementing policies to respond effectively to emerging health threats (*2*). Among these initiatives, the Japanese government resolved to establish a new research institute, subsequently named the *Kokuritsu Kenko Kikikanri Kenkyu Kikou* (国立健康危機管理研究機構) in Japanese and the Japan Institute for Health Security (JIHS) in English (*3*). This institute will be formed through the merger of the National Center for Global Health and Medicine (NCGM) and the National Institute of Infectious Diseases (NIID) and will officially commence operations on April 1, 2025.

The establishment of JIHS aims to strengthen Japan's capabilities as a center of excellence for infectious disease control (*2*). It is envisioned as a hub for providing scientific insights, evaluating epidemic trends, advancing clinical research and trials, and supporting rapid development of medical countermeasures such as diagnostics, therapeutics and vaccines. Its creation acknowledges the need for an organization capable of informing governmental decision-making and addressing health crises with agility and innovation. This paper examines the background leading to establishment of JIHS, outlining its goals, organizational structure, and future priorities.

Reforming the new structure of the government architecture after reflecting on the COVID-19 response

The origins of reforming the new structures initiative can be traced back to October 6, 2020, when a subcommittee of the Liberal Democratic Party's Policy Research

Council proposed measures to address vulnerabilities exposed by the COVID-19 pandemic (*4*). Subsequently, on June 15, 2022, Prime Minister Fumio Kishida announced plans for a new institute by integrating NCGM and NIID to establish a so-called "Japan CDC" under the Minister of Health, Labour, and Welfare (MHLW) (*5*).

On September 2, 2022, the government's COVID-19 Response Headquarters, which Prime Minister Fumio Kishida chaired, unveiled the "Specific Measures to Prepare for the Next Infectious Disease Crisis" (*6,7*). This plan explicitly outlined the establishment of a control tower, the Cabinet Agency for Infectious Disease Crisis Management (CAICM), to centralize the planning and formulation of government policies while coordinating efforts among relevant ministries and agencies for infectious disease crisis responses directed by the Prime Minister (*8*). It also included upgrading the divisions related to infectious diseases to the Department of Infectious Disease Prevention and Control within the Health Service Bureau in MHLW (*9*). The department conducts integrated activities such as analyzing and understanding the characteristics of infectious diseases, testing, vaccinations, support for public health centres, risk communication and quarantine measures and leads the coordination of infectious disease crises. Both organizations were established on 1st September 2023. Figure 1 shows the Government Organizational Framework for Infectious Disease Crisis Response in Japan as of 4th Sep 2023 (*9*). To strengthen the collaboration between the two agencies, under the Chief Medical and Global Health Officer in MHLW, who also serves as the Cabinet Infectious Disease Crisis Management Officer in CAICM, the Department of Infectious Disease Prevention and Control will collaborate closely with the CAICM.

Simultaneously, a new expert organization called JIHS focused on infectious diseases was announced (*6*). JIHS will provide scientific insights to the Prime Minister (*via* the CAICM) and the MHLW (*via* the Infectious Disease Control Department). Its key functions will include infectious disease intelligence activity, research and development, comprehensive medical services and human resource development and international cooperations.

Brief history and core functions of NCGM

NCGM traces its origins to the Army Temporary Hospital, established in 1868 and was renamed the Army Center Hospital in 1873 (Table 1) (*10*). In 1929, it moved to its current location in Toyama, Shinjuku, Tokyo. After World War II, it was transferred to the Ministry of Health and Welfare in 1945 and renamed the National Tokyo Daiichi Hospital. The institute has continuously evolved to meet changing demands of the times and implement key government policies. In 1974, it became the National Medical Center Hospital. Over the years, it expanded its scope, establishing the AIDS Medical Information Center in 1988 and founding the International Medical Center of Japan in 1993. In 2010, it was restructured as the National Research and Development Agency, NCGM.

NCGM includes the Center Hospital in Shinjuku, which has 749 beds, including a special infection care

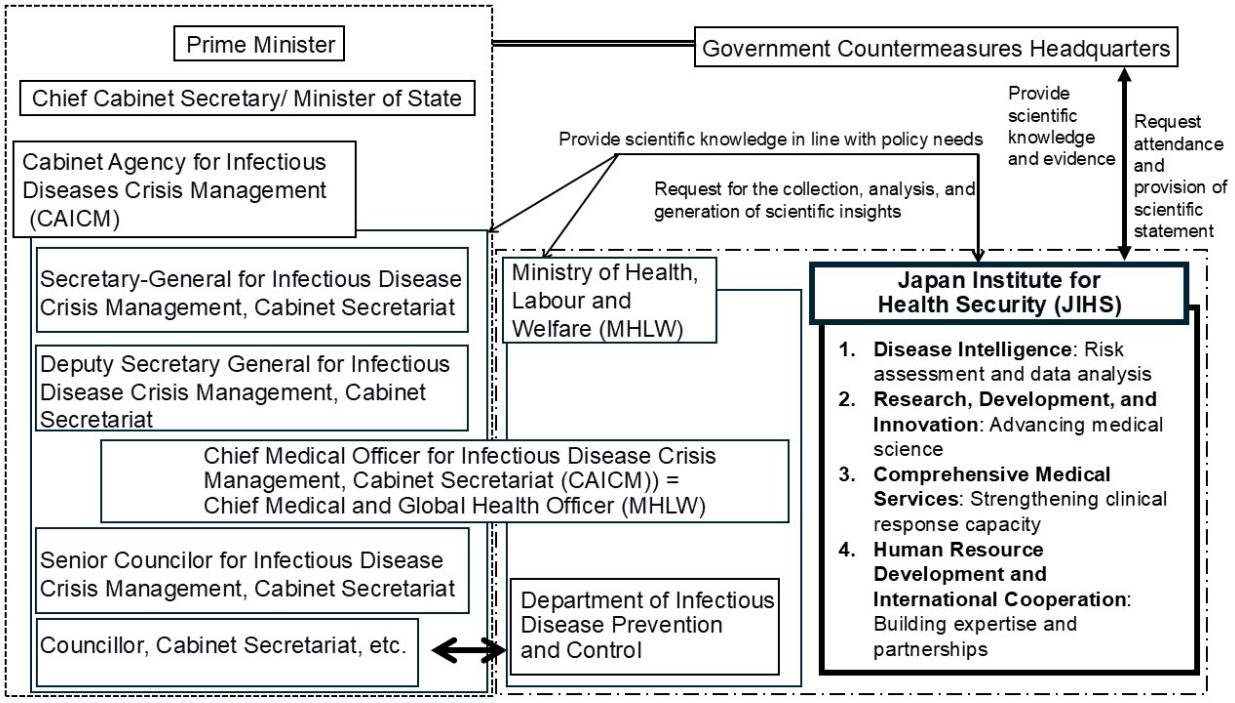

Figure 1. Government organizational framework for infectious disease crisis response in Japan.

unit (4 beds), and provides advanced and specialized medical care. During the COVID-19 pandemic, NCGM led efforts to care for infected patients from early 2020, contributed to developing clinical guidelines, and provided technical input for public health policies for the MHLW, and the Tokyo Metropolitan Government.

NCGM comprises several centers, including the AIDS Research Center (ACC), Disease Control and Prevention Center (DCC), Emergency Medical Care Center, Kohnodai Hospital, Research Institutes for Hepatitis and Immunology, Diabetes Research Center, and the Center for Clinical Sciences (CCS), as well as the Bureau of International Health Cooperation and the National College of Nursing. NCGM is also a World Health Organization (WHO) Collaborating Center for: *i*) Health Systems Development, *ii*) Prevention, Preparedness, and Response to Emerging Infectious Diseases, and *iii*) Prevention, Preparedness and Response to Antimicrobial Resistance.

Brief history and core functions of NIID

In 1947, the National Institute of Health (NIH) was founded as a research institute affiliated with the Ministry of Health and Welfare, Japan for conducting: *i*) fundamental and applied research on infectious diseases, which are recognized as a high priority for establishing a safe and secure society after World War II, and *ii*) national test for lot release and development of antibiotics and vaccines. NIH initially included three departments (research department, quality control department, and pilot production section) (Table 2) (*11*). The institute established the Murayama Branch Laboratories in 1961 to cope with the large-scale poliomyelitis epidemic in 1958.

This institute transferred the main functions of the present site, Toyama Research Laboratories, located in Shinjuku, Tokyo, right next to the NCGM in 1992. Then, in April 1997, the NIH was renamed the National Institute of Infectious Diseases (NIID) and opened the Infectious Disease Surveillance Center to collect all the information on incidents of infectious diseases. The NIID opened additional functions, such as the Influenza Virus Research Center in 2009, the Designation of a Biosafety level (BSL)-4 facility at Murayama Branch in 2015, and the AMR Research Center in 2017. During the COVID-19 pandemic, an increased number of research staff have been allocated to strengthen public health response capacity, with the establishment of the Center for Emergency Preparedness and Response (CEPR) in 2020 and the Center for Field Epidemic Intelligence, research, and professional development (CFEIR) in 2021. Furthermore, the Research Center for Drug and Vaccine Development and the Research Planning and Coordination Center were established to promote research, development, and collaboration.

Table 1. Brief History of National Center for Global Health and Medicine (NCGM)

Year	Event
1868	Opened as an Army Temporary Hospital
1873	Renamed the Army Center Hospital
1929	Relocated to the current site in Toyama, Shinjuku, Tokyo
1945	Transferred to the Ministry of Health and Welfare as the National Tokyo Daiichi Hospital
1947	Opened a subsidiary nursing school
1974	Renamed the National Medical Center Hospital
1988	Established the AIDS Medical Information Center
1993	Founded International Medical Center of Japan
2001	Opened the National College of Nursing
2003	Designated a medical institution for specified infectious diseases
2010	Reorganized as an Independent administrative agency, the National Center for Global Health and Medicine (NCGM)
2015	Renamed as a National Research and Development Agency, NCGM

Table 2. Brief History of National Institute of Infectious Diseases (NIID)

Year	Event
1947	Established as the National Institute of Health (NIH)
1961	Established labs for quality control of polio vaccines in Musashimurayama, Tokyo
1988	Established the AIDS Research Center
1992	Relocated to the current site in Toyama, Shinjuku, Tokyo
1997	Renamed to the National Institute of Infectious Diseases (NIID)
	Affiliated Leprosy Research Center
	Established Infectious Disease Surveillance Center
2009	Established Influenza Virus Research Center
2015	Designated as BSL-4 facility at Murayama Branch
2017	Established AMR Research Center
2020	Established Center for Emergency Preparedness and Response (CEPR)
2021	Established Center for Field Epidemic Intelligence, Research and Professional Development (CFEIR)

NIID has been nominated as 4 WHO Collaborating Centers for virus reference and research (enterovirus), reference and research on influenza, standardization and evaluation of biologicals, and AMR surveillance and research. NIID is also a reference laboratory for Japanese Encephalitis Global specialized laboratory, Polio Global Specialized Laboratory, Polio Regional Reference Laboratory, National Polio Laboratory, measles and Rubella Global Specialized Laboratory, Measles and Rubella Regional Reference Laboratory, Human Papillomavirus Laboratory Network Western Pacific Regional reference laboratory, H5 Influenza reference laboratory, Essential regulatory laboratory, WHO Coronavirus network reference laboratory, and WHO global surveillance of drug resistance in leprosy.

The institute traces its origins to the Institute for Infectious Disease, established in 1892 by Dr. Shibasaburo Kitasato as a private research institute affiliated with the Hygiene Society of Japan (*11*). It later came under the supervision of the Ministry of Home Affairs, facilitating its transformation into the Imperial Institute of Infectious Disease. Subsequently, it was transferred to the Ministry of Education and integrated into Tokyo Imperial University as the Institute for Infectious Disease in 1914 up to 1946.

Goals and priorities of JIHS

Mission

The mission of the JIHS is to contribute to building a resilient and secure society through the implementation of research and development (R&D) on infectious diseases and other diseases, as well as the provision of medical care.

Vision

The vision of the JIHS is to become an "Integrated Science Center for Infectious Diseases" in Japan that leads the world in infectious diseases countermeasures, with world-class capabilities in information collection, analysis and risk assessment, research and development, and clinical functions. JIHS will prioritize the following four core pillars:

i) *Disease intelligence: information collection, analysis and risk assessment*

JIHS will be a central hub for infectious disease intelligence, conducting data collection, analysis and assessment while fostering collaboration with domestic and international partners. The institute will deliver scientific insights to inform government decision-making and also provide the public with clear, accessible information.

ii) *Research, development, and innovation*

JIHS aims to establish itself as a global leader in research by creating a world-class environment for advancing scientific discovery. Its efforts will span from foundational research and the development of medical countermeasures to clinical trials. JIHS will act swiftly as a research and development hub during infectious disease crises, leveraging a robust domestic and international network to coordinate efforts, including clinical trials.

Figure 2. Logo of Japan Institute for Health Security.

iii) *Comprehensive medical services*

Advanced clinical capabilities are crucial for addressing infectious disease crises. JIHS will build upon and enhance NCGM's general hospital functions to safeguard public health and provide top-tier medical care. During surges of patients during a pandemic or infectious disease crisis, NCGM will shift to treating moderate and severe cases of infected patients and coordinate a local and regional network that stratifies multiple hospitals by function to ensure adequate medical service capacity.

iv) *Human resource development and international cooperation*

JIHS will focus on cultivating and retaining experts across various disciplines, including healthcare professionals, researchers, and public health responders. This will be achieved through international exchanges and partnerships among industry, government, and academia. Additionally, JIHS will promote global health initiatives through active international cooperation.

On this occasion of the JIHS establishment, the new logo was created. It embodies the unification of organizations: the NIID and NCGM (Figure 2). The outer circle represents a culture dish, symbolizing NIID's scientific research and the Earth, reflecting NCGM's global health mission. The inner red circle evokes Japan's national flag, signifying JIHS's role as a national institution. The crossed lines symbolize the merger, representing our commitment and aspiration to advance infection control measures as a unified entity.

Organizational structure of JIHS

The organizational structure of JIHS will be divided into the control bureau and the organization. The control bureau will establish five new bureaus on 1st April 2025: *i*) Health Security and Management (General Coordination), *ii*) Research and Development, *iii*) Medical Services, *iv*) Human Resource Development, and *v*) System Infrastructure Development. JIHS organization will comprise the following institutions: *i*) National Institute of Infectious Diseases (NIID), *ii*) National Institute of Global Health and Medicine (currently the Research Institute, NCGM), *iii*) National

Center for Global Health and Medicine (currently Center Hospital), *iv*) National Kohnodai Medical Center (currently Kohnodai Hospital), *v*) Center for Clinical Sciences, *vi*) Bureau of Global Health Cooperation (currently the Bureau of International Health Cooperation), and *vii*) National College of Nursing.

The JIHS will be the center of excellence for infectious disease control domestically and internationally. Through integration, JIHS aims to enhance existing systems while fostering synergy between basic and clinical research. JIHS will strengthen the hospital's ability to respond to the crisis and maintain the function of providing advanced medical service as the hospital. By acting as a hub for domestic and international networks for infectious diseases, the institute will consolidate critical information, drive innovative research, and generate transformative solutions for health security.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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[#]*Current affiliation*: Japan Institute for Health Security.
**Address correspondence to*:
Norihiro Kokudo, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: kokudo.n@jihs.go.jp

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Enhancing health security against infectious diseases: Perspectives on the emergency operations capabilities of the Japan Institute for Health Security

Tomoya Saito[1,*,#], Tomimasa Sunagawa[2,#], Motoi Suzuki[3,#], Tetsuro Matano[4,#], Takaji Wakita[4,#]

[1] Center for Emergency Preparedness and Response, National Institute of Infectious Diseases, Japan;
[2] Center for Field Epidemic Intelligence, Research, and Professional Development, National Institute of Infectious Diseases, Japan;
[3] Center for Surveillance, Immunization, and Epidemiologic Research, National Institute of Infectious Diseases, Japan;
[4] National Institute of Infectious Diseases, Japan.

Abstract: The Japan Institute for Health Security (JIHS) will be established in April 2025 by merging the National Institute of Infectious Diseases (NIID) and the National Center for Global Health and Medicine (NCGM). JIHS aims to enhance health security against infectious disease crises by integrating NIID's surveillance, epidemiologic investigation, and research expertise with NCGM's clinical care and research capabilities. An effective response to an infectious disease crisis depends on robust intelligence, systematic data analysis, and surge capacity – the ability to rapidly scale responses through mobilization of resources and an established infrastructure. An Emergency Operations Center (EOC), which centralizes emergency response coordination, is critical to harmonizing these diverse capabilities, enabling technical experts to focus effectively on specialized tasks. NIID has contributed to disease prevention through surveillance, laboratory reference services, and devising medical countermeasures. The establishment of NIID's Center for Emergency Preparedness and Response (CEPR) in 2020 and the EOC in 2021 markedly improved crisis management in the NIID, as demonstrated during events like Tokyo 2020 and the SARS-CoV-2 Omicron variant outbreak. These experiences highlight the importance of centralized coordination, which is being incorporated in the operational framework of the newly established JIHS. This article reviews NIID EOC's evolution and its crucial role in enhancing Japan's health security by consolidating lessons learned from recent public health crises.

***Keywords*:** National Institute of Infectious Diseases, National Center for Global Health and Medicine, crisis management, emergency operations center

Introduction

The Japan Institute for Health Security (JIHS) was established through the integration of the National Institute of Infectious Diseases (NIID) and the National Center for Global Health and Medicine (NCGM) in April 2025 (*1*). JIHS is expected to play a central role in health security particularly in infectious disease crises by integrating NIID's expertise in surveillance, epidemiological investigations, and research and development with NCGM's expertise in infectious disease clinical care and research. This integration aims to enhance its intelligence capacity and enable a more comprehensive response to infectious disease crises – including pandemics – and increase surge capacity.

Health security from infectious disease crises requires a comprehensive societal approach that builds upon infectious disease control while also encompassing measures to sustain economic activities and social functioning during emergencies. To effectively intervene in infectious disease crises and minimize their negative impact on society, intelligence derived from systematic information collection, analysis, and assessment is essential. Additionally, ensuring surge capacity – the ability to respond rapidly and at scale during a crisis – requires enhancing logistics to mobilize resources, pre-establishing a scalable response infrastructure, and obtaining the necessary resources for large-scale emergency operations. In order to harmonize these diverse operational capabilities, robust coordination is indispensable, thereby underscoring the importance of an Emergency Operations Center (EOC).

An EOC is a place within which, in the context of an emergency, personnel responsible for planning, coordinating, organizing, acquiring, and allocating resources and providing direction and control can focus

their activities on responding to the emergency (*2*). Such emergency operations capacity and capabilities are required not only by public health authorities but also by technical agencies like JIHS, which will need similar coordination to capitalize on its integrated strengths.

Drawing on its experience, NIID has played a crucial role in infectious disease prevention and control by operating infectious disease surveillance under the Infectious Diseases Control Act, providing laboratory reference services, and conducting research and development on medical countermeasures. By centralizing coordination, the EOC has enabled NIID experts to concentrate on their specialized roles, thereby maximizing operational effectiveness. The establishment of the Center for Emergency Preparedness and Response (CEPR) in 2020 and the EOC in 2021 was a pivotal step in enhancing crisis management operations at the NIID. These experiences underscore the importance of effective coordination – a lesson now being incorporated in the emergency operations capabilities of the newly formed JIHS, which is expected to further enhance Japan's health security.

This article provides an overview of NIID CEPR's activities over the past five years (Figure 1), with a focus on the evolution of its EOC, which has served as a central platform for NIID's responses to high-risk mass gatherings – such as the Tokyo 2020 Olympic and Paralympic Games (Tokyo 2020) – and outbreaks like the emergence of the Omicron variant of SARS-CoV-2. The article further discusses lessons learned from the EOC's establishment and its operations in the NIID over the past four years and offers insights on the role of emergency operations capabilities in enhancing health security through the JIHS.

Establishment of the CEPR in the NIID

Before the CEPR's establishment, the NIID primarily consisted of laboratories focused on pathogen research and wet lab studies, except for the Infectious Disease Surveillance Center, which was responsible for national surveillance and field epidemiology and related research. The CEPR was established to enhance disease control capabilities by enhancing crisis management capabilities, such as preparedness, response coordination, and the emergency laboratory response networks in the NIID. In response to the growing need to enhance crisis management capabilities during the early stage of the COVID-19 pandemic, the CEPR was expanded in April 2021. It was reorganized into eight offices under three group directors (Figure 2).

Development of the EOC in the NIID

The physical EOC space was first established in July 2021 in preparation for Tokyo 2020. The largest conference room on the NIID Toyama Campus was renovated to include an operations room surrounded by two medium-sized and two small meeting rooms, 2 single working booths, and a media monitoring room (Figure 3). During normal times, CEPR Office 2 leads the activation of the EOC structure with the cooperation of the relevant departments and centers. This office is a focal point for the consolidation of a variety of information – ranging from surveillance, investigations, and research on diseases and pathogens to media reports – from both internal and external sources. CEPR Office 1 maintains the EOC facilities and manages logistics, while CEPR Office 3 oversees media monitoring and risk communications. CEPR Office 5 handles the planning and support of exercises and training for EOC operations.

Microsoft Teams serves as the virtual platform for EOC operations, ensuring real-time sharing of information and communication among EOC members. Through several operation experiences, an activation/

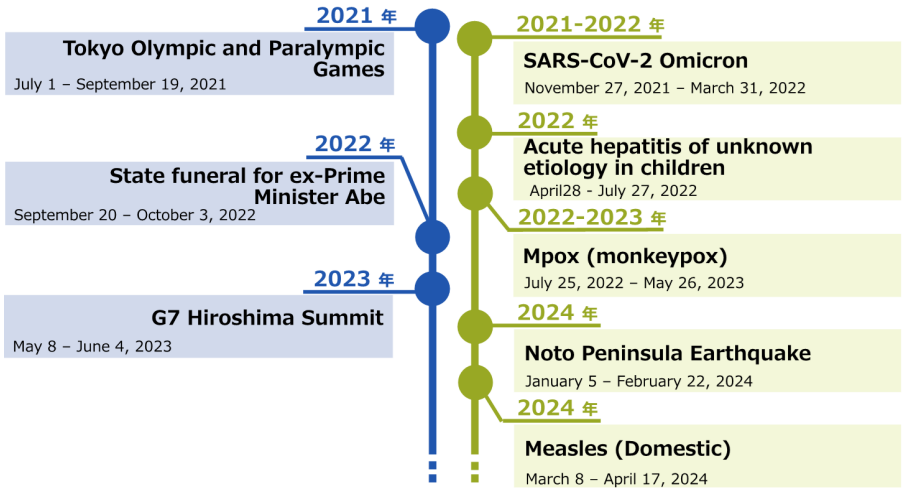

Figure 1. Activation of the Emergency Operations Center at the National Institute of Infectious Diseases, 2021 to 2024.

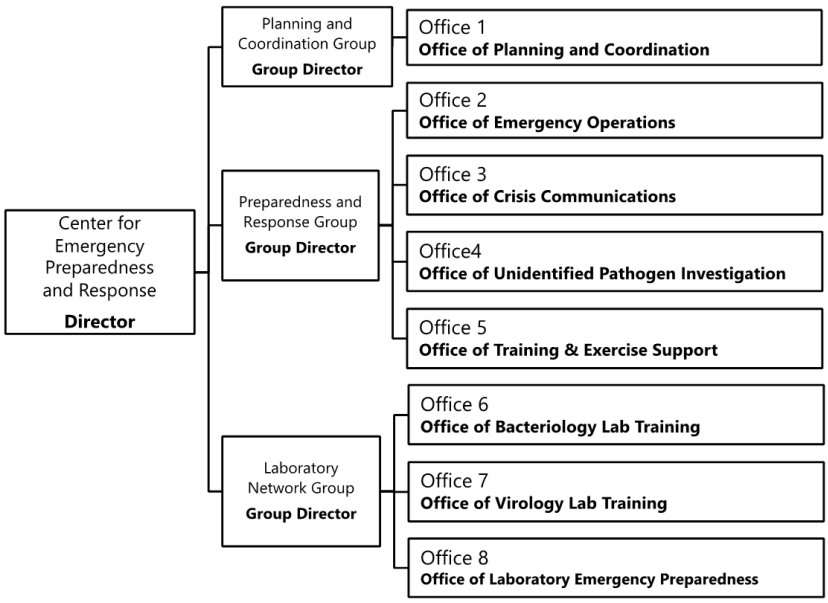

Figure 2. The organizational chart of the Center for Emergency Preparedness and Response, National Institute of Infectious Diseases from April 2021 to March 2025.

Figure 3. Emergency Operations Center at the National Institute of Infectious Diseases.

deactivation protocol, standard operating procedures, and a prototype organization chart were drafted and refined through after-action-reviews and exercises. The decision to activate/deactivate the EOC is guided by a situational assessment of the risk of an event, the expected response by the NIID, and the NIID's capabilities and readiness, using the NIID EOC Operational Risk Assessment Tool (NEORAT) (*3*) (Table 1).

History of activation of the NIID EOC and its activities

Tokyo 2020 Olympic and Paralympic Games, 2021

The NIID EOC was first activated from July 1 to September 19, 2021, in preparation for Tokyo 2020. The NIID EOC for Tokyo 2020 aimed to enhance surveillance, support response efforts, and enhance a cross-divisional response system (*4*). It mobilized personnel from multiple specialized departments within the NIID, established a cross-divisional incident management framework, and operated under a structured system organized by function. Additionally, the NIID EOC also served as a communication hub with external organizations by publishing daily reports.

To ensure efficient operations, three major functional groups were established and then further divided into specialized teams (*5*). The Surveillance and Assessment Group conducted enhanced surveillance to monitor potential infectious disease cases and events that were related to or could impact Tokyo 2020 and carried out timely risk assessments (*6*). The Event Response Group was responsible for supporting field investigations, surveillance, and risk assessments at local health departments and the Tokyo 2020 Games Health and Hygiene Support Tokyo Branch (Tokyo HHB), and at the Infectious Disease Control Centre of the Tokyo 2020 Organising Committee (IDCC) (*7*). It also provided consultations on infection control and prevention and conducted genomic epidemiology analyses of COVID-19 cases related to Tokyo 2020. The Logistics Group played a role in facility management, personnel management, document control, and general administration, including the organization of regular and *ad hoc* meetings (*5*).

Although this was the first activation of the NIID EOC, the decision-making process was well-defined, enabling the swift and efficient execution of cross-departmental operations during this high-profile mass gathering. In particular, logistics played a crucial role in ensuring the seamless and efficient implementation of specialized operations by experts (*5*).

SARS-CoV-2 Omicron, 2021 to 2022

Table 1. Overview of the NIID EOC Operational Risk Assessment Tool (NEORAT)*

No	Questions
1	Is the risk of the event high? - Probability of its occurrence - Probability of spread - Impact such as its clinical severity - Risk perception
2	Are internal departments' roles and coordination systems well organized? - Are roles of departments clarified? - Are the coordination and collaboration systems established?
3	Is the external communication system well organized? - Are communication needs (*e.g.*, the need for regular reporting) high? - Is the communication system established?
4	Is collaboration beyond the normal scope of the department's responsibilities needed? - Does the burden of the responsible department exceed its capacity? - Is there a need to activate a business continuity plan?
5	Is an out-of-business-hours response expected? - Is a response expected late at night, early in the morning, on weekends, and on public holidays?

*modified from Reference (*3*).

On November 26, 2021, the World Health Organization (WHO) designated the newly identified SARS-CoV-2 lineage B.1.1.529 as Omicron and classified it as a Variant of Concern (VOC). To facilitate rapid information collection and countermeasure planning, the NIID activated the EOC on November 27, 2021, prior to detection of the first Omicron case in Japan (*8*). In addition to surveillance, risk assessment, and support for field investigations of clusters, the EOC coordinated laboratory and epidemiological investigations at the NIID in collaboration with clinical investigations at the National Center for Global Health and Medicine, and the Ministry of Health, Labor, and Welfare (MHLW), to conduct the First Few Hundred (FF100) study on the SARS-CoV-2 Omicron (*9*). Given the anticipated rapid escalation in the volume and urgency of related tasks, the organizational structure of the EOC was expanded to include two additional groups beyond those established for the NIID EOC during Tokyo 2020: "Special Studies & Other Activities" and "Laboratory Response". These groups consist of highly specialized personnel from various departments and research centers within the NIID (*8*). These experts were tasked with facilitating the active sharing of information and rapidly characterizing the Omicron variant's properties and transmission dynamics to facilitate decision-making on control measures. As sufficient information on the Omicron variant was obtained and an appropriate response framework was established, the EOC was deactivated on March 31, 2022. During the 125-day activation period, a total of nine risk assessment reports on the Omicron variant were issued, with the sixth report receiving the highest number of webpage views (460,000 as of late April 2022) (*8*).

Acute hepatitis of unknown etiology in children, 2022

In early April 2022, cases of severe acute hepatitis of unknown etiology in children were reported in the United Kingdom of Great Britain and Northern Ireland. In response, the collection and sharing of information among relevant departments at the NIID began on April 7, 2022. On April 25, NIID published a summary of information from Europe and the United States, along with a mini-review on adenoviruses and hepatitis, which were suspected causes (*10*). Although there were no indications that a similar increase in cases had been observed domestically, since efforts to identify cases may lead to an increase in the number of reported cases and consultations, the NIID EOC was activated on April 28 for a better institute-wide response (*11*). The EOC's activities were relatively smaller in scale than during the previous two events. The main task was to conduct a situational assessment, integrate the domestic reporting of cases, and to clarify the lab consultation process for those reported cases. After three situational reports in April (*10*) and May (*12,13*) and an interim report on a domestic investigation (*14*) were published, the NIID EOC was deactivated on July 27, 2022 since a monitoring framework had been established at the MHLW and NIID (*11*).

Mpox, 2022 -2023

In May 2022, the United Kingdom reported mpox cases that were unrelated to travel to endemic countries (*15*). Subsequently, a significant number of cases were reported, primarily among men who have sex with men (MSM) in Europe and the United States, with no history

of travel to endemic regions. In response, the NIID worked on revising the mpox fact sheet on its website, publishing situation reports in May (*16*) and July (*17*) and issuing guidance on infection control measures for confirmed and suspected mpox cases in collaboration with the Disease Control Center of the NCGM in June (*18*). Additionally, efforts were made to establish a laboratory diagnosis protocol and provide reagents to local public health institutes (*19*). On July 23, 2022, the outbreak was declared a Public Health Emergency of International Concern (PHEIC). Following the PHEIC declaration and the identification of the first domestic case, the NIID EOC was activated on July 25, 2022 (*11*).

After its activation, the EOC facilitated the review of epidemiological and laboratory findings, investigations of domestic cases, diagnostic testing at the NIID upon request from local governments, and support for establishment of diagnostic capabilities at local public health laboratories. Development of an mpox vaccine was a key focus of the response, leading to the establishment of a vaccine team at the NIID to support a clinical study on the efficacy of the LC16m8 vaccine for mpox prevention (*20*). As a part of its EOC response, three additional risk assessment reports (*21-23*) and a Q&A document for the general public (*24*) were published. One notable aspect of the mpox response was risk communication and community engagement activities (*25*). The EOC engaged in community-based communication efforts aimed at facilitating informed decision-making among MSM. These efforts were carried out in collaboration with the MHLW, the Tokyo Metropolitan Government, the NCGM, and community-based organizations (CBOs) dealing with MSM, utilizing media, websites, and educational materials. After the PHEIC was lifted on May 10, 2023, the mpox situation stabilized both globally and domestically, and the NIID EOC was deactivated on May 26, 2023 (*11*). With experience from three prior EOC activations, the NIID staff had become familiar with inter-departmental collaboration, and many preparatory activities were completed efficiently before the formal activation of the EOC. Nonetheless, the activation reinforced the prioritization of activities for the mpox response at the NIID and cross-departmental activities for an effective mpox response

State funeral for a former Prime Minister, 2022

For the state funeral of former Prime Minister Shinzo Abe on September 27, 2022, the NIID EOC was activated from September 20 to October 3, 2022, to address infection control measures and risk management particularly with regard to COVID-19 (*11*). As usual, a risk assessment was conducted in collaboration with relevant departments and centers. While these types of short-term VIP events, including the subsequent G7 Hiroshima Summit in 2023, are considered low risk in terms of infectious disease control, they are high-profile events requiring a swift response and vigilance, particularly with regard to potential bioterrorism threats. To ensure clarity in roles and responsibilities among centers and departments involved in EOC activities, a standard operating procedure (SOP) was developed in advance. Additionally, potential scenarios involving bioterrorism or other unusual events were considered.

This event was the first time a pre-event exercise was conducted. The framework for sharing information, communicating with external agencies, and laboratory testing capabilities was reviewed and strengthened through a pre-event mini simulation exercise with local public health departments (*11*).

G7 Hiroshima Summit, 2023

In May 2023, the G7 Hiroshima Summit was held in Hiroshima City. Given the summit's status as a high-profile event, the NIID EOC was activated from May 8 to June 4, 2023 to ensure comprehensive readiness and a swift response to infectious disease outbreaks that could disrupt the event, including potential bioterrorism threats. As has been done before the state funeral, a pre-event exercise was conducted to assess the communication and coordination framework among internal and external stakeholders, including local public health laboratories. in preparation for emergency testing related to bioterrorism or severe infectious diseases. During the summit, EOC staff members were deployed to the medical response headquarters on-site to provide technical support. Simultaneously, the EOC conducted enhanced surveillance for infectious disease outbreaks and monitored media and other sources to maintain real-time situational awareness (*25*).

Noto Peninsula Earthquake, 2024

On January 1, 2024, a major earthquake struck the Noto Peninsula in Ishikawa Prefecture, Japan. The prolonged evacuation period following the disaster necessitated infection control measures in shelters and enhanced collaboration with relevant organizations in the affected areas (*25*). Recognizing the need for a cross-departmental public health response, the NIID EOC was activated on January 5, 2024. The NIID EOC provided logistical support to NIID staff deployed to the response headquarters on-site, where they contributed to *ad hoc* enhanced surveillance efforts in the affected areas. Additionally, the NIID published two risk assessment reports on infection risks in the affected areas and evacuation shelters (*26,27*). To support infection control efforts on the ground, an infection prevention advisory document for volunteers was also prepared and disseminated (*28*). With significant progress in the restoration of public infrastructure and improvements in infection control measures at evacuation shelters,

NIID's deployment concluded on February 21, 2024. As no further urgent coordination efforts were required, the NIID EOC was deactivated on February 22, 2024.

Measles, 2024

Since 2023, there have been frequent reports of measles outbreaks worldwide. In February 2024, a case of imported measles was reported in Japan, with confirmation that the patient had traveled on an international flight during the infectious period. Along with cases linked to this case of imported infection, there were concerns about additional imported cases and the potential for further domestic spread. Given the risk of a measles outbreak in Japan, the need for clear communication through situational updates and timely risk assessments, and the necessity of preparedness for a large-scale or prolonged response, the NIID EOC was activated on March 8, 2024 (*29*).

During the activation period, the EOC's mission was defined as follows: *i*) situation awareness and early alerting, *ii*) technical support for domestic cases, *iii*) epidemiological investigations, and *iv*) research to identify unknown public health aspects of the measles response. A weekly EOC meeting was held six times to review the response and plans of relevant departments And develop a common situational awareness at the NIID. An advisory document was issued to enhance awareness and preparedness at healthcare facilities (*30*). The EOC also coordinated genomic epidemiological investigations across relevant departments (*29*). The measles clusters were considered to have been contained after the health monitoring period for contacts ended by mid-April, so the EOC was deactivated on April 17, 2024.

Perspectives on JIHS's crisis management role and capabilities

Effective crisis management in infectious disease emergencies requires a well-defined chain of command, streamlined consolidation of information, and efficient sharing of information–challenges that became evident through the NIID's experience with EOC operations. Additionally, fostering broader awareness and understanding of the EOC concept and incident management is crucial to improving overall readiness.

The establishment of the JIHS through the integration of the NIID and the NCGM represents a significant step toward enhancing Japan's health security framework. By combining the NIID's strengths in surveillance, epidemiological investigations, and research and development with the NCGM's expertise in clinical care and infectious disease research, the JIHS aims to create a more comprehensive response system for infectious disease crises, including pandemics, while also increasing surge capacity.

To operationalize these expanded capabilities within a robust governance structure, the JIHS will establish the control bureau as its coordinating body. Within this framework, executive directors will also serve as bureau directors, ensuring consistency in the chain of command during both emergency and non-emergency operations (*31*). The Bureau of Health Security and Management, a key division within the control bureau, will function as both an intelligence hub and the crux of integrated emergency operations. To enable the JIHS to efficiently conduct large-scale responses, particularly during pandemics, centralized consolidation of information and coordination will be essential. By assuming coordination and logistical responsibilities, the EOC will allow JIHS experts to focus on their specialized tasks, thereby maximizing operational efficiency during public health emergencies. The lessons learned from the NIID EOC's operations have underscored the importance of structured coordination, intelligence gathering, and surge capacity in crisis management. Building upon these foundations, the JIHS will refine emergency response capabilities, enhance Japan's health security framework, and develop an agile and scalable rapid response system — ensuring preparedness for future infectious disease threats.

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[#]*Current affiliation*: National Institute of Infectious Diseases, Japan Institute for Health Security.
**Address correspondence to*:
Tomoya Saito, Center for Emergency Preparedness and Response, National Institute of Infectious Diseases, Japan Institute for Health Security, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162-0052, Japan.
E-mail: saito.t@jihs.go.jp

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Capacity development of nursing professionals for the next pandemic: Nursing education, on-the-job training, and networking

Mami Kayama[1], Kyoko Sudo[1,*], Kumiko Kamata[2], Kumiko Igarashi[3], Tomohiro Nakao[4], Shigeaki Watanuki[1]

[1] National College of Nursing, Japan, Tokyo, Japan;
[2] Japan Public Health Association, Tokyo, Japan;
[3] National Institute of Public Health, Saitama, Japan;
[4] Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Abstract: The COVID-19 pandemic highlighted the essential role of nursing professionals in infection control and patient care across various healthcare settings in Japan. Despite their dedication, the crisis exposed significant gaps in preparedness, training, and leadership development. This paper examines the challenges nurses and public health nurses faced during the pandemic and proposes a framework for strengthening capacity development to enhance future public health emergency responses. Fundamental infection control education must be systematically incorporated into basic nursing curricula, equipping nurses with essential skills such as proper use of personal protective equipment, zoning principles, and infection prevention strategies. Simulation-based training should complement theoretical instruction to ensure practical application. Continuous professional development through structured on-the-job training is crucial, particularly for smaller hospitals and elderly care facilities where infection control expertise remains limited. Public health nurses require specialized training in epidemiological investigations and outbreak management to coordinate community health responses effectively. Leadership in clinical settings and public health must be reinforced. The Infectious Disease Health Emergency Assistance Team (IHEAT) and supervisory public health nurses played key roles in the pandemic response. Still, challenges in rapid deployment and infrastructure readiness hindered their effectiveness. Strengthening managerial education and crisis response training will be critical to improving future outcomes. Additionally, networking and knowledge-sharing systems should be expanded to enhance communication and coordination. Mental health support for nursing professionals engaged in infection control must also be prioritized. This paper advocates a comprehensive approach to nursing education, training, and leadership development to fortify Japan's healthcare system against future pandemics.

***Keywords*:** capacity development, nursing professionals, nursing education, on-the-job training, networking

Introduction

During the COVID-19 pandemic, nursing professionals in Japan played a crucial frontline role, demonstrating their commitment and resilience in various healthcare settings. Japan's national nursing licenses include public health nurses, midwives, and registered nurses. While registered nurses work primarily in hospitals and home care settings, public health nurses are employed by local government offices at the prefectural and municipal levels, as well as in occupational health settings (*1*). Public health centers play a key role in infection prevention, response, and containment in local communities, with public health nurses addressing these challenges within their jurisdictions.

To enhance specialized nursing capabilities, the Japanese Nursing Association operates a certification system for nurses with advanced expertise in specific fields, such as infection control nursing (*2*). Certified Nurse Specialists (CNS) are highly trained professionals who apply their deep knowledge and clinical skills to provide high-quality nursing care to individuals, families, and communities facing complex health challenges (*2*). They obtain certification after completing a master's program, acquiring relevant work experience, and passing a national credentialing examination (*2*). Similarly, Certified Nurses (CN) are expected to provide high-level nursing care in specialized fields, utilizing advanced nursing techniques and knowledge. They achieve certification by accumulating practical

experience after obtaining their national nursing license. Public health nurses play a critical role in community health, focusing on disease prevention, health promotion, and governmental support not only for medical care but also for welfare services. Their responsibilities span public health centers, municipal health offices, industries, and some hospital settings (*2*). In infection control, public health nurses possess specialized skills in contact tracing, epidemiological surveillance, health education, and risk communication, which are essential for managing public health emergencies.

During the pandemic, registered nurses contributed to a wide range of settings beyond hospitals, including elderly care facilities and home care, although they faced significant challenges in infection control (*3*). Moreover, public health nurses collaborated with local governments and healthcare institutions to implement public health measures effectively. The crisis underscored the need for specialized infection control knowledge and skills, but conventional in-person training programs were difficult to conduct. Instead, online education, particularly e-learning, became an essential tool for providing necessary education and training.

The COVID-19 pandemic highlighted the essential role of infection control in nursing and revealed gaps in preparedness across all levels of nursing. On the basis of this experience, we recognize the need to integrate infection control education into basic nursing education, postgraduate education, and continuous professional development. It is also crucial to establish advanced training systems to equip nurses with the skills necessary to respond effectively to future health emergencies.

In response to these challenges, the Japanese government established the Japan Institute for Health Security (JIHS). The JIHS, set to launch on April 1, 2025, will serve as a central body for research, medical care, international cooperation, and workforce training in infectious diseases and other emerging health threats. The organization will conduct epidemiological surveys and clinical research and provide scientific knowledge to strengthen the nation's health security system. The JIHS will integrate the National Institute of Infectious Diseases and the National Center for Global Health and Medicine, with the aim of enhancing Japan's response capabilities for future pandemics (*4*).

This paper outlines the difficulties faced by Japanese nursing professionals during the COVID-19 pandemic and provides recommendations for a capacity development system to better prepare for future pandemics.

Education for infection control during normal phase

Basic nursing education: training for registered nurses and public health nurses

At the beginning of the pandemic, registered nurses in clinical settings were required to support infection control efforts, including working in dedicated COVID-19 wards. Many people required on-the-job training in essential practices such as donning and doffing personal protective equipment (PPE) and implementing standard infection control measures (*5*). Public health nurses faced extreme challenges in managing health monitoring and hospitalization coordination of infected individuals while handling call center duties at public health centers. During the COVID-19 pandemic, many public health nurses allocated to municipalities lacked experience in epidemiological investigations and implementing infection control measures, which made their roles particularly demanding. These challenges are not unique to Japan and reflect the difficulties that nursing professionals faced globally during the pandemic (*6*). The infection control skills required during pandemics must be systematically incorporated into basic nursing education. Essential competencies should include proper PPE use, zoning principles, and standard precautionary measures. To enhance practical application, nursing curricula should integrate simulation-based training alongside theoretical instruction, ensuring that nurses develop the hands-on expertise required for real-world infection control situations (*7*).

On the job training for nurses and public health nurses

During the pandemic, public health nurses played a pivotal role in advising households on infection prevention, monitoring mild cases, and helping prevent the spread of the virus. In hospitals, strengthening infection control skills among all nurses is essential. Effective infection control requires not only basic knowledge but also practical management skills. Many smaller hospitals, psychiatric hospitals, and elderly care facilities lacked Certified Nurses in infection control, highlighting the need for outreach support (*8*). To enhance infection control capabilities at all levels, structured training programs should be developed and led by infection control-Certified Nurse Specialists as well as Certified Nurses in infection control. These programs should include PPE training, zoning management, and simulation-based response drills. For new nurses, early exposure to PPE protocols and basic infection control techniques should be integrated into on-the-job training programs, ensuring continuous skill development across all hospital departments. Additionally, low nurse-to-patient ratios in ICUs have been associated with decreased care implementation rates (*9*). In comparison to other countries, Japan's low nurse-to-ICU bed ratio requires reassessment to optimize critical care responses. Encouraging generalist nurses to gain experience in critical care can be another effective strategy. Furthermore, strengthening infection control personnel in local healthcare settings is essential, particularly through outreach training programs for smaller hospitals

and nonspecialist facilities. Public health nurses should receive practical training in epidemiological investigations, cluster outbreak response, and infection control interventions. Existing e-learning resources (*10,11*), developed during the COVID-19 pandemic, should be leveraged to increase accessibility and efficiency in training programs.

Expected leadership in public health centers and hospitals: supervising public health nurses and nursing administrators

Public health nurses played a critical role in responding to the COVID-19 pandemic through the Infectious Disease Health Emergency Assistance Team (IHEAT) program (*12*). IHEAT is a mechanism that mobilizes regional public health nurses and other specialized professionals to support public health centers during public health emergencies, such as infectious disease outbreaks. When local governments with public health centers struggle to manage the response, they can request support from IHEAT personnel. Additionally, IHEAT members are required to undergo preparatory training to ensure that they can provide effective assistance when deployed. When public health centers were overwhelmed, IHEAT personnel were dispatched to assist. To ensure rapid deployment, IHEAT members were required to undergo specialized training. During the COVID-19 pandemic, IHEAT public health nurses were instrumental in conducting epidemiological investigations and managing home-care patients. However, despite the establishment of a registration and dispatch system, challenges arose due to insufficient training infrastructure and unprepared local governments, which hindered timely deployment in some cases during the pandemic.

Currently, supervisory public health nurses are assigned to each prefecture and municipality, leading public health strategies at the regional level. Their expertise in disease management and response is particularly crucial. In times of health crisis, public health centers play a key role in coordinating with medical institutions and local governments to implement effective infection control measures. To increase pandemic preparedness, it is essential to cultivate strong management skills in public health nurses with who will coordinate resources and implement effective response strategies in collaboration with municipalities. At the prefectural level, supervisory public health nurses have a broader perspective on regional public health and must be able to assess challenges across municipalities, facilitate rapid decision-making, and strengthen interregional collaboration to ensure an effective response system.

In hospitals, infection control leadership roles are filled by Certified Nurses in infection control and infection control-Certified Nurse Specialists, alongside nursing administrators. Currently, Certified Nurses in infection control and infection control- Certified Nurse Specialists are present in fewer than 40% of hospitals across Japan. Consequently, these professionals not only contribute to in-hospital infection control but also provide outreach support to smaller hospitals and healthcare facilities (*8*).

On the other hand, nursing administrators are responsible for overseeing infection control in hospitals and care facilities. They must ensure that staff are adequately trained and that crisis response capabilities are continually enhanced (*13*). One major challenge during the COVID-19 pandemic was that many hospitals operated with a minimal workforce during normal periods, making it difficult to scale up infection control management when crises emerged. To address this, nursing administrators must possess strong resource management skills, ensuring that hospitals can adapt quickly and deploy personnel to ICUs, other hospitals, and home care nursing stations when necessary. Strengthening rapid decision-making and personnel allocation capabilities will be essential for future pandemic preparedness.

Response to health emergencies: networking and mental health support

Rapid and effective information-sharing networks are essential during pandemics. Leveraging existing networks efficiently can improve response efforts. During the COVID-19 pandemic, many directives and official communications were issued daily by the Cabinet Office and the Ministry of Health, Labour and Welfare, requiring public health centers to adapt their responses accordingly. The ever-changing information created confusion in the field. To address this confusion, key information relevant to nursing professionals was extracted from these communications and disseminated through networks (*14*). During a pandemic, it is crucial not only to gather and distribute necessary and critical information but also to prioritize and explain essential content for nursing professionals. Providing this information in an accessible manner to infection control leaders and nursing administrators ensures a more effective and streamlined response. Additionally, the Japanese Nursing Association has received numerous inquiries regarding the expanded roles of nurses, including administering intravenous fluids and oxygen therapy at quarantine facilities (*15*). Lessons from the Disaster Support Nurses Program and IHEAT (*12*) suggest that structured information sharing, needs-based rapid response, and optimal personnel allocation are necessary for future crises.

Moreover, mental health support for nursing professionals engaged in infection control is a critical issue. Nurses, including public health nurses, who were in prolonged contact with infected patients experienced significant psychological stress, including anxiety about transmitting the virus to their families and distress from

inadequate end-of-life care for patients. As a result, they were identified as a high-risk group for suicide and mental health disorders (*16,17*). In Japan, the Disaster Psychiatric Assistance Team (DPAT) provided acute psychiatric care during the crisis (*18*), and various organizations, such as academic associations, offered online counseling and guidelines (*19*). Going forward, it is essential to enhance the existing support systems while strengthening cooperation between the Ministry of Health, Labor and Welfare and professional organizations. This includes establishing a structured counseling system and implementing stress reduction programs to ensure the mental wellbeing of nursing professionals engaged in infection control.

Sharing good practices and strengthening networks

The COVID-19 pandemic has provided valuable lessons for nursing professionals. Building networks that enable nurses to learn from different approaches taken by hospitals and municipalities can enhance their ability to respond effectively. Therefore, it is vital to systematically share good infection control practices nationwide so that they can be adapted at local levels. Having such a system in place during normal phases will facilitate the rapid exchange of good practices during emergencies. For example, there were cases in which successful outreach support models led by Certified Nurses in infection control, as mentioned previously, were actively compiled and used to refine training programs (*15*). Additionally, strengthening networks both within and across organizations is highly desirable. In one municipality, public health nurses successfully utilized an SNS communication tool, LINE, to rapidly share information with medical and welfare service providers, which significantly improved coordination. To enhance preparedness, it is essential to establish a system that allows public health centers, medical institutions, and nursing associations to maintain regular communication beyond organizational and sectional boundaries.

Furthermore, networks among hospitals, academic societies, and other professional organizations have proven effective. By leveraging these networks, training opportunities can be expanded nationwide, and a framework for collecting and sharing essential information can be developed. This not only facilitates seamless communication but also contributes to swift and well-coordinated responses during emergencies.

Policy recommendations

To respond effectively to future health emergencies, the JIHS must play a key role in implementing the following measures: *i*) Infection control skills should be integrated into basic nursing education (for public

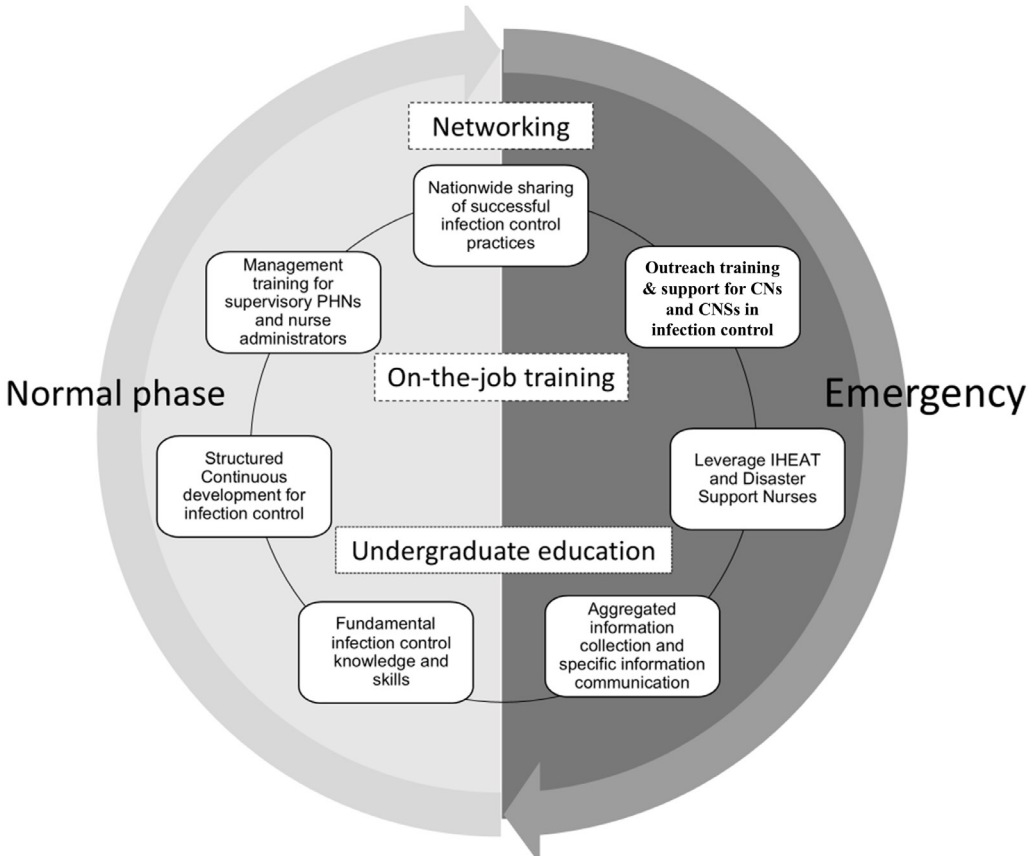

Figure 1. A comprehensive training platform for infection control to respond effectively to future health emergencies.

health nurses, midwives, and registered nurses), and practical simulation-based training should be enhanced; *ii*) Develop and organize structured training programs for continuing education and new nurse training, ensuring accessibility for nurses in small- and medium-sized hospitals, as well as welfare and long-term care facilities (mainly generalist nurses); *iii*) The training and management education of supervisory public health nurses should be strengthened, and their capacity to lead infection control measures at public health centers and at the local government level should be increased; *iv*) IHEAT and Disaster Support Nurses should be encouraged to reinforce emergency network collaboration systems while expanding mental health support programs; *v*) Organize and utilize training programs required for infection control-Certified Nurse Specialists and Certified Nurses in infection control engaged in outreach support for welfare and long-term care facilities; *vi*) Facilitate the nationwide sharing of successful infection control practices and strengthen network collaboration between medical institutions and local governments; *vii*) The official notifications, directives, and administrative communications issued by the cabinet office and the Ministry of Health, Labor and Welfare during emergencies should be aggregated and interpreted, ensuring that relevant information is effectively communicated to nursing professionals.

To fulfill these roles, it is suggested that the JIHS establish a comprehensive training platform (Figure 1) for infection control, which would serve as a hub for disseminating the latest information on infection nursing during health emergencies, compiling existing e-learning materials, and facilitating communication, information-sharing, and professional exchange.

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**Address correspondence to*:
Kyoko Sudo, National College of Nursing, Japan, 1-2-1 Umezono Kiyose-shi, Tokyo 204-8575, Japan.
E-mail: sudoky@adm.ncn.ac.jp

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How to build a better clinical trial ecosystem for future infectious disease emergencies in Japan: Findings from a narrative review and stakeholder meetings

Hiroki Saito[1,2,§,*], Kazuaki Jindai[3,§], Taro Shibata[4], Miwa Sonoda[5], Tatsuo Iiyama[5]

[1] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada;
[2] Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, Kawasaki, Japan;
[3] Department of Virology, Tohoku University Graduate School of Medicine, Sendai, Japan;
[4] Biostatistics Division, Center for Research Administration and Support, National Cancer Center, Tokyo, Japan;
[5] Department of International Trials, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: The COVID-19 pandemic posed a serious challenge to national and global pandemic preparedness and response (PPR). Timely identification and development of diagnostics, therapeutics and vaccines through prompt evidence generation from clinical trials was recognized as an important health security agenda. In 2022, under the guidance of Japan Ministry of Health, Labour and Welfare (MHLW), a health policy research team was convened to analyze the COVID-19 related clinical trial ecosystem in the context of PPR in Japan and abroad with a focus on clinical trials for therapeutics. The research mainly composed of the following: a narrative review of relevant peer reviewed journals and grey literature, interview of global experts and stakeholders including those from the United States and the United Kingdom, and a culminating meeting in Japan with various stakeholders. Based on the outcomes of this research, the team makes the following three recommendations: (1) Strengthen the leadership group's role in infectious disease clinical trials, (2) Promote sustained coordination and collaboration among stakeholders, and (3) Apply innovative clinical trial designs and create an enabling research environment. Clinical trials, as a public health good, must be further integrated into healthcare. The team advocates for the implementation of these recommendations at the policy level to help improve the clinical trial ecosystem for future health emergencies in Japan.

***Keywords*:** COVID-19, pandemic preparedness and response, health emergencies, clinical trial ecosystem

Introduction

The COVID-19 pandemic has posed a significant challenge to national and global pandemic preparedness and response (PPR). During the early phase, diagnostics, therapeutics and vaccines were developed rapidly in addition to the various public health measures deployed. Japan also conducted numerous research activities, but it lagged its peer countries in development of essential vaccines and therapeutics.

In 2021, G7 countries set up the 100 Days Mission (100DM), aiming "to develop safe and effective diagnostics, therapeutics and vaccines available within the first 100 days of a future pandemic threat being identified (*1*)". Japan reaffirmed its commitment to PPR and 100DM in 2023 when the G7 summit was held in Japan (*2,3*). World Health Organization (WHO) also emphasizes strengthening of global clinical trial ecosystem as an important global health agenda for PPR (where the clinical trial ecosystem was defined as "the sum of all elements required to fund, prioritize, design, conduct, monitor and report scientifically and ethically appropriate, well-designed, and well-implemented clinical trials as well as features necessary for oversight and coordination") (*4*). Nationally and globally, building of a better clinical trial ecosystem is recognized as of critical importance, which enables rapid development and deployment of medical countermeasures (MCMs) under pandemic conditions.

In 2022, under the guidance of Japan Ministry of Health, Labour and Welfare (MHLW), a health policy research team was convened to investigate the COVID-19 related clinical trial ecosystem in the context of PPR in Japan and abroad. The team was composed of fiver members whose expertise included research and development (R&D) management in multi-country clinical trials, health emergencies, infectious disease epidemiology and biostatistics. The team reviewed the

COVID-19 related R&D activities in various countries, interviewed stakeholders across the globe, and developed policy level recommendations that are supported by various experts. The manuscript summarizes the research findings and sets forth the recommendations as a guide for better PPR through MCMs.

Outline of research project

Narrative review

First, a narrative review was conducted to compare Japan and other countries on clinical trials for therapeutics and vaccines with a focus on the United States (US) and the United Kingdom (UK). The scope included policies relevant to R&D for COVID-19, and supportive infrastructure such as research funding and regulations. The narrative review included articles in peer reviewed journals accessed through PubMed and grey literature such as governmental documents and reports accessed through Google search. Additional relevant literature was identified from key articles and documents. The US and the UK were selected as comparisons to Japan as they were considered to have outperformed Japan in COVID-19 related clinical trials using different approaches (*5-7*). The review also helped to identify potential contacts for the stakeholder/expert interviews.

Interviews of global stakeholders and experts

Second, interviews and focus group discussions with stakeholders were conducted by two research members (HS and KJ). The aim was to further clarify challenges and identify learnings regarding the clinical trial infrastructure through experiences of the COVID-19 pandemic. Potential interview candidates were contacted by email. Additional candidates were contacted as a snowballing sampling where appropriate. The interviews were conducted in person or online with each interview lasting for 30 to 60 minutes. Meeting notes were taken in English or Japanese, and the interviews were recorded when appropriate. After each interview, a summary was created by the interviewers. A total of 27 interviews were conducted (Japan: 16, the US: 7, and the UK: 4).

Culminating meeting in Japan

Lastly, findings from the literature review and the interviews were summarized for policy implications. The recommendations to the government (MHLW) and the after-mentioned leadership group were drafted by the team thereafter. A group of Japanese experts/stakeholders were invited to a culminating meeting to obtain further input and to reach a consensus on the proposed recommendations as a group. The meeting participants were selected among the interviewees based on their technical expertise and backgrounds, ensuring a diverse set of perspectives. The meeting was held on February 15, 2023, attended by 29 participants (5 from the team; 10 experts/stakeholders including infectious disease specialists, an intensive care unit physician, basic researchers, an expert from an Academic Research Organization (ARO), a representative from a pharmaceutical company and officials from a national funder; 5 from MHLW and 8 observers). A follow-up email was sent and each participant accepted the meeting minutes.

For the purposes of this research, the following findings and recommendations are presented mainly regarding clinical trials on therapeutics, both investigational new drugs and repurposing drugs (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=97*). The recommendations also have some relevancy to the early outbreak observational research for evaluation of epidemiology (*e.g.*, 'first few hundred study') and pathophysiology. The decision to focus mainly on therapeutics in this research was made because the vaccine development had already been addressed separately at the national level such as the foundation of Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response (SCARDA) (*8*).

Findings and recommendations

The team focused on the following three areas from policy implications perspective: (1) Strengthen the leadership group's role in infectious disease clinical trials, (2) Promote sustained coordination and collaboration among stakeholders, and (3) Apply innovative clinical trial designs and create an enabling research environment. Each area was divided into sub-categories, and the recommendations of each sub-category were presented as action items with consideration to the priorities and feasibility at policy level (Table 1).

Strengthen the leadership group's role in infectious disease clinical trials

Reflecting upon the COVID-19 experience, Japanese government has announced establishment of the Department of Infectious Diseases Prevention and Control within MHLW and the creation of Japan Institute for Health Security (JIHS) consolidating the National Institute of Infectious Diseases and National Center for Global Health and Medicine to prepare for pandemics. JIHS and MHLW are expected to lead research pursuits for MCMs. For the purpose of this report, we refer to those groups collectively as the "leadership group". This leadership group will need to take on following roles in a pandemic:

i) Early detection of infectious diseases of a pandemic potential and prioritization of medical countermeasures: Infectious diseases cross borders. Surveillance activities

Table 1. Action items for better clinical trials ecosystem in Japan

Areas / Sub-categories	Action Items
(1) Strengthen the leadership group's role in infectious disease clinical trials	
i) Early detection of infectious diseases of a pandemic potential and prioritization of medical countermeasures	• Establish a process to agree on a prioritization of R&D seeds where the leadership group monitors and analyzes information that comes in from around the globe. • Strengthen trust and collaborative relationships with organizations such as WHO, health agencies in peer countries, local research institutes (ASEAN CDC, Pasteur Institute, Noguchi Memorial Institute for Medical Research, *etc.*) by sending researchers from the leadership group on secondment.
ii) Development of MCMs portfolio	• Researchers from the leadership group participates in considering MCMs portfolio with international stakeholders such as WHO R&D blueprint[1] and share ideas with industry partners and academia.
iii) Funding strategy and its flexibility	• Strengthen funding schemes that can support infectious disease R&D over multiple years. • Establish a body that can provide continuous and flexible funding support for therapeutics and diagnostics development as SCARDA plays a role in vaccine development. This could be achieved by either expanding SCARDA's scope or creating a framework that works closely with SCARDA.
iv) Support and coordination	• Create a function that specializes in research coordination such as CRN in the UK. • Build expertise in clinical trial functions, such as statistical analysis, data management, study management, and ethics review at leadership group. • Engage AMED as a national funding agency and PMDA as a regulatory body to work with the leadership group closely in order to collaborate with academia and industry. • Provide sufficient resources to facilitate and sustain communication with all stakeholders.
(2) Promote sustained coordination and collaboration among stakeholders	
i) Merge academia and industry networks	• Further strengthen a system where AROs can support investigator initiated clinical trials. In addition to setting up appropriate environment, provide sufficient funding and development seeds strategically to academia in order to cultivate talent who can lead clinical trials. • Share available infectious disease seeds between industry and academia to promote collaboration and matching. • Involve the network of local governments and health centers in the clinical trial ecosystem. For example, determine roles of each hospital in a region so eligible patients can be appropriately transferred. Similarly, better understand challenges among various stakeholders, including leadership organization, local governments, and medical institutions in the inter-pandemic period, and take appropriate measures.
ii) Talent exchange and career path design	• Increase opportunities for exchange and improve the flow of talent across public, academia, industry, and clinical sectors. It would be especially beneficial for those from the public sector to gain experience in the private sector. • Design a clear career path for experts in clinical trials and clinical trialists in collaboration with Ministry of Education, Culture, Sports, Science, and Technology. • Ensure benefits, welfare and working environment so that high retention can be achieved for diverse talent within the ecosystem. One idea might be to establish an expert certification system such as CRP in the UK.[2] • Expand programs such as IDES training and FETP to contribute to the clinical trial ecosystem. Design the programs so that their experiences can be effectively utilized in a pandemic. • Send public officials to where clinical trials take place, such as Infectious Disease Designated Hospitals and Clinical Research Core Hospitals, not just during a pandemic but during the inter-pandemic period.
iii) Collective experience and expertise	• Allocate large enough research funds to academia that can be used in the inter-pandemic period. • Review KPIs of Clinical Research Core Hospitals and design incentives such that they conduct large scale clinical trials in a pandemic. • Establish a consortium made up of the stakeholders. (Specific actions described in "(3) Apply innovative clinical trial designs and create enabling research environment"). • Create opportunities to exchange ideas on the clinical trial network from other clinical areas (*e.g.*, cardiovascular, cancer[3], *etc.*).
iv) Seamless data sharing	• Reconstruct how to effectively use data owned by different sectors. Consider establishing a specific team for the data consolidation/sharing.

[1]*https://www.who.int/teams/blueprint/* [2]*https://www.ahcs.ac.uk/registration/psa-accredited-register/clinical-research-practitioners/* [3]*https://jcog.jp/en/* AMED: Agency for Medical Research and Development; AROs: Academic Research Organizations; ASEAN CDC: Association of Southeast Asian Nations Centers for Disease Control and Prevention; CRN: Clinical Research Network; CRP: Clinical Research Practitioner; FETP: Field Epidemiology Training Program; ICH-GCP: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice; ICMRA: International Coalition of Medicines Regulatory Authorities; IDES: Infectious Disease Emergency Specialist; KPIs: key performance indicators; MCMs: medical countermeasures. PMDA: Pharmaceuticals and Medical Devices Agency; PPIE: Patient and Public Involvement and Engagement; R&D: Research and Development; UK: United Kingdom; SCARDA: Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response; WHO: World Health Organization.

Table 1. Action items for better clinical trials ecosystem in Japan (continued)

Areas / Sub-categories	Action Items
v) Communication with patients and the public	• Develop guidelines for promotional activities related to clinical trials and PPIE, and proactively use mass media especially in a pandemic to gain understanding for clinical trials. • Promote the importance of PPIE by building PPIE programs into medical education and post-graduate medical trainings.
vi) Networks with stakeholders abroad	• Strategically send researchers and public officials overseas to enhance global research networks. • Develop strategies to support more researchers and experts leading and or participating in global research networks (including securing budget and support). It may be worthwhile to designate a few locations as strategic sites. • Encourage and support Japanese researchers to apply not only to domestic grants, such as AMED, but also overseas funding in partnership with overseas partners.
(3) Apply innovative clinical trial designs and create an enabling research environment	
i) Infrastructure of academia and medical institutions	• Identify hospitals and clinics that can participate in clinical trials through pragmatic approach and create a roadmap to build a broad network of clinical trials. • Reassess research function of specified/class 1/class 2 Infectious Disease Designated Hospitals as well as other hospitals.
ii) Data reliability and flexible regulatory affairs	• Make scenarios where data compiled through pragmatic approach is utilized for emergency approval process in a pandemic, and reach a consensus on its feasibility and the strategies for safety data among stakeholders including PMDA, leadership group, academia, and industry in the inter-pandemic period. • Participate in global discussions related to revisions of ICH-GCP and apply the global standards into redesigning clinical trial infrastructure that also enables pragmatic approach. Continue to work on standardization of regulatory and approval processes using the ICMRA framework. • Have PMDA participate in the research group (consortium) made up on stakeholders within the clinical trial ecosystem (as discussed "(2) Promote sustained coordination and collaboration among stakeholders") or have regular exchange opportunities with PMDA.
iii) Preparation of protocols and simulation	• Have research group (consortium) develop various scenarios in terms of location of outbreak, potential pathogens, and prepare protocols. Hold regular meetings and workshops to conduct simulations. • Have research group (consortium) collaborate with the leadership group as well as funders in order to conduct and review clinical trials based on developed protocols like "drills".

[1]*https://www.who.int/teams/blueprint/* [2]*https://www.ahcs.ac.uk/registration/psa-accredited-register/clinical-research-practitioners/* [3]*https://jcog.jp/en/* AMED: Agency for Medical Research and Development; AROs: Academic Research Organizations; ASEAN CDC: Association of Southeast Asian Nations Centers for Disease Control and Prevention; CRN: Clinical Research Network; CRP: Clinical Research Practitioner; FETP: Field Epidemiology Training Program; ICH-GCP: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice; ICMRA: International Coalition of Medicines Regulatory Authorities; IDES: Infectious Disease Emergency Specialist; KPIs: key performance indicators; MCMs: medical countermeasures. PMDA: Pharmaceuticals and Medical Devices Agency; PPIE: Patient and Public Involvement and Engagement; R&D: Research and Development; UK: United Kingdom; SCARDA: Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response; WHO: World Health Organization.

should be strengthened through collaborations with WHO and other countries' surveillance activities led by the leadership group (*9,10*). By using more accurate information obtained in a timely manner, the leadership group will be able to assess the risks of a potential pandemic. This can be shared with stakeholders, such as academia and private industries, to help them determine appropriate R&D priorities.

ii) Development of medical countermeasures portfolio: The leadership group should prepare a therapeutic R&D portfolio based on various pandemic scenarios through clinical trials for promising MCMs. Several stakeholders pointed out that one of the reasons why Japan fell behind in COVID-19 therapeutics and vaccines development was due to the lack of candidate MCMs portfolio at the time when the outbreak was detected (*11*).

iii) Funding strategy and its flexibility: Planning a budget requires a national health security perspective when it comes to R&D activities in infectious diseases. It also requires continued support as R&D activities typically span across multiple years. The our review revealed that more than half of the COVID-19 related grants in Japan did not last for a year, unlike the US and the UK (Figure 1). While such foresight and commitment are necessary to ensure fruitful outcomes from these R&D activities, due to the unpredictable nature of a pandemic, it is often challenging for academia or industry to make such investments proactively. To ensure an effective PPR, aggressive financial support should be made by the government into areas prioritized by the leadership group. Financial support should be both Push (during R&D phase) and Pull (*e.g.*, advanced purchase commitment by the government) to minimize the risks associated with R&D. Keeping the infectious disease R&D infrastructure "warm" even during

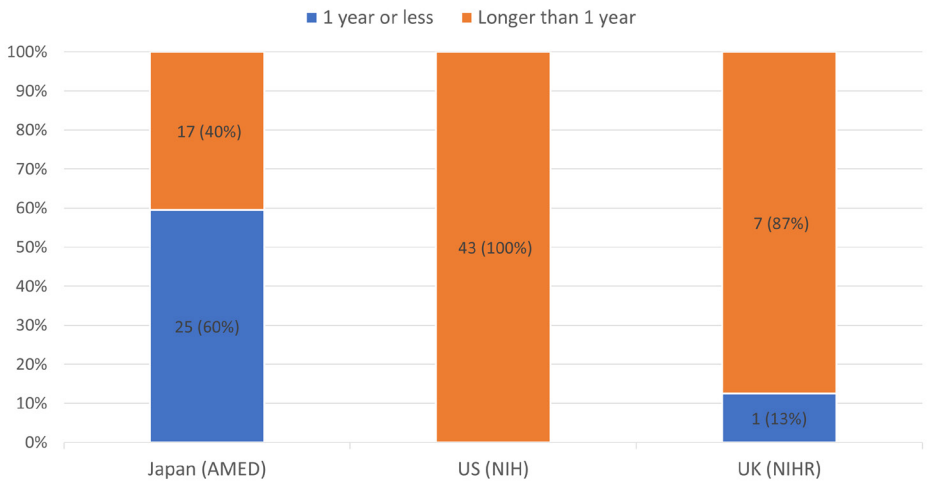

Figure 1. Number and proportion of the funding period of COVID-19 related grants in Japan, the US and the UK. AMED: Agency for Medical Research and Development; NIH: National Institutes of Health; NIHR: National Institute for Health and Care Research.

the inter-pandemic period will ensure that the R&D portfolio continues to evolve and talent development is uninterrupted.

iv) Support and coordination: The leadership group should coordinate and cultivate relationships with R&D stakeholders. Top-down direction can be effective during a pandemic; however, support for the R&D stakeholders during the inter-pandemic period can help clarify their needs. In the UK, clinical trials were prioritized by Urgent Public Health (UPH) Panel, convened from the members of Department of Health and Social Care (DHSC) and the National Institute for Health and Care Research (NIHR) early in the COVID-19 pandemic (*6*). In emergencies prior to the COVID-19 pandemic, Scientific Advisory Group for Emergencies (SAGE) in the Cabinet Office Briefing Rooms (COBR) was consulted for policy decision making (*12*). In addition, the US and the UK regulatory and funding agencies appeared to have provided more direct, tangible support to academia and industry compared to the Japanese agencies. This likely formed a closer relationship between the equivalent leadership groups and R&D stakeholders in the respective countries. It should also be made easy to provide feedback in both directions to enable continuous communication and collaboration. The leadership group is expected to unite all stakeholders, secure resources, and work with funding and regulatory agencies in order to quickly push promising MCMs to be made available and accessible in a pandemic.

Promote sustained coordination and collaboration among stakeholders

A stakeholder map of infectious diseases clinical trials in Japan was created across 3 topics: R&D, epidemiology/public health, and clinical care (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=97*). To establish a system that enables swift conduct of clinical trials during a pandemic, the stakeholders need regular coordination and collaboration in the inter-pandemic period to establish a working relationship. Below factors are essential to promote stakeholder collaboration:

i) Merge academia and industry networks: Contract Research Organizations (CROs), Site Management Organizations (SMOs), and other medical institutions work together in an industry sponsored clinical trial. Infectious disease R&D activities during a pandemic, however, are not always incentivizing for industries. On the other hand, investigator initiated clinical trials and Specified Clinical Trials (*13,14*) as well as international clinical trials may also be conducted during a pandemic, creating competition for often scarcely available resources. For a pragmatic approach that enables maximum benefit to the citizens, an efficient clinical trial ecosystem needs to be established across all the stakeholders to avoid duplicative work and foster collaborative efforts where appropriate. Academia and medical institutions often lack necessary resources to conduct clinical trials on their own. AROs, in the sense of clinical research support function, are often optimized to conduct industry sponsored clinical trials, leaving them with limited resources left for other clinical research such as investigator initiated clinical trials (*15*). In a pandemic, activities by industry and academia both become vital to the country. These networks should be merged so that roles and responsibilities can be shared and clarified while the leadership group lead these efforts overall (Figure 2).

ii) Talent exchange and career path design: The clinical trial ecosystem is rooted in personal connections. Continuous effort should be made to increase the touchpoints between those who are part of the network. For example, the 100DM provided opportunities for

stakeholders, including policy makers and experts, to meet and discuss the shared goal for Japan. In addition to providing opportunities for people to connect within the network, talent should move from one sector to another to be able to share "lived experiences". This can help activate multi-sectoral collaboration within the ecosystem (*16*). This can help avoid duplicative clinical trials through facilitation of a more collaborative research environment rather than a competitive one.

iii) Collective experience and expertise: While promoting fluid movement of talent, experience and expertise should be systematically accumulated in each organization. While the leadership group should possess the functions and talent in conducting clinical trials, the various stakeholders that are hands-on conducting clinical trials should have the expertise themselves as well. For example, academia should be able to conduct clinical trials on their own and not be dependent on CROs. It is especially important that Clinical Research Core Hospitals, as determined by Medical Care Act, can conduct infectious diseases clinical trials during a pandemic as core of research activities, in collaboration with other community hospitals and clinics (*17*).

iv) Seamless data sharing: Patient data should be more easily sharable among stakeholders for research purposes. This includes data standardization, electronic health records, consent, and ethics review. As an example, in the UK, Health Data Research UK (HDRUK) under Medical Research Council oversees data management. NHS electronic medical records summaries are shared nationally. Clinical trial data is not owned by a specific research organization but is held by NHS. Researchers routinely connect to clinical data collected on the NHS database, which enables analysis of outcome data and helps to avoid additional burden of data collection for research purposes. NHS's digital data is supported by Office for National Statistics (ONS), which is similar to Japan's Statistics Bureau. In Japan during the COVID-19 pandemic, where clinical care was provided (*e.g.*, Designated Medical Institution for Infectious Diseases) (*18*), where patient information was accumulated (*e.g.*, local public health centers), and where clinical trials were conducted (*e.g.*, Clinical Research Core Hospitals) were not functionally well connected, which became a hurdle for conducting clinical trials. There are limitations, such as where Health Center Real-time Information-sharing System on COVID-19 (HER-SYS) and other patient information/management support systems used by local governments cannot be used for research purposes even within the same facility.

v) Communication with patients and the public: A clinical trial ecosystem requires cooperation from the patients, the public, and frontline healthcare providers. Understanding of what a clinical trial entails among them becomes even more critical in a pandemic. As such, Patient and Public Involvement and Engagement (PPIE) activities are crucial in order to cultivate a cooperative culture. In the UK where PPIE activities are promoted, clinical trials are perceived as part of health care, and the people understand the importance of participating in clinical trials (*19*).

vi) Networks with stakeholders abroad: The clinical trial ecosystem does not conclude within Japan. In fact, infectious disease R&D should be global. Japanese researchers should actively participate in expert networks, international collaborative frameworks such as GloPID-R, and international platform trials. Increasingly, low and middle income countries in Asia and Africa are also establishing foundations for clinical trials, and many major industries and universities from Western countries are conducting clinical trials across continents.

Apply innovative clinical trial designs and create an

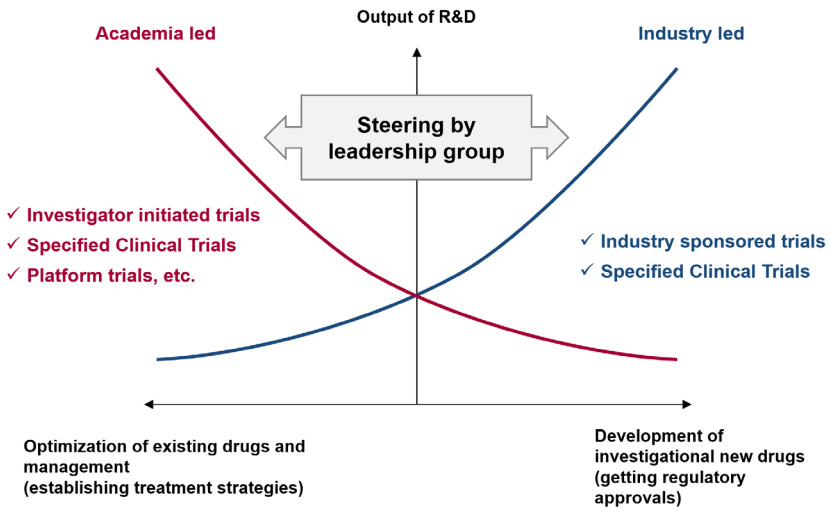

Figure 2. Roles and responsibilities of academia and industries on a clinical trial ecosystem.

enabling research environment

To conduct clinical trials promptly in a pandemic, innovative approaches in trial designs and conducts are essential. In general, evaluation of efficacy of candidate therapeutics is conducted through conventional, strictly managed randomized control trials (RCTs). In the COVID-19 pandemic, however, numerous small non-RCT clinical trials were conducted for the same interventions and was difficult to establish broadly effective evidence (*20*). In a pandemic, efforts need to be made not only to save patients but also to build evidence. Such evidence can be reflected onto the constantly updating therapeutic management strategy to immediately benefit patients (*21*).

One case example that succeeded in doing this was UK's RECOVERY trial (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=97*). RECOVERY trial showed effectiveness of dexamethasone only 3 months into the pandemic, contributing to saving an estimate of over 1 million deaths (*22*). RECOVERY took a pragmatic approach that enabled more subjects to enroll under less strict eligibility criteria compared to a conventional double-blind RCT (rigorous approach).

While the rigorous approach aims mainly to evaluate a specific intervention and obtain regulatory approval, the pragmatic approach aims to find the most beneficial treatment approach for patients (*i.e.* comparative effectiveness research) (Table 2). Investigational new drugs that have been approved through the rigorous approach may go through another clinical trial using the pragmatic approach to optimize its use (*23*). Research based on the pragmatic approach using real world data may also lead to new evidence (*24*).

On the other hand, the US conducted platform trials, such as Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV). This was a public private partnership scheme that kept some elements of the rigorous approach. The two countries had different approaches: the UK promoted public and academia led clinical trials using the pragmatic approach, and the US promoted clinical trials using the rigorous approach supported by public entities such as National Institutes of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA). The difference between the US and the UK in clinical trial design and conduct may be attributed to the differences in healthcare systems and the existing clinical trial infrastructures.

Based on these examples, Japan should consider promoting clinical trials with the pragmatic approach in addition to the more commonly practiced rigorous approach. Building evidence effectively in a pandemic by leveraging the advantages of both types of trials

Table 2. Characteristics of rigorous *vs.* pragmatic approach

Characteristics	Rigorous Approach	Pragmatic Approach
Purpose	• Obtain regulatory approval • Mainly approval for investigational new drugs, approval for additional indications	• Identify effective/optimal drugs among already approved drugs (comparative effectiveness) • Mainly drug repurposing
Method, Form of clinical trials*	• RCT (often, one to one comparison)	• Platform Trial, *etc.* (multiple arm comparisons)
Study population, Control group	• Concurrent control • Placebo, Standard of Care	• Concurrent or non-concurrent control • Standard of Care
External validity, Generalizability	• Low (strict eligibility criteria)	• High (simple eligibility criteria)
Obtaining consent	• Compliant with ICH-GCP (In Japan, Ministerial ordinance GCP compliant)	• While ICH-GCP is the standard, operate flexibly based on the circumstances
Trial conductor	• Industry sponsored trials: pharmaceutical companies, CRO • Investigator initiated trials: medical institutions, academia → if clinical trials with similar disease conditions and/or interventions, they can become "competitive"	• Medical institutions, academia → if participating in the same platform trial, becomes "collaborative"
Flexibility in protocol	• In principle, stick with the plan/protocol created prior to the trial initiation	• Can adapt flexibly based on accumulated data
Burden on participating sites	• High (need to secure resources for research conduct)	• Low
Cost per case	• High	• Low

*For the purpose of this table, clinical trials are categorized into two groups; however, not all clinical trials are strictly categorized into one or the other. CRO: Contract Research Organization; GCP: Good Clinical Practice; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; RCT: randomized control trial.

would require solving the following challenges:

i) Infrastructure of academia and medical institutions: As discussed in "*Merge academia and industry networks*", it is difficult to incentivize industries to evaluate the efficacy of existing drugs through pragmatic approach, and thus such clinical trials are often led by academia in other countries. However, in Japan, the academic institutions, such as Clinical Research Core Hospitals, who should be leading such pragmatic approach clinical trials have historically focused on using rigorous approach. Meanwhile, majority of hospitals and clinics that provide clinical care do not necessarily have the resources to conduct clinical trials. The current system is not set up for all stakeholders to be easily engaged in both types of clinical trials. Strengthening of academic institutions that lead clinical trials with rigorous approach and building a broad network of hospitals and clinics that can participate in clinical trials with pragmatic approach will both be important. Particularly, the latter broad research network needs to be promoted in the inter-pandemic period so that participation into clinical trials including platform trials can be possible in an actual pandemic (Figure 3).

ii) Data reliability and flexible regulatory affairs: Pragmatic approach employs a more relaxed eligibility criteria and minimizes additional data collection. This opens a potential risk that it may not have sufficient and accurate safety data. Whether or not evidence collected through pragmatic approach can meet requirements for drug approval process is a topic of debate (*25-27*). On the other hand, just conducting numerous small scale RCTs with rigorous approach may not lead to effective and efficient evidence generation overall. While there are some opposing aspects of the two approaches, how to improve data reliability through pragmatic approach will be a major challenge. This will also require regulatory affairs that can be flexible, reflecting societal needs.

iii) Preparation of protocols and simulation: While the total cost for a platform trial may be lower, the initial cost and time to prepare for a platform trial with pragmatic approach may be greater than multiple conventional RCTs (*28*). In addition, a large-scale trial would require buy-in from medical institutions, patients, and civil society. Time is of essence once a pandemic has begun; protocols should be established prior, and ideally, with ethics review (*29*). Operations and statistical analysis for a platform trial would also be more complex, so additional planning and simulating may be needed.

Conclusions

In this health policy research, the COVID-19 related R&D activities in various countries were reviewed, multiple interviews with experts and stakeholders were conducted, and the findings were confirmed and summarized at the culminating meeting for future policy implications. As a result, the research team proposed the following recommendations to the government and the leadership group for better PPR through MCMs: (1) Strengthen the leadership group's role in infectious disease clinical trials. The leadership group must take a proactive role in early detection of outbreak, prioritization of MCMs, portfolio development, strategic and flexible funding support, and robust support and coordination for all the stakeholders. (2) Promote sustained coordination and collaboration among stakeholders. Stakeholders in all three areas of R&D, epidemiology/public health, and clinical care should coordinate on a regular basis so that a clinical trial infrastructure can be built that enables rapid launch and conduct of clinical trials in a collaborative manner amid a pandemic. (3) Apply innovative clinical trial designs and create an enabling research environment. The leadership group should employ innovative clinical trial designs and create an enabling research environment (including funding and regulatory support) that helps to generate

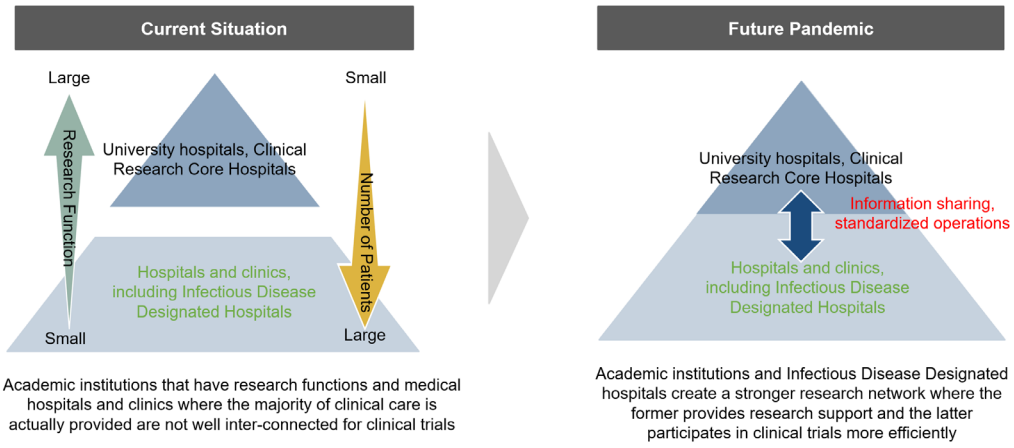

Figure 3. Current situation and future direction of clinical trial infrastructure.

valid evidence promptly, which is then directly reflected onto future clinical practice.

Though available resources are variable between Japan and other countries, the review and stakeholder meetings confirmed that numerous stakeholders in Japan were engaged in the COVID-19 pandemic response. For better future PPR, the discussions converged towards not only the "creation" of a new body or "innovative" solutions but also resource optimization and reallocation where needed. What's critically missing in Japan was the notion that the clinical trials infrastructure should be part of PPR at the policy level, and therefore, the available resources were not designed or well-connected to function efficiently and effectively under the clinical trial ecosystem.

A critical point is that a better clinical trial ecosystem must be promoted even in the inter-pandemic period, actively and constantly conducting clinical trials in infectious disease areas so that MCMs can be tested and brought in as quickly as possible in the event of a pandemic. To do so, in addition to the establishment of the leadership group that is already being discussed, an appropriate enabling environment must be cultivated such that stakeholders involved in infectious disease clinical trials can collaborate flexibly.

Another key point is to foster a "Made WITH Japan" mentality. Monitoring of outbreaks globally and networking with international frameworks as well as international collaborative clinical research groups is crucial. It is not necessary for R&D to be "Made in Japan" or "All Japan".

"Trials save lives (*30*)". Clinical trials as public health good must be further integrated into health care. The research team advocates the recommendations being implemented in a sustained manner in pursuit of a healthier society for Japan.

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[§]*These authors contributed equally to this work.*
**Address correspondence to*:
Hiroki Saito, Interdepartmental Division of Critical Care Medicine, University of Toronto, 200 Elizabeth Street, Toronto, Ontario, M5G 2C4, Canada.
E-mail: hiroki.saito@mail.utoronto.ca

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Resilience building in public health rapid response teams in urban multi-hazard scenarios: Pathways and strategies from Shanghai, China

Xiaoyan Huang[1,*], Qian Wu[1], Yang Dai[2], Huanyu Wu[1]

[1] Division of Emergency Management, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China;
[2] Medical Emergency Office, Shanghai Municipal Health Commission, Shanghai Municipal Health Commission, Shanghai, China.

Abstract: Urban centers face a complex and multifaceted array of public health threats from infectious disease outbreaks and incidents of foodborne pathogens to health crises due to disasters, posing grave risks to people's health and societal stability. As the operational backbone of emergency response systems, public health rapid response teams are mission-critical in performing disease surveillance, outbreak containment, and clinical case management across all phases of emergencies. Nevertheless, persistent structural barriers including workforce deficits and competency mismatches constrain operational effectiveness during large-scale health emergencies. To address these challenges, this study proposes a resilience-building framework for public health rapid response teams that takes into account multi-hazard scenario planning and the evolving nature of events. Key interventions including institutional capacity building, strategic foresight initiatives, cross-sector policy integration, and tiered resource allocation systems have been implemented in order to enhance the core resilience dimensions of withstanding shocks, agile adaptability, and restoration of functioning.

***Keywords*:** public health rapid response teams, resilience building, multi-hazard scenarios

Introduction

Over the past few years, the frequent occurrence of major public health emergencies worldwide (*1-3*) has posed unprecedented challenges to human health, social stability, and economic development (*4*). The COVID-19 pandemic has exposed the fragilities inherent in the global public health system, rigorously testing the emergency management capabilities of nations and regions worldwide. In this context, effective mitigation of the impacts of significant public health risks from the perspective of urban governance has become an urgent issue requiring prompt resolution.

During public health emergencies, professional and efficient public health rapid response teams can promptly mobilize to mitigate and control the spread of public health risks. Public health rapid response teams are defined as trained and equipped teams with the capacity to deploy rapidly, efficiently, and effectively respond to public health emergencies in coordination with other response efforts (*5*). However, when confronting increasingly complex and evolving disaster scenarios, multiple limitations in team building and management, such as insufficient workforce deployment during mass-casualty incidents, lack of cross-disciplinary expertise and coordinated operational capabilities in addressing complex disasters, and occupational burnout arising from prolonged high-intensity responses, have become apparent.

To address diverse disaster risks, Shanghai has issued guidelines to promote the construction of a new urban infrastructure to develop a resilient city (*6*), systematically enhancing the city's capacities to withstand, adapt to, and rapidly recover from disruptive conditions and to develop sustainably. By integrating resilience principles into the creation of public health rapid response teams, the city aims to establish an operational team system with reinforced adaptive capacity, restorative capability, and organizational learning capacity. This system is designed to enable a rapid response, provide sustained mitigation, and conduct scenario-adapting operations when confronting acute public health crises or enduring chronic public health risk pressures in varying contexts (*7*).

Connotations and theoretical foundations of resilient public health rapid response teams

Resilience building in public health systems

Originating from the fields of engineering and ecology (*8,9*), resilience is a ubiquitous concept that has been increasingly applied to the area of public health and development in recent years (*10*). A resilient health system is typically characterized as one that recognizes its inherent strengths and vulnerabilities; safeguards people's health during public health crises; responds effectively to public health crises of all types, learns from them, and turns lessons into better preparedness, and integrates diverse stakeholders and initiatives into coordinated efforts through systemic learning mechanisms (*11,12*). Such a system includes a wide variety of actors and actions in a coordinated effort to yield positive health outcomes.

Resilience building in public health rapid response teams

Public health rapid response teams refer to professionally trained units capable of rapidly deploying during public health emergencies to provide technical support and coordinate response efforts (*13*). Team members routinely provide healthcare during normal times and can be mobilized either full-time or part-time for emergency operations when required. To enhance the resilience of urban public health rapid response teams, strategies should focus on enhancing three core capacities: stress resistance (withstanding acute shocks), adaptability (adjusting to evolving threats), and the capacity for recovery (restoring functions post-crisis). This ensures agile responses to complex and dynamic emergencies while safeguarding public safety.

Strategies for building resilient public health rapid response teams

Resilience building with public health emergency response teams requires a multi-dimensional approach to establish a system that is highly adaptable and able to restore functioning.

Risk profiling and scenario mapping

Urban risks and disaster scenarios need to be systematically identified and catalogued, and demand for public health emergency response capabilities needs to be forecast.

Goal-oriented capacity planning

To achieve the dual objectives of a rapid response to small-scale incidents and sustained resilience in response to prolonged large-scale emergencies, a goal-oriented approach is required to develop and manage public health emergency response teams. This entails ensuring that both front-line teams and reserve forces meet critical criteria including sufficient workforce capacity to rapidly mobilize, adaptive competencies that align with evolving threats, and geographic distribution to ensure the coverage of vulnerable populations.

Establishing multi-sectoral collaboration mechanisms

The development of public health emergency response teams is inherently systemic. Adopting a systems thinking approach ensures integrated and coordinated efforts that integrate governmental agencies, healthcare facilities, community organizations, and civil society stakeholders through societal engagement models.

Enhancing competencies through iterative learning

The technical and professional competencies of public health rapid response teams need to be continuously enhanced, with a priority on enhancing community-based public health emergency teams to accelerate localized responses. Lessons learned from varied incident responses need to be adopted institutionally to iteratively improve operational mechanisms and workforce capabilities, such as implementing structured post-event debriefing protocols to codify operational lessons.

Shanghai's approach to building resilient public health rapid response teams

Delineating urban risks

Shanghai faces public health emergencies that may cause severe threats to people's health, including: major outbreaks of infectious diseases (*e.g.*, epidemics involving novel pathogens); clusters of diseases of unknown origin; serious incidents of foodborne and occupational diseases; health hazards triggered by natural disasters (*e.g.*, typhoons and urban waterlogging) and industrial accidents (*e.g.*, chemical leaks).

Analyzing scenario-specific demands on public health rapid response teams

Public health rapid response teams serve as the core operational force in managing public health emergencies, functioning during every phase — prevention, response, rescue, and recovery — with scenario-specific demands.

i) Routine/normal risk scenarios. During periods of sporadic disease outbreaks or incubation of latent risks, public health rapid response teams must focus on priority capacity-building objectives: enhancing future adaptability through quality system development and enabling early detection, identification, and mitigation of latent public health risks at the community level to prevent risk proliferation or incident escalation.

ii) Small-scale incident scenarios. Community-based public health rapid teams must demonstrate resilience to diverse risks, delivering a timely and coordinated response while ensuring operational stability. If initial

containment measures fail to effectively control the event, resulting in a rapid increase in cases exceeding the community's capacity, additional teams must be mobilized regionally. These teams should rapidly assemble and adeptly conduct case management, epidemiological investigations, close contact tracing, environmental disinfection, *etc*.

iii) Large-scale incident scenarios. During catastrophic events such as pandemics or major natural disasters, public health rapid response teams must demonstrate robust resilience to withstand sustained systemic shocks. During such crises, risks propagate citywide, characterized by exponential surges in cases that trigger cascading societal disruptions and impose an overwhelming strain on the urban healthcare system. To address these challenges, coordinated mobilization of all municipal public health emergency teams is imperative, ensuring optimal resource allocation through centralized command systems. Moreover, social mobilization protocols should be activated when necessary, including the strategic deployment of reserve forces from emergency response personnel pools to augment frontline capacities.

iv) Post-crisis reconstruction scenarios. During the transition from emergency to routine operations, efforts must focus on consolidating containment, preventing a resurgence, and restoring social order. Concurrently, lessons learned from public health emergency responses should be systematically identified through debriefing and evaluation of team performance, with mechanisms tailored to enhance daily preparedness and further response capabilities.

Key measures to enhance resilience building in public health rapid response teams

Integrated policy and planning

Policy support (*e.g.*, through the Shanghai Municipal Regulations on Public Health Emergencies) needs to be enhanced to mandate the establishment of a public health governance framework, a centralized emergency command system to coordinate multi-sectoral responses, and a specialized and multidisciplinary public health workforce with dual-role capabilities that integrate peacetime preparedness and emergency response. Standardized emergency management protocols shall be followed, including the creation of a tiered public health emergency response plan framework specifying operational requirements and task allocation matrices for varied incident scenarios. Municipal and district health authorities need to develop versatile and comprehensive public health teams capable of responding to multiple scenarios on-site. Additionally, all healthcare facilities should create specialized emergency response teams or rapid response units to ensure system-wide preparedness, thereby advancing a well-rounded public health emergency response system.

Establishing a tiered and categorized team system

Based on the characteristics and demands of public health emergency work in multiple scenarios, the rapid response team system should be structured through classification by function and stratification by administrative level. Teams should be classified by specialization or mission into infectious disease control teams, medical rescue teams, laboratory testing teams, sanitation and quarantine teams, and psychological crisis intervention teams, operating synergistically to achieve mission objectives. A three-tiered hierarchical structure is established at the municipal, district, and community level corresponding to administrative levels. Municipal-level teams coordinate responses to large-scale incidents and provide technical guidance, while district and community-level teams take primary responsibility for on-site emergency operations within their jurisdiction, ensuring localized containment and recovery. A scenario-driven mechanism to dispatch public health emergency response teams is needed, enabling rapid deployment of required units based on incident-specific scenarios and achieving optimized allocation of emergency resources in alignment with the city public health emergency response framework.

Enhancing district and community-level teams

District-level public rapid response teams provide guidance to community teams on preparedness and response operations. Each district-level team should maintain a reserve capacity of at least three times the size of the core team to ensure rapid augmentation of personnel in the event of surges.

Community-level teams conduct health education campaigns, risk surveillance, and reporting during routine operations. During localized incidents, these teams perform early detection, provide timely reporting, and implement initial containment measures. During large-scale emergencies, they conduct emergency response operations within designated zones.

Additionally, a standardized equipment configuration for district and community-level teams is needed, ensuring robust support in communication and command systems, field investigations, on-site operations, and logistical support.

Enhancing capacity development

A resilience-oriented mindset and culture of crisis learning should be fostered within healthcare systems by integrating public health emergency response capacity building into the routine development of healthcare frameworks through institutionalized training and scenario-based drills (*14*). General and tailored training programs and curriculum systems should be developed to foster a specialized and multidisciplinary emergency workforce. An online training platform should be constructed and hybrid training models should be adopted to expand training coverage and enhance

operational efficiency.

A city-wide annual operational plan for public health emergency response team exercises and mobilization should be formulated, mandating that all teams conduct at least one full-scale exercise annually in a scenario involving a large-scale incident. These measures ensure a rapid transition between routine and emergency modes while enhancing capabilities in cross-functional coordination, adaptive problem-solving, and scenario-specific responses under abnormal conditions.

Establishing a supportive social environment

Public health rapid response teams should be designated as high-risk occupational groups under legal regulations, mandating comprehensive safeguards for occupational safety and mental health. This includes the provision of biosafety-compliant personal protective equipment (PPE) and field investigation and response facilities. Financial and career incentives such as targeted subsidies and performance-based rewards should be offered during emergency operations. Career advancement opportunities for team members should be provided, such as professional advancement or prioritized promotions for frontline responders. A dedicated merit-based reward fund should be established to recognize individuals and units making exceptional contributions during public health crises. Strategic partnerships with academic and research institutions need to be formed to establish public health workforce pipelines *via* specialized training centers, ensuring sustained capacity development that is responsive to evolving public health threats (*15*).

Establishing a reserve workforce

A baseline assessment of healthcare professionals throughout the municipality must be prioritized through systematic workforce mapping, with targeted capacity-building in public health emergency preparedness and response delivered *via* degree-granting academic programs, credentialed residency training, and lifelong learning initiatives.

Reserve mechanisms and emergency medical reserve teams should be created to ensure capacity in the event of surges. This initiative will establish dual-role workforce reserve pools and multi-tiered emergency public health teams. At the same time, volunteer teams should be systematically created through formalized collaborations with civil society organizations. Volunteers should be strategically deployed in the following roles, with task assignments based on competency assessments and supervision by public health professionals: health education and risk communication, community containment measures, crowd control and logistical coordination, port-of-entry quarantine operations, psychological first aid, and epidemiological field investigations (Figure 1).

Limitations and priority areas for further development

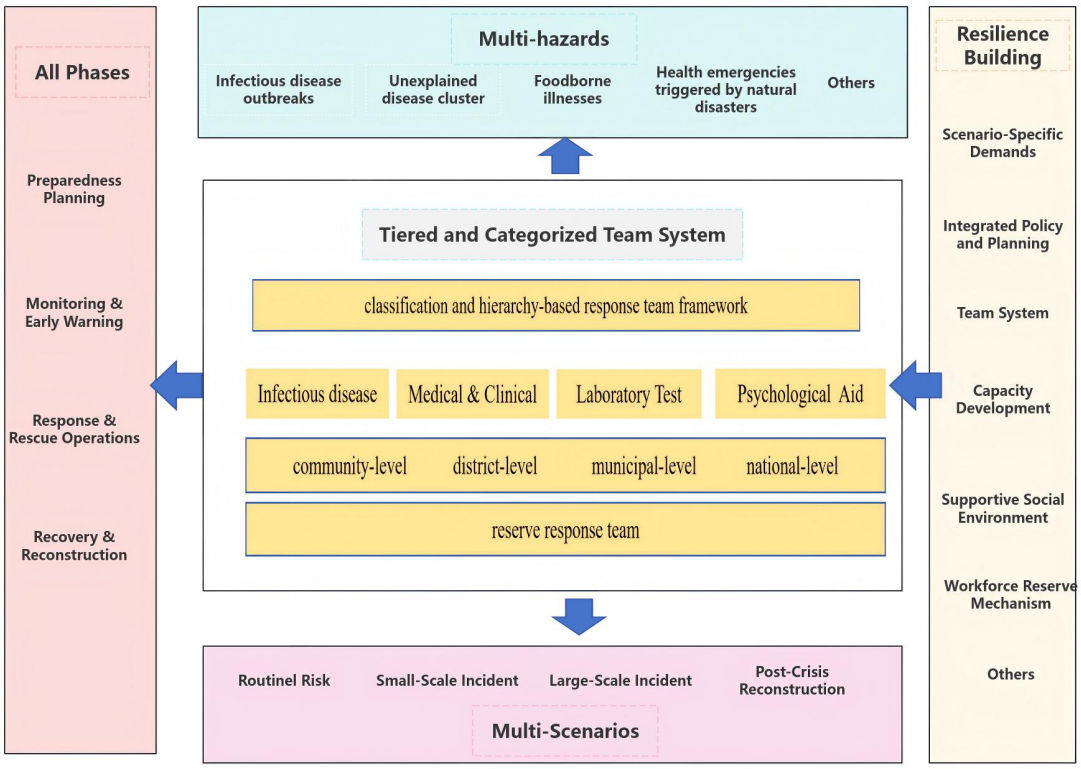

Figure 1. Core elements of resilience building. This figure comprehensively illustrates the key elements of resilience development in public health emergency response teams across multiple hazards, scenarios, and phases.

Health system resilience remains an emerging field with limited dedicated policy frameworks and implementation case studies globally. Future efforts to enhance resilience in public health rapid response teams face critical challenges, particularly in:

i) Balancing routine provision of healthcare with crisis response, especially during large-scale emergencies where evidence-based countermeasures (*e.g*., vaccines and targeted therapies) are not yet unavailable. Implementing tiered emergency response mechanisms (*16*), coupled with structured protocols for team rotation, replenishment, and cross-sector coordination to sustain essential healthcare during prolonged crises.

ii) The ability to scientifically assess evolving trajectories of public health emergencies and conduct intelligent command-dispatch operations is critical to rationally allocating emergency response teams and optimizing emergency management efficiency. The potential for further innovation lies in advances in emerging technologies to build resilience, including AI-optimized emergency decision-making architectures and blockchain-secured emergency supply chains. These technologies can catalyze intelligent operationalization of public health emergency response systems while addressing current gaps in dynamic resource coordination.

iii) Given the significant international divergence in understanding the concept of resilience and its implementation, there is a pressing need for research on quantitative assessment of resilience building in public health rapid response teams. Such research will provide data-driven support and evidence-based decision-making tools to optimize systemic adaptability and resource prioritization. Concurrently, enhanced international collaboration and exchanges of knowledge, adoption of advanced public health emergency management frameworks and technologies, and fostering strategically minded public health emergency personnel will help to enhance the systemic capabilities of rapid response teams and drive holistic improvements in public health resilience.

Conclusion

Building a resilient urban public health rapid response system is a complex, iterative systems engineering process. To ensure a rapid response to and effective mitigation of diverse urban risk scenarios, public health rapid response teams need prioritized investments in proactive preparedness including scenario-specific capacity building, stockpiling of resources for surges, and pre-determined response protocols to enhance systemic resilience. When confronted with sustained shocks and stressors, public health rapid response teams can maintain operational continuity and sustain core functions through tiered team development and integrated support mechanisms. Various strategies and methods can be used to enhance the adaptive capacity of rapid response teams, such as conducting after-action analyses, establishing institutional mechanisms to learn from crises, and implementing data-driven policies.

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**Address correspondence to*:
Xiaoyan Huang, Division of Emergency Management, Shanghai Municipal Center for Disease Control and Prevention, No. 1399 Shenhong Road, Minhang District, Shanghai 201107, China.
E-mail: huangxiaoyan@scdc.sh.cn

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Overview of global governance, capacity, and health systems implication of pandemic prevention, preparedness, and response: A narrative review and descriptive analysis of open-source data

Tetsuya Miyamoto[1,#], Masami Fujita[1,#], Masahiko Hachiya[1,#], Yuta Yokobori[1,#], Kenichi Komada[1,#], Hitoshi Murakami[1,#,2,*]

[1] Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan.
[2] School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan.

Abstract: The COVID-19 pandemic has highlighted the importance of pandemic prevention, preparedness, and response (PPPR) in global health. This review first examined global health governance (GHG) for PPPR, identifying its core-satellite structure. Key GHG functions include rule-setting, resource mobilization, medical countermeasures (MCMs) supply, surveillance and data/pathogen sharing with rapid response, and One Health. Major gaps exist in global collaboration, enforcement of the International Health Regulations (IHR), and the World Health Organization's (WHO) capacity. The most urgent issue is pathogen access and benefit-sharing (PABS). Second, the PPPR capacity across world regions were assessed using two public datasets: eSPAR and GHS Index. Sub-Saharan Africa requires urgent support to strengthen most PPPR aspects, while epidemiological and laboratory surveillance, infection prevention and control (IPC), and regulatory functions need improvement in low- and middle-income countries (LMICs) in various regions outside Europe. Japan, with its strong PPPR capacity, is well-positioned to assist. Lastly, the review explored the link between PPPR and health systems strengthening (HSS). PPPR must be firmly integrated into HSS to ensure resilience, equity, inclusiveness, continuity of care, and sustainability. Core health system components — service delivery, workforce, health information systems, MCMs access, and governance — along with communication and trust-building, effectively contribute to PPPR. However, pandemic exceptionalism and the over-securitization of PPPR and health security may hinder coordination. The enhanced GHG for PPPR, led by the empowered WHO, should effectively facilitate and coordinate technical assistance to LMICs to strengthen their PPPR capacities and promote PPPR-HSS integration by bringing together the often-divided health security and HSS communities.

***Keywords*:** pandemic prevention, preparedness and response (PPPR), health security, global health governance, IHR core capacities, health systems, Universal Health Coverage (UHC)

Introduction

Pandemics are global events that require global actions in prevention, preparedness, and response (*1*) based on multilateralism, shared responsibility, and mutual accountability among countries (*2*). Since the Coronavirus Disease 2019 (COVID-19) pandemic, reflections on its devastating public health and socioeconomic impacts, as well as the deficiencies in the global preparedness and response system, have brought pandemic prevention, preparedness, and response (PPPR) to the forefront of global health discussions, leading to the emergence of various international initiatives.

Against this backdrop, this review contributes to the *Global Health and Medicine*'s topic issue of "Health Security and Infectious Diseases" from a global health perspective through three key approaches. First, it examines global health governance (GHG) for PPPR, focusing on its structure, functions, and existing gaps through a narrative review of relevant literature. We focused on global health governance because the existing governance architecture largely determines the feasibility of the global actions required for PPPR. Second, it assesses the status of PPPR capacities across regions of the world through a descriptive analysis of open-source data from the electronic State Parties Self-Assessment Annual Reporting (eSPAR) on core capacities under the International Health Regulations (IHR) and the Global Health Security (GHS) Index. Through this analysis, we sought to elucidate the existing gaps in global PPPR capacities. Lastly, it explores the interconnections between PPPR and health systems strengthening (HSS) in the global context through a narrative review. We explored this aspect because HSS is considered a

tangible action point for addressing the PPPR capacity gaps identified in the second section.

Global health governance (GHG) for pandemic prevention, preparedness, and response (PPPR): structure, functions, and existing gaps

The United Nations Development Programme (UNDP) defines governance as the mechanisms, processes, and institutions through which citizens and groups articulate their interests, exercise their legal rights, meet their obligations, and mediate their differences (*3*). There is no universally accepted formal definition of GHG. However, it is generally defined as the use of formal and informal institutions, rules, and processes by states, intergovernmental organizations, and non-state actors to address health challenges that require cross-border collective action for effective resolution (*4*). In the following subsections, we will examine the structure, functions, and existing gaps of GHG in relation to PPPR.

Structure of GHG for PPPR

Global health is not governed by a single regime but rather by a "regime complex", a collective of partially overlapping and non-hierarchical regimes (*5*). Here, a regime refers to a set of principles, norms, rules, and decision-making procedures around which actors' expectations converge within a given issue area of international relations (*6*).

Indeed, in GHG for PPPR, multiple regimes operate in a partially overlapping and non-hierarchical manner. These include the United Nations (UN) system, which encompasses the World Health Organization (WHO), World Bank, United Nations Children's Fund (UNICEF), Food and Agriculture Organization (FAO), World Organisation for Animal Health (WOAH), and United Nations Environment Programme (UNEP); groups of nations such as the G7 and G20; and public-private partnerships (PPPs) such as the Pandemic Fund, Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), Global Alliance for Vaccine and Immunization (Gavi), Coalition for Epidemic Preparedness Innovations (CEPI), Global Health Security Agenda (GHSA), and Unitaid.

The WHO, as the sole entity authorized to establish legally binding instruments such as the so-called pandemic treaty — formally known as the WHO Convention, Agreement, or Other International Instrument on Pandemic Prevention, Preparedness, and Response (WHO CA+) — and the International Health Regulations (IHR), holds a uniquely central position in GHG for PPPR due to its comprehensive representation of 194 member states. Its central role in GHG is rooted in the widely held belief in its instrumental legitimacy (*7*). A Delphi survey of global health experts confirmed that the WHO is both the current and future leading actor in stewardship, guideline and policy development, and the promotion of solidarity and collaboration in global PPPR (*8*). The WHO's centrality in GHG for PPPR will be further reinforced by the anticipated adoption of WHO CA+ at the 78th World Health Assembly (WHA78) in May 2025. Additionally, the 2024 amendments to the IHR have strengthened the WHO's regulatory authority.

We can recognize a core-satellite structure within the existing GHG for PPPR, where the WHO serves as the central core, while other UN agencies, the G7/G20, and PPPs function as surrounding satellites with partially overlapping mandates and functions in a nonhierarchical order. These satellites are not under the direct command or control of the WHO as the central core but instead operate autonomously, sometimes without proper coordination.

Functions of GHG for PPPR

Based on a review of existing literature through Google Scholar searches using the keywords "global health governance"' AND ("pandemic"' OR "'pandemic prevention" OR "'pandemic preparedness"' OR "'pandemic response"), as well as websites and documents published by major actors in GHG for PPPR, we have identified five key functions and the major actors associated with each, as presented in Table 1. Below, we will examine each of these functions in detail.

Rule-setting

Since 2024, a trilogy of global health law reforms — including the formulation of the WHO CA+, the revision of the IHR, and the implementation of the GHSA's Legal Preparedness Action Package (LPAP) — has taken place, aiming to support global solidarity and establish a comprehensive legal framework for global PPPR (*9*). The WHO CA+ seeks to prevent pandemics, save lives, reduce disease burdens, and protect livelihoods by strengthening global capacities for PPPR (*10*). The agreement encompasses achieving equity, strengthening and sustaining PPPR and health system recovery capacities, enhancing coordination, collaboration, and cooperation for PPPR, securing financing for PPPR, and establishing governance mechanisms. The most debated issue within the WHO CA+ has been the pathogen access and benefit-sharing (PABS) mechanism. This issue is further analyzed in the subsection "Global supply of medical countermeasures (MCMs)" below.

A far-reaching and decisive package of amendments to improve the IHR was agreed upon at WHA77, underscoring the commitment to solidarity and equity, particularly in relation to access to medical products and financing, the establishment of the States Parties Committee to facilitate the effective implementation of the amended IHR, and the creation of National IHR Authorities (*11*). The amendments primarily expand assurances of equity, enhance global oversight of the

Table 1. Key functions of global health governance (GHG) for pandemic prevention, preparedness, and response (PPPR) and major actors

Key functions	Major actors
1. Rule-setting	WHO, GHSA
2. Resource mobilization, particularly surge finance	Pandemic Fund, World Bank, WHO, Gavi, Global Fund, GHSA, G20
3. Global supply of medical countermeasures (MCMs)	i-MCM-Net, WHO (CFE), G7, Unitaid, GO2AL, Gavi, CEPI, UNICEF
4. Surveillance and data/pathogen sharing with rapid response and containment	WHO (IHR, GOARN, IPSN & GISRS), US-CDC, FAO, WOAH
5. One Health	WHO, FAO, WOAH, UNEP, GHSA

WHO: World Health Organization; GHSA: Global Health Security Agenda; Gavi: Global Alliance for Vaccine and Immunization; i-MCM-Net: Interim Medical Countermeasures Network; CFE: Contingency Fund for Emergencies; GO2AL: Global Oxygen Alliance; CEPI: Coalition for Epidemic Preparedness Innovations; IHR: International Health Regulations; GOARN: Global Outbreak Alert and Response Network; IPSN: International Pathogen Surveillance Network; GISRS: Global Influenza Surveillance and Response System; US-CDC: United States Centers for Disease Control and Prevention; FAO: Food and Agriculture Organization, WOAH: World Organisation for Animal Health; UNEP: United Nations Environment Programme.

regulations' implementation, and increase authorization for national-level implementation, reflecting the stagnation in IHR core capacity building in low- and middle-income countries (LMICs) over the past 20 years.

The GHSA is an international collaboration launched in 2014 to strengthen global capacities to prevent, detect, and respond to infectious disease threats. The LPAP was introduced in March 2022 to address gaps in national legal capacities for public health security by providing technical tools and resources to help countries strengthen their public health laws. It aims to bring together state and non-state actors to advocate for legal preparedness and support countries in enhancing their legal frameworks for future health emergencies (*9*). However, unlike the WHO CA+ and IHR, it provides guidance and best practices rather than imposing binding legal requirements.

The UN itself, rather than its specialized agencies, has also sought leadership and rule-setting in PPPR. In September 2023, the UN General Assembly convened a High-Level Meeting on PPPR and issued a Political Declaration. However, this meeting ultimately failed to generate strong commitment and momentum for global health emergency governance due to diplomatic tensions, disagreements among member states, and the weakness of the Political Declaration (*12*). In 2022, the G7, under Germany's presidency, introduced the Pact for Pandemic Readiness to enhance the global landscape for pandemic preparedness. However, it failed to gain significant global momentum.

In the rule-setting process for GHG concerning PPPR, equity is emerging as a key concern, as reflected in the content of the WHO CA+ and the amended IHR. Assurance of equal access to vaccines has been strongly advocated by countries in the Global South (*13*). The issue of global equity is closely interlinked with other aspects of GHG, such as governance structures, political and economic power, laws and regulations, private investment and PPPs, and partnership and solidarity (*14*). Civil society engagement has been proposed to ensure that the equity concerns are properly addressed (*15*).

Resource mobilization, particularly surge finance

The Pandemic Fund, WHO, and Gavi currently have tangible global financing mechanisms for PPPR. The Pandemic Fund was established in 2022 by renaming the World Bank's Financial Intermediary Fund for PPPR. It can allocate up to US$25 million for single-country projects and up to US$40 million for multi-country projects in principle. The fund places a relatively greater emphasis on financing prevention and preparedness rather than response, as these are recognized as being more cost-effective (*16*). In 2015, the WHO launched the Contingency Fund for Emergencies (CFE) in response to the Ebola crisis in West Africa. The fund allows the WHO to respond rapidly to disease outbreaks and health emergencies often within 24 hours (*17*). Gavi launched the Day Zero Financing Facility in 2024 to provide rapid funding for vaccine procurement in response to global pandemics. It has already been applied to recent Mpox outbreaks in Africa (*18*).

The Global Fund launched the COVID-19 Response Mechanism (C19RM) in 2020 to combat COVID-19, adapt essential human immunodeficiency virus (HIV), tuberculosis, and malaria programs, and strengthen health systems (*19*). However, the Global Fund is no longer accepting new C19RM applications.

The GHSA and G20 are also active in pandemic financing, though they do not have any tangible financing mechanisms. In 2019, GHSA launched the Sustainable Financing for Preparedness Action Package Working Group to strategically mobilize global, regional, and country-level resources to achieve sustainable financing for PPPR. In 2021, the G20 notably launched the High-Level Independent Panel (HLIP) on Financing the Global Commons for Pandemic Preparedness and Response, aiming to identify global financing gaps and propose actionable solutions to address them (*20*). Coordinating the various financing mechanisms mentioned in the previous paragraphs will be a key challenge for GHG in PPPR over the coming decades.

Global supply of medical countermeasures (MCMs)

The US Food and Drug Administration (US-FDA) defines medical countermeasures (MCMs) as biologics, drugs, and devices that may be used in response to a potential public health emergency caused by terrorism or a naturally occurring emerging disease (*21*). In response to the COVID-19 pandemic, the WHO established the Interim Medical Countermeasures Network (i-MCM-Net), which became operational by early 2024. It is a network of UN agencies, PPPs, civil society organizations (CSOs)/non-governmental organizations (NGOs), regional bodies, industry, and the private sector, aimed at enhancing collaboration for timely and equitable access to MCMs during public health emergencies (*22*).

Japan launched the "MCM Delivery Partnership for Equitable Access (MCDP)" based on the "G7 Hiroshima Vision for Equitable Access to Medical Countermeasures (MCMs)" announced at the G7 Hiroshima Summit in 2023. The initiative aims to ensure the equitable distribution of MCMs, address all stages from research and development to manufacturing and last-mile delivery, and facilitate the mobilization of financial resources (*23*). During the COVID-19 pandemic, Unitaid co-led the Therapeutics Pillar of the Access to COVID-19 Tools (ACT) Accelerator to ensure equitable access to vaccines, tests, and treatments (*24*). It also launched the Oxygen Emergency Taskforce to address critical shortages of medical oxygen, which later evolved into the Global Oxygen Alliance (GO2AL) (*25*).

The COVID-19 pandemic has sparked much debate over the equitable global supply of COVID-19 vaccines. As previously mentioned, the most heated debate during intergovernmental negotiations on the WHO CA+ has centered around the PABS mechanism. LMICs have expressed concerns that, despite obligations to share pathogen samples and genetic data, they may not receive timely and affordable access to the resulting medical products (*26,27*). Conversely, high-income countries (HICs) and pharmaceutical companies argue that the proposed PABS may contradict existing intellectual property laws. The draft treaty suggests that manufacturers provide a minimum of 20% of their pandemic-related products — split between donations and affordable pricing — to the WHO for distribution based on public health needs (*28*).

The COVID-19 Vaccines Global Access (COVAX) Facility, coordinated by Gavi and involving the WHO, CEPI, and UNICEF, was the first global effort to ensure access to COVID-19 vaccines for all countries worldwide (*27*). Although it significantly contributed to delivering vaccines to LMICs, various operational shortcomings were identified. According to a scoping review, the primary implementation challenge was vaccine nationalism and hoarding by HICs. Governments of HICs with purchasing power signed bilateral agreements with vaccine manufacturers to secure supplies for their populations before they were made available to LMICs through COVAX, resulting in a "too little, too late" delivery to LMICs (*29*). Others point out governance issues inherent to PPPs, such as conflicts of interest among suppliers sitting on the governing board (*30*). However, the COVAX model is likely to be relevant for future pandemics, particularly as an effort to ensure the PABS mentioned above.

Surveillance and data/pathogen sharing with rapid response and containment

The WHO hosts several reporting mechanisms for public health emergencies, including pandemics. First, the IHR requires member states to notify the WHO of any events that may constitute a public health emergency of international concern (PHEIC) through the National IHR Focal Point within 24 hours (*31*). Second, the Global Outbreak Alert and Response Network (GOARN), a network of expert institutions primarily focused on responding to and controlling outbreaks by rapidly deploying experts to outbreak sites, also works on alerting and risk assessments through weekly operational calls since 2017. These calls facilitate the sharing of alerts and operational information to ensure that all stakeholders are informed about emerging epidemic threats (*32*). Third, the International Pathogen Surveillance Network (IPSN), a global network of pathogen genomic communities including governments, academia, the private sector, civil society, and international organizations, was launched in 2023 to facilitate the early detection of new epidemic threats through global genomic surveillance (*33*). Fourth, although its scope is limited to influenza, the Global Influenza Surveillance and Response System (GISRS), established in 1952, monitors and analyzes influenza viruses to detect emerging strains with pandemic potential (*34*).

The United States Centers for Disease Control and Prevention (US-CDC) operates the Global Disease Detection (GDD) Program since 2004, aiming to detect and stop infectious diseases at the source before crossing international borders through the network of CDC technical experts stationed worldwide (*35*). In the field of One Health, the Global Early Warning System (GLEWS), a collaboration between WHO, FAO, and WOAH launched in 2006, is operating to track zoonotic diseases (*36*). Notably, GOARN, GDD, and GLEWS provide frameworks for rapid response and containment of pandemics.

A study identified governance and coordination, health systems infrastructure and resources, and community engagement as the three key areas needing improvement in global health information systems to optimize PPPR (*37*). A commentary by authors, including the former Director of the US-CDC, based on lessons learned from COVID-19, advocates for global information-sharing and collaboration, and more specifically, the prototype pathogen approach. This strategy involves selecting and studying virus families with high pandemic potential in order to preemptively

gather information on basic virology, diagnostic assays, animal models, antigenic targets, optimal vaccine platforms, and potential immune correlates for the rapid development of MCMs when pandemics occur (*38*).

One Health

One Health is defined as a holistic, systems-based approach that recognizes the interconnection between the health of humans, animals, plants, and the environment. This concept has gained renewed attention and evolved over the past decade due to the increased frequency and severity of threats that link the health of humans, animals, plants, and the environment (*39*). One Health, along with measures to prevent antimicrobial resistance (AMR), is one of the few approaches that directly address the "prevention" aspect of PPPR.

Among the existing global One Health initiatives, the most notable is the One Health Joint Plan of Action (OHJPA) led by the UN quadripartite organizations: WHO, FAO, WOAH, and UNEP (*39*). The One Health High-Level Expert Panel (OHHLEP) was launched in 2021 by the same four UN agencies to provide scientific guidance on One Health risks and policy recommendations. The multisectoral and transdisciplinary expertise of OHHLEP members spans a wide range of fields, including animal, human, and environmental health, biodiversity conservation, and social sciences (*40*). The Zoonotic Disease Action Package (ZDAP) of the GHSA involves countries and organizations around the world, aiming to support its members in developing and strengthening their capacity to prepare for, prevent, detect, and respond to zoonotic disease threats using a One Health approach (*41*).

Several pieces of literature highlight the weaknesses of the global governance of One Health. One source identifies four key issues: *i*) sectoral, professional, and institutional silos, along with tensions between human, animal, and environmental health; *ii*) challenges posed by the international legal system and state sovereignty; *iii*) asymmetry in power between countries represented in multilateral institutions; and *iv*) chronic underinvestment (*42*). Another source points out the lack of global governance over wildlife trade for human consumption to prevent zoonotic spillovers (*43*). The third specifically identified the relative lack of integration of environmental and social sciences compared to human and animal health (*44*).

Existing gaps of GHG for PPPR

Literature has identified various existing gaps in GHG for PPPR, particularly those that arose in response to the COVID-19 pandemic. Three broad categories of gaps are mentioned across multiple articles. The first is the lack of global collaboration, coordination, and partnership. This category encompasses two distinct dimensions: *i*) dyscoordination among governance actors (*45*), and *ii*) dyscoordination among governance subjects, most notably national governments (*46*). The former is specifically illustrated by the differing and fragmented responses of the WHO, the European Union (EU), and the International Monetary Fund (IMF)/ World Bank to COVID-19. The latter is manifested in the lack of coordination between HICs and LMICs (*46*), the domination of HICs (*47*), rivalry between powerful countries (*48*), and inequitable representation (*49*).

The second gap is the lack of enforcement of global rules, particularly the IHR, and the compliance of countries. Although the IHR is legally binding regulations, the WHO has limited enforcement power over its member states. As a result, the level of voluntary implementation and compliance among countries remains low (*50-52*). This situation is rooted in the world order dominated by sovereign nations, where the obligations stipulated in the IHR can only be achieved by balancing national and global interests (*46*). The UN Charter explicitly prohibits the UN from intervening in matters that are essentially within the domestic jurisdiction of any state (*53*). Several proposals have been made to address this issue, including incentives for participation, penalties for non-compliance (*52*), independent rapporteurs with investigatory missions, a formal structure for civil society reporting and accountability, and trust-building activities between the WHO and countries (*54*).

The third gap is the insufficient capacity of the WHO, which forms the central core of the GHG architecture for PPPR. Insufficiencies identified include conflicts of interest and political bias, a more political than technical orientation (*50*), ineffective communication of crucial scientific information, a small budget that largely depends on voluntary contributions (*48*), and delayed declarations of PHEIC, as seen in the case of the West Africa Ebola crisis in 2014 (*55*).

From the review above, it is apparent that the future GHG for PPPR must confront the daunting task of effectively coordinating among governance actors, as illustrated in Table 1, as well as among governance subjects, including national governments, private corporations, and civil society, and between governance actors and subjects. With the anticipated adoption of the WHO CA+ in May 2025, it is crucial to revisit the issues of enforcement and compliance, alongside those related to the amended IHR, and ideally develop innovative solutions to this longstanding problem. The WHO must be empowered in terms of authority, operations, and financial resources to function effectively as the central hub of the GHG for PPPR. Finally, the most pressing issue within the GHG for PPPR — the PABS — must be effectively resolved within the framework of the WHO CA+.

Overview of the status of PPPR capacities across world regions: A descriptive analysis of open-source data

This section examines the status of PPPR capacities across world regions and identifies major gaps through a descriptive analysis of the electronic State Party Self-Assessment Annual Reporting (eSPAR) for the IHR and the Global Health Security (GHS) Index. Table 2 compares the 15 IHR core capacities assessed in eSPAR with the six categories of the GHS Index. Generally, the former provides a more detailed breakdown of specific aspects, while the latter takes a more aggregated approach.

A major difference between the two datasets is that while eSPAR covers non-biological threats, such as chemical events and radiation emergencies, the GHS Index focuses specifically on infectious diseases. A large proportion of the components overlap. For example, "5. Surveillance" in eSPAR corresponds to "2. Early detection and reporting" in the GHS Index, while "1. Policy, legal, and normative instruments to implement IHR" in eSPAR aligns with "5. Commitments to improve national capacity, financing plans to address gaps, and adherence to global norms" in the GHS Index. Risk communication, explicitly covered as Capacity 10 in eSPAR, is also included under Category 3 (Rapid response) in the GHS Index.

PPPR capacities across world regions assessed by the electronic State Parties Self-Assessment Annual Reporting (eSPAR)

The IHR mandates member states to report to the World Health Assembly on the implementation of the Regulations. Between 2010 and 2017, an IHR monitoring questionnaire was sent to IHR National Focal Points. In 2015, the comprehensive IHR Monitoring and Evaluation Framework (IHRMEF) was introduced, which included the State Parties Self-Assessment Annual Reporting (SPAR), Joint External Evaluation (JEE), after-action reviews, and simulation exercises. SPAR is a mandatory, country-led, multisectoral review of progress toward IHR core capacity implementation. In contrast, the JEE is an external review of a country's progress conducted every 4-5 years. To facilitate SPAR, the electronic State Party Self-Assessment Annual Reporting (eSPAR) tool was implemented in 2018 (*56*).

The eSPAR generates scores for each of the 15 IHR core capacities for all countries worldwide, making it suitable for assessing status of IHR core capacity implementation across world regions. However, due to its self-reporting nature, SPAR scores are susceptible to overreporting by countries. In contrast, the JEE is more objective and less prone to bias. Indeed, a study comparing SPAR and JEE scores revealed an average difference of 18%, with the average JEE score at 56% and the average SPAR score at 75% in 2017 (*57*). Nevertheless, since the JEE is conducted only once every 4-5 years for any given country, its annual coverage is limited, making it unsuitable for assessing the cross-sectional status of world regions. Existing literature has found a high correlation between JEE and SPAR scores (*56,58*). For these reasons, we used eSPAR rather than JEE scores to assess the PPPR status of different world regions.

The Sustainable Development Goals (SDGs) have set Target 3.d, "Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction, and management of national and global health risks", as one of the means of implementation targets. This target has two indicators: 3.d.1 measures IHR capacity and health emergency preparedness, monitored through eSPAR, while 3.d.2 tracks the percentage of bloodstream infections caused by selected antimicrobial-resistant organisms, monitored by the

Table 2. Comparison of IHR core capacities in eSPAR and categories in GHS Index

IHR core capacities in eSPAR[a]	Categories in GHS Index[a]
1. Policy, Legal and normative Instruments to implement IHR	1. Prevention of the emergence or release of pathogens
2. IHR Coordination, National IHR Focal Point functions and advocacy	2. Early detection and reporting epidemics of potential international concern
3. Financing	3. Rapid response to and mitigation of the spread of an epidemic
4. Laboratory	4. Sufficient and robust health system to treat the sick and protect health workers
5. Surveillance	5. Commitments to improve national capacity, financing plans to address gaps, and adhering to global norms
6. Human resources	6. Overall risk environment and country vulnerability to biological threats
7. Health emergency management	
8. Health services provision	
9. Infection prevention and control (IPC)	
10. Risk communication and community engagement (RCCE)	
11. Points of entry (PoEs) and border health	
12. Zoonotic diseases	
13. Food safety	
14. Chemical events	
15. Radiation emergencies	

IHR: International Health Regulations; eSPAR: electronic State Parties Self-Assessment Annual Reporting; GHS: Global Health Security. [a]The numbers of the 15 IHR core capacities in eSPAR (left column) and the six categories in GHS Index (right column) do not correspond to each other.

Global Antimicrobial Resistance and Use Surveillance System (GLASS).

The eSPAR currently consists of 15 IHR core capacities and 35 indicators. Each indicator is scored from 1 to 5 based on predetermined rating scale definitions and then converted into a percentage (0-100%). Capacity scores are calculated as the arithmetic mean of all indicator scores (%) within each capacity (*59*). The total eSPAR score (%) for a country is obtained by calculating the arithmetic mean of the 15 capacity scores, rounded up to the nearest integer. The aggregated scores for the six WHO Regions are calculated as the arithmetic mean of the total scores of all countries within each Region. Figure 1 presents the map of the six WHO Regions.

Figure 2 illustrates the trend in the total average score (%) of the 15 IHR core capacities reported by eSPAR across the six WHO Regions and Japan from 2021 to 2023. Revisions to categories and indicators occurred between 2017 and 2018, and again between 2020 and 2021. In particular, the number of core capacities increased from 13 to 15 between 2020 and 2021. Given this inconsistency in the timeline, we focused only on data from 2021 to 2023. There are four major findings. First, Japan consistently scored much higher than the averages of all six WHO Regions. Second, among the six Regions, the European Region (EUR) had the highest scores throughout the three years. Third, the African Region (AFR) consistently had the lowest scores during the period. Lastly, the scores of the remaining four Regions — the Americas Region (AMR), Eastern Mediterranean Region (EMR), South-East Asia Region (SEAR), and Western Pacific Region (WPR) — were closely grouped, positioned just below those of EUR.

Japan's high scores can be partly explained by the fact that each WHO Region includes LMICs among its members. Even EUR encompasses LMICs in Central Asia. SEAR has no HICs, AFR has only Seychelles as an HIC, and AMR, EMR, and WPR consist of a mix of HICs and LMICs. These findings clearly indicate that AFR should be a priority for support to strengthen its IHR core capacities for improved PPPR, particularly through assistance from Japan.

PPPR capacities across world regions assessed by Global Health Security (GHS) Index

The GHS Index is an initiative led by the Nuclear Threat Initiative (NTI) and the Johns Hopkins Center for Health Security (JHU), in collaboration with The Economist Intelligence Unit (EIU). It represents the first comprehensive evaluation and comparison of health security and related capacities across 195 countries. The Index is based solely on publicly available information, including data that countries have either disclosed themselves or that has been provided to or documented by international organizations (*60*). Given the complexity of global health security, a multidimensional analytical framework was employed for an objective, country-level assessment. An international panel of experts provided insights and recommendations on the Index's structure, questions, and data sources. The EIU conducted research to generate the Index scores. Countries were given the opportunity to review and comment on preliminary results, but score changes were considered only if publicly available evidence was provided that had not been previously identified by the research team (*61*).

The GHS Index is also susceptible to overreporting by countries due to its reliance on open-source data. However, it is considered more objective than eSPAR because data are researched and scored consistently by a third party, and a multidimensional analysis is conducted on collected data to generate scores. While eSPAR primarily reflects government authorities, the GHS Index mainly reflects evaluations by foreign experts. A study found a low correlation between SPAR and GHS Index scores, suggesting that they measure different aspects of PPPR capacities (*58*).

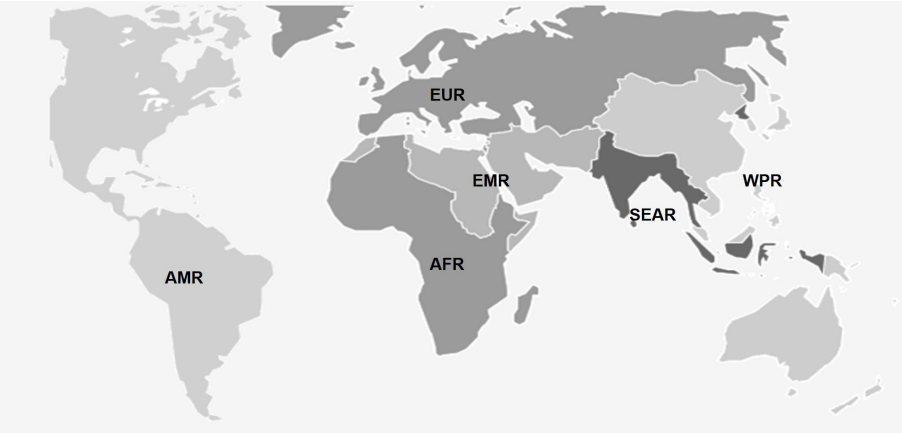

Figure 1. Map of WHO Regions. Data Source: WHO MiNDbank (*https://extranet.who.int/mindbank*). AMR: Americas Region; AFR: African Region; EUR: European Region; EMR: Eastern Mediterranean Region; SEAR: South-East Asia Region; WHO: World Health Organization; WPR: Western Pacific Region.

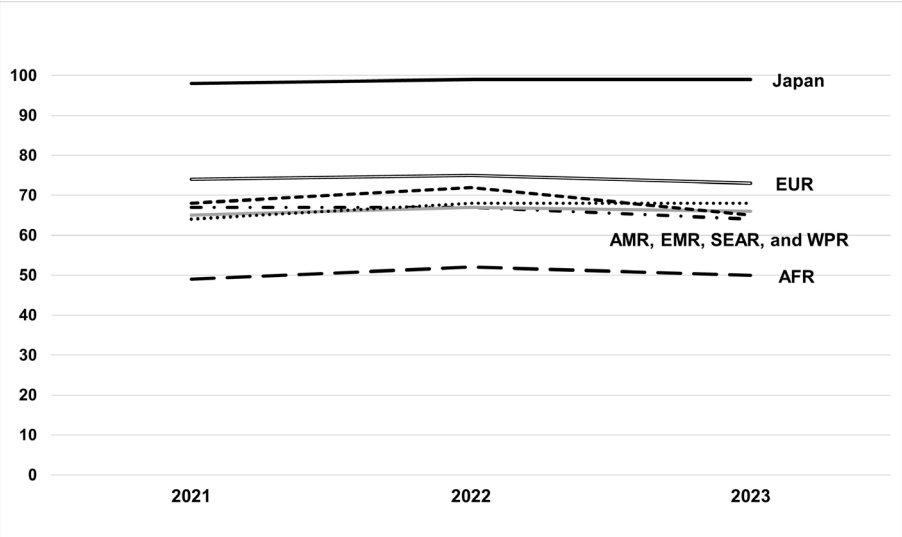

Figure 2. Trend of total average score (%) of 15 IHR core capacities reported by eSPAR by WHO Regions and Japan (2021-2023). IHR: International Health Regulations; eSPAR: Electronic State Parties Self-Assessment Annual Reporting; AMR: Americas Region; AFR: African Region; EUR: European Region; EMR: Eastern Mediterranean Region; SEAR: South-East Asia Region; WHO: World Health Organization; WPR: Western Pacific Region.

The Index consists of six categories and 37 indicators, which are further subdivided into 96 sub-indicators and 171 questions. Different indicators use different rating scales, but all scores are normalized to a range of 0 to 100. When aggregating indicator scores to calculate category scores, different weighting principles were applied to reflect varying assumptions about relative importance of indicators. These principles included equal weighting, expert-informed panel weighting, and weighting based on Principal Components Analysis. Consequently, category scores were calculated as weighted means of indicator scores, as determined by the weighting profile. Total GHS Index score for a country was also calculated as the weighted mean of the six category scores (*61*).

Figure 3 illustrates the trend in the total average scores (%) of the six GHS Index categories by WHO Region and Japan from 2019 to 2021. The aggregated scores for the six WHO Regions were calculated as the arithmetic means of the total scores of all countries within each Region, ensuring consistency with eSPAR. Findings reflect three key patterns observed in the eSPAR data analysis: Japan's higher scores, EUR's position as the highest-scoring Region, and AFR's position as the lowest-scoring Region in both years. However, while the scores for AMR, EMR, SEAR, and WPR were closely grouped in the eSPAR analysis, they were more dispersed in the GHS Index. EMR ranked as the second-lowest, followed by WPR. Overall, these four Regions scored significantly lower and were positioned closer to AFR than to EUR. This last finding may reflect a reduced impact of overreporting by countries in AMR, EMR, SEAR, and WPR in the GHS Index compared to eSPAR.

Based on the assumption that the GHS Index is more objective than eSPAR, discrepancies in the GHS Index scores, averaging the 2019 and 2021 figures for all six categories, between Japan and the six Regions were examined to identify the categories most in need of assistance (Table 3). EUR scored highest in all six categories, while AFR scored lowest in four out of six categories. When examining discrepancies of more than 25 percentage points (pp) between Japan and the Regions, AFR showed discrepancies greater than 25pp in five out of six categories, except for Category 5: Commitments to Improve National Capacity. This indicates an urgent need for support in sub-Saharan African countries to enhance most aspects of PPPR. For Category 2: Early Detection and Reporting (Surveillance), all Regions except EUR showed discrepancies greater than 25pp. For Category 4: Sufficient and Robust Health Systems, AFR, EMR, and WPR exhibited discrepancies greater than 25pp. Several Regions require support to strengthen these two categories.

For Categories 2 and 4, we examined discrepancies at the indicator level to gain a better understanding. For Category 2, the arithmetic means of the six indicator scores for Japan and all countries in AFR, AMR, EMR, SEAR, and WPR were compared. For Category 4, the arithmetic means of the seven indicator scores for Japan and all countries in AFR, EMR, and WPR were compared. Among indicators for Category 2 (Surveillance), discrepancies greater than 50pp were observed in laboratory supply chains (62.1pp), real-time surveillance and reporting (66.0pp), and surveillance data accessibility and transparency (57.3pp). Countries in AFR, AMR, EMR, SEAR, and WPR require support for both epidemiological and laboratory surveillance for early detection and reporting. Among the indicators for Category 4 (Health Systems), discrepancies greater

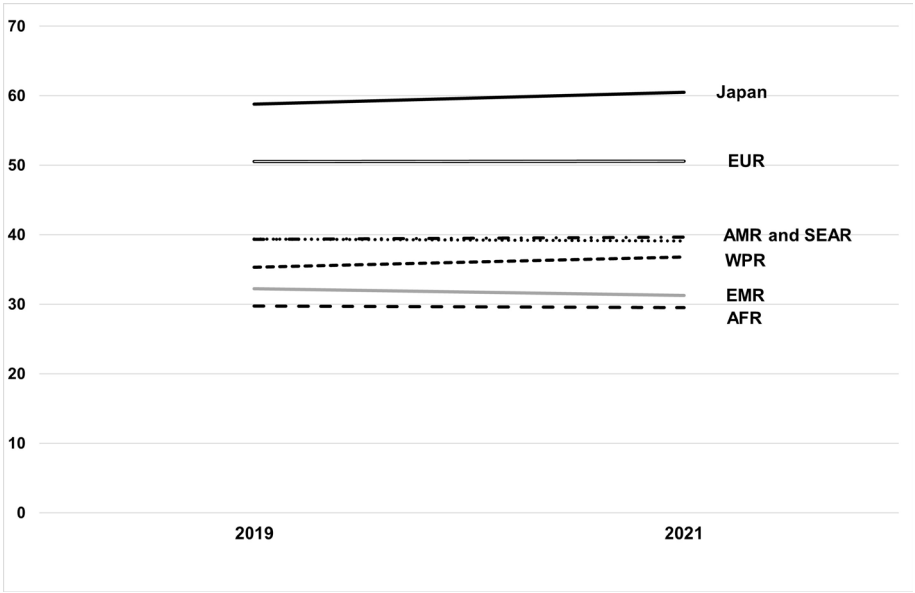

Figure 3. Trend of total average score (%) of six GHS Index categories by WHO Regions and Japan (2019 and 2021). GHS: Global Health Security; AMR: Americas Region; AFR: African Region; EUR: European Region; EMR: Eastern Mediterranean Region; SEAR: South-East Asia Region; WHO: World Health Organization; WPR: Western Pacific Region.

than 50pp were observed in infection control practices (83.9pp) and capacity to test and approve new medical countermeasures (64.3pp). Countries in AFR, EMR, and WPR need support for infection prevention and control (IPC) in medical facilities and for strengthening regulatory functions.

In summary, the above analysis indicates that countries in sub-Saharan Africa urgently need support to enhance most aspects of PPPR, so they do not become the weakest link in the chain of global PPPR. AFR, AMR, EMR, SEAR, and WPR require support on epidemiological and laboratory surveillance, while AFR, EMR, and WPR need support on IPC and regulatory functions. Japan is well-positioned to provide such support, given its strong performance in nearly all aspects of PPPR.

Interconnections between PPPR and Health Systems Strengthening (HSS) in the global context

In 2000, the WHO defined a health system as encompassing all activities whose primary purpose is to promote, restore, or maintain health in the World Health Report 2000. The report outlined three fundamental objectives of health systems: *i*) improving the health of the population, *ii*) responding to people's expectations, and *iii*) providing financial protection against the costs of ill health (*62*). In 2010, the WHO introduced Health Systems Framework, which identifies six building blocks of health systems: *i*) service delivery, *ii*) health workforce, *iii*) health information systems, *iv*) access to essential medicines, *v*) financing, and *vi*) leadership/ governance (*63*).

The Ebola virus disease outbreak in West Africa (2014-2016) and the COVID-19 pandemic have highlighted the crucial role of health system capacity and resilience in PPPR, underscoring need for stronger integration between PPPR and health system strengthening (HSS) (*64-66*). Indeed, the 15 core capacities of the IHR include health service provision, human resources, financing, and policy, as well as legal, normative, and legislative instruments — all of which are components of health systems (Table 2).

Based on a review of existing literature through Google Scholar searches using the keywords ("pandemic prevention, preparedness, and response" OR "health security") AND ("health systems strengthening" OR "universal health coverage" OR "'primary health care"), in the following subsections, we will examine the concept of interconnections between PPPR and HSS, the tangible contributions of health systems to PPPR, and potential barriers to effective PPPR-HSS coordination.

Conceptual relationship between HSS, Universal Health Coverage (UHC), Primary Health Care (PHC), and health security

In 2016, Kutzin and Sparkes argued that HSS comprises the means or policy instruments, while Universal Health Coverage (UHC) serves as a framework for defining policy objectives. UHC means that all people have access to the health services they need without financial hardship (*67*). They further explained that HSS represents actions taken, whereas UHC, health security, and resilience represent desired outcomes (*68*).

At the WHA 75 in 2022, Dr. Tedros Ghebreyesus, Director-General of the WHO, reported on strengthening global architecture for health emergency preparedness,

Table 3. Discrepancies of GHS Index scores for six categories between Japan and six WHO Regions (average of 2019 and 2021)

Regions	Category 1		Category 2		Category 3		Category 4		Category 5		Category 6	
	Scores	Discrepancy (pp)	Scores	Discrepancy (pp)	Scores	Discrepancy (pp)	Scores	Discrepancy (pp)	Scores	Discrepancy (pp)	Scores	Discrepancy (pp)
Japan	45.2	NA	63.6	NA	61.3	NA	50.5	NA	66.7	NA	70.6	NA
EUR	45.2	0.0	40.7	-22.9	46.4	-14.9	47.1	-3.3	55.9	-10.8	68.0	-2.6
AFR	15.0	-30.2	23.7	-39.9	32.1	-29.2	17.5	-33.0	45.5	-21.2	44.0	-26.6
AMR	29.9	-15.2	29.5	-34.1	41.0	-20.3	31.4	-19.0	48.9	-17.8	56.3	-14.3
EMR	22.8	-22.3	23.6	-40.0	35.2	-26.1	23.6	-26.9	36.9	-29.8	48.4	-22.2
SEAR	29.3	-15.8	37.4	-26.2	39.6	-21.7	30.4	-20.1	46.2	-20.5	52.8	-17.8
WPR	22.7	-22.4	28.4	-35.2	40.6	-20.7	23.9	-26.5	42.4	-24.3	58.3	-12.3

Discrepancy of more than 25 percentage points (pp) are highlighted by bold letters. GHS: Global Health Security; WHO: World Health Organization; PP; percentage points; European Region; AFR: African Region; AMR: Americas Region; EMR: Eastern Mediterranean Region; SEAR: South-East Asia Region; WPR: Western Pacific Region. Category 1: Prevention of the emergence or release of pathogens. Category 2: Early detection and reporting epidemics of potential international concern. Category 3: Rapid response to and mitigation of the spread of an epidemic. Category 4: Sufficient and robust health system to treat the sick and protect health workers. Category 5: Commitments to improve national capacity, financing plans to address gaps, and adhering to global norms. Category 6: Overall risk environment and country vulnerability to biological threats.

response, and resilience. He emphasized that health security, Primary Health Care (PHC), and health promotion should be built upon a solid foundation of strong health systems (*69*). PHC refers to healthcare provided as close as possible to people's everyday environment, encompassing health promotion, disease prevention, treatment, rehabilitation, and palliative care (*70*). Several articles have also highlighted critical interconnections between health security, UHC, and HSS (*71,72*). Based on the above, HSS is regarded as a concrete action point in achieving aspirational objectives of UHC, PHC, and health security, including PPPR.

A proposal has been made to integrate core capacities of global health security into comprehensive UHC systems as a robust defense against future pandemics. Such integration simultaneously strengthens both global health security and UHC, ensuring long-term resilience and equity (*73,74*). Similarly, PHC has been proposed as a crucial component of health system resilience due to its inclusiveness and ability to ensure continuity of care during pandemics (*75,76*).

Tangible health systems contributions to PPPR

Numerous articles elaborate on contributions of health systems to PPPR, primarily based on past pandemic experiences, including the West African Ebola outbreak and the COVID-19 pandemic. Figure 4 summarizes the contributions of health systems components and functions to PPPR. Among the six building blocks of health systems, five have been identified in several studies as direct contributors to PPPR. The first is service delivery, often discussed in the context of ensuring continuity and scalability of routine services during pandemics (*77-79*). The second is the health workforce, with particular emphasis on its surge capacity (*77,80,81*). The third is the health information system, particularly — but not limited to — disease surveillance (*78-81*). The fourth is supply chain management, especially regarding MCMs, with a focus on equitable distribution (*77,78,80,81*). The last is leadership and governance, encompassing issues such as command and control, jurisdictional authority across administrative levels, and coordination (*78,80,81*). The remaining building block, financing, has not been extensively addressed in the existing literature but is also critical for PPPR.

In addition to the components of health systems, two key functions have been identified as notable contributors during pandemics. The first is communication, which includes risk communication strategies, community engagement, and partnerships with the media (*80,81*). Community engagement is particularly important for ensuring equity in service delivery and promoting social justice. The second is trust-building, which involves fostering trust in health systems among the public and trust in management among healthcare workers (*80,81*).

Recognizing that health system resilience is key

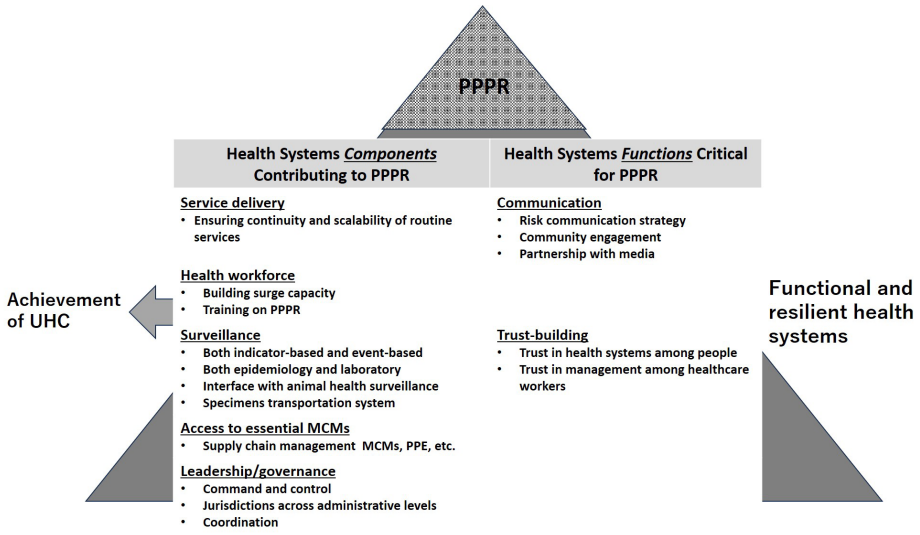

Figure 4. Contributions of health systems components and functions to pandemic prevention, preparedness, and response (PPPR). MCMs: medical countermeasures; PPE: personal protective equipment; UHC: Universal Health Coverage.

to effective PPPR, several articles have elaborated on factors contributing to resilience during pandemics. These factors include multi-sectoral responses, adaptation of health system capacity to evolving situations, strengthening of PHC, and increasing and sustaining public financing through domestic resource mobilization for health and social protection (*75,82,83*).

To safeguard surge capacity of the health workforce and contingency financing for pandemics, redundancy in human resources and budgets is necessary. However, ensuring redundancy presents a challenge due to the continuous demand for efficiency, which often involves reducing redundancy in health systems and health facility management.

Potential barriers to PPPR-HSS coordination

Several potential barriers to PPPR-HSS coordination are noted in existing literature. The first is the exceptionalism of PPPR and health security (*84*). The mentality that pandemics are exceptional events requiring exceptional measures may lead to deprioritization of sustainable and stable resource allocation to health systems, as it overlooks the functions of existing health systems.

The second is the over-securitization of PPPR and health security by framing them as part of the national security agenda. This can cause countries to prioritize national interests over global public goods and view LMICs as security threats rather than partners (*84*). Furthermore, norms, values, and approaches of the health sector may be eroded by the increased presence of security actors, primarily from the defense and intelligence communities, within the health-security nexus (*85,86*).

In contrast to a narrow, state-centric approach to health security, the concept of universal health security has been proposed as a more inclusive and people-centered framework that aligns closely with the principles of human security (*85,87,88*). Rather than prioritizing national interests over global public goods, universal health security emphasizes equitable access to essential health services, strengthened global cooperation, and resilient health systems that protect all populations, particularly those in vulnerable settings. By integrating health security into the broader framework of human security, this approach highlights the need to address structural determinants of health, promote international solidarity, and ensure that PPPR efforts are guided by principles of equity and sustainability, rather than narrowly defined national security agendas. The Government of Japan has been actively promoting the concept of human security (*89*), along with UHC.

Conclusion

Aiming to provide an overview of PPPR from a global health perspective, this review first examined the GHG for PPPR, focusing on its structure, functions, and existing gaps. Actors within the GHG for PPPR form a core-satellite structure, with the WHO as the core, while other UN agencies, the G7/G20, and PPPs function as satellites with partially overlapping mandates in a non-hierarchical order. They mainly fulfill five key functions: *i*) rule-setting, *ii*) resource mobilization, particularly surge finance, *iii*) global supply of MCMs, *iv*) surveillance and data/pathogen sharing with rapid response and containment, and *v*) One Health. Major gaps include: *i*) global collaboration, coordination, and partnership, *ii*) enforcement of global rules, particularly the IHR, and countries' compliance, and *iii*) capacity of the WHO. The most pressing issue within the GHG for PPPR is the PABS mechanism.

Second, it assessed the status of PPPR capacities across the six WHO Regions through a descriptive

analysis of eSPAR and GHS Index data. Results indicated that countries in sub-Saharan Africa urgently need support to strengthen most aspects of PPPR. Epidemiological and laboratory surveillance, IPC, and regulatory functions require support across various Regions, except for EUR. Japan is well-positioned to provide such support, given its strong performance in nearly all aspects of PPPR as measured by both eSPAR and the GHS Index.

Lastly, it explored the interconnections between PPPR and HSS in the global context. HSS was regarded as a concrete action point in achieving the aspirational objectives of UHC, PHC, and health security, including PPPR. Almost all health systems building blocks — namely service delivery, health workforce, health information systems, access to essential MCMs, and leadership/governance — as well as two key functions, communication and trust-building, were identified as health systems contributors to PPPR. Multi-sectoral responses, adaptation to evolving situations, strengthening PHC, and domestic resource mobilization for health and social protection were identified as factors contributing to health systems' resilience during pandemics. Pandemic exceptionalism and the over-securitization of PPPR and health security were acknowledged as potential barriers to PPPR-HSS coordination.

These findings provide the following critical directions for future global PPPR: *i*) GHG for PPPR must enhance coordination among governance actors, governance subjects, and between the two. It should also revisit the enforcement of global rules, including the amended IHR and the forthcoming WHO CA+, while strengthening the WHO's authority, operational capacity, and financial resources; *ii*) Technical assistance for PPPR capacity-building is particularly needed in the African Region, as well as in other LMICs, with a specific focus on surveillance, IPC, and regulatory functions; *iii*) PPPR must be firmly integrated into HSS, UHC, and PHC to ensure resilience, equity, inclusiveness, continuity of care, and sustainability. Ideally, the enhanced GHG for PPPR, led by the empowered WHO, should effectively facilitate and coordinate technical assistance to LMICs to strengthen their PPPR capacities and promote PPPR-HSS integration by bringing together the often-divided health security and HSS communities.

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[#]*Current affiliation*: Japan Institute for Health Security (JIHS).
**Address correspondence to*:*
Hitoshi Murakami, Bureau of International Health Cooperation, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: murakami.h@jihs.go.jp

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The world preparing for future pandemics and public health emergencies of international concern: Comparison of various multilateral access and benefit-sharing mechanisms and the impact of a new WHO mechanism for pathogens with pandemic potential on Japanese access and benefit-sharing policy

Saki Nakamura[1,*], Makiko Matsuo[2]

[1] Institute for Future Initiatives, The University of Tokyo, Tokyo, Japan;
[2] Graduate School of Public Policy, The University of Tokyo, Tokyo, Japan.

Abstract: Currently, there is a member-state-led discussion in the Intergovernmental Negotiating Body of the World Health Organization (WHO) to draft and negotiate a convention, agreement, or other international instrument under the Constitution of the WHO to strengthen global pandemic prevention, preparedness, and response (WHO CA+). An access and benefit-sharing (ABS) mechanism for pathogens is likely to be a key element of this instrument, as it may provide legal certainty for rapid pathogen sharing and global access to medical countermeasures against future pandemics and in some cases public health emergencies of international concern, which are expected to be provided to countries in need. A multilateral ABS mechanism may resolve issues arising from the bilateral nature of the current ABS mechanism established under the Nagoya Protocol (which requires recipients to decipher the complex web of ABS legislation, thereby preventing rapid access to pathogens), and may also improve uneven global access to medical countermeasures during pandemics. This study analyzes the ongoing WHO discussion on ABS mechanisms while reviewing other examples of such mechanisms, including those outside the health sector. Additionally, there is a growing global interest in mapping national policies on ABS, as discussions on international policies are ongoing in multiple fora. This study furthermore introduces Japan's ABS policy, which is not widely known, and explores how the new WHO mechanism could affect Japan, namely highlighting the importance and the challenges of participating in such a system for industry and academia in the context of a developed country.

***Keywords*:** Nagoya Protocol (NP), WHO CA+, genetic sequence data (GSD), digital sequence information (DSI), pandemic treaty, pandemic instrument

Introduction

The rapid sharing of pathogens and their genetic sequence data (GSD) is crucial for countries to effectively respond to health emergencies. This has been emphasized on various occasions in the international community, including during the COVID-19 pandemic (*1-5*). Currently, the World Health Organization's (WHO) Intergovernmental Negotiating Body (INB) is drafting and negotiating a convention, agreement, or other international instrument to strengthen pandemic prevention, preparedness, and response (hereafter, the WHO CA+). The access and benefit-sharing (ABS) mechanism for pathogens with pandemic potential is being considered as a key element of this new instrument (*6*). The ongoing WHO negotiation of the ABS mechanism for pathogens with pandemic potential is important; as much as this ABS mechanism can globally facilitate access to medical countermeasures against pandemics, it could also encumber pathogen sharing and complicate the already-complex landscape of ABS legislation.

Although prior studies (*7-13*) have been conducted from the perspective of international organizations, studies comparing different ABS mechanisms developed or under development in various intergovernmental organizations are lacking. This includes work focusing on the pandemic instrument currently being discussed at the WHO. Moreover, there is a growing global interest in mapping national policies on ABS due to the ongoing discussions on ABS mechanisms in multiple international fora (*14*); yet, the literature on Japan's ABS policy is

limited (*15*). Identifying incentives and challenges for industry and academia to participate in the ABS mechanism for pandemics in the context of a developed country is enabled by providing comprehensive information on the Japanese ABS policy in a universal language, as well as exploring how the new ABS mechanism could affect Japan.

Therefore, the present study reviews the debate on ABS within the context of the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization of the Convention on Biological Diversity (hereafter, the Nagoya Protocol [NP]), particularly focusing on pathogens, the WHO's Pandemic Influenza Preparedness Framework (PIPF), and other ABS mechanisms discussed in other forums, such as the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGR) and the Agreement under the United Nations Convention on the Law of the Sea on the Conservation and Sustainable Use of Marine Biological Diversity of Areas beyond National Jurisdiction (BBNJ Agreement). These documents are summarized in Table 1. Subsequently, the potential new ABS mechanism for pathogens with pandemic potential that is currently being discussed at the WHO is analyzed in relation to other ABS mechanisms, as well as how the new ABS mechanism could potentially affect Japan's ABS policy. Information regarding the WHO CA+ in this article is based on the latest available information as of March 31, 2025.

The ABS mechanism for pathogens

Currently, no international laws require states to share pathogens or GSD. The WHO's International Health Regulations (2005), which apply to all WHO-member states and are "designed to prevent the international spread of disease", do not have a provision that explicitly requires the sharing of pathogen samples and GSD. They only require the sharing of "public health information" regarding events that may constitute a public health emergency of international concern (Article 6) (*16*).

During the COVID-19 pandemic, expert groups stressed the need for clear obligations for access to pathogens and GSD as well as sharing of vaccines, therapeutics, and diagnostics (VTDs) during health emergencies (*9,17*). Rourke *et al.* (2020) appealed the necessity for an adequate legal framework that cultivates mutual trust and equitable scientific collaboration and enables sharing of, and access to, pathogens and GSD for rapid research and development of VTDs. The Independent Panel for Pandemic Preparedness and Response (2021) proposed a framework convention-protocol approach and suggested to consider legal mechanisms for rapid sharing of sequence data and samples and the equitable sharing of VTDs. This issue is not new in the field of public health, as it first garnered widespread attention in 2006 when Indonesia refused to share its influenza A virus (known as H5N1) samples with the WHO for risk assessment through the WHO global influenza surveillance response system (WHO GISRS) — a voluntary network of laboratories and institutions sharing influenza samples (*18*). This barrier to rapid access to influenza virus samples originated from a sense of inequity and the undermining of sovereignty in developing countries. Indonesia argued that while they made information and samples available through the WHO GISRS, they could seldom afford the medical countermeasures that were developed and patented by pharmaceutical companies in industrialized countries (*19*). To resolve this issue, an ABS mechanism for influenza viruses with pandemic potential (IVPP) — the PIPF — was developed in 2011, following the adoption of a resolution by the World Health Assembly — issued in May 2007 — that stressed the need for "the timely sharing of viruses and specimens" through the WHO GISRS and the promotion of "transparent, fair and equitable sharing of the benefits arising from the generation of information, diagnostics, medicines, vaccines and other technologies" (*20,21*). Although limited to IVPP, the PIPF is the first reported ABS mechanism for pathogens.

The implications of the NP — a supplementary agreement to the Convention on Biological Diversity (CBD) — for pathogen sharing have been debated and analyzed by the WHO since 2010, triggered by Indonesia's refusal to share its H5N1 samples (*22,23*). The NP's objective is to implement "the fair and equitable sharing of benefits arising out of the utilization of genetic resources, thereby contributing to the conservation and sustainable use of biodiversity", which is among the three objectives of the CBD (*24*). In the CBD, "genetic resources" refer to any material of plant, animal, microbial, or other origin containing functional units of heredity (genetic material) of actual or potential value (Article 2); additionally, it stipulates that states have sovereign rights over their natural resources (Article 15) (*25*). The NP sets out obligations for parties to take measures related to access to genetic resources (*e.g.*, Article 6), fair and equitable benefit-sharing (*e.g.*, Articles 5, 10, and 14), and compliance (*e.g.*, Articles 15 and 18). It requires each party to establish measures to ensure prior informed consent (PIC) before granting/being granted access to genetic resources, which would be agreed upon by the provider and recipient of the resources (Article 6).

As pathogens contribute to neither the protection nor the conservation of biological diversity, but rather the opposite by threatening biological diversity and impacting wildlife, questions have been raised regarding the status of pathogens as genetic resources under the CBD (*18,26*). The ambiguity of the NP has created a patchwork of ABS laws for pathogens (*27*), where certain countries are implementing domestic ABS legislation by

Table 1. Key global agreements on access and benefit sharing (ABS) systems issued by intergovernmental organizations

Year	Organization	Key features / Summary (*Ref.*)
1. The Convention on Biological Diversity (CBD) (*24*)		
1992	CBD Secretariat (UNEP*)	- Three objectives: "the conservation of biological diversity, the sustainable use of its components, and the fair and equitable sharing of benefits arising from the utilisation of genetic resources" - Entered into force on December 29th, 1993. *United Nations Environment Program
2. Treaty on Plant Genetic Resources for Food and Agriculture (ITPGR) (*48*)		
2001	FAO	- Objective: "conservation and sustainable use of plant genetic resources for food and agriculture and the fair and equitable sharing of the benefits arising out of their use, in harmony with the Convention on Biological Diversity, for sustainable agriculture and food security" - Establishes a multilateral ABS mechanism for plant genetic resources (no DSI). Recipients gain access from a common pool without bilateral negotiations with providers - Recipients deposit a portion of the profits into a fund if new varieties of plants are developed and commercialized to support agricultural projects in developing countries
3. WHA60.28 Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits (*21*)		
2007	WHO	- A resolution adopted by the Sixtieth World Health Assembly - Stressed the need for "the timely sharing of viruses and specimens" through the WHO GISRS and the promotion of "transparent, fair and equitable sharing of the benefits arising from the generation of information, diagnostics, medicines, vaccines and other technologies"
4. the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization of the Convention on Biological Diversity (the Nagoya Protocol) (*24*)		
2010	The CBD Secretariat (UNEP)	- A supplementary agreement to the CBD, which was opened for signature in 1992 - Objective: to implement "the fair and equitable sharing of benefits arising out of the utilization of genetic resources, thereby contributing to the conservation and sustainable use of biodiversity" - Sets out obligations for parties to take measures related to access to genetic resources, fair and equitable benefit-sharing, and compliance - Requires each party to establish measures to ensure prior informed consent before granting/being granted access to genetic resources, which would be agreed upon by the provider and recipient of the resources
5. Pandemic Influenza Preparedness Framework (PIPF) (*20*)		
2011	WHO	- Objective: to improve "pandemic influenza preparedness and response, and strengthen the protection against pandemic influenza by improving and strengthening the WHO global influenza surveillance and response system ('WHO GISRS'), with the objective of a fair, transparent, equitable, efficient, effective system for, on an equal footing: *i*) the sharing of H5N1 and other influenza viruses with human pandemic potential; and *ii*) access to vaccines and sharing of other benefits" - Manufacturers are required to sign a Standard Material Transfer Agreement with the WHO to receive influenza samples, which includes commitments to set aside specific quantities of vaccines, antivirals, or diagnostic kits for donation or purchase in the event that influenza pandemic emerges and to provide an annual partnership contribution, which would be allocated to pandemic influenza preparedness capacity-building, response activities, and the implementation of the PIPF
6. United Nations Convention on the Law of the Sea on the Conservation and Sustainable Use of Marine Biological Diversity of Areas beyond National Jurisdiction (BBNJ Agreement) (*54*)		
2023	United Nations	- Objective: "to ensure the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction, for the present and in the long term, through effective implementation of the relevant provisions of the Convention and further international cooperation and coordination" - Establishes a multilateral ABS mechanism for marine genetic resources in areas beyond national jurisdiction and their DSI - Establishes a financial mechanism where developed parties are required to make annual contributions to the fund

extending the NP to pathogens and GSD (*14*). For this reason, the NP has been criticized for hindering rapid access to pathogens, thereby impeding scientific research, particularly in the health emergency context (*28,29*). There have been reports regarding delays in sharing samples of seasonal and pandemic influenza, SARS-CoV-2, Zika, mpox, Japanese encephalitis, foot and mouth disease, African swine fever, and bacterial isolates that are important for assessing antimicrobial resistance (*12,30*). The current practice entails pathogens to be handled according to the laws of national jurisdiction (*23*) and, as no established multilateral ABS mechanisms currently exist for pathogens (except for the PIPF), recipients — including researchers and manufacturers — are required to bilaterally obtain PIC from the provider when accessing pathogens depending on the country of origin's ABS legislation. Japan is a party to the NP, but the PIC is not required to obtain access to genetic resources within its national jurisdiction (*31,32*).

Features of the NP relevant to the pandemic instrument currently under discussion

Two articles of the NP are relevant to the WHO CA+. Article 4.4 of the NP stipulates that the protocol does not apply to genetic resources covered by other international ABS instrument(s) (hereafter, specialized international instrument [SII]) as long as they are "consistent with, and does not run counter to the objectives" of the CBD and the NP (*24*). Consequently, some parties of the NP, including the EU and Japan, have designated the PIPF as an SII (*33,34*). Due to the differences among the parties with respect to the interpretation and the implementation of this article, an attempt to develop an internationally agreed upon criteria for a SII has been initiated. The NP Subsidiary Body on Implementation has noted a list of "indicative criteria" in March 2022, which remains to be discussed in the CBD (*35*). Article 8 (b) provides special considerations for health emergencies when developing and implementing ABS legislation in each party. It also touches upon the need for expeditious access to genetic resources and fair and equitable sharing of benefits arising out of the use of genetic resources, including access to affordable treatments, especially in developing countries (*24*). Nevertheless, the implementation of these special considerations is unclear and left to domestic jurisdictions. The WHO CA+ may establish an ABS mechanism for pathogens with pandemic potential that may also be designated as an SII, therefore allowing recipients in NP parties to avoid the complex PIC process and mutually agreed terms (MATs) from the provider country.

ABS mechanism for data

Since the adoption of the CBD and NP, science and technology have advanced substantially. A significant increase in the value of data, including GSD, for product development has been observed, particularly in the biological and agricultural sectors. This has fostered a discussion on the need to consider an ABS mechanism for "digital sequence information" (DSI) in the CBD and the NP. As mentioned previously, "genetic resources" are defined as any material containing functional units of heredity (Article 2) in the CBD. Whether this term includes information such as GSD is unclear. However, provider countries of genetic resources have voiced concerns that recipients and users avoid or circumvent the ABS of genetic resources under the CBD and NP by utilizing DSI, and the benefits that would otherwise arise from the use of genetic resources are being compromised. In the CBD, a difference exists in the interpretation of genetic resources between developing and developed countries, where the former claim the inclusion of DSI while the latter claim exclusion, as information is not considered material (*36,37*). However, a decision was made in the fifteenth meeting of the Conference of the Parties (COP) to the CBD to establish "a multilateral mechanism for benefit-sharing from the use of digital sequence information on genetic resources, including a global fund", "recognizing the different understandings of the concept and scope of DSI on genetic resources, and the range of views regarding the need to define such concept and scope". An ad hoc open-ended working group was established to make recommendations on such a multilateral mechanism to the COP at its sixteenth meeting (*38*). The sixteenth COP held from October to November 2024 decided that parties would encourage DSI users including those from the pharmaceutical industry to contribute a portion of their profits to the global fund (the Cali Fund), supporting the objectives of the CBD (*39*).

As of March 31, 2025, no agreement has been reached on the definition of DSI. Workstreams under the CBD discussed the definition for two years before the COP's fifteenth meeting. The list developed by the Ad Hoc Technical Expert Group on DSI of genetic resources contained definitions ranging from nucleic acid sequence reads and associated data to macromolecules and cellular metabolites (*40*). This was eventually narrowed down to four different groups, the narrowest being DNA and RNA (*38*). The COP agreed with the decision regarding the continuing use of the term DSI for further discussions (*41*).

Existing ABS mechanisms and their implications for ABS for pathogens with pandemic potential

The PIPF

The PIPF was adopted at the World Health Assembly of the WHO in May 2011, to improve "pandemic influenza preparedness and response, and strengthen the protection against pandemic influenza by improving and strengthening the WHO global influenza surveillance and response system ('WHO GISRS'), with the objective of a fair, transparent, equitable, efficient, effective system for, on an equal footing: i) the sharing of H5N1 and other influenza viruses with human pandemic potential; and *ii*) access to vaccines and sharing of other benefits" (*20*). The PIPF is a non-binding instrument on ABS. Since the early 1950s, WHO-member states, through their national influenza centers, have voluntarily shared representative influenza viruses detected through national surveillance with the WHO Collaborating Centres in the WHO GISRS. Twice a year, in February and September, scientists from the Collaborating Centres attend a meeting organized by the WHO to review global flu data and make recommendations on specific vaccine viruses that would compose seasonal flu vaccines (*42*). Since the PIPF's adoption, influenza laboratories that have been designated or recognized by the WHO and have accepted to work under agreed WHO terms of reference are required to sign a standard material transfer agreement (SMTA) within the WHO GISRS, while manufacturers are required to sign an SMTA outside the WHO GISRS with the WHO to receive influenza samples from the

WHO GISRS. The latter SMTA includes commitments to set aside specific quantities of vaccines, antivirals, or diagnostic kits for donation or purchase in case an influenza pandemic emerges, as well as to provide an annual partnership contribution (PC), which would be allocated to pandemic influenza preparedness capacity-building, response activities at the time of a pandemic, and the Pandemic Influenza Preparedness Secretariat for the implementation of the PIPF (*43*). The sum of the annual PC equals 50% of the running cost of the WHO GISRS, which was estimated to be 56.5 million USD in 2010, setting the annual PC to 28 million USD. The amount contributed by each manufacturer is calculated using a weighted formula that considers the contributor's average annual influenza product sales for four years (*44-46*). Noteworthily, if required under the NP, then PIC and MATs from the provider country must be obtained for manufacturers to receive influenza virus samples other than H5N1 and influenza viruses of pandemic potential from the WHO GISRS (*47*). Additionally, the term GSD is used instead of DSI in the PIPF (to the best of the authors' knowledge, DSI has never been used in WHO's previous technical documents before the WHO CA+), and laboratories are expected to share "GSD and analyses arising from that data, relating to H5N1 and other influenza viruses with human pandemic potential", "in a rapid, timely and systematic manner with the originating laboratory and among WHO GISRS laboratories" (*20*). An ABS mechanism within the different drafts of the WHO CA+ is clearly informed by the PIPF model. However, because the WHO CA+ targets pathogens with pandemic potential, their countermeasures and the manufacturers of these countermeasures cannot be identified. Unlike influenza viruses of pandemic potential, adapting the PIPF model — including the determination of the PC — poses many challenges. The details of these challenges will be covered in detail in later sections.

The ITPGR

The ITPGR was adopted in 2001 by the thirty-first Food Agricultural Organization Conference with the objective of "conservation and sustainable use of plant genetic resources for food and agriculture and the fair and equitable sharing of the benefits arising out of their use, in harmony with the Convention on Biological Diversity, for sustainable agriculture and food security" (*48*). Japan became a member of the treaty in October 2013 after the approval of the 183rd Ordinary Session of the Diet (*49*). The treaty facilitates access to plant genetic resources for food and agriculture for research and breeding, particularly to those important from the perspective of food security listed in Annex I as a "list of crops covered under the Multilateral System". The treaty furthermore establishes a Multilateral System of Access and Benefit-sharing to ensure that benefits accrued from these plant genetic resources are shared fairly and equitably. This multilateral system enables access to plant genetic resources provided by Contracting Parties from a common pool by signing an SMTA, which allows recipients to avoid bilateral negotiations on the terms and conditions for every access. Recipients are expected to deposit a portion of the profits into a Benefit-sharing Fund if new varieties are developed and commercialized (*50*). This fund supports agricultural projects in developing countries contributing to the conservation and sustainable use of plant genetic resources in food and agriculture (*51*). Japan recognizes the ITPGR as an SII under Article 4, Paragraph 4 of the NP (*49,52*).

The establishment of a pool of plant genetic resources available for access and a fund for capacity-building, observed in the ITPGR, is a potential ABS model that the pandemic instrument could apply. However, there are three challenges: *i*) difficulties in characterizing and identifying pathogens that would fall under the scope of the multilateral ABS system, *ii*) processing SMTAs for each access, and *iii*) handling of GSD in the multilateral system. A possibility exists that the ABS mechanism in the WHO CA+ could be applied to a list of pathogens that fulfill certain criteria similar to the ITPGR's approach; however, the scope of the pathogens is still under debate. Would the list encompass only pathogens with pandemic potential, or would it be significantly broader? How would the WHO and member states develop criteria for pathogens with pandemic potential which include unknown pathogens that may cause future pandemics? The list of priority pathogens with pandemic potential that the WHO is currently developing as part of its regular normative work (*53*) may help inform the INB's work. Secondly, although a bilateral negotiation on access and benefits between a provider and a recipient is not required in the ITPGR, an SMTA still needs to be concluded for every access. A simpler procedure for access may be needed in the pandemic instrument to incentivize the industry's participation. Lastly, because the ITPGR was developed more than 20 years ago, DSI is not currently within the scope of the Multilateral System of Access and Benefit-sharing.

The BBNJ agreement

The BBNJ agreement was agreed upon by the Intergovernmental Conference in June 2023 "to ensure the conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction, for the present and in the long term, through effective implementation of the relevant provisions of the Convention and further international cooperation and coordination" (*54*). The first organizational meeting was convened in April 2018; the agreement was adopted by consensus after five sessions, with two resumed fifth sessions and the fourth meeting postponed from 2019 until 2022 (*55*).

The BBNJ agreement includes two features relevant to the WHO CA+. First, it includes the principle of fair and equitable sharing of benefits as one of the general principles and approaches of the agreement. Second, it establishes a multilateral ABS mechanism for marine genetic resources in areas beyond national jurisdiction and their DSI (*54*). Notably, although the BBNJ agreement uses the term "equity", it is not defined. Meanwhile, the same term is used in the drafts of the WHO CA+, and WHO member states are actively debating its definition.

In the ABS mechanism of the BBNJ agreement, a clearing-house mechanism was established whereby parties are required to provide information regarding the collection of marine genetic resources six months or as early as possible before the collection. Subsequently, the clearinghouse mechanism automatically generates a BBNJ-standardized batch identifier. Parties are expected to report the following information with their BBNJ standardized batch identifier: the repository or database where DSI on marine genetic resources is deposited, and the location where all the collected marine genetic resources are deposited. A report with details regarding the geographical area from which the marine genetic resources were collected is also required for submission to the clearinghouse mechanism. Non-monetary benefits include access to sample collections, marine technology transfer, and capacity building; monetary benefits from the utilization of marine genetic resources in areas beyond national jurisdiction and their DSI, including commercialization, are expected to be shared fairly and equitably through a financial mechanism established in the BBNJ agreement. Until new modalities for monetary benefit-sharing are adopted, developed parties are required to make annual contributions to the fund, which comprise 50% of the party's assessed contribution to the budget adopted by the COP (*54*). No SMTA has been developed in the BBNJ agreement, while modalities for capacity building and the transfer of marine technology are provided in articles 42 and 43 of the agreement. The ABS mechanism under the BBNJ agreement is different from that under ITPGR, as it has no list of genetic resources covered because the scope of marine genetic resources of areas beyond national jurisdiction to be targeted and collected is unlimited. This is another model that the pandemic instrument could apply, as developing a list of pathogens that would fall under the scope of the instrument could be difficult.

This section provides an overview of the existing ABS mechanisms agreed in several international fora, namely the PIPF, the ITPGR, and the BBNJ agreement. The key elements of the ITPGR and the BBNJ agreement and their implications for an ABS mechanism for pathogens with pandemic potential are summarized in Table 2. The elements of the PIPF are presented separately in Table 3, along with details on the challenges of incorporating the PIPF elements into an ABS mechanism for pathogens in the pandemic instrument. These challenges are detailed in later sections.

Negotiation of the WHO CA+

Pandemic-related ABS mechanism discussed in WHO CA+

In a special session held in December 2021, the World Health Assembly (WHA) adopted a decision to establish the INB to draft and negotiate the WHO CA+ (*56*). The first meeting was held in February 2022, and two co-chairs — one from the Netherlands and one from South Africa — and four vice-chairs — from Brazil, Egypt, Thailand, and Japan — were elected to comprise the INB bureau (*57*). At the second meeting, held in July 2022, the INB agreed that the new instrument should be legally binding (*58*). The INB has been discussing several texts during its negotiating process: the conceptual zero draft developed in November 2022 (*59*), the zero draft developed in February 2023 (*60*), the bureau's text developed in April 2023 (*61*), and the negotiating text developed in October 2023 (*6*), while an ABS mechanism for pathogens with pandemic potential has been a part of these texts. The INB was unable to reach an agreement by the Seventy-seventh WHA in May 2024 as originally planned. It is continuing its negotiations by building upon text submitted to the assembly that contains some provisionally agreed upon contents (*62*), to finish its work by the Seventy-eighth WHA in May 2025 or earlier (*63*).

Challenges in developing an ABS mechanism for pathogens in the pandemic instrument

The ABS mechanism in the draft texts of the pandemic instrument adopts a structure similar to that of the PIPF. For example, the "proposal for negotiating text of the WHO pandemic agreement", issued on October 30, 2023, provides for: *i*) the establishment of a WHO-coordinated laboratory network (WCLN), which comprises recognized laboratories where parties may share pathogen samples through relevant public health authorities and authorized laboratories; and *ii*) the development of an SMTA to be used with the transfer of samples from a laboratory in the WCLN to a recipient. The SMTA is expected to include the commitments of recipients to set aside a minimum of 20% (10% as a donation and 10% at affordable prices to the WHO) of the production of pandemic-related products for real-time access by the WHO in the event of a pandemic, as well as to provide an annual contribution based on the recipient's nature and capacity (*6*). Although the ABS provisions were significantly reduced immediately before the WHA in 2024 in an attempt to reach a consensus by deferring the discussion of details to a separate document, the draft still contains the concept of the WCLN and descriptions

Table 2. Existing ABS mechanisms and their implications for ABS for pathogens with pandemic potential

Elements of the agreement (*Ref.*)	Implications of the agreement to the WHO CA+
Treaty on Plant Genetic Resources for Food and Agriculture (ITPGR) (*48*)	
- Facilitates access to plant genetic resources for food and agriculture for research and breeding, particularly to those important from the perspective of food security listed in Annex I as a "list of crops covered under the Multilateral System".	The ABS mechanism in the WHO CA+ could be applied to a list of pathogens that fulfill certain criteria similar to the ITPGR's approach; however, the scope of the pathogens is still under debate.
- Establishes a multilateral ABS mechanism for plant genetic resources (no DSI), where recipients gain access from a common pool without bilateral negotiations with providers.	Although a bilateral negotiation on access and benefits between a provider and a recipient is not required in the ITPGR, an SMTA still needs to be concluded for every access. A simpler procedure for access may be needed in the pandemic instrument to incentivize the industry's participation.
United Nations Convention on the Law of the Sea on the Conservation and Sustainable Use of Marine Biological Diversity of Areas beyond National Jurisdiction (BBNJ agreement) (*54*)	
- Establishes a multilateral ABS mechanism for marine genetic resources in areas beyond national jurisdiction and their DSI. The ABS mechanism has no list of genetic resources covered because the scope of marine genetic resources of areas beyond national jurisdiction to be targeted and collected is unlimited.	The intergovernmental negotiating body could decide not to apply the ABS mechanism in the pandemic instrument to a list of pathogens, as developing a list of pathogens that would fall under the scope of the instrument could be difficult.
- Establishes a clearing-house mechanism in the ABS mechanism whereby parties are required to provide information including the repository or database where DSI on marine genetic resources is deposited, and the location where all the collected marine genetic resources are deposited.	The pandemic instrument could develop a mechanism where parties are required to provide information on the database where GSD (or more broadly DSI) on pathogens with pandemic potential is deposited.
- Establishes a financial mechanism where monetary benefits from the utilization of marine genetic resources and their DSI, including commercialization, are expected to be shared fairly and equitably. Until new modalities for monetary benefit-sharing are adopted, developed parties are required to make annual contributions to the fund.	The pandemic instrument could establish a financial mechanism where the monetary benefits from the utilization of pathogens and their GSD, including commercialization, are expected to be shared by the user as well as annual contributions from parties to the fund.

*For elements and implications of the Pandemic Influenza Preparedness Framework (PIPF) (*20*), refer to Table 3.

of the set-asides (*62*). Following the PIPF's success, this new ABS mechanism for pathogens seems to be a feasible idea at first glance; however, it has numerous inherent challenges in addressing pandemics (Table 3).

First, in contrast to influenza, pathogens that will cause future pandemics or public health emergencies of international concern cannot be identified before their occurrence. This notion also extends to the countermeasures that will be effective in combating these health emergencies — including prophylaxis, diagnostics, and treatment. Therefore, it would be challenging for the WHO and relevant parties to identify manufacturers who would sign the SMTA during the pre-pandemic period. Additionally, incentives are low for manufacturers to sign the SMTA and obtain samples of unknown pathogens, as manufacturers cannot predict the type of pathogens they would gain access to through the WCLN and the future market value of the product they may develop against the pathogen in question. Third, in contrast to the PIPF, the calculation of a partnership contribution to the WCLN is impossible because the products required to counter the pandemic are currently unknown; therefore, product sales — part of the PC calculation formula — cannot be determined. Finally, if capacity building of the WCLN were to become part of the non-monetary benefits of the new ABS mechanism, the WCLN's broad scope may not be appealing to manufacturers considering participating in the system. Incentives for the PIPF contributors to pay their PC include their targeted allocation to capacity building for strengthening global influenza surveillance, which would, in turn, enable manufacturers to access important influenza pathogen samples. However, industry participation is essential to the success of the pandemic ABS mechanism; thus, the INB and the WHO Secretariat would need to address these challenges. In addition, industry engagement at the negotiation stage is key to ensuring that the mechanism provides incentives.

Although the WHO CA+ cannot simply copy the PIPF for the above reasons, the two instruments partially overlap in their scope, as the PIPF itself is an instrument on pathogens with pandemic potential, namely IVPP. Therefore, the WHO CA+ should not contain contradicting provisions, and its relationship with the PIPF needs to be clearly defined.

Uncertainty also stems from the operational and governance perspectives regarding the ABS mechanism proposed in the pandemic instrument's draft texts. For example, according to Article 21, Chapter III of the negotiating text: the COP can "establish subsidiary bodies to carry out the work of the COP", which may include "a panel of experts to provide scientific advice and a WHO Pathogen Access and Benefit-Sharing System Expert

Table 3. Challenges in developing an ABS mechanism for pathogens in the pandemic instrument, as compared to the Pandemic Influenza Preparedness Framework (PIPF)

Elements of the PIPF (An ABS mechanism for influenza viruses with pandemic potential)	Elements of the draft CA+ agreement (An ABS mechanism for any pathogens with pandemic potential)	Implementation Challenges
Establishes the WHO global influenza surveillance response system (WHO GISRS) as a voluntary network of laboratories and institutions sharing influenza samples.	Proposes to establish a WHO-coordinated laboratory network (WCLN) comprised of recognized laboratories where parties may share pathogen samples.	Manufacturers with the capacity to develop influenza vaccines have the incentive to sign an SMTA for gaining access to influenza samples from the WHO GISRS. In contrast, incentives are low for manufacturers to sign an SMTA to obtain samples of unknown pathogens, as manufacturers cannot predict the type of pathogens they would gain access to through the WCLN and the future market value of the product they may develop against the pathogen in question.
A Standard Material Transfer Agreement (SMTA) is signed by manufacturers with the WHO to receive influenza samples from the WHO GISRS. It includes commitments to set aside specific quantities of vaccines, antivirals, or diagnostic kits for donation or purchase by WHO in the event that an influenza pandemic emerges.	Recipients are granted access to pathogen samples by signing an SMTA that includes commitments to set aside a minimum of 20% of the pandemic-related products produced by the recipient as a result of using that pathogen including its sequence data for real-time access by the WHO during the pandemic.	For influenza, manufacturers who would have the most interest in signing the SMTA during the pre-pandemic period are manufacturers of influenza products. In contrast, identifying manufacturers who would sign the SMTA in the WHO CA+ during the pre-pandemic period would be challenging for two reasons: one, pathogens that will cause future pandemics or PHEICs cannot be identified before their occurrence; and two, the countermeasures that will be effective in combating these health emergencies also cannot be identified during the pre-pandemic/PHEIC period.
The SMTA also includes commitments of manufacturers to provide an annual partnership contribution (PC), which would be allocated to pandemic influenza preparedness capacity-building, response activities at the time of a pandemic, and the implementation of the PIPF.	Recipients are granted access to pathogen samples by signing an SMTA that includes commitments to provide an annual contribution based on the recipient's nature and capacity.	1. Product sales (as part of the PC calculation formula) can be estimated for manufacturers who sell seasonal influenza vaccines. In contrast, the calculation of a partnership contribution to the WCLN is impossible because the products required to counter the pandemic are currently unknown; therefore, product sales cannot be determined. 2. Manufacturers have the incentive to pay their PC to the PIPF because it will strengthen global influenza surveillance specifically, improving their chances of accessing important influenza samples. In contrast, the WCLN's broad scope to cover pathogens with pandemic potential may not be as attractive to manufacturers because their annual contribution would not be targeted to improve global surveillance for a specific type(s) of pathogens.

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Advisory Group" (*6*), but the nature and the function of such an advisory group remains unclear. The Bureau's text (*61*), which is an older draft than the negotiating text, contained a stand-alone article on a Benefit-Sharing Expert Committee (Article 25), which was provided with a mandate "to establish guidelines for benefit sharing, providing transparency and ensuring a fair and equitable sharing of benefits, and to report to the COP, as well as discharge all functions set out in the WHO CA+ and respond to the requests of the COP". Such committees are possibly envisioned to develop modules and materials to facilitate a deeper understanding of the provisions such as to achieve the effective implementation of the instrument, similar to various modules developed by the ITPGR Secretariat (*64,65*), FAQs developed by the PIPF Secretariat (*66*), or various guides and toolkits, including the International Health Regulations (2005) Toolkit for Implementation in National Legislation, developed by the WHO Secretariat (*67,68*).

Challenges in addressing an ABS mechanism for GSD of pathogens in the pandemic instrument

As mentioned previously, a multilateral mechanism for benefit-sharing through the use of DSI on genetic resources is currently being discussed in an ad hoc open-ended working group in the CBD, in parallel with the INB's work at the WHO. This raises additional issues.
The member states of the INB are actively discussing whether the ABS system in the WHO CA+ should be recognized as "a specialized international access and benefit-sharing instrument within the meaning of paragraph 4 of Article 4 of the Nagoya Protocol" (*6,62*). Theoretically, designating the WHO CA+ as an SII in the context of the NP is certainly helpful, as it will exempt those who are parties to both the NP and the pandemic instrument from benefit-sharing provisions under the NP with respect to the specific genetic resources covered by — and for the purpose of — the specialized instrument; these are, in this case, pathogens related to pandemics. However, clearly distinguishing whether a certain pathogen and its GSD would be considered under the ABS mechanism of the pandemic instrument or the multilateral benefit-sharing mechanism for DSI considered under the CBD may be challenging. For example, recent developments in vaccine research have focused on the highly conserved regions of various human pathogenic coronaviruses, which may be considered useful for developing a universal vaccine to protect populations against beta coronaviruses in general, rather than against a specific virus (*69*). Additionally, the difference between DSI (the term used in the CBD) and GSD (which can be considered to be narrower in definition) may also complicate ABS legislation for pathogens related to pandemics if the INB decides to use GSD in its final text, in line with other WHO documents including the PIPF.

Sections 4.2 and 4.3 discuss two sets of challenges that arise in the development of an ABS mechanism for pathogens in the pandemic instrument. One is attributed to the scope of this instrument to address pandemics broadly, rather than pandemics caused by specific pathogens, such as IVPP. Another is related to the parallel discussions happening in the CBD regarding an ABS mechanism for DSI (Table 4).

Possible scenarios for the ABS mechanism in the pandemic instrument

There are a few possible scenarios for, and elements from other existing ABS mechanisms that the INB could incorporate into, the ABS mechanism in the pandemic instrument. These approaches are not mutually exclusive, and pandemic instruments can adopt combinations of different approaches and elements.

The first is an ABS mechanism similar to the PIPF, as proposed in different versions of texts discussed by the INB (*6,60-62*). The structural similarity and feasibility challenges related to this approach were described extensively in the previous two sections — difficulties in identifying pathogens with pandemic potential, their countermeasures, and manufacturers of these countermeasures during the pre-pandemic period.

Second, the pandemic instrument could adopt the ITPGR's approach, which could be considered a variation of the PIPF model, wherein recipients are required to sign an SMTA to gain access to a list of pathogens related to pandemics, which would be covered

Table 4. Challenges in developing an ABS mechanism for pathogens in the pandemic instrument

Points	Challenges
1	There are inherent challenges in addressing pandemics broadly compared to influenza pandemics. The PIPF cannot simply be made to apply to an ABS mechanism for pathogens with pandemic potential because pathogens that will cause future pandemics or PHEICs cannot be identified before their occurrence. In addition, the countermeasures that will be effective in combating these health emergencies cannot be identified during the pre-pandemic period.
2	A multilateral mechanism for benefit-sharing through the use of DSI on genetic resources is currently being discussed in a working group in the CBD, in parallel with the INB's work at the WHO. These mechanisms have to be structured to avoid a situation in which a given pathogen with pandemic potential and its GSD/DSI is subject to both the ABS mechanism of the pandemic instrument and the multilateral benefit-sharing mechanism for DSI considered under the CBD.

under a multilateral ABS system. Recipients would be expected to deposit a portion of their profits to a benefit-sharing fund in the multilateral system if new products were developed and commercialized. The fund would support capacity building for pandemic preparedness and response (*50*). The problem with this approach is that the limited scope of enlisted pathogens may become a hurdle for inviting recipients, as opportunities to develop countermeasures and sales are predicted to be infrequent. Furthermore, the need for recipients to sign an SMTA for every access may disincentivize their participation.

Lastly, the pandemic instrument could incorporate elements from the BBNJ agreement, wherein monetary benefits — from the utilization of pathogens and their GSD (or more broadly DSI), including commercialization — are expected to be shared fairly and equitably by the user through a financial mechanism established in the instrument. Developed parties are also expected to make annual contributions to the fund, comprising 50% of the party's assessed contribution to the budget adopted by the COP (*54*). The scope of ABS could be broad, as there would be no list of pathogens, in contrast to the ITPGR. This approach could be beneficial, as capturing pathogens that may cause a pandemic — including those that are currently unknown — in a list is unrealistic. Additionally, providing access to a wide range of pathogens may be a greater incentive for the industry than providing access to a small list of pathogens.

In any approach, the INB may inevitably decide to adopt ABS for pathogens, including a provision on benefit-sharing for the utilization of GSD or, more broadly, DSI, considering the current movement of discussion on ABS for DSI in the CBD and the fact that not only the virus sample but also their sequence data are required for vaccine sequence design in the production of mRNA vaccines, which played a unique role in controlling the COVID-19 pandemic (*70*). In this regard, there is an urgent need to analyze the potential effects of an ABS mechanism for pandemics on Japan's ABS policy and to identify the merits and challenges in the context of a developed country.

The impact of a new WHO mechanism for pathogens with pandemic potential on Japanese ABS policy

As ABS mechanisms are actively discussed in many fora, including the INB in the WHO, there is growing interest and value in mapping national policies on ABS (*14*). Therefore, it is important that information regarding Japan's ABS policy is accessible in a universal language. As previously mentioned, Japan has established national guidelines (not legislation), pertaining to genetic resource access and the fair and equitable sharing of benefits arising from their utilization for the NP's national implementation, issued jointly by the Ministry of the Environment; the Ministry of Health; the Ministry of Finance; the Ministry of Agriculture, Forestry and Fisheries; the Ministry of Education, Culture, Sports, Science and Technology; and the Ministry of Economy, Trade and Industry (*32*). The government of Japan does not require PIC with respect to genetic resources — a practice observed in numerous European countries, including the UK, where access controls are not put in place, thereby providing free access to genetic resources (*32,71,72*). Japan has historically supported SII recognition, designating the PIPF and ITPGR as SIIs under Article 4.4 (*33,52*). Designating the pandemic instrument as an SII allows recipients in NP parties to avoid the complex PIC process and mutually agreed terms from the provider country. Therefore, if Japan decides to become a member of a pandemic instrument, the authors assess that it will designate the pandemic instrument domestically as an SII.

Two issues related to recognizing the pandemic instrument as an SII are expected (Figure 1). First, because parties to the NP need to designate SIIs through and in accordance with their national ABS policy, a situation will arise where there will be a mix of countries that have designated the pandemic instrument as an SII versus those that have not. Potential recipients, particularly the industry including those in Japan, will be cautious about participating in the new ABS mechanism in fear that they will be responsible for benefits under two international agreements—the NP and the pandemic

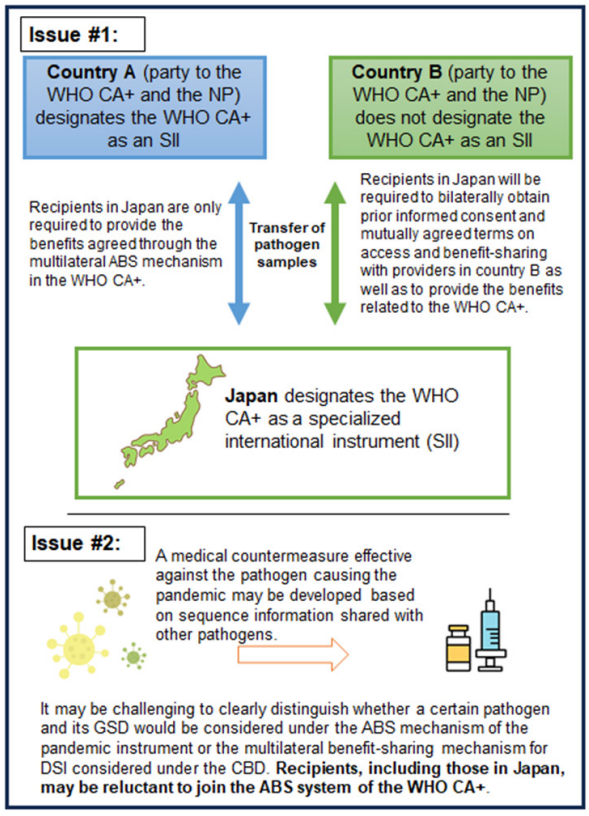

Figure 1. Potential issues caused by an ABS mechanism for pathogens with pandemic potential to Japanese policy implementation.

instrument — for the same pathogen and its DSI/GSD. Ensuring that ABS rights and obligations are not duplicated in the domestic implementation of the NP and other ABS agreements is important for participation. Second, because a clear-cut line is lacking between genetic resources of the NP and pathogens related to pandemics, recipients may still be reluctant to participate even if the pandemic instrument is designated as an SII in most NP parties. As highlighted previously, a situation may arise wherein a vaccine against a pandemic pathogen is developed using a conserved region of the virus family (*69*), thereby making it difficult to identify the pathogen and/or GSD originally utilized for product development. In this hypothetical situation, one may argue that benefits should be shared under the NP, whereas others may argue that benefits should be shared in accordance with the pandemic instrument. In the future, these issues related to legal certainty need to be thoroughly discussed among member states and also with potential recipients such as industry and academia to establish an effective ABS mechanism where pathogens are readily accessible and benefits are equitably shared. Structuring an effective ABS mechanism for pandemics is time-consuming; however, as the ABS mechanism is merely one component among the many arrangements in the agreement on pandemic prevention, preparedness and response, there is a risk of compromising the details for the sake of consensus.

This review presented an up-to-date account of recent developments of the ABS mechanisms in different international fora to highlight their relevance to the ongoing negotiations occurring in the health sector and to identify Japan's expected challenges with a new WHO ABS mechanism. While analysis in the Japanese context is helpful for understanding similar challenges faced by other developed countries, nation-specific analyses are essential as the ABS mechanism will impact countries differently depending on factors such as presence/non-presence of industry and its scale, and the status of domestic ABS legislation. Conducting such analyses in different country contexts will support an evidence-based approach towards building an ABS mechanism that ensures rapid access to pathogens and GSD as well as benefit-sharing that includes equitable access to medical countermeasures during pandemics.

Conclusion

The rapid sharing of pathogens and their GSD is essential for an effective response to health emergencies, and this aspect of access to pathogens, as well as benefit-sharing from their utilization, is a potential core element of the WHO CA+ that is currently being discussed in the WHO's INB. There are elements from the existing ABS mechanisms — including the PIPF, ITPGR and the BBNJ agreement — that the INB could incorporate to develop a new ABS system for pathogens related to pandemics. Additionally, the simultaneous discussion in the CBD to establish a multilateral benefit-sharing mechanism for DSI may further complicate the already-complex web of ABS legislation implemented by parties to the NP, if implemented alongside the new ABS mechanism for pandemics. Japan and some European countries, which do not require PIC for access to their genetic resources in their ABS policy, will continue contributing to the rapid provision of access to genetic resources, promoting surveillance, research, and development, while establishing bilateral negotiations with countries that require PIC and MATs under their ABS legislation. A need exists for facilitating global awareness of the ongoing negotiations at the WHO on ABS for pathogens with pandemic potential, particularly for industry and academia, which may facilitate rapid access to pathogens by providing legal certainty within the complex landscape of ABS legislation, as well as promote global equitable access to medical countermeasures against future pandemics.

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**Address correspondence to*:
Saki Nakamura, Institute for Future Initiatives, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.
E-mail: saki.nakamura@gmail.com

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Effect of the establishment of the Korea Centers for Disease Control and Prevention/Korea Disease Control and Prevention Agency from the perspective of global health security

Chaeshin Chu*

Division of International Affairs, Department of Planning and Coordination, Korea Disease Control and Prevention Agency, Cheongju, Korea.

Abstract: The Korea Centers for Disease Control and Prevention (KCDC) was established in 2004 after the SARS epidemic. As a national disease control agency, KCDC strengthened its capacities for global health security based on experiences from some important issues such as the Influenza A/H1N1 pandemic (2009), the Middle East Respiratory Syndrome outbreak in Korea (2015), the Zika epidemic (2016), and COVID-19 pandemic (2020-2024). KCDC can make or revise infectious disease prevention and control related law, and collect, manage and analyze disease data from all the local public health centers and medical institutions in Korea. Based on the indicator-based surveillance, event-based surveillance and laboratory-based surveillance, KCDC conducts risk assessment for public health threats and has full responsibility as a competing authority in responding to outbreaks on a legal basis, which is specified in the national disaster framework. All quarantine stations in airports and sea ports belong to KCDC, and individual international travel history data at point of entries are linked to the National Health Insurance Services Database and medical doctors can access the database when the symptomatic individual visits the clinics/hospitals to check his/her travel history in the affected countries. This is a backbone to identify and notify imported infectious diseases from local clinic/hospitals to KCDC. Based on risk assessment in KCDC, KCDC triggers the Emergency Operations Center to respond. This KCDC-centered public health governance with centralized, comprehensive surveillance and response is one of the model cases from the health security perspective to consider for countries that are to establish new national public health institutes in the post-COVID-19 era.

***Keywords*:** emerging infectious diseases, national public health institute, health security

Introduction

The World Health Organization (WHO) revised the international Health Regulations (IHR) (2005) to strengthen the member states' core capacities for monitoring, laboratory diagnosis, prevention and response to infectious diseases in preparation for potential global and regional public health threats after the severe acute respiratory syndrome (SARS) epidemic (*1*). Each member state is required to submit a self-assessment report annually to the WHO on implementation of the IHR core capacity. In 2014, the Ebola epidemics in West Africa raised the limitations of IHR self-assessment, thus prompting establishment of a new mechanism to evaluate and further strengthen capacities for response to public health emergencies across all member states (*2*).

With the existing IHR monitoring and evaluation framework, WHO created the Joint External Evaluation (JEE) tools in 2016 with the Global Health Security Agenda. WHO recommended member states to participate in JEE on a voluntary basis to assess the extent of their core capacities and reflect evaluation outcomes accordingly in national plans (*3*).

The Republic of Korea (ROK) acknowledged the necessity for a unified public health agency with a systematic national disease control system against emerging infectious disease threats. The Korea Centers for Disease Control and Prevention (KCDC) was established in 2004, and it covered disease prevention and response, quarantine, and research (*4*). The Middle East respiratory syndrome (MERS) outbreak in 2015 stimulated the government of ROK to reform the National Infectious Disease Control System to be able to respond to emergencies. Reshaping efforts were made in the legal system, protocols/ guidelines, the quarantine system, information sharing and collaboration between different sectors, collaboration between central and regional governments, inter-ministerial and muti-sectoral collaboration, the national laboratory system, surveillance, health workforce, and risk communication.

This reform enhanced the national capacity to respond to public health emergencies during the early state of COVID-19 (*5*). To prevent and prepare for a future pandemic, the KCDC, an affiliated organization of the Ministry of Health and Welfare, upgraded to an independent government agency with the name of the Korea Disease Control and Prevention Agency (KDCA) in 2020. KDCA oversaw regulations such as the infectious disease control and prevention act and has practical authority over infectious disease policies and enforcement. Epidemiological investigations, disease control research and projects and health promotion are also carried out under the authority of the KDCA (*6*).

In this article, the author reviewed the background in establishing KCDC/KDCA after major emerging infectious disease outbreaks, and summarized the technical areas to strengthen the prevention, detection and response capacities in ROK with the aim of measuring the effect of establishing a national public health institute to detect and respond to COVID-19.

Literature search and effect measurement

Literature Search Strategy

The author searched for all the white papers of the KCDC/KDCA since its inception with special attention to the year when the major public health events such as Influenza A/H1N1, Zika, MERS outbreak, and COVID-19 (*7-12*). To find the effect of the reform, mainly focused on the restructuring of KCDC, the author checked the JEE mission report of the Republic of Korea published in 2017 (*5*) and IHR States Parties Self-Assessment Annual Reports (SPAR) on the WHO website during the COVID-19 pandemic (*13*).

Measuring the Effect of Establishing KCDC/KDCA

To measure the effect of establishment of a disease control agency in the context of global health security, the author followed the JEE evaluation tool and compared the scores in the selected comparable technical area of JEE and SPAR. ROK's JEE scores in 2017 and SPAR scores during the COVID-19 pandemic era (2021-2023) were used for comparison. Based on the JEE tool (first edition), the author chose the relevant technical areas in which KCDC was the main actor in the preparedness and response for infectious disease threats in ROK. 14 out of 19 technical areas were selected to measure the effect of KCDC/KDCA establishment (Table 1) (*14*) . The mean scores of all indicators in a technical area of JEE were taken and converted into a 100-point scale to compare with SPAR scores.

Strengthened capacities

National legislation, policy and financing

The ROK had a comprehensive and concrete legal basis to implement the IHR (2005). For human infectious diseases, the Ministry of Health and Welfare (MOHW) and the KCDC/KDCA operate under the Infectious Disease Control and Prevention Act and the Quarantine Act. For animal diseases, there was the Act on the Prevention of Contagious Animal Diseases. Ministries from other sectors conducted their activities according to the IHR (2005) all hazards approach under various laws such as the Nuclear Safety Act and Chemicals Control

Table 1. Summary of JEE Scores and SPAR scores of the Republic of Korea

Technical Area	JEE[a] 2017 (*5*)	SPAR (*36*)		
		2021	2022	2023
PREVENT				
National Legislation Policy and Financing	100	60	100	100
IHR Coordination, Communication and Advocacy	100	87	87	93
Antimicrobial Resistance[b]	95	100	100	100
Zoonotic Disease	80	100	100	100
Biosafety and Biosecurity	90	NA	NA	NA
Immunization	100	NA	NA	NA
DETECT				
National Laboratory System	95	100	100	100
Real time Surveillance	95	100	100	100
Workforce Development	93	90	100	100
RESPOND				
Emergency Response Operations[c]	90	100	100	100
Linking Public Health and Security Authorities	100	NA	NA	NA
Risk Communication	93	100	93	93
POINTS of ENTRY	100	100	100	100

Data source: WHO (*5,36*). [a]Although JEE and SPAR are based on a 5-point scale, the WHO SPAR website converted the scores into a 100-point scale with mean scores of each technical area; [b]In JEE, Infection Prevention and Control are included in AMR; [c]Emergency Response Operations are included in Health emergency management in SPAR (See Discussion). *Abbreviations:* JEE: Joint External Evaluation, SPAR: States Parties Self-Assessment Annual Report, IHR: International Health Regulations. NA: Not Available.

Act (*5*).

The ROK regularly reviewed and revised relevant laws to align with requirements under the IHR (2005) and after major public health events to incorporate lessons learned into the existing legal system. This includes a major revision or amendment of the relevant laws in 2005 after IHR (2005) were adopted, after the Middle East Respiratory Syndrome (MERS) outbreak in 2015 and COVID-19 in 2020 (*15-18*). In the 2020 amendment, KDCA had full responsibility in the outbreak response (*18*).

The ROK allocated regular annual budgets with reserve funds and supplementary budget for health and relevant ministries to prepare, detect, and respond to public health emergencies (*5*).

IHR coordination, communication and advocacy

The KCDC/KDCA was the national IHR focal point (IHR NFP) in ROK and had a well-established system with high-level expertise for IHR coordination, communication, and advocacy. Since the MERS outbreak in 2015, a dedicated division in the KCDC was established for systematic domestic and international information collection and risk assessments. Since 2016, the dedicated division in the Center for Public Health Emergency Preparedness and Response in KCDC served as IHR NFP and oversaw the ROK's progress for IHR (2005) implementation (*5,9*). During the initial stage of the COVID-19 pandemic in 2020, the division conducted risk assessment and based on their assessment appropriate countermeasures were conducted (*19*).

Antimicrobial resistance

For the first stage of the National Antimicrobial Resistance Safety Management Program (2003-2007), antibiotic consumption volume and antimicrobial resistance in human, animals, food and agricultural production were assessed to devise national action plans in both clinical and nonclinical settings, improve public awareness, promote education, and build international collaboration. A national surveillance system was implemented to monitor cases of healthcare-associated infections, and a new pharmaceutical law regulating the collection, disposal, and small packaging of drugs, as well as the transport and disposal of hazardous drugs were legislated (2006).

In the second stage (2008-2012), a legal framework for infection control was established. A dedicated surveillance system for healthcare associated infection was implemented, and specialized education programs for infection control were offered. The Korean Antimicrobial Resistance Monitoring System (KARMS) Annual Report was published, and the Culture Collection of Antimicrobial Resistant Microbes was opened, together providing the foundation for research and development in the field.

Based on WHO's Global Action Plan on Antimicrobial Resistance, ROK developed the National Antimicrobial Resistant Management Action Plan (2016-2020) in 2016 to prevent the emergence and spread of AMR pathogens in humans and animals (*5,20*).

Zoonotic disease

As most recent emerging and re-emerging infectious diseases are zoonotic, there has been growing emphasis on the significance of zoonotic disease control in public health emergencies (*21*). The ROK designated ten priority zoonotic diseases including anthrax, severe acute respiratory syndrome (SARS), animal influenza with human infection, tuberculosis (Mycobacterium bovis), Enterohemorrhagic Escherichia coli, Japanese encephalitis, brucellosis, rabies, variant Creutzfeldt-Jakob disease, and Q fever with disease-specific guidelines for notification, epidemiological investigations, laboratory diagnosis, and control measures. The KCDC and the Animal and Plant Quarantine Agency (APQA) established the Zoonotic Disease Committee to facilitate information sharing and collaboration for the detection, prevention and response to zoonotic disease events between the human and animal health sectors (2004). The National Institute of Environmental Research (NIER) joined the committee (2017) to apply a One Health Approach for zoonotic disease.

Investigations in animals were carried out by the Ministry of Agriculture, Food and Rural Affairs (MAFRA) and APQA. Laboratory tests for known and novel zoonotic pathogens were carried out by the KCDC/KDCA and the 17 Research Institutes of Health and Environment (RIHEs) for human specimens and by APQA for animal specimens. The Infectious Disease Integrated Management System of the KCDC and the Korea Animal Health Integrated System (KAHIS) of the APQA linked to share animal and human health data (*5,10*).

Biosafety and biosecurity

The KCDC/KDCA regulated the human pathogens under the Infectious Disease Control and Prevention Act and the Act on the Promotion of Collection, Management, and Utilization of Pathogen Resources. The MAFRA regulated animal pathogens and plant pathogens under the Act on the Prevention of Contagious Animal Diseases, the Plant Protection Act, and the Act on the Preservation, Management and Use of Agro-bioresources.

Laboratories and research facilities in the ROK were registered with the government and required to keep biosafety and biosecurity regulations under the jurisdiction of different ministries depending on the biosafety level (BSL) and depending on whether they

are commercial or public facilities with their own guidelines for laboratory biosafety and biosecurity management based on KCDC/KDCA's Laboratory Biosafety Guidelines according to the latest international regulations. Laboratory facilities of BSL 2 and above should designate an institutional biosafety officer and establish an Institutional Biosafety Committee which had the authority to stop the proposed work in case of biosafety or biosecurity concerns. Transportation of select agents was also strictly controlled under the Infectious Disease Control and Prevention Act and the Guidelines for Safe Transport of Infectious Substances. Transportation of high-risk pathogens (HRPs) were required by the approval of the Institutional Biosafety Committee. The ROK government designated several private institutions to conduct biosafety and biosecurity training and provided a budget to fund these activities (*5,22*).

Immunization

In ROK, the National Immunization Program (NIP) started in 1954 under the Prevention of Contagious Diseases Act, designating routine immunization against seven infectious diseases, including smallpox and diphtheria. A total of 20 vaccines were included in the NIP, of which 18 vaccines were provided for free as of 2024. Free vaccination services were expanded to the 19,700 private clinics to tackle financial barriers and improve accessibility from 2014 onwards.

The IT based Immunization Registry Information System enabled real-time monitoring of national or regional immunization coverage as well as the status of vaccine supply. Resident registration information helped identify the number of target people for immunization, thus providing reliable vaccination coverage. The Immunization Registry system shared registration information with relevant organizations.

Since 1995, the KCDC/KDCA operated the National Compensation System for Adverse Events Following Immunization (AEFI) with respect to the NIP. In 2000, the Comprehensive Plan for the AEFI Management was established to support the adverse events surveillance and management system to respond promptly to a serious adverse event.

The ROK cared for foreign residents, who might not have easy access to NIP services, by enabling them to receive free immunizations regardless of possession of an alien registration card and by offering vaccination guidelines in 9 languages nationwide.

The ROK maintained a high vaccination coverage of 95% or above for each vaccine for children. For those who were born in 2013, the fully vaccination coverage for BCG, hepatitis B (HBV), DTaP (Diphtheria, Tetanus and acellular Pertussis) and IPV (inactivated polio) vaccine, which were recommended up to 12 months of age, was 95.9% and 89.2% for 8 vaccines (above mentioned 5 vaccines and MMR, Japanese Encephalitis vaccine) recommended up to 36 months of age. The ROK declared itself measles free in 2006, and, in 2014, was the first nation in the Western Pacific Region to be certified as having eliminated measles (*5,23*).

National laboratory system

The national laboratory system of the ROK consisted of the KCDC/KDCA, Research Institute of Health and Environment (RIHE), and public health centers, where KCDC served as the national reference laboratories. Public health laboratories in 256 public health centers and RIHEs conducted the laboratory testing of infectious diseases and laboratory-based surveillance of the national notifiable infectious diseases in collaboration with the hospitals under the supervision of KCDC/KDCA. As the national reference laboratories, KCDC/KDCA performed the laboratory testing of infectious diseases, quality control and quality assurance of laboratory tests, laboratory-based surveillance, and related training for capacity building. Laboratory testing for 80 national notifiable infectious diseases was performed at public health centers and private sector medical institutions, and the respective costs for laboratory testing were supported as specified in the Infectious Disease Control and Prevention Act.

To control zoonotic diseases, ROK designated major zoonotic diseases as national notifiable infectious diseases. According to the Infectious Disease Control and Prevention Act, the committee for zoonotic disease, composed of experts in public and animal health, was operated. In addition, public human health and animal health laboratories shared data and collaborated for specific diseases on an ad-hoc base through forming consultative groups.

Distribution of public and private sector laboratories was relatively even and easily accessible in all provinces in ROK. The national specimen referral and transfer system was well-established for public health purposes (*5,24*).

Real time surveillance

ROK established an infectious disease surveillance system based on laws/acts. In 2000, the KCDC established an IT-based system capable of reporting in real time, thus ensuring the timeliness and completeness of surveillance data and promoting integration with other surveillance data.

The national notifiable infectious disease surveillance system in ROK had a mandatory surveillance system, and a sentinel surveillance system. 80 types of national notifiable infectious diseases (120 diseases total) were required to be reported in accordance with the Infectious Disease Control and Prevention Act (*5*). The mandatory surveillance system monitors Class 1 to Class

4 infectious diseases. The sentinel surveillance system monitored seasonal influenza, and Class 4 infectious diseases (*25,26*). Since 2016, The MOHW/KCDC imposed private diagnosis laboratories with the duty of reporting notifiable infectious disease pathogens upon their confirmation to prevent delays and unreported cases.

Since the surveillance system was operated through an IT-based system, the reporting of healthcare facilities to local public health centers was shared immediately with provincial governments as well as KCDC/KDCA.

The event-based surveillance system and syndromic surveillance system were in operation to detect potential public health threats. Event-based surveillance collected information from media reports, research papers, and incident reports from healthcare facilities, the Korea-China-Japan network, and inter-governmental information sharing (*27*). A dedicated analysis team integrated indicator-based surveillance data with event-based surveillance data to assess risks and produce reports on a daily, weekly, monthly and annual basis (Figure 1 and Figure 2). Also, the emergency room based syndromic surveillance system was operated in preparation for bioterrorism.

The data gathered through the indicator-based surveillance provided infectious disease statistics to the public in real time through the infectious disease web statistics system, and these data were analyzed on a weekly basis to provide weekly infectious disease statistics through the Public Health Weekly Report (Figure 3). The data collected through event-based surveillance and syndromic surveillance were integrated and assessed for risks and distributed internally, as well as externally with relevant agencies, to transmit timely information regarding infectious diseases that required the attention of the public (Figure 1 and Figure 2) (*5,25-27*).

Workforce development

The KCDC/KDCA was responsible for prevention, investigation, quarantine, testing, and research of infectious diseases. The Department of Public Health and the Research Institute of Health and Environment at the provincial level and public health centers at the district level were responsible for public health services. The KCDC/KDCA had a workforce of about 1,400 people including contracted employees. In local governments, a total of 115 people in 17 provinces, 136 people in 17 Research Institutes of Health and Environment, and 1,181 in 256 public health centers oversaw managing infectious diseases. In particular, the epidemiological intelligence service programme to conduct epidemiological investigations, has operated since 2000 by KCDC/KDCA. There were 102 Epidemic Intelligence Officers (EIOs) in ROK, including FETP trainees. Fifty of them worked at the central government and 46 officers are at the local and provincial levels (*5*).

To foster the public health workforce in ROK, various educational programs are being operated

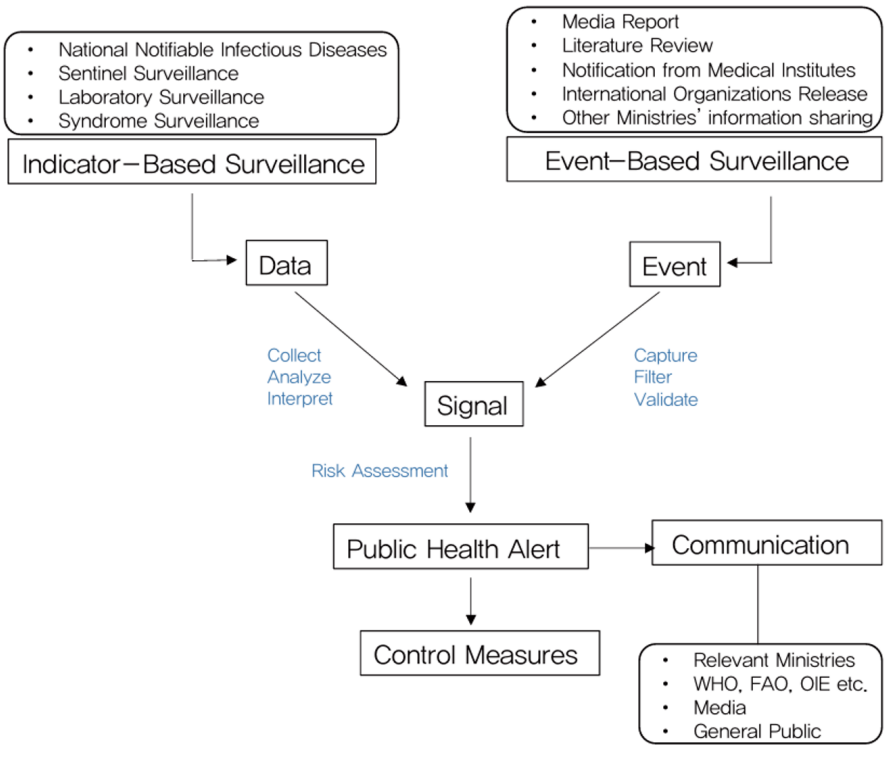

Figure 1. Flowchart of event-based surveillance and indicator-based surveillance. Indicator-based surveillance is a main source of information gathering for risk assessment, but event-based surveillance has its own role as in the early detection of COVID-19.

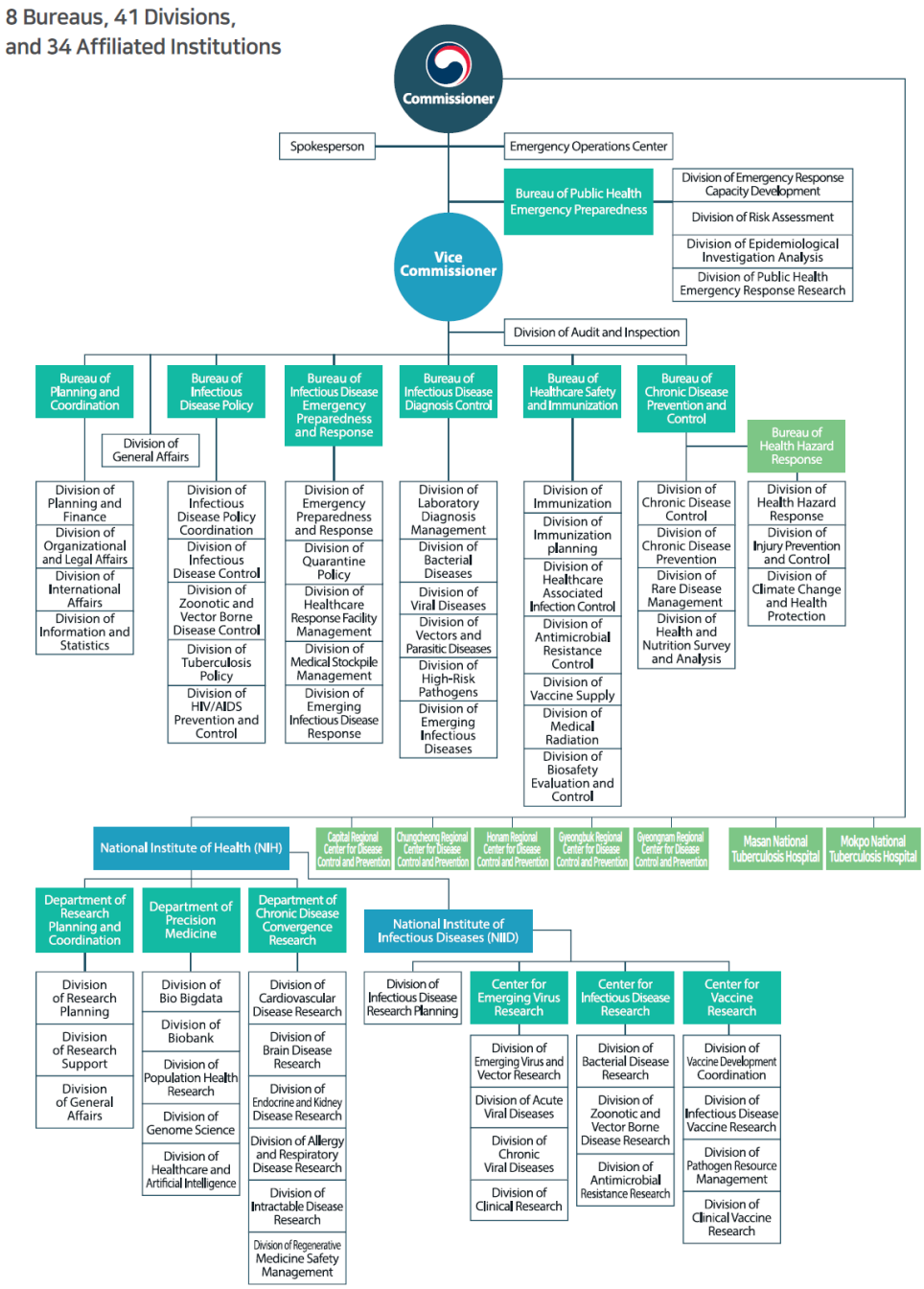

Figure 2. KDCA and its affiliated organizations . KDCA has 8 bureaus and 41 divisions and 34 affiliated institutions. KDCA is a main agency to respond to infectious diseases. It also covers non-communicable diseases and national health and nutritional survey. National Institute of Health (NIH) and National Institute of Infectious Diseases (NIID) are included for research. *Data source: Ref. 37.*

directly or through outsourcing. Typical examples are the public health basic courses operated by the Korea Human Resource Development Institute for Health and Welfare (KOHI), the Field Management Training Program (FMTP) to train personnel in charge of infectious disease management, and the Field Epidemiology Training Program (FETP) to enhance capacity for epidemiology investigation. After the 2015 MERS outbreak, the minimum number of FETP fellows was fixed by law in ROK. Additional medical professionals could be urgently mobilized in addition to healthcare personnel in the public sector, so the capacity to cope with the surge in human resources demand was strengthened (*5*).

Emergency response operations

The Emergency Operations Center (EOC) was established at KCDC in 2016 after the MERS outbreak to support the inter-governmental coordination of information and resources regarding public health emergencies by sharing information on infectious disease

Figure 3. The Public Health Weekly Report (PHWR). PHWR is a weekly publication of KDCA including weekly statistics on the national notifiable infectious disease incidence, policy, and case report launched in 2008. It started with Korean only version, but international requests have made KDCA publish both Korean and English version since 2021. *Data source: Ref. 28.*

events among the relevant ministries/agencies. When the risk of detected events was recognized through a rapid risk assessment as high enough to cause a public health emergency, a MOHW/KCDC internal risk assessment meeting was convened to determine its emergency level in accordance with the Framework Act on the Management of Disasters and Safety and the Standard Manual for Infectious Disease Emergency Management. If the level was determined as Yellow or above, EOC was activated according to the manual. The EOC operation manual has been prepared to specify the procedures for responses to each type of emergency and the roles of the EOC staff in the case of EOC activation. The information system for emergency management was established to enable the EOC to carry out its roles more systematically in the collection and analysis of information, and the supporting of on-site responses (*28*).

Linking public health and security authorities

ROK established Comprehensive Bioterrorism Plan in 2001 to prepare for the threat of North Korea's terrorist attacks to the world and the overall increase in global terrorism risks. Thereafter, manuals and guidelines on bioterrorism were published and are periodically revised. The MOHW announced 8 kinds of biological infectious diseases (Anthrax, Botulinum, Plague, Marburg Fever, Ebola fever and Lassa fever) and established the Infectious Disease Emergency Management Plan in collaboration with the Infectious Disease Control Committee to prepare for large-scale bioterrorism-affected patients in 2016. The Infectious Disease Emergency Management Plan and the Guideline for Bioterrorism preparedness and response against public health emergencies were established.

KCDC/KDCA's Guideline for Bioterrorism Preparedness and Response identified the roles of the central government and local governments in detail for public health emergencies or bioterrorism. KCDC/KDCA jointly conducted a simulation exercise with related ministries every year (*5*).

Risk communication

The KCDC established a dedicated division on risk communication after the 2015 MERS outbreak and published the Risk Communication Guideline for Public Health Emergencies and the Standard Operating Procedure for Risk Communication for Public Health Emergencies, containing details about the risk communication system and strategy, basic principles, communication networks, and evaluation to prepare for emerging infectious diseases.

The risk communication channels for information dissemination included media, Internet, and social networks, and the KCDC/KDCA call center (1339). KCDC/KDCA conducted user-friendly and accessible risk communication by providing various disease information, latest press releases, and content on disease prevention and health information.

KCDC/KDCA monitored major rumors or inaccurate information through the media, Internet, social networking, and 1339 call center. The press releases were disseminated against inaccurate information with reliable information including Q&A sheets were quickly provided through all communication (*5*).

Point of entry

The KCDC/KDCA had 13 quarantine stations (11 quarantine branch offices) installed at airports and seaports nationwide to systemically carry out entry screening toward entrants, along with local governments, and hospitals.

The KCDC/KDCA sent text messages to overseas travelers urging them to report to the KCDC 1339 Call Center if they experienced any symptoms. The quarantine management system that provided travelers' information to medical institutions was to rapidly detect suspected cases and prevent further transmission. When suspected cases were detected at the point of entry (PoE), patients were transferred immediately to nearby hospitals with national designated isolation units. The KCDC/KDCA designated affected areas based on the Quarantine Act, which required travelers to complete a health questionnaire when entering the country.

The KCDC/KDCA established a comprehensive response plan to prepare for and respond to public health emergencies at PoE. The KCDC/KDCA and the Animal and Plant Quarantine Agency (APQA) maintained a cooperative system with the Ministry of Justice and the Customs Service and organize the QIC (Quarantine, Immigration and Customs) institutional council to regularly hold meetings for the exchange of information (*5*).

Discussion

The Global Health Security Agenda developed a new approach to the emerging and reemerging infectious diseases, AMR and biothreats. The global public health emergency can be avoided by preventing avoidable outbreaks, detecting early and responding rapidly to the public health event (*29*). The ROK showed high scores in JEE and SPAR after the 2015 MERS outbreak. Legal basis for case isolation and contact tracing is important and financial compensation during the quarantine period of the suspected cases or contacts with sustainable financing. Conformity to routine vaccination was another predicting factor. For the emerging infectious diseases, early detection and rapid response was a key to containing the outbreak (Table 1 and Figure 4).

Lesson learned from the 2015 MERS outbreak in ROK

An imported case of MERS in 2015 exposed the gaps in the public health system of the ROK. The case visited a primary clinic to a tertiary hospital until he was identified as the MERS infected case. 186 confirmed cases and 38 deaths infected with MERS were a critical failure of the ROK public health system. The KCDC did not detect at PoE the suspected case. The doctors in the hospital and clinics had no information on the patient's travel history and found no clue about this emerging infectious disease. The patients in the emergency room in the tertiary hospital were exposed because there was no triage for respiratory patients with fever. What made the situation worse was the mistrust of the public. The public did not believe what the public health authority said. An epidemilogical investigation to identify contact, contact tracing and quarantine based on mobile phone location and credit card transaction history lacked legal basis (*30*) . The 2015 MERS outbreak was just like what we saw during the COVID-19 pandemic in the world

Reform to the national public health emergency systems in ROK

KCDC has a strong web-based indicator-based surveillance system, or integrated Public Healthcare Information System (PHIS) and is used by more than 3,500 health organizations (*31*). KCDC needed to strengthen the event-based surveillance system with risk assessment, which could complement the indicator-based surveillance. KCDC established a new dedicated division responsible for event-based surveillance and risk assessment. The information with risk assessment was

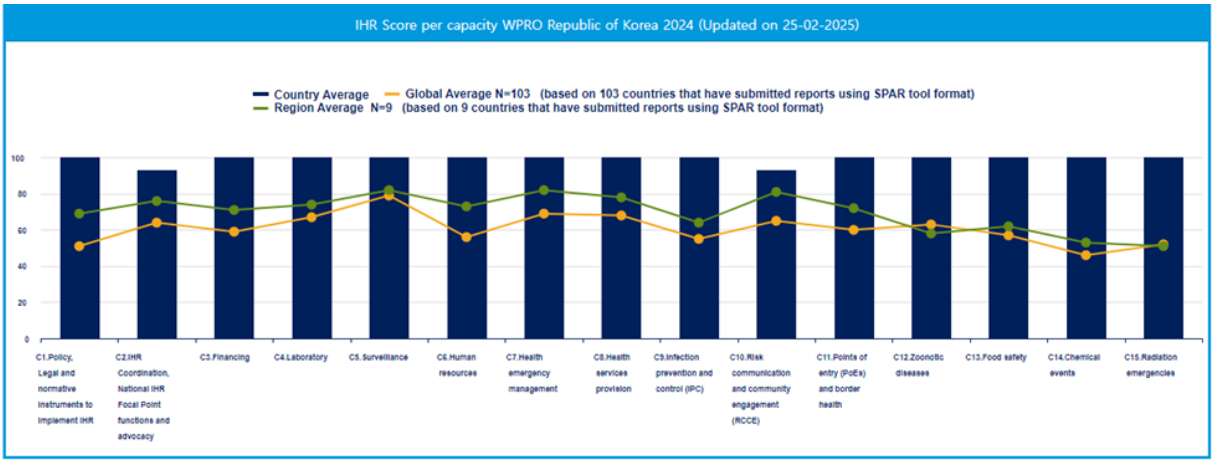

Figure 4. The Republic of Korea's Scores of the IHR States Parties Self-Assessment Annual Report (SPAR) in 2024. ROK has developed and sustained the IHR core capacities scores compared to the global average in all 15 SPAR technical areas.

distributed to relevant ministries/agencies and medical doctors. Together with the Korea Medical Association, the division published a weekly report on overseas emerging infectious disease (Figure 1 and Figure 2) (*27*).

MOHW/KCDC revised the legal gap in contact tracing by revising the Infectious Disease Control and Prevent Act not to violate the personal information law by inserting special situations of infectious disease outbreak so that mobile phone location and credit card transaction history can be traced on a concrete legal basis (*17*). The dedicated risk communication which hired former journalists and public relation experts contributed to enhancing the credibility of KCDC activities (*5*).

Lesson learned from COVID-19 pandemic in ROK

KCDC detected an outbreak in Wuhan on December 31, 2019 through its event-based surveillance system and communicated with China IHR National Focal Point (NFP) to request information on this and shared information on diagnostics and epidemiological investigation with Japan, Taiwan and Thailand with several risk assessments (*19*). KCDC detected the first imported case at a point of entry on January 20, 2020 and conducted case isolation and contact tracing with its advanced ICT technology (*32*). ROK's IHR NFP in KCDC/KDCA notified the information on foreign national cases and contacts detected in ROK or in the inbound flights to the relevant IHR NFPs and ships (*33*). The KCDC shared contact tracing strategy and experience with the United Kingdom Health Security Agency (*10*), and worked together with the United States (US) Department and Human Health Services and US Centers for Disease Control and Prevention for establishing a global health security office (*22,23*). The KDCA hosted the GHSA ministerial meeting in Seoul (*33*) and announced the launching of the Global Health Security Coordination Office in 2022 (*34*). The KDCA actively has taken a leader role in global health security during the COVID-19 pandemic and in a post-COVID-19 era (*35*).

KCDC has developed a mid-and long-term preparedness and response plan for emerging infectious diseases. The key tasks include: *i*) Proactively preparing for and responding to infectious disease outbreaks, *ii*) Controlling and eliminating infectious disease risk factors, *iii*) Preparing for disease and protecting vulnerable groups for healthcare in the super-aging society, *iv*) Enhancing national health care research capabilities, and *v*) Leading global public health cooperation (*35*).

In conclusion, the establishment of KCDC/KDCA showed a significant advancement in global health security because it strengthened South Korea's capacity to respond to infectious diseases while fostering collaboration, innovation, and preparedness at both regional and global levels. In an era where infectious diseases has no borders, the KCDC/KDCA's role is integral to safeguarding public health worldwide.

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**Address correspondence to*:
Chaeshin Chu, Division of International Affairs, Department of Planning and Coordination, Korea Disease Control and Prevention Agency, 187 Osongsaengmyeong 2-ro, Osong-eup, Chengju, Chungcheongbuk-do 28159, Korea.
E-mail: cchu@korea.kr

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Large-scale screening of SARS-CoV-2 variants in Tokyo, Japan: A 3-year and 9-month longitudinal survey

Junko S. Takeuchi[1,#], Kei Yamamoto[2,#], Masami Kurokawa[3,#], Kento Fukano[1,#], Azusa Kamikawa[1,#], Emiko Hatano[1,#], Sakino Takayanagi-Nishisako[1,#], Ayano Motohashi[3,#], Yuki Takamatsu[4,#], Hiroaki Mitsuya[4,#], Norio Ohmagari[2,#], Moto Kimura[1,#], Wataru Sugiura[5,*,#]

[1] Biorepository and Research Laboratory, Department of Academic-Industrial Partnerships Promotion, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan;
[3] Department of Laboratory Testing, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan;
[4] Department of Refractory Viral Diseases, National Center for Global Health and Medicine Research Institute, Tokyo, Japan;
[5] Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Over nearly four years (March 10, 2021–December 31, 2024), we performed a comprehensive longitudinal analysis of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants among patients in a single hospital in Tokyo, Japan. Using RT-qPCR and Sanger sequencing, complemented by whole-genome sequencing, we tested nasopharyngeal swab samples (n = 4,628) and tracked the emergence and evolution of variants of concern (VOCs). The findings demonstrate the utility of a hospital-based SARS-CoV-2 variant surveillance system for informing clinical decision-making and public health settings, including: *i*) serving as a reference for selecting appropriate treatments, *ii*) enabling early detection of VOCs, *iii*) contributing to the development of hospital infection control guidelines, *iv*) fostering cooperation with local governments, *v*) supporting cohort studies, and *vi*) identifying long-term SARS-CoV-2 infections. This work underscores the importance of real-time variant monitoring for mitigating the effects of pandemics and provides essential epidemiological and clinical data that can guide future outbreak management and policy development.

***Keywords*:** COVID-19, variant of concern (VOC), sequencing, epidemiology, clinical data

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19 (*1*), continues to mutate as the infection spreads. Since the Alpha variant (PANGO lineage B.1.1.7) (*2*) was designated a "Variant of Concern (VOC)" at the end of 2020, the Delta (B.1.617.2, AY sublineages) (*3*) and Omicron (B.1.1.529, BA sublineages) (*4*) variants were identified in May and November 2021, respectively. Subsequently, various sublineages of the Omicron variant, including BA.1, BA.2, BA.4, BA.5, and other recombinant strains, have been reported (*5*). When VOCs emerge independently, each may become regionally or globally dominant, replacing earlier variants. The replacement of these mutant strains has caused successive "waves" of infection, significantly burdening healthcare systems (*6,7*). By the end of 2024, Japan had faced eleven major SARS-CoV-2 epidemic waves. Each dominant variant exhibits unique clinical characteristics, including disease severity, immune evasion, transmissibility, and sensitivity to vaccines or therapeutics (particularly monoclonal antibodies) (*8*). In clinical settings, identifying the infecting variant can be crucial for determining treatment strategies for patients with underlying conditions or comorbidities, as well as for controlling the spread of infection within hospital wards (*9*).

The National Center for Global Health and Medicine (NCGM), Tokyo, one of four Designated Medical Institutions for Specified Infectious Diseases in Japan, has been involved in the COVID-19 response since the outbreak began. Activities included health checkups and RT-qPCR testing for returnees on chartered flights from Wuhan, China (*10*), and medical care for patients from the Diamond Princess cruise ship (*11*). In hospitals treating a large number of COVID-19 cases, it is particularly important to understand the circulating

variants with distinct virological characteristics in a clinical setting. During the early years of the pandemic, SARS-CoV-2 variant monitoring in Japan was documented using whole-genome sequencing-based (*12*) and Sanger sequencing-based methods (*13*). However, reports on the longitudinal surveillance of variants within a single medical institution remain limited.

This study aimed to develop a rapid and efficient SARS-CoV-2 variant monitoring system within a clinical setting and evaluate its impact on patient management and hospital infection control. Beginning on March 10, 2021, NCGM initiated SARS-CoV-2 variant testing using residual nasopharyngeal swab samples from COVID-19 patients with RT-qPCR-based kits or Sanger sequencing to monitor variant trends within the hospital. Additionally, we report findings from a large-scale screening of SARS-CoV-2 variants among hospitalized patients at NCGM over a period of three years and nine months, discussing how variant information was utilized in clinical settings. This study provides insights into the role of real-time variant surveillance in hospital settings, offering a model that could be applied to future infectious disease outbreaks.

Materials and Methods

Participants in the study

Between March 10, 2021, and December 31, 2024, we tested 4,628 residual nasopharyngeal swab samples from patients (both outpatients and inpatients) diagnosed with COVID-19 at NCGM in Tokyo, Japan.

RT-qPCR-based method

The VirSNiP SARS-CoV-2 Spike kits (Roche Diagnostics Corp., Tokyo, Japan) were used per the manufacturer's protocol.

Nucleic acid extraction and Sanger sequencing

Nucleic acid (50 µL) was extracted from 200 µL of nasopharyngeal swab samples using a KingFisher APEX System (Thermo Fisher Scientific, Waltham, MA, USA) and the MagMAX Viral/Pathogen Nucleic Acid Isolation Kit (Thermo Fisher Scientific). Subsequently, 15 µL of the extracted nucleic acid was used for cDNA synthesis using PrimeScript™ IV 1st Strand cDNA Synthesis Mix (Takara Bio, Shiga, Japan) with a random hexamer. A total of 1 µL of cDNA was amplified through 1st and 2nd PCR reactions using PrimeSTAR® Max DNA Polymerase (Takara Bio). The primer sets are listed in Table 1. These sets amplified approximately a 0.6 Kbp fragment of the receptor binding domain (RBD) of the *spike* (S) gene to identify SARS-CoV-2 variants (Figure 1A, Fragment 2). Since September 2024, an additional S gene region (Figure 1A, Fragment 1; N-terminal domain covering amino acid residues 1-70) has been analyzed to distinguish

Table 1. Primer sets used in this study

Fragment 1 (for XEC)			
5'- to 3'-	**PCR**	**Direction**	**Period**
ATGTCATGCATGCAAATTACATATTTTGGA	1st	Forward	week 35 of 2024 ~
AATTCACAGACTTTAATAACAACATTAGTAGCG	1st	Reverse	
TTGTCTTCCTATTCTTTATTTGACATGAGT	2nd	Forward	
TCTAAAGTAGTACCAAAAATCCAGCCTC	2nd	Reverse	
Fragment 2 (for Receptor Binding Domain)			
5'- to 3'-	**PCR**	**Direction**	**Period**
ACTTGTGCCCTTTTGGTGAAGT	1st/2nd	Forward	week 17 of 2021 ~
TGCTGGTGCATGTAGAAGTTCA	1st/2nd	Reverse	
ACTTGTGCCCTTTTGRTGAAGT	1st/2nd	Forward	week 48 of 2021 ~
TGCTGGTGCATGTAGAAGTTCA	1st/2nd	Reverse	
TCCTTCACTGTAGAAAAAGGAATCTATCA	1st	Forward	week 43 of 2022 ~
GTCCACAAACAGTTGCTGGTG	1st	Reverse	
GATTTCCTAATATTACAAACTTGTGCC	2nd	Forward	
TGCTGGTGCATGTAGAAGTTCA	2nd	Reverse	
TCCTTCACTGTAGAAAAAGGAATCTATCA	1st	Forward	week 46 of 2023 ~
GTCCACAAACAGTTGCTGGTG	1st	Reverse	
GTTAGATTTCCTAATATTACAAACTTGTG	2nd	Forward	
TGCTGGTGCATGTAGAAGTTCA	2nd	Reverse	
CGTTGAAATCCTTCACTGTAGAAAAAGG	1st	Forward	week 41 of 2024 ~
TCCACAAACAGTTGCTGGTGC	1st	Reverse	
GAGTCCAACCAACAGAATCTATTGTTAGAT	2nd	Forward	
TCAAAAGAAAGTACTACTACTCTGTATGGTT	2nd	Reverse	

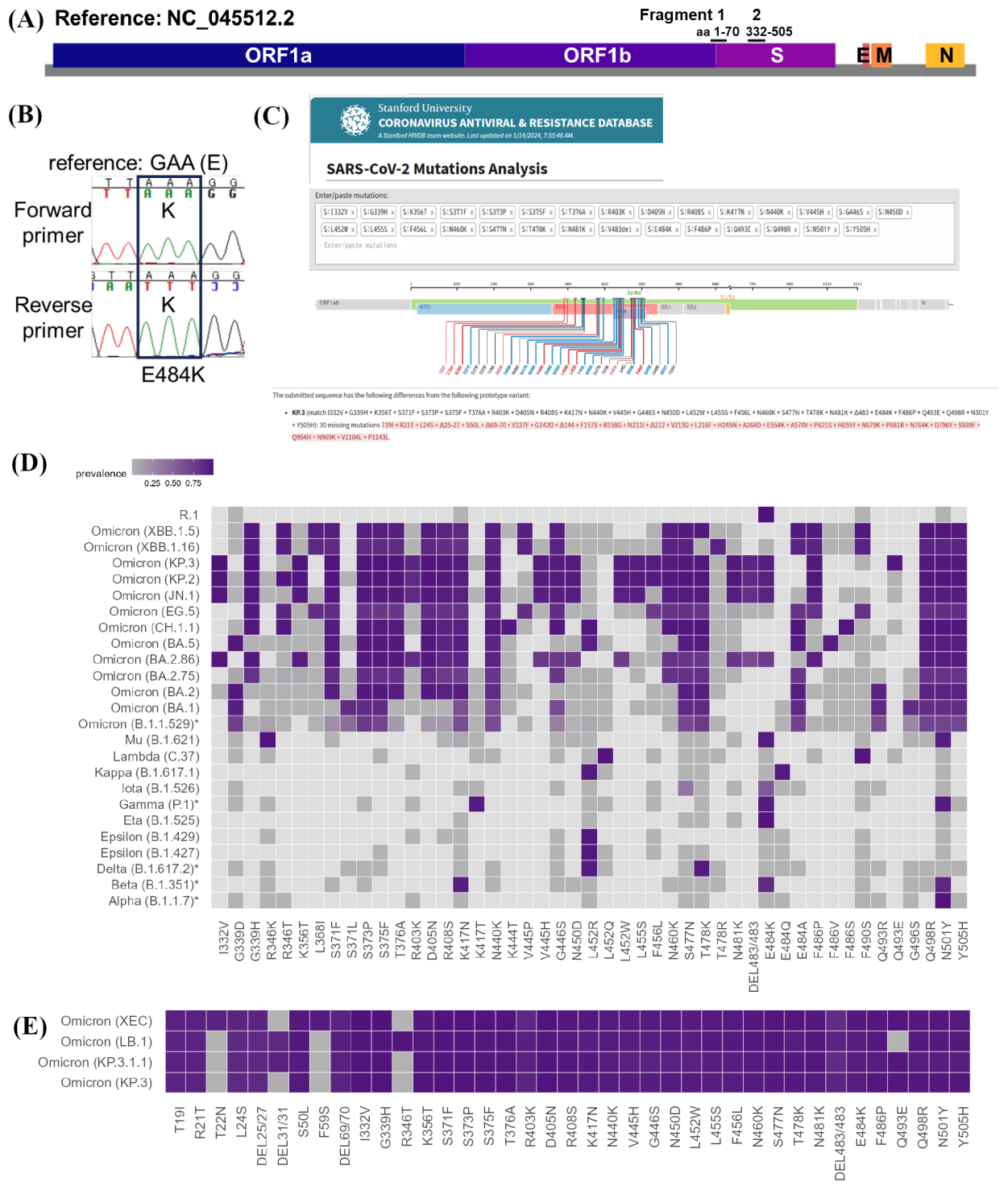

Figure 1. Inferring SARS-CoV-2 variants using Sanger sequencing. (A) RT-PCR amplification regions targeted in this study. Fragments 1 (covering amino acid residues 1–70) and 2 (covering amino acid residues 332–505) include key mutations that enable the identification of XEC and VOC, respectively. **(B)** The resulting sequence electropherograms were aligned with the Wuhan-Hu-1 reference sequence (NC_045512.2). **(C)** SARS-CoV-2 variants were inferred based on mutation patterns using the Stanford SARS-CoV-2 Mutations Analysis tool. **(D, E)** Prevalence of mutations within the sequenced S region for Variants of Concern (VOC), Variants of Interest (VOI), and the R.1 variant, one of the dominant variants during Japan's 4th wave, is shown. Mutations present in at least 75% of the sequences associated with each lineage are displayed. For VOC, an asterisk (*) is attached to each notation. Data were obtained from GISAID (accessed on 14 March 2025). The heatmap was generated using the R package outbreakinfo 0.2.0 (*42*). aa: amino acid residues.

between KP.3, KP.3.1.1, LB.1, and XEC variants (Figure 1E). Positive PCR products were validated *via* agarose gel electrophoresis, purified using a Millipore Multiscreen-HTS-PCR 96-well plate (Millipore, Billerica, MA, USA), and sequenced with the BigDye™ Terminator v3.1 Cycle Sequencing Kit (Thermo Fisher Scientific). The resulting electropherograms were aligned to the Wuhan-Hu-1 reference sequence

(NC_045512.2) using Sequencher 5.4.6 (Hitachi Software Engineering Co., Ltd., Yokohama, Japan) (Figure 1B). Variant inference was based on mutation patterns using the Stanford SARS-CoV-2 Mutations Analysis tool (*14*) (Figure 1C).

Whole-genome sequencing

Using nucleic acid from nasopharyngeal swab samples, cDNA synthesis, target amplification, and library preparation were performed according to the Illumina COVIDSeq Test Reference Guide (Illumina Inc., San Diego, CA, USA) with ARTIC primers (V3, 4, 4.1, or 5.3.2). SARS-CoV-2 genome sequencing was conducted on the Illumina iSeq 100 system, and results were analyzed using the Illumina DRAGEN COVID Lineage software.

Quantification of the virus

RT-qPCR testing was conducted using the SARS-CoV-2 Detection Kit -Multi- (NCV-403, TOYOBO CO., LTD., Osaka, Japan) and a LightCycler 96 System (Roche Diagnostics Corp.), following the manufacturer's instructions. Briefly, 10 μL of extracted nucleic acid was mixed with 40 μL of reaction mixture. The cycle quantification (Cq) values were obtained by amplifying two regions (N1 and N2 primer/probe sets) from the N gene.

Database analysis

The SARS-CoV-2 lineage distribution in Japan and worldwide during the study period was analyzed using data from the Global Initiative on Sharing All Influenza Data (GISAID) EpiCoV database (*15*) as of January 9, 2025. The following criteria were applied: "Collection date" between March 10, 2021, and December 31, 2024, or between January 1, 2020, and December 31, 2024. "Sequence length" ≥ 27,000, and "Passage details/history" is Original. For domestic sequences, "Location" was set to Japan.

Data visualization was performed using R 4.3.1, and statistical analyses were conducted using GraphPad Prism 9.3.0. (GraphPad Software Inc., San Diego, CA, USA).

Results

A total of 4,628 nasopharyngeal swab samples from COVID-19-diagnosed cases at NCGM were included in this study. Among these, the SARS-CoV-2 variants of 3,423 samples (74.0%) were inferred (Figure 2A). The World Health Organization (WHO) categorized certain variants as VOCs and variants of interest (VOIs) to enhance global monitoring (*16*). The Sanger sequencing protocol used in this study could distinguish the VOCs and VOIs, including those that did not spread domestically in Japan, except in cases where R.1 and Eta (B.1.525) could not be distinguished (Figure 1D). At NCGM, prior to the emergence of the Delta variant, variants for each sample were identified using RT-qPCR-based kits, such as the VirSNiP SARS-CoV-2 Spike kits (Roche Diagnostics Corp.). If the N501Y mutation was detected, the variant was classified as Alpha, while the presence of the E484K mutation identified it as R.1, one of the dominant variants during Japan's 4th wave. However, as the mutation patterns of the virus diversified, classifying variants based solely on a single mutation in the S gene became increasingly challenging (Figure 1D).

From May 2021 onward, when RT-qPCR-based kits could not determine variants, the Sanger sequencing protocol was adopted. On May 19, 2021, the first Delta variant case, initially detected in India on October 5, 2020 (*3*), was confirmed at NCGM. By late July 2021, just before the Tokyo Olympic and Paralympic Games, all samples at NCGM underwent Sanger sequencing. On December 2, 2021, the first Omicron variant case, originally identified in South Africa on November 25, 2021 (*5*), was detected at NCGM. Starting June 10, 2022, foreign tourists on package tours were allowed to enter Japan. Shortly thereafter, on June 14, 2022, the first BA.4/BA.5 Omicron sublineage was detected at NCGM.

The distribution of SARS-CoV-2 lineages in Japan during the study period was analyzed using all domestic SARS-CoV-2 genome data (≥27,000 nucleotides, n = 642,096) registered in the GISAID EpiCoV database (Figure 2B). While the data from NCGM primarily focused on hospitalized patients with severe cases, the data from GISAID comprises a broader range of data, including epidemiological surveys and quarantine data. Nevertheless, the trends in variant prevalence were consistent across both datasets. Relative fluctuations in the number of newly infected cases in Japan and Tokyo closely aligned with the sequencing data from NCGM and GISAID during Japan's 4th (Alpha) and 5th (Delta) epidemic waves (Figure 2, Figure 3). This is consistent with earlier reports indicating that the number of confirmed COVID-19 cases and the number of sequenced SARS-CoV-2 genomes were well correlated for the 1st to 5th (Delta) waves in Japan, with approximately 10% of confirmed cases being sequenced (*17*).

After the emergence of Omicron sublineages, the Sanger sequencing protocol used in this study could no longer differentiate between certain sublineages, such as BA.1 and BC.1, or BA.4/BA.5 and BF.x (*e.g.*, BF.5), due to the limited sequencing region (0.6 Kbps of the *spike* gene), unlike GISAID, which sequences the entire SARS-CoV-2 genome. For example, samples initially identified as BA.4/BA.5 through Sanger sequencing were later found to include BF.2 or BF.5

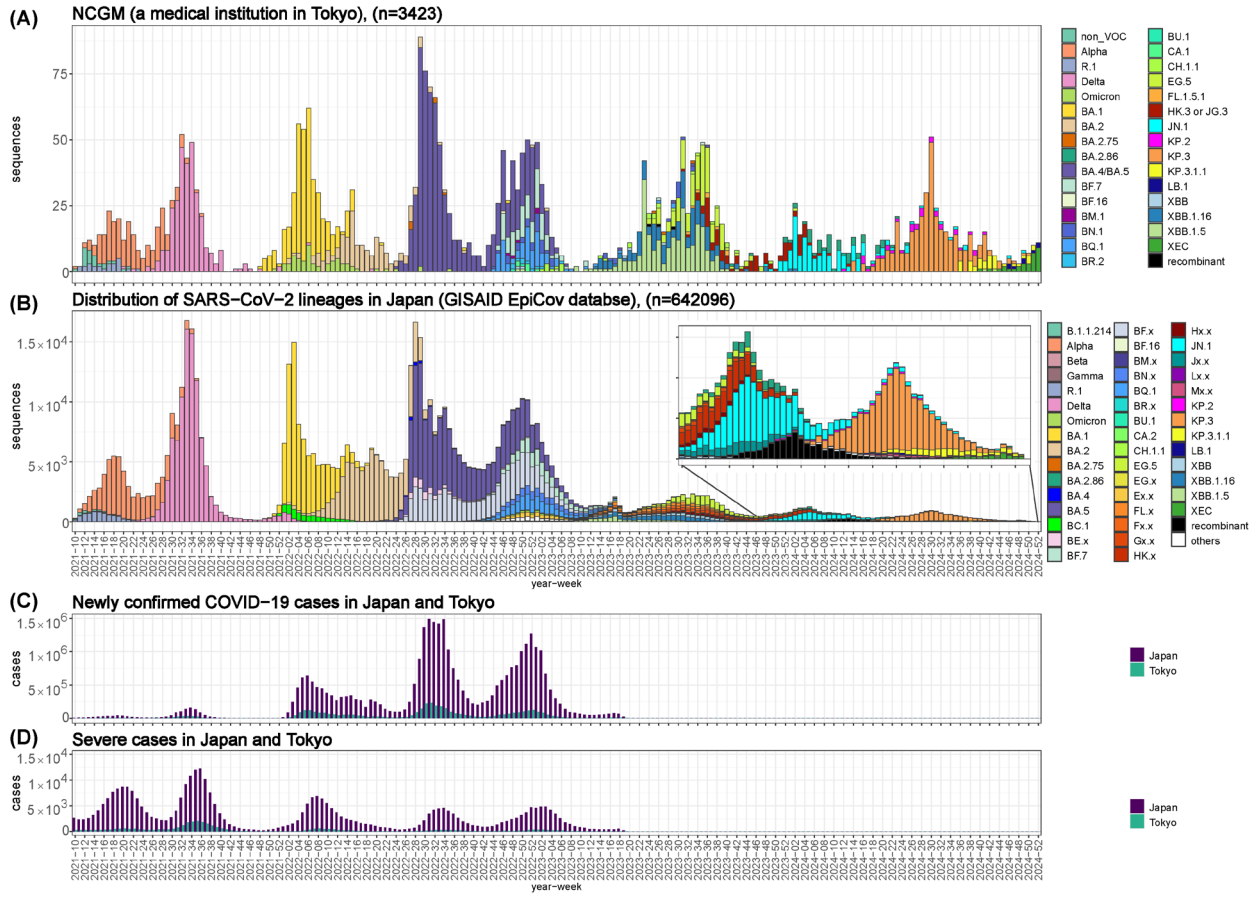

Figure 2. Weekly epidemiological distribution of SARS-CoV-2 variants between March 10, 2021, and December 31, 2024. **(A)** Data derived from patients diagnosed with COVID-19 at NCGM, Tokyo, Japan (n = 3,423). Sequences with no detectable single mutations were classified as "non_VOC". **(B)** All domestic samples (≥ 27,000 nucleotides) registered in the GISAID EpiCoV database (n = 642,096). A magnified view of the data from week 46 of 2023 onward is shown in the upper-right corner. **(C, D)** The number of new SARS-CoV-2 infections and severe cases in Japan and Tokyo based on open data from the Ministry of Health, Labour and Welfare (*43*).

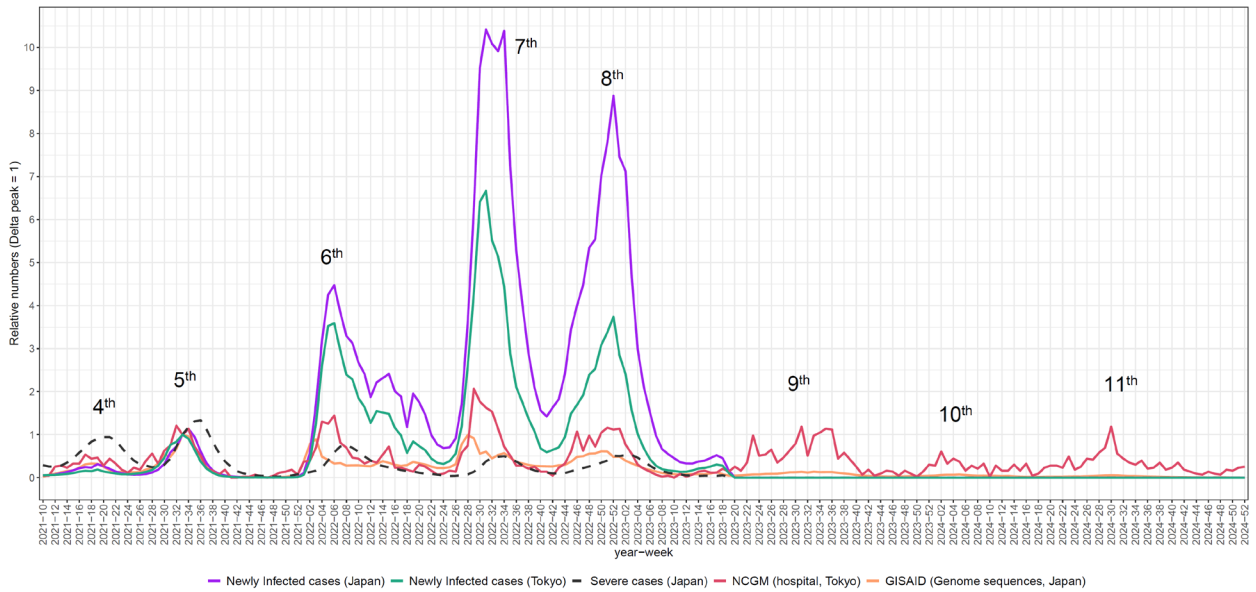

Figure 3. Relative numbers of newly infected cases in Japan (solid purple), in Tokyo (solid green), severe cases in Japan (dashed black), SARS-CoV-2 variants inferred at NCGM (solid red), and domestic genome sequences registered in the GISAID database (solid orange) are shown. The Y-value at the peak of the 5th wave (Delta peak, week 33 of 2021) is set to 1.

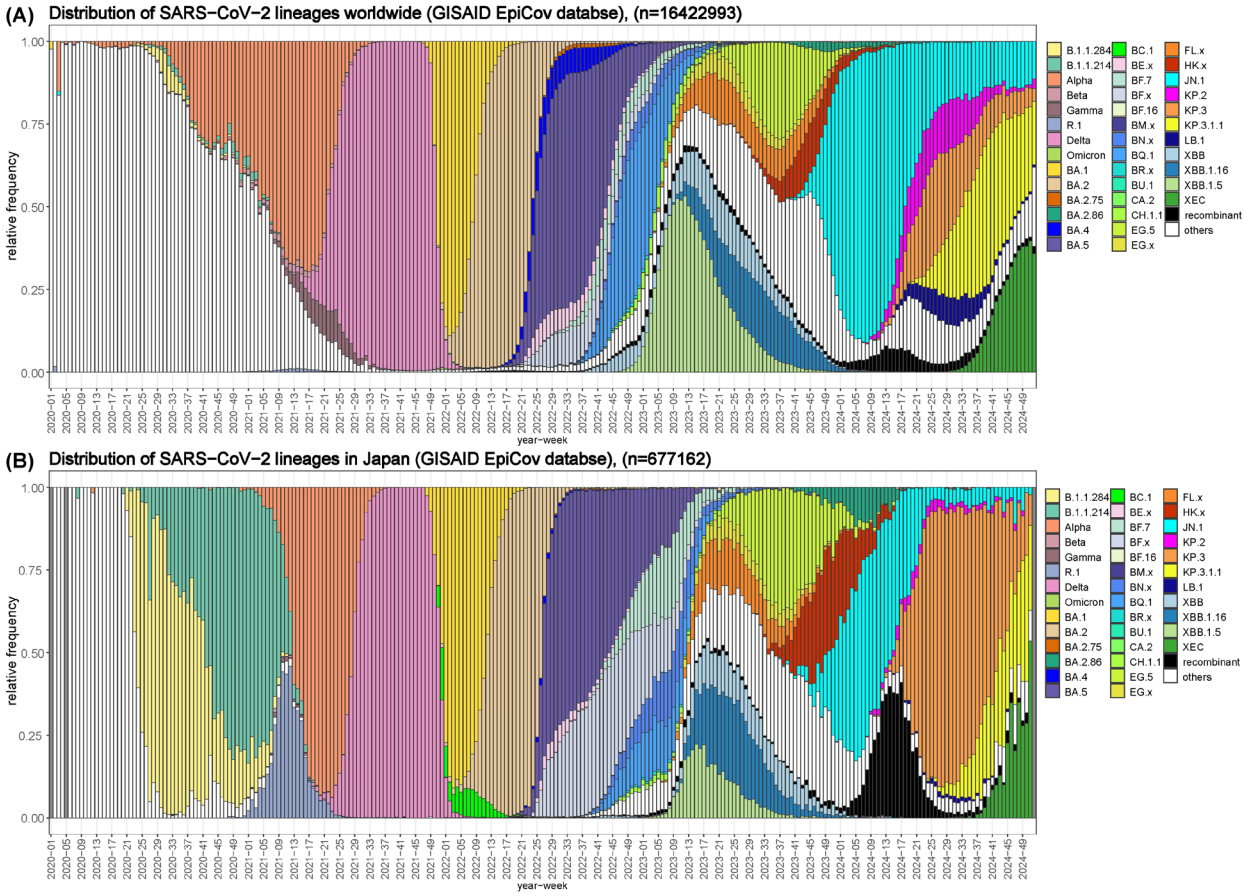

Figure 4. Weekly epidemiological relative frequency of SARS-CoV-2 variants between January 1, 2020, and December 31, 2024. (A) All worldwide (*n* = 16,422,993) and **(B)** domestic (*n* = 677,162) samples (≥ 27,000 nucleotides) registered in the GISAID EpiCoV database.

upon whole-genome sequencing. Nonetheless, NCGM data successfully captured the overall trends of SARS-CoV-2 variants.

On May 8, 2023 (week 19 of 2023), the Japanese government reclassified COVID-19 as a "Class 5 disease" under the Infectious Diseases Control Law, equating it to seasonal influenza (*18,19*). Consequently, COVID-19 surveillance in Japan transitioned from a notifiable system to a sentinel-based system (*20*), and reporting all detected COVID-19 cases was no longer mandatory. As a result, the proportion of sequences registered in GISAID decreased after the 9th wave (Omicron XBB.1.5/EG.5.1) compared to NCGM data. In NCGM data, the peak case numbers of the 8th and 9th waves were nearly identical. However, in GISAID data, the peak of the 9th wave was reduced to one-quarter of that of the 8th wave, suggesting that while both NCGM and GISAID captured domestic outbreak waves, GISAID had a lower capture rate compared to NCGM.

Next, regarding a comparison of trends between Japan and global data, Figure 4 presents the distributions of SARS-CoV-2 lineages between January 1, 2020, and December 31, 2024. Several differences were noted: *i*) detection of region-specific minor strains and other VOCs, such as the Beta (B.1.351) and Gamma (P.1) variants, during the pre-Delta period; and *ii*) variations in the frequency of Omicron sublineages. Conversely, transition to the Delta variant and subsequent spread of the Omicron BA.1 and BA.2 variants followed consistent patterns worldwide.

Finally, both NCGM and GISAID (Japan and worldwide) datasets demonstrated that when variants with higher transmissibility or basic reproduction numbers (R_0) emerged, their replacement of previous variants was clearly observable, as documented in prior studies (*21*). For example, the transmission advantage of BA.1 (170%) is approximately double that of Delta (85%), and more recent Omicron variants, such as XBB (280%), exhibit significantly greater transmissibility.

To investigate the underlying cause of amplification failure in some samples during the 2nd PCR step of Sanger sequencing, we quantified the viral load of 60 nasopharyngeal swab samples using RT-qPCR testing. All of these samples were derived from the same epidemic wave (8th wave) and amplified using the same primer sets. Of these, 30 were sequentially extracted from the period with low amplification efficiency (3/30, weeks 8-10 of 2023), while the remaining 30 were sequentially extracted from the period with high amplification efficiency (27/30, weeks 47-48 of 2022).

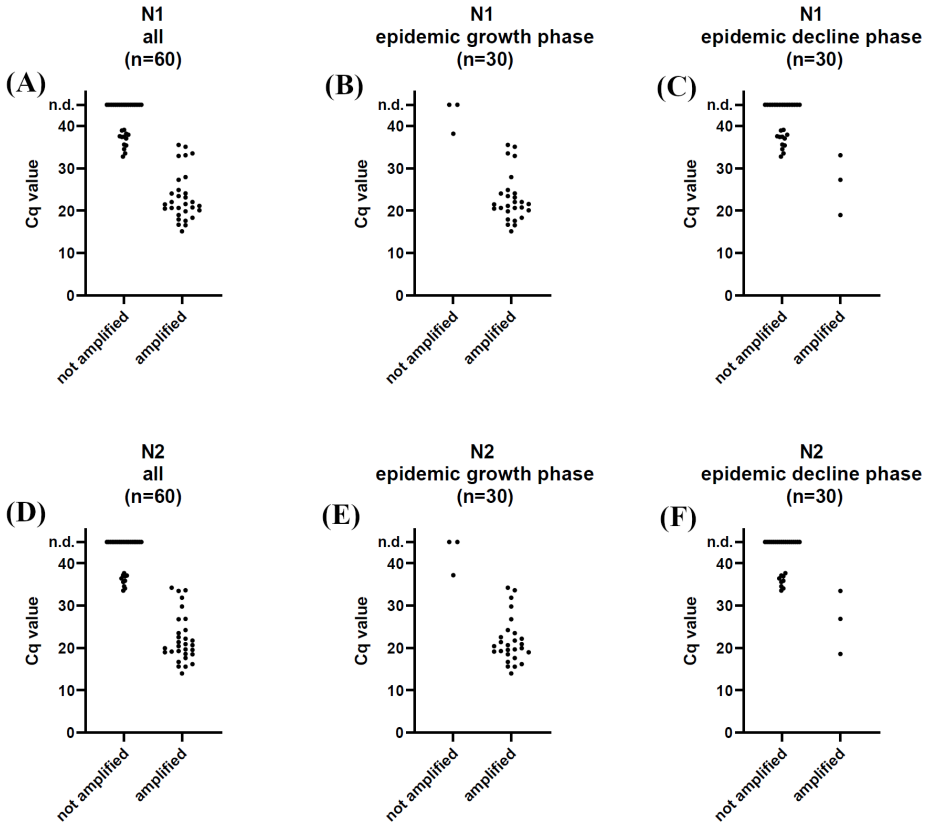

Figure 5. (A, D) Comparison of Cq values between successfully amplified (n = 30) and not amplified (n = 30) samples during the 2nd PCR. Among the 60 samples, **(B, E)** samples collected during the epidemic growth phase of the 8th wave (weeks 47-48 of 2022) and **(C, F)** samples collected during the epidemic decline phase (weeks 8-10 of 2023) are shown separately. Cq values were quantified using the SARS-CoV-2 Detection Kit -Multi- (TOYOBO) by amplifying two regions (N1 and N2 primer/probe sets) derived from the N gene. n.d.: not detected.

As expected, samples with lower Cq values (indicating higher viral loads) were more likely to be amplified (Figure 5). Among the non-amplified samples, 17 out of 30 for N1 and 20 out of 30 for N2 were below the detection limit. Median Cq values for N1 and N2 in the non-amplified samples were 37.42 (interquartile range [IQR]: 34.98-38.06) and 36.14 (IQR: 34.41-37.13), respectively, which were significantly higher than those of successfully amplified samples, whose medians were 21.54 (IQR: 19.62-25.49) for N1 and 20.55 (IQR: 18.55-24.85) (both $p < 0.0001$).

Interestingly, among the 60 samples, those collected during the epidemic's growth phase (weeks 47-48 of 2022) exhibited higher viral loads (Figure 5B, E), while those collected during the decline phase (weeks 8-10 of 2023) showed lower viral loads (Figure 5C, F). This observation aligns with previous findings that the early phase of an epidemic wave often involves a higher proportion of recently infected individuals with higher viral loads, whereas the late phase sees a greater proportion of individuals with relatively older infections and lower viral loads (*22*). Our data further confirmed differences in viral copy numbers between samples collected during the epidemic expansion and contraction phases.

Discussion

At NCGM, variant information was provided in real-time as a reference for the Center Hospital, the Laboratory Testing Department, and the Infection Control Team. Additionally, upon request, this information was supplied to local governments. Representative applications include the following: *i*) Since the Omicron variant and its sublineages are resistant to monoclonal antibody treatments (*23-25*), variant information was used as a reference for selecting appropriate treatments; *ii*) The variant information facilitated the early detection of Delta and Omicron cases in Japan (*26-28*); *iii*) In cases of COVID-19 outbreaks within the Center Hospital, suspected samples were analyzed in detail, including whole-genome sequencing and phylogenetic analysis. These findings were shared with the Infection Control Team to trace virus transmissions within wards, contributing to the development of hospital infection control guidelines; *iv*) At the request of local governments, whole-genome sequencing of samples from severe COVID-19 cases was performed and registered in the GISAID database; *v*) Some data were utilized in cohort studies of breakthrough infections,

particularly in relation to vaccination or prior infection among NCGM staff (*29-31*); *vi*) Long-term SARS-CoV-2 infection cases were identified as part of variant surveillance efforts (*32*). On a global scale, examining the genetic changes in SARS-CoV-2 has significantly enhanced public health responses. A notable example is the development of mRNA vaccines. The Delta variant, for instance, demonstrated increased transmissibility and virulence, which was associated with higher morbidity rates (*33,34*). These findings prompted intensified vaccination efforts. In countries such as the United Kingdom and the United States, vaccination campaigns were accelerated to mitigate severe COVID-19 outcomes (*35*). Similarly, Japan successfully implemented the primary COVID-19 vaccination series (first and second doses), achieving 75% coverage by the end of November 2021 (*36,37*). The effectiveness of the primary series of COVID-19 mRNA vaccines against symptomatic infection in Japan was reported at 89.8% during the Delta wave. In contrast, during the Omicron wave, the effectiveness dropped to 21.2%, but with the administration of a third dose, it rose to 71.8% (*38*). These findings underscore the necessity of booster doses, and Japan began administering the third dose in December 2021. However, the effectiveness of this dose waned over time, particularly against Omicron sublineages (*39*). In response to the reduced vaccine effectiveness, bivalent mRNA vaccines (containing Spike-encoding mRNA of both the original SARS-CoV-2 strain and Omicron-BA.1 or -BA.4/5) and additional Omicron-XBB.1.5 or -JN.1 monovalent mRNA vaccines have been developed (*39,40*).

As demonstrated, the capability to analyze SARS-CoV-2 variants within a hospital and the establishment of a collaborative team to share real-time information can be critical for optimizing treatment strategies, controlling the spread of infections in healthcare settings, understanding regional variant trends, and advancing epidemiological and clinical research. However, this study has several limitations. First, since it was conducted at a single medical institution in Tokyo, Japan, the findings on SARS-CoV-2 variant trends may not be generalizable to other regions or countries. Second, the testing methods changed throughout the study. Initially, the RT-qPCR method was used, but from May 2021, it was replaced with the Sanger method. Third, the Sanger method used in this study only covers approximately 0.6 Kbps of the S gene, which limits the resolution of lineage identification. While lineage estimation is possible, precise identification requires next-generation sequencing (NGS)-based full-genome analysis for more detailed information.

In conclusion, our study highlights the utility of RT-qPCR and Sanger sequencing, complemented by whole-genome sequencing, in screening SARS-CoV-2 variants, both in clinical settings and for gaining epidemiological and medical insights. By tracking nearly all patient samples from a Tokyo hospital over three years and nine months, we acquired valuable insights into the turnover of variants in symptomatic patients, including those with severe cases. The WHO declared a Public Health Emergency of International Concern for COVID-19 on January 30, 2020, which was officially lifted on May 5, 2023. However, the WHO emphasized that emergence of new variants still poses a potential risk of renewed surges in cases and deaths (*41*). Our findings improve the understanding of SARS-CoV-2 variant trends in Tokyo, Japan, and will assist in detection of emerging variants in the future.

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[#]*Current affiliation*: Japan Institute for Health Security.
**Address correspondence to*:*
Wataru Sugiura, Center for Clinical Sciences, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: sugiura.w@jihs.go.jp

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COMMENTARY
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Health system analysis for pandemic policies: Suggestions for the Japan Institute for Health Security (JIHS)

Michael R. Reich*

Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

Abstract: This commentary introduces an approach to health systems analysis and reform, presents the implications of the health systems approach for pandemic preparedness and responses, and offers potential suggestions for the Japan Institute for Health Security (JIHS) to consider adopting in its activities for pandemic policies and health systems. The paper examines actions for health system strengthening that have important implications for pandemic preparedness and responses in five areas of policy intervention (according to the book *Getting Health Reform Right*: *A Guide to Improving Performance and Equity*): *i*) *financing*, how funds are mobilized, placed in risk pools, and allocated in a health system; *ii*) *payment*, how different actors and institutions in a health system are paid; *iii*) *organization*, how a health system is organized and managed; *iv*) *regulation*, how government rules are used to change the actions of both private and public institutions; and *v*) *persuasion*, how information and targeted interventions are used to change the choices and behaviors of specific actors in a health system. The commentary also makes four tentative suggestions for JIHS: mobilize expertise in all health system areas, develop a new unit for health system analysis, establish global relevance, and merge the two organizations effectively.

***Keywords*:** health system analysis, pandemic preparedness and responses, Japan Institute for Health Security (JIHS)

Introduction

The establishment of the Japan Institute for Health Security (JIHS) marks a major turning point in Japan's institutions and policies for global health. Japan's decision to create this new organization is especially important given the sudden disengagement of the United States from global health.

Upon assuming power on January 20, 2025, President Donald Trump took two critical actions in this arena on his first day in office: first, issuing an executive order to withdraw the United States from the World Health Organization (*1,2*), and second, issuing an executive order to freeze all funds for foreign assistance for 90 days, effectively halting all activities of the U.S. Agency for International Development (USAID) (*3*). President Trump subsequently announced his intention to close the agency (*4*) and to terminate nearly all of its 10,000 staff, keeping only around 290 people (*5*). On March 10, Secretary of State Marco Rubio announced that 83% of USAID programs were closed (canceling 5,200 contracts) and that the remaining programs would be managed directly in the Department of State (*6*). The implications of these decisions are still unfolding around the world but clearly will have negative impacts on the health and well-being of vulnerable populations in low- and middle-income countries, as projected in a memorandum prepared by a USAID official before he was fired (*7*). These and other shifts in U.S. policy and strategy will also create significant challenges and opportunities for high-income nations, including Japan.

JIHS was created by merging two existing organizations: the National Center for Global Health and Medicine (NCGM) and the National Institute of Infectious Diseases (NIID). The full details of this merger are presented in other articles in this special issue. As with any organizational merger, many issues will need to be sorted out. Some are logistical and administrative (such as reporting structure, personnel contracts, how to deal with overlaps, how to deal with gaps, budgeting processes, *etc*.). Other issues may emerge related to integrating the mission, programmatic strategies, and organizational culture. I have a few suggestions on key issues and useful approaches for JIHS to use as it works through inevitable challenges.

My first suggestion for JIHS is to clarify the organization's name in English and Japanese. Various definitions of "health security" have been proposed in the international literature. It will be important for JIHS to specify its definition of "health security" in

both conceptual and operational terms. Considering the institute's name in Japanese complicates this further. A direct translation into English of the Japanese name of *Kokuritsu Kenko Kiki Kanri Kenkyu Kiko* (国立健康危機管理研究機構) is closer to "National Institute for Health Crisis Management and Research". Notably, the English name emphasizes the strategic aspects of protecting health security (a broad system-level concept), while the Japanese name highlights the importance of managing and researching health risks (a more technical and intervention-focused concept). The two names of JIHS in English and Japanese have been confirmed by the government and officially adopted for use. However, it still may be helpful for JIHS to clarify the meanings of the two different names as the organization moves forward with its operations.

My second suggestion is for Japan to learn about the institutional challenges of managing health security risks from other countries. What lessons can be learned from countries, such as the United States, that were not initially successful in dealing with the COVID-19 pandemic?

One lesson from the U.S. experience is that the existence of an institute does not automatically result in success in managing health crises. Consider the example of the U.S. Centers for Disease Control and Prevention (the CDC). In December 2022, over two years into the COVID-19 pandemic, the U.S. House of Representatives Select Subcommittee on the Coronavirus Crisis released a staff report on its findings. It cited details on over 80 incidents of political interference by the (first) Trump administration in the federal government's public health efforts to manage and control the pandemic in 2020. Committee chair Representative James E. Clyburn made this statement (*8*): "The Select Subcommittee's investigation has shown that the [first Trump] administration engaged in an unprecedented campaign of political interference in the federal government's pandemic response, which undermined public health to benefit the former president's political goals. As today's report shows, President Trump and his top aides repeatedly attacked CDC scientists, compromised the agency's public health guidance, and suppressed scientific reports in an effort to downplay the seriousness of the coronavirus. This prioritization of politics, contempt for science, and refusal to follow the advice of public health experts harmed the nation's ability to respond effectively to the coronavirus crisis and put Americans at risk".

When the second Trump administration took office in January 2025, they began a new round of extremely aggressive attacks on public health institutions and rejecting the use of science in making public policy. In February 2025, for example, the Trump administration appeared ready to fire many of the 135 members of the Epidemic Intelligence Service at the CDC, the "disease detectives" responsible for pandemic investigation and control in the U.S. and around the world (*9*) – but then one week later apparently decided not to eliminate the positions. The U.S. experience should be studied as JIHS considers potential political challenges in the future and develops strategies to protect public health institutions from potential political interference.

Health system analysis and reform

My main suggestions (below) are responses to the original question: how can health systems be improved to more effectively deal with pandemics? This is a critical topic, but so complex that it cannot be adequately addressed in a short essay. My goal here, therefore, is to introduce one approach to health system analysis, consider the implications for how health systems intersect with pandemics, and offer potential suggestions for what JIHS might do in this field.

Since the mid-1990s, I have been working with colleagues at Harvard University and the World Bank to develop and refine an approach to health system analysis and reform (*10*). This approach provides an action-oriented, structural method for assessing health system performance. It also recommends measures to address specific performance problems and improve overall system performance based on many countries' experiences. The approach is explained in detail in the book *Getting Health Reform Right*: *A Guide to Improving Performance and Equity* (*11*), which was published in 2004, and serves as the basis for a more recent publication targeted at practitioners, *Health Reform Manual: Eight Practical Steps* (*12*). The method has been widely used for training government officials on how to manage health system performance, and for assessing both national and sub-national health systems (for an example, see Ref. *13*).

This approach to health system analysis and reform uses five areas of policy interventions, shown in Figure 1, to influence three intermediate performance measures (efficiency, quality, and access) in order to improve three health system performance objectives: health status, public satisfaction, and financial risk protection. The five areas of policy interventions (also called control knobs) are (*11*): *i*) *Financing*: the sources of money for the health system, along with its risk pools and allocation; *ii*) *Payment*: how different actors and institutions in the health system are paid; *iii*) *Organization*: how the system is organized (including centralized versus decentralized, and public versus private sectors) and managed; *iv*) *Regulation*: the use of government rules to change the actions of both private and public institutions; *v*) *Persuasion*: efforts to change the choices and behavior of specific actors (providers, patients, consumers, and prescribers) through targeted interventions.

Two distinctive features of this approach to health system analysis and reform are worth noting. The first is its emphasis on considering different kinds of interventions throughout the policy cycle (problem

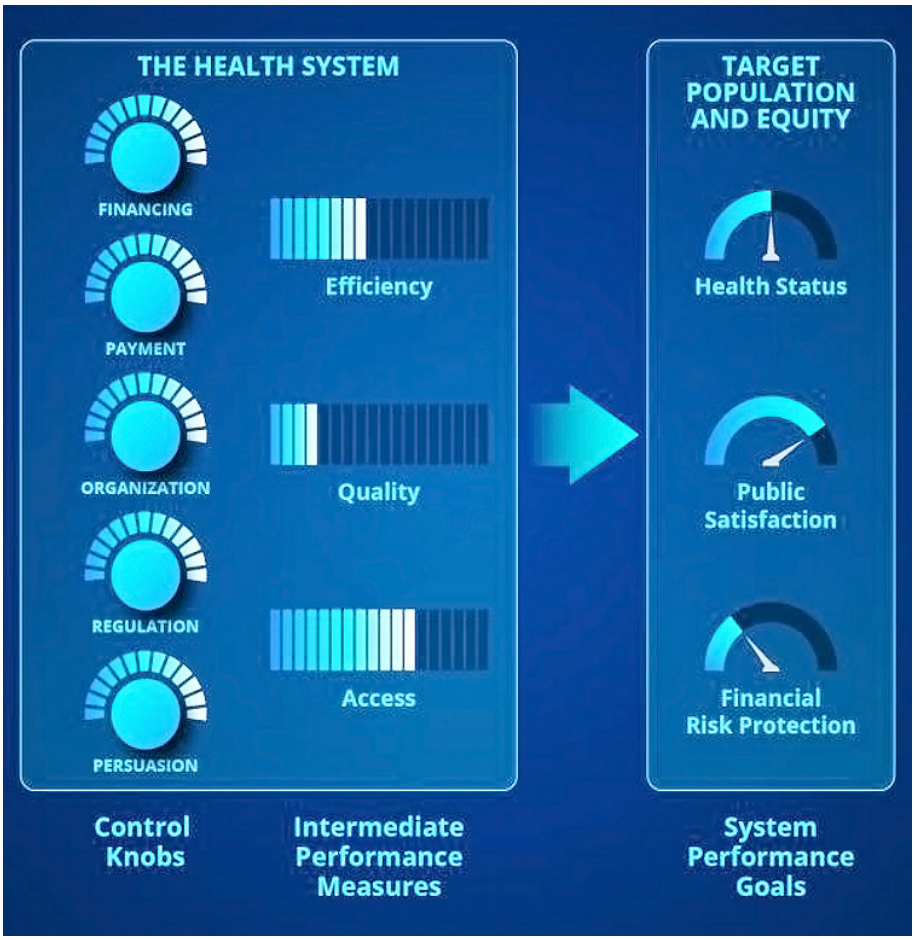

Figure 1. Framework for health system analysis and reform. Source: Reich *et al*., Health Reform Manual: Eight Practical Steps (*Ref. 12*); adapted from Roberts *et al*. (*Ref. 11*).

definition, diagnosis, policy development, political decision, implementation, and evaluation). The different stages of the policy cycle are incorporated into the eight steps of the *Health Reform Manual* (*12*). The second distinctive feature is that the approach incorporates three different kinds of analysis in health reform: technical (including epidemiological and economic assessments); ethical (with an introduction to applied philosophy); and political analysis (including how to do applied policy analysis (*14*)).

Health systems and pandemics

How can this approach to health system analysis be used in pandemic preparedness and responses? And how can it be used to suggest potential actions for JIHS?

First, let's consider how the three health system performance goals are related to pandemics. In terms of health status, a health system leader would probably seek to reduce infection rates, control the spread of infectious agents, and adopt measures that reduce morbidity and mortality following infection. Regarding public satisfaction, it would be important to communicate consistently and provide easily understood information (in order to promote public trust and encourage compliance with the desired pandemic interventions). For financial risk protection, it is important to design measures that assure patients do not bear the costs of prevention (such as immunization) or face burdensome costs of illness if they become sick, while also ensuring that access to diagnostics is financially accessible so that individuals can be identified and isolated in a timely manner to reduce further spread.

Next, let's explore the various policy intervention areas (the five dials at the left of Figure 1) and the implications of health system strengthening for pandemic preparedness and responses.

Financing involves collecting money, pooling it, and allocating it for health system functions. An important feature of financing for pandemics is the creation of dedicated pandemic emergency funds. These assure rapid resource mobilization at the national level and can then be distributed to local authorities for action. This requires flexible funding mechanisms to address new or unexpected needs. It is also likely that mechanisms will be required to allow for disbursing funds directly to people who have unexpected out-of-pocket pandemic-related expenses. Financing also has to be available for the implementation of epidemic surveillance systems, to rapidly develop real-time data systems for emerging

infectious agents, and for creating integrated data platforms for monitoring and rapid response. A third important activity for financing is long-term support for epidemiology training. A distinguished example is the U.S. CDC's long-standing and successful financing of the Epidemic Intelligence Service, although its future is uncertain under the current administration (*9*).

Payment involves the disbursement of funds to health facilities and providers to compensate them for services and commodities; payment modalities create incentives that shape individual and organizational behaviors. For pandemic preparedness and responses, it is important to use available funds to pay institutions and individuals to prevent and treat infectious diseases. Payment can also be used to provide fair compensation to frontline workers, especially when they experience heightened stress and personal risks during a pandemic. During the COVID-19 pandemic, burnout and inadequate pay led to healthcare workers' strikes around the world (including in Bosnia, Hong Kong, South Korea, Kenya, Peru, Spain, the U.S., and Zimbabwe (*15*)). In Japan, burnout became a major problem among public health nurses, who play an important community role in the Japanese health system (*16*) and bore the brunt of many frontline actions for COVID-19 (*17*). Payment also includes mechanisms for strategic purchasing, which allow timely procurement of essential supplies (including vaccines, personal protective equipment, and other critical resources). Payment mechanisms can also be used to stabilize market dynamics and ensure equitable access to pandemic control resources.

Organization involves structural decisions about the health system at the macro, meso, and micro levels, including what happens in the public versus the private sector and which decisions are made at each level of the health system. For pandemics, this includes the establishment and sustainability of emergency response units, with dedicated resources, staff, and protocols for efficient mobilization during a crisis. Organization involves addressing various questions, including: Who do these units report to? How are they funded? Where do they sit within different institutions? For example, Japan's experience with using its Disaster Medicine Assistance Teams (DMATs) – mainly intended for natural disasters – in the early responses to COVID-19 suggests that these response teams can also be helpful in pandemic response (*18*). Another important organizational goal is to ensure the continuation of essential health services during a pandemic, even during pandemic surges, for example, through plans for hospital load balancing (*19*). Enabling the use of flexible organizational models for health services (such as telemedicine and mobile clinics) to reach vulnerable populations in pandemics can also be important. Finally, public and private sector interactions during a pandemic can create both opportunities and challenges, particularly in terms of how they share (or hoard) resources, including medical countermeasures such as protective equipment, vaccines, medicines, diagnostics, and other essential supplies.

Regulation involves the use of government rules to change the actions of private and public institutions. For pandemics, it is important to streamline research and regulatory approvals for diagnostics, treatments, and vaccines. This can involve accelerating approval processes during health emergencies. Government agencies can create pre-approval frameworks that allow for the rapid evaluation and deployment of emergency-use technologies. One example of this accelerated regulatory approach was South Korea's legislation for reverse transcription polymerase chain reaction (RT-PCR) emergency use authorization and contact-tracing methods (prior to COVID-19), which allowed the country to mount a swift and effective response using the strategy named "3T–Test, Trace, and Treat" (*20*). How JIHS approaches regulation will be especially important, given its new role in the research and development of vaccines and treatments.

Persuasion, the fifth area of policy intervention, encompasses how government can influence the behaviors of people to engage in pandemic preparedness at the individual and community levels. Persuasion strategies can help shape individual behavior to promote effective pandemic responses. Clear communication and transparency about decisions and actions can also contribute to social trust in government action during pandemics. This is one area where Japan was particularly successful during the COVID-19 pandemic. The "Three Cs" campaign represented an effective form of policy communication (*21*) for persuasion. The Three Cs urged people to avoid *closed* spaces, *crowded* places, and *close-contact* settings. This became a catchy policy slogan in Japanese, based on its repeated use of the *kanji* 密 [mitsu] to signify "density", to encourage avoiding the 三つの密 (the three densities), pronounced as *mittsu* no *mitsu* or 三密 [*san mitsu*] (This was recognized as the Words of the Year for 2020!). This policy communication, combined with the existing habit of wearing masks as an "historically embedded social practice" (*22*), helped create an effective pandemic response in Japan.

Tentative suggestions for JIHS

What are the practical implications of this approach to health systems analysis and reform for pandemic preparedness and responses in general, and especially for the newly established JIHS? Here are four tentative suggestions, offered with humility, for JIHS to consider.

i) *Mobilize expertise in all health system areas*: Taking on new challenges requires new expertise. To strengthen the new organization's capacity in health system analysis for pandemic preparedness and responses, JIHS will require technical specialists for all five areas of policy intervention (financing, payment,

organization, regulation, and persuasion), as well as people with expertise in political and ethical analysis methods. This will require cultivating significant expertise in social science (such as economics, political science, organizational behavior, and policy communication), which may not have existed previously in either of the two organizations.

ii) *Develop a new unit for health system analysis*: Pandemic institutions (in Japan and elsewhere) need to create robust health system analysis units for pandemic policies. If JIHS seeks to provide ongoing strategic advice about how to prevent and manage pandemic outbreaks, it will need an established group assigned to this task. The unit would do well to foster both domestic and international experience, since JIHS may be called on to act within Japan as well as with other countries. This unit could provide training courses domestically and internationally on strategies for pandemic prevention and responses.

iii) *Establish global relevance*: JIHS could create a new model for transforming health systems to address pandemic preparedness that is relevant for Japan and adaptable for other countries worldwide. This role would be particularly important given the current international context, as the Trump administration removes the U.S. government from many global health organizations and from the broader sphere of international cooperation. The gaps created represent a strategic opportunity for Japan to use JIHS to expand its global role in pandemic preparedness and health systems. These global activities could include, for example, funding pandemic preparedness initiatives in other countries, establishing global courses on health systems and pandemic policies, creating regional partnerships for pandemic preparedness and health system strengthening, and fostering regulatory harmonization across countries related to pandemic policies.

iv) *Merge the two organizations effectively*: Combining two existing organizations (with different histories, cultures, and missions) and transforming them into a single new entity is an ongoing challenge, for both public and private sectors. JIHS no doubt is drawing the lessons from other contexts about how to manage this complicated process (*23*). One area of particular interest will be the role of the general hospital (which belonged to NCGM before the merger) to advance health system analysis for pandemic policies. This is an area that is not possessed by the U.S. CDC, and so could represent a significant potential advantage for the JIHS.

While the next global pandemic may or may not resemble the one we just experienced with COVID-19, it is important to learn from our recent experiences to prepare for a more effective response next time. I hope that some of the ideas presented above, about how health system strengthening relates to pandemic policies, are helpful in structuring and managing Japan's new institute for health security.

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Address correspondence to:
Michael R. Reich, Taro Takemi Professor of International Health Policy, Emeritus; Department of Global Health and Population, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA.
E-mail: michael_reich@harvard.edu

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COMMENTARY
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Clinical considerations for the next pandemic: Japan's current challenges and strategic preparedness

Norio Ohmagari*,#

Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: This commentary aims to reflect on the clinical implications of past pandemics and discuss Japan's preparedness for future pandemics, with a specific focus on enhancing national countermeasures through clinical, infrastructural, and systemic reforms. By analyzing pandemics including the Spanish flu (1918), Asian flu (1957), Hong Kong flu (1968), H1N1 influenza (2009), and COVID-19 (2019-), the article discusses their clinical features, societal impacts, and the factors that drive the spread of infectious diseases. With Japan's clinical context as a case study, this commentary emphasizes the importance of enhancing healthcare systems to accommodate sudden surges in cases, with a focus on expanding infrastructure and ensuring rapid access to diagnostics, treatments, and vaccines. The commentary also advocates for improved early detection systems, effective global sharing of information, and the training of healthcare professionals to respond to emerging threats. This article argue that pandemic preparedness should go beyond lessons from COVID-19, promoting a comprehensive and flexible approach that can be adapted to a range of potential future scenarios. Such measures will help ensure that healthcare systems remain resilient and capable of mitigating the impact of future pandemics.

***Keywords*:** pandemic preparedness, Japan, clinical infrastructure, infectious diseases, healthcare policy

Introduction

Multiple global pandemics over the past century, including the Spanish flu (1918), Asian flu (1957), Hong Kong flu (1968), H1N1 influenza (2009), and COVID-19 (2019-) (*1-5*), have increasingly revealed that global healthcare systems must be robust, responsive, and forward-looking. Influenza and coronaviruses remain the primary threats, with emerging pathogens such as the Nipah virus, Ebola virus, and engineered bioweapons posing additional risks. Factors that accelerate pandemics include globalization, urbanization, climate change, and misinformation. Rapid international travel enables the rapid spread of diseases, whereas urban density exacerbates transmission. Climate-related changes increase the risk of mosquito-borne diseases and zoonotic spillovers.

The next pandemic could overwhelm healthcare systems, causing shortages in beds, intensive care units (ICUs), ventilators, and medical staff. High mortality rates can destabilize societies, whereas prolonged lockdowns can damage mental health, education, and economies. Supply chain disruptions can limit access to vaccines and medicines and exacerbate global inequality.

This commentary sought to clarify the clinical aspects of pandemics and discuss measures needed to prepare for the next one. Specifically, it: *i*) summarized past pandemics and outlined their clinical features, *ii*) discussed characteristics of infectious diseases caused by potential pandemic pathogens, *iii*) raised issues regarding Japan's clinical response to the current pandemic, and *iv*) discussed what measures Japan will need to take in the event of a future pandemic.

Lessons from historical pandemics

Spanish flu (1918)

This pandemic was caused by an influenza outbreak during World War I. Various theories have been proposed to explain the origin of this outbreak. Approximately one-third of the world's population was estimated to be infected, with 20-50 million deaths. The fatality rate was extremely high (> 2%), with many victims being mature adults in their 20s-40s. In Japan, approximately 23.8 million people were infected, and approximately 390,000 died (*6*). No vaccines or antivirals were available at the time, and non-drug measures against infection were implemented in many areas, including quarantines, masks, and bans on gatherings.

Asian influenza (1957)

The influenza A (H2N2) pandemic began in 1957. It is known as the "Asian flu." This new strain of influenza was first identified in Hong Kong and Singapore in the spring, and it spread worldwide to Europe and the United States in approximately 6 months. Although the fatality rate was low at approximately 0.2% (*7*), there were a vast number of infected people, resulting in many deaths. Vaccine development progressed in many countries, and the epidemic was controlled over a relatively short period.

Hong Kong influenza (1968)

This pandemic, also known as the Hong Kong flu, was caused by influenza A(H3N2) and occurred in 1968. A new strain, confirmed in Hong Kong, spread from Asia to Europe and the United States, and the global death toll was estimated to be at least 1 million (*8*). The symptoms were relatively mild and the fatality rate was low, but the death toll increased in the second wave through the winter of 1969. The H3N2 virus subsequently became a seasonal influenza virus and it has been circulating yearly.

H1N1 influenza (2009)

This pandemic, caused by influenza A(H1N1)pdm09, emerged in the spring of 2009. A new strain of influenza A(H1N1)pdm09 was identified in Mexico, and it spread worldwide in a short period of time. The highest alert level was declared during Phase 6 in June. Although young people were primarily infected, a few cases of infection among older adults were reported. The estimated global mortality was 201,200 (range 105,700-395,600) (*4*). In Japan, an estimated 20 million people were infected in over a year, with 203 deaths reported; therefore, the death rate per population was lower than that in other countries (*9*). The epidemic subsided within a few months, and the H1N1pdm strain was subsequently incorporated into seasonal influenza strains.

COVID-19 (2019-)

COVID-19 was first identified in Wuhan, China at the end of 2019 and eventually became a global pandemic. The virus responsible, SARS-CoV-2, is transmitted mainly by infectious particles containing the pathogen, through their mouth or nose and can spread asymptomatically; the World Health Organization (WHO) declared COVID-19 a pandemic in March 2020, and there were multiple waves of outbreaks worldwide. Countries implemented strict countermeasures such as urban blockades and border closures but were unable to completely prevent the spread of the virus. A vaccine was developed and administered after late 2020, and severe infections were suppressed, but the pandemic was prolonged by continued reemergence due to mutations of Delta, Omicron, and other strains. Preliminary estimates suggest that the total number of global deaths attributable to the COVID-19 pandemic was at least three million on May 20, 2021, representing 1.2 million more deaths than officially reported (*10*).

Assumptions regarding the next pandemic

Pathogens likely to cause the next pandemic

Diseases that have been identified as pandemics thus far include acute respiratory infections. However, other infectious diseases can lead to pandemics. Based on past cases, the next pandemic is likely to be caused by an emerging virus. The most typical pandemic occurs when an animal influenza virus, such as avian influenza, mutates and becomes persistently transmissible from person to person. In the past, all pandemics have been caused by influenza viruses, and currently, there are warning signs of the potential emergence of zoonotic viruses, such as the highly pathogenic H5N1 avian influenza virus.

Based on the examples of severe acute respiratory syndrome, Middle East respiratory syndrome, and COVID-19, coronaviruses are pathogens with a high potential for causing pandemics. An unknown coronavirus in nature could spread to humans; if a new virus emerges that is as lethal as severe acute respiratory syndrome or Middle East respiratory syndrome virus and that is as infectious as the virus that caused COVID-19, it could cause a serious situation.

Other potential viruses include enteroviruses, paramyxoviruses like the Nipah virus, and filoviruses like the Ebola virus. All of these viruses have thus far only caused local epidemics, but they could cause global pandemics if they mutate and become more infectious. In addition, the use of artificially modified pathogens and bioweapons poses a potential threat. Moreover, the emergence of unknown viruses is possible.

Factors contributing to the spread of infection

Factors unique to modern society will be responsible for the emergence and spread of the next pandemic. The global situation is rapidly changing, and the probability of a pandemic is increasing. In addition, the speed at which infectious diseases spread and their impact on human health and society is greater than ever before. Below are some of the specific factors:

With the development of transportation and logistics, people and goods move around the globe by air, and infectious diseases spread rapidly worldwide. In the modern era, the time from the first case to a pandemic is extremely short.

Economic growth is accompanied by large cities,

which are the centers of the economy; those cities are densely populated and a virus can, once introduced, spread rapidly. Moreover, public health measures may be inadequate in areas with rapid population growth. Such environments have poor sanitation and can serve as breeding grounds for the spread of infection.

Global warming will expand the habitats of mosquitoes and other vectors and increase the period of their annual activity, which may lead to the spread of mosquito-borne infectious diseases, such as dengue fever and malaria. Deforestation increases the risk of wildlife–human encounters. This means that humans will be increasingly exposed to zoonotic pathogens, and, as a result, so-called viral spillovers from animals to humans are more likely to occur. Climate change leads to disasters such as floods, which are more likely to trigger outbreaks of infectious diseases. Several post-disaster cholera outbreaks have occurred worldwide in recent years.

In areas with poverty or conflict, containing infectious diseases is difficult because of weak healthcare systems. Supply chain disruptions can lead to shortages in medical supplies. One can see an example in the recent worldwide outbreak of cholera, much of which occurred in conflict zones.

Information disseminated during a pandemic can have an impact on the spread of infection because it has a significant effect on people's behavior. Misinformation and disinformation are serious issues. If misinformation or disinformation causes panic and people avoid taking measures to prevent infection, preventing infection becomes more difficult.

Potential public health impacts

The next pandemic is expected to have the following severe impacts on public health:

i) A rapid increase in the number of patients over a short period of time will lead to a shortage of hospital beds, ICUs, and ventilators and exhaust medical personnel. The lack of appropriate treatment in a timely manner can result in the loss of life.

ii) The nature of the pandemic will change depending on the populations susceptible to this infectious disease. In the case of COVID-19, many older people have been affected, with significant morbidity and mortality, whereas many children became ill during the 2009 H1N1 influenza pandemic. The influenza epidemic that swept through the early 19th century, known as the Spanish flu, infected and killed many young people.

iii) If the fatality rate of an infectious disease is high, a sudden increase in the number of deaths can shock society and cause social chaos. Conversely, a low fatality rate but a high rate of infection would result in an increase in deaths, with long-term, significant losses due to health problems caused by aftereffects and loss of labor.

iv) Lockdowns, school closures, and suspensions to control the pandemic will severely restrict people's lives and cause the stagnation of economic activity. If prolonged, the measures could have serious impact, such as worsening mental health, loss of educational opportunities, and widening of social divisions. These problems became apparent during the COVID-19 pandemic.

v) Production may be unable to keep up with the sudden increase in demand for diagnostics, therapeutics, and vaccines, and the limited supply may flow only to countries with large economies. This can lead to international conflict. If vaccines and medicines do not reach low-income countries, the virus will persist in those regions. If the virus persists in some parts of the world, containing it globally may be difficult.

What preparations should be made?

Countermeasures have been developed based on lessons learned from the preceding pandemic. If, however, only the immediate preceding pandemic is the point of reference, then the countermeasures will be biased and insufficient to respond to the next pandemic. Therefore, a wide range of scenarios must be considered, and a flexible system that can be deployed to respond to various situations must be developed. In preparation for the next pandemic, the following measures should be taken from a medical perspective:

Enhancing research and development for diagnostics, pharmaceuticals, and vaccine production systems

Investment in research and development and manufacturing infrastructure during normal times is imperative; as a result, diagnostics, pharmaceuticals, and vaccines can be promptly supplied in the early stages of a pandemic. In Japan, the Strategic Center for Biomedical Advanced Vaccine Research and Development for Preparedness and Response was established to facilitate the development of promising vaccine technologies and new modalities (*11*). A similar system needs to be established for diagnostic approaches and therapeutics. Domestic production systems for raw materials and containers should be established within Japan, and public–private partnerships should be promoted to obtain the necessary quantities in the event of an emergency.

Healthcare infrastructure

A flexible healthcare system that can withstand the rapid increase in the number of patients, including the planned expansion of beds for patients with infectious diseases, ICUs, and ventilators; the formulation of a plan to set up temporary medical facilities on short notice; and the establishment of a network to dispatch support medical personnel is needed. Therefore, a mechanism

of coordination that can flexibly allocate staff and inpatient beds at medical facilities to treat patients with infectious diseases during a pandemic is needed. Striking a balance with non-infectious disease care is crucial. Such coordination is not easy, and administrative agencies must be closely involved. Japan's new National Action Plan for Pandemic Influenza and New Infectious Diseases includes training and enhancing cooperation during normal times; local governments must work with relevant organizations to promptly set up medical and inspection systems in the event of an outbreak (*12*).

Human resource development

Government officials, researchers, and healthcare professionals involved in public health response, treatment, and research and development of infectious diseases should be trained effectively. This objective has not yet been achieved. A major problem is the lack of jobs and positions for these individuals. Industry, academia, and the government must take this issue seriously and build an ecosystem in which the pool of talent can evolve and grow.

Planned stockpiling and ensuring production lines for supplies

Planned stockpiling and ensuring production lines for supplies such as masks and protective equipment, test reagents, therapeutics, ventilators, and daily necessities, which are in short supply during a pandemic, are necessary. Starting in normal times, national and local governments should cooperate to maintain appropriate inventories and diversify supply networks. This strategy reduces the dependence on imports of raw materials for pharmaceuticals and vaccines and ensures domestic production and alternative sources of procurement.

Establishment of early detection/warning systems and rapid sharing of information

A system for the early detection of and the rapid sharing of information on emerging infectious diseases must be established. In Japan, the government is currently enhancing the surveillance of acute respiratory infections to detect respiratory infections of unknown etiologies in a timely fashion. In Japan, there is a system of "suspected case surveillance." This surveillance system is designed to monitor patients exhibiting severe symptoms of unknown origin to detect and prevent potential infectious disease outbreaks. Designated medical facilities must promptly report such suspected cases to public health authorities. This proactive approach facilitates a rapid response, thereby safeguarding public health. Health surveillance, which integrates animal and human health information, is extremely important from the perspective of monitoring spillovers from animals to humans. To make these surveillance activities effective, a genome analysis network should be operational staring in normal times to speed up the detection of pathogens and the surveillance of mutant strains of emerging and re-emerging infectious diseases. The Japan Institute for Health Security (JIHS) (*13,14*) operates the Infectious Disease Clinical Research Network with a national repository. Funded by the Ministry of Health, Labor, and Welfare, this is a project for a clinical research network to act as a platform for rapid tallying of cases in an emergency. Moreover, Japan should comply with the obligation to report information to the WHO and develop a platform for the real-time sharing of data with other countries. Departments of the JIHS should function as hubs for infectious disease information, provide scientific advice to governments, and disseminate information to the public and international community.

Conclusion

This commentary examined past pandemics and discussed the measures that Japan will need to adopt in the future. What are required are measures, systems, and policies that are not biased from experience with COVID-19; these efforts need to be comprehensively developed to respond to future emergencies. However, responding flexibly and quickly is easier said than done. To ensure that actual operations are as smooth as possible, the processes of planning, checking progress, and confirming proficiency through training and revision of countermeasures should be repeated. These measures should be incorporated into daily healthcare and implemented regularly. These steps will enable us to respond flexibly to various emerging infectious diseases and build sustainable healthcare systems.

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[#]*Current affiliation*: Japan Institute for Health Security.
**Address correspondence to*:*
Norio Ohmagari, Disease Control and Prevention Center, National Center for Global Health and Medicine, Japan. 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: ohmagari.n@jihs.go.jp

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A perspective on field epidemiology in Japan: Insights from human resource development in the Field Epidemiology Training Program

Tomimasa Sunagawa*,#

Center for Field Epidemic Intelligence, Research and Professional Development, National Institute of Infectious Diseases, Japan.

Abstract: The establishment of the Center for Field Epidemic Intelligence, Research, and Professional Development (CFEIR) within the National Institute of Infectious Diseases (NIID) in 2021 marked a significant advancement in the country's epidemiological training capacity. Japan's Field Epidemiology Training Program (FETP), launched in 1999, has since trained 128 epidemiologists as of 2025, strengthening outbreak response efforts nationwide. The COVID-19 pandemic highlighted the acute shortage of field epidemiologists, emphasizing the need for FETP expansion and regional training initiatives. The introduction of the 1+1 training model and establishment of regional training spots in Osaka and Okinawa have diversified the participant base, increasing local outbreak response capacity. Since 1999, FETP trainees have been deployed to 419 outbreak investigations, including COVID-19, measles, food poisoning, and emerging infectious diseases. With the upcoming launch of the Japan Institute for Health Security (JIHS) in April 2025, efforts will focus on strengthening human resource development using field epidemiology and integrating applied epidemiology approaches such as One Health, disaster epidemiology, and risk communication. Strengthening international collaboration, particularly in the Western Pacific and Southeast Asia, remains a key priority. This paper underscores the evolving role of field epidemiology in Japan and the necessity of sustained investments in epidemiological training, digital tools, and global health partnerships to ensure preparedness for future pandemics.

***Keywords*:** field epidemiology, FETP, infectious diseases, applied epidemiology, health security

Introduction

In April 2021, the Center for Field Epidemic Intelligence, Research, and Professional Development (CFEIR) was established within the National Institute of Infectious Diseases (NIID), marking the first institution in Japan dedicated to "field epidemiology". The concept of "shoe-leather epidemiology" – a core principle of field epidemiology which has been used by Epidemic Intelligence Service (EIS) at the U.S. Centers for Disease Control and Prevention (CDC) since 1951 — had already entered Japan in the 1950s under the term "Waraji-Ekigaku" (straw-sandal epidemiology) (*1*). However, with improved sanitation in the 1970s, infectious diseases declined. In the 1990s, concerns about emerging infectious diseases grew in many countries. In Japan, a large-scale outbreak of enterohemorrhagic *Escherichia coli* O157 occurred in Sakai City (1996) (*2*). Multiple countries had established Field Epidemiology Training Programs (FETPs) modeled after the U.S. EIS at that time. In Japan, the Infectious Diseases Control Law was enacted in April 1999 (*3*). Following this, in September 1999, Japan launched its own FETP within the NIID, modeled on the EIS.

What do Field Epidemiologists do?

Since 1999, FETP has trained field epidemiologists rapidly to detect, assess and respond to infectious disease threats, strengthening response to national outbreaks (*4*). Japan's FETP is a two-year on-the-job training (OJT) program covering six core competencies: surveillance, outbreak investigation, epidemiological research, risk communication, and network strengthening. The work of field epidemiologists is sometimes described as the four Cs: Count (descriptive epidemiology), Compare (analytical epidemiology), Communicate, and Collaborate (*5*).

The COVID-19 pandemic in 2020 exposed a shortage of field epidemiologists, highlighting the FETP's importance. As of March, 2025, 128 trainees had completed FETP, approaching the 157 field epidemiologists needed to cover public health offices, though still below the 600 recommended under the International Health Regulations (one per 200,000 people) (*6*).

Who are the participants in Japan's FETP?

As of 2024, FETP had its highest-ever enrollment (30 trainees), with 22 seconded from local governments and other institutions and eight NIID employees. Since CFEIR's launch in 2021, the number of annual trainees increased from 4.3 to 12.5 per year. Initially dominated by physicians, FETP now includes more public health officials. The 1+1 training model and regional training spots in Osaka and Okinawa have expanded training outside Tokyo. Regional training now accounts for 33% of participants, improving responsiveness to local mass gatherings and health crises such as the FIBA Basketball World Cup (Okinawa), the Noto Peninsula earthquake in 2024, and the Kobayashi red yeast rice scandal (Osaka) (*7*).

Overview of outbreak response by Japan's FETP

Since 1999, Japan's FETP has supported 419 outbreaks as of November 2024, including COVID-19, measles, food poisoning, Antimicrobial Resistance and emerging infectious diseases (Figure 1) (*8*). The median number of outbreak investigations per year was 7.5, with the lowest recorded in 1999 (1 event) and the highest in 2020 (138 events). FETP trainees provide technical assistance in active case-finding, contact tracing, database development, descriptive and analytical epidemiology and coordination with other municipalities and relevant organizations. During the COVID-19 pandemic, FETP alumni collaborated to support outbreak investigations.

Notable outbreak response activities over the past decade

In 2014, Japan's first domestically transmitted dengue fever case since the 1950s led to an epidemiological investigation (*9*), resulting in updated mosquito-borne diseases guidelines (*10*). The 2014 Ebola virus disease epidemic in West Africa prompted the World Health Organization (WHO) to declare a Public Health Emergency of International Concern (PHEIC), and Japan sent a team including FETP staff members and alumni to Sierra Leone (*11*). This experience contributed to the establishment of Japan's Infectious Disease Response Team under the Japan Disaster Relief (JDR) framework.

During the early period of COVID-19, FETP provided assistance primarily in epidemiological investigations, and occasionally in infection control and maintenance of facility function. In the case of the Delta variant, analysis of transmission routes identified seven major outbreak origins, six of which were successfully contained (*12*). FETP played a key role in supporting field responses in many of these events. Similarly, the Omicron (BA.1) spread was mitigated through public health efforts, with FETP providing essential technical support (*13*).

These experiences highlighted that while viral influx can overwhelm containment and mitigation measures, effective border controls, national consensus, and technical collaboration between NIID, national and local governments can help slow transmission.

Perspectives on applied epidemiology with a focus on field epidemiology

Field epidemiology has evolved as a practical discipline to guide public health actions. CFEIR's three divisions enhance field epidemiology through training (FETP), data analysis and dissemination, and global health workforce development.

With the launch of the Japan Institute for Health Security (JIHS) in April 2025, CFEIR will continue its

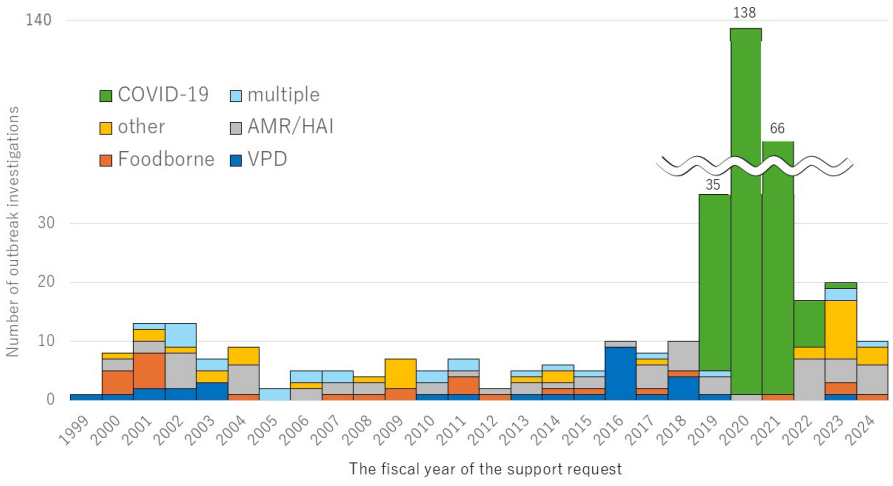

Figure 1. Yearly trend of FETP outbreak response deployments as of November 2024 (*n* = 419). *Note: Figure based on publicly available data from the NIID website as cited in reference (8). Website currently being migrated; new version forthcoming.*

core mission of training and developing highly skilled field epidemiologists, strengthening domestic public health networks, and expanding training programs to better address emerging infectious diseases. While preserving the fundamental principles of "Shoe-leather Epidemiology" through rigorous descriptive epidemiology, efforts will also focus on actively integrating digital technologies into training and outbreak response strategies. The program aims to standardize in-house local government training, expand continuing education for alumni, and strengthen regional collaboration frameworks.

Japan's FETP has historically focused on epidemic intelligence and outbreak investigations, with an emphasis on capacity building. JIHS will broaden efforts within Applied Epidemiology, integrating One Health (a multisectoral approach that addresses health threats at the interface of humans, animals, and ecosystems), disaster epidemiology, infectious disease policy, and risk communication. Strengthening international collaboration remains a priority, particularly in the Western Pacific and Southeast Asia.

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#*Current affiliation:* National Institute of Infectious Diseases, Japan Institute for Health Security.
**Address correspondence to*:
Tomimasa Sunagawa, Center for Field Epidemic Intelligence, Research and Professional Development, National Institute of Infectious Diseases, Toyama 1-23-1, Shinjuku-ku, Tokyo 162-8640, Japan.
E-mail: sunatomi@niid.go.jp

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The Japanese initiative for the Global Research Network and Link on Infectious Diseases (J-GRID+) Program and its prospects

Miyako Otsuka*,#, Koji Wada#, Masaki Omori#, Teiji Takei#, Norihiro Kokudo#

National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: In response to the urgent need to strengthen Japan's capabilities in vaccine and pharmaceutical development for future infectious disease outbreaks, a global research "network" aimed at enhancing international collaboration was conceived. As a result, the Japanese initiative for the Global Research Network and Link on Infectious Diseases (J-GRID+), funded by the Japan Agency for Medical Research and Development (AMED), was launched in 2023. The aim of this article is to share our initiative to strengthen the global research network to prepare for infectious disease crises. Institutions participating in the J-GRID+ network have been conducting infectious disease research hubs under the previous "Japan Initiative for Global Research Network on Infectious Diseases (J-GRID project)" which supported over 20 years. The J-GRID+ was established for two key components: *i*) the "Overseas Research Centers Development", which strengthens research capacities in regions affected by infectious diseases through collaboration between Japanese universities and overseas research institutions, and *ii*) the "Operation of the J-GRID+ Network Core Center" to strengthen the monitoring of the information of signs of infectious disease outbreaks globally, to support each research center, and to strengthen communication as a global network. In April 2025, the newly established Japan Institute for Health Security (JIHS) will serve as the core center. With this outlook, J-GRID+ strives to be an enduring platform that supports global health security while respecting and strengthening international relationships.

Keywords: J-GRID+, infectious disease research network, health security, Japan

Introduction

The COVID-19 pandemic has had a profound global impact, exposing vulnerabilities in various systems worldwide. Japan was no exception (*1*). The pandemic revealed weaknesses within our healthcare and public health systems, prompting recognition of the need for substantial revisions and the construction of more resilient frameworks. Among the key areas identified was the need to enhance Japan's vaccine research, development, and production capacity. As a result, in 2021, the Japanese government adopted the "Strategy to Strengthen Vaccine Development and Production Systems" as a long-term national strategy. A central policy under this strategy was the expansion of monitoring systems, which are essential for the swift development and distribution of vaccines (*2*).

In response to the urgent need to strengthen Japan's capabilities in vaccine and pharmaceutical development for future infectious disease outbreaks, a global research "network" aimed at enhancing international collaboration was conceived. As a result, the Japanese initiative for the Global Research Network and Link on Infectious Diseases (J-GRID+), funded by the Japan Agency for Medical Research and Development (AMED), was launched in 2023 and operated by National Center for Global Health and Medicine (NCGM) and National Institute of Infectious Diseases (NIID) which will going to be Japan Institute for Health Security (JIHS) from 1st April 2025. Its primary goal was to reinforce existing collaborations between domestic universities and overseas institutions by networking these relationships to maximize the benefits of mutual research endeavors and lay the groundwork for rapid and coordinated responses to future health crises (*2,3*). The aim of this article is to share our initiative to strengthen the global research network to prepare for infectious disease crises.

Brief history: Toward the establishment of J-GRID+

Institutions participating in the J-GRID+ network have been conducting infectious disease research for the past 20 years with support from public research funding (*4*).

Phase 1 (2005-2009): The program to establish overseas research centers for emerging and reemerging infectious diseases was implemented by the Ministry

of Education, Culture, Sports, Science and Technology (MEXT). This phase focused on promoting cross-border collaborative research on infectious diseases. Its key components include establishing joint research centers between Japanese universities/research institutions and their counterparts in Asia and Africa, based on mutual benefit, with researchers from both sides working together on a daily basis.

Phase 2 (2010-2014): This phase is the so-called "Program to Promote the Establishment of Strategic Research Centers for Global Infectious Diseases" and aims to strengthen and solidify the established research hubs. The program provided a foundation for sustainable research activities, deepened collaborations with domestic and international institutions, and promoted the accumulation of knowledge and technologies in basic, clinical, and applied research. It also prioritized fostering the next generation of globally active experts in the field of infectious diseases, contributing to both international public health efforts and safeguarding Japan's health security.

Phase 3 (2015-2019): With the establishment of AMED in 2015, the program evolved into the "Japan Initiative for Global Research Network on Infectious Diseases (J-GRID)" (*5*). During this phase, epidemiological studies and basic research on diagnostics, therapeutics, and vaccines were conducted at overseas research centers across Asia and Africa. The program prioritized developing new technologies for infection control, advancing human resource development, and strengthening collaborative research frameworks with Japanese universities and research institutions.

After 15 years' J-GRID program to establish the research platform and infrastructure and to implement the research, the new program called "Japan Program for Infectious Diseases Research and Infrastructure" was launched in 2020. This new program aims to promote the participation of a diverse range of researchers and accelerate collaboration with countries conducting advanced research. These efforts will strengthen Japan's infectious disease research capabilities by fostering the development of new talent equipped with advanced skills and expertise, encouraging the involvement of young researchers, and facilitating innovative research (*6*).

List of research sites of J-GRID+

The current J-GRID+ program includes ten Japanese universities and 11 overseas research centers. Table 1 shows the list of Japanese universities with corresponding counterpart institutions and the contents of their research (*7-15*), and Figure 1 illustrates the locations of overseas research centers and the core centers (J-GRID+).

Under the "Overseas Research Center Development", Japanese researchers are, in principle, stationed locally and engage in collaborative research with trusted local universities and research institutions aiming to reinforce the research capabilities of Japanese universities' overseas centers. This long-standing, trust-based collaboration allows for access to invaluable resources such as clinical samples, epidemiological data, and patient information from infectious disease hotspots. These data would otherwise be unattainable within Japan. For instance, Osaka University has maintained a relationship with Thai research institutions since 1958, while several other centers boast similarly long-standing ties. Recently, Nagasaki University also established a new research hub in Brazil, marking a significant expansion into Latin America.

Details of each center, including their respective partnerships and research highlights, are published on the J-GRID+ website and are aavailable for public viewing (*16*). The program emphasizes the importance of nurturing respectful relationships with overseas counterparts, particularly when sensitive tasks such as sharing infectious disease information or biological samples are involved. Careful consideration is given to avoid undermining established relationships, ensuring mutual benefit, and minimizing the burden on partner institutions.

The prospect of J-GRID+ Network Core Center

The J-GRID+ Network Core Center, which has been jointly managed by NCGM and NIID, will transition to the Japan Institute for Health Security (JIHS) on April 1, 2025. The JIHS is tasked to serve as a knowledge hub for infectious diseases, integrating high-quality scientific evidence and swiftly providing this information to the Ministry of Health, Labour and Welfare (MHLW) and other relevant bodies. While NCGM and NIID have historically focused on strengthening monitoring systems and research networks, JIHS will expand these efforts. It will prioritize facilitating collaboration between domestic and international research institutions and private-sector companies engaged in developing vaccines, diagnostics, and therapeutics. Furthermore, JIHS will play a crucial role in pandemic preparedness by collecting and analyzing epidemiological data, monitoring global infectious disease policy trends, and supporting research and development initiatives.

The J-GRID+ Network Core Center in JIHS would continue *i*) to strengthen the monitoring of the information of signs of infectious disease outbreaks globally, *ii*) to support each research center, and to strengthen communication as a global network. One example of strengthening the relationship is a meeting held in November 2024, where the J-GRID+ Network Core Center organized a meeting in Zambia, bringing together researchers from participating Japanese universities and overseas research centers. This meeting proved highly effective in strengthening inter-hub collaboration, resulting in new discussions for joint

Table 1. List of J-GRID+ Japanese universities with corresponding counterpart institutions and the contents of their research

Japanese university Representative of the project	Country: counterpart institutions, (year of establishment)
Nagasaki University (*7*) Prof. Futoshi Hasebe	Vietnam:National Institute of Hygiene and Epidemiology, Viet Nam (Since: 2005)
Infectious diseases handled: Mosquito-borne viral infections (dengue fever, Zika fever, chikungunya fever, Japanese encephalitis, *etc.*), respiratory viral infections (COVID-19, influenza, respiratory syncytial virus infection, *etc*.), enteric viral infections (norovirus infection, rotavirus infection, enterovirus infection, *etc*.), zoonotic viral infections (Nipah virus infection, Hantavirus infection, rabies, *etc.*), diarrhea-causing bacteria (Vibrio bacteria, pathogenic *E. coli*, *etc.*)	
Osaka University (*8*) Prof. Tetsuya Iida	Thailand: National Institute of Health of Thailand (Since: 2005)
Infectious diseases handled: Diarrhea (cholera, dysentery, salmonella, norovirus, rotavirus, *etc.*) and mosquito-borne viral infections (dengue virus, chikungunya virus, *etc.*)	
The University of Tokyo (*9*) Prof. Yasushi Kawaguchi	China: Institute of Microbiology, Chinese Academy of Sciences; Harbin Veterinary Research Institute, Chinese Academy of Agricultural Sciences (Since: 2005)
Research: Basic research on the development of new treatments and diagnostic methods for enveloped viruses, such as influenza viruses, flaviviruses, and herpes viruses, which are currently circulating or are expected to become circulating in the future and may cause imported infectious diseases, with a focus on SARS-CoV-2, in collaboration with Chinese research centers, domestic institutions, the National Institute of Infectious Diseases, and overseas research centers of other universities are dealt.	
Hokkaido University (*10*) Prof. Hirofumi Sawa	Zambia: School of Veterinary Medicine, University of Zambia (Since: 2007)
Infectious diseases handled: Viral zoonoses (arthropod-borne infections, hemorrhagic fever, respiratory infections, intestinal infections, hepatitis, rabies, *etc.*), bacterial zoonoses (tuberculosis, relapsing fever, rickettsiosis, cholera, anthrax, AMR, *etc*.), protozoal zoonoses (leishmaniasis, trypanosomiasis, cryptosporidiosis, *etc.*)	
Kobe University (*11*) Prof. Yasuko Mori	Indonesia: Airlangga University Institute of Tropical Disease (Since: 2007)
Research: Research into the discovery of new pathogens (zoonotic pathogens) in monkeys living in Indonesia, epidemiological surveys of viral diarrhea, trends in AMR, and elucidation of the pathogenesis of dengue hemorrhagic fever.	
Okayama University (*12*) Prof. Shinichi Miyoshi	India: National Institute for Research in Bacterial Infections (Since: 2007)
Infectious diseases handled: Cholera and Vibrio infections, pathogenic *E. coli* infections, AMR infections, Salmonella infections (typhoid fever), viral diarrhea, rotavirus infections	
Institute of Science Tokyo (*13*) Prof. Toshihiko Suzuki	Ghana: Noguchi Memorial Institute for Medical Research, University of Ghana (Since: 2008)
Infectious diseases handled: Mosquito-borne viral infections (dengue virus, yellow fever virus, *etc.*), rotavirus infection, falciparum malaria, bacterial infections (Buruli ulcer, AMR, *etc.*)	
Tohoku University (*14*) Prof. Hitoshi Oshitani	Philippines: Research Institute for Tropical Medicine (Since: 2008)
Infectious diseases handled: Pediatric respiratory infections (RS virus, enterovirus, rhinovirus, influenza virus, human metapneumovirus, parainfluenza virus, adenovirus, human coronavirus), pediatric diarrhea (norovirus, sapovirus, rotavirus), *etc.*	
Niigata University Prof. Reiko Saito	Myanmar: National Health Laboratory (Since: 2015)
Infectious diseases handled: Respiratory infections (influenza virus, respiratory syncytial virus, SARS-CoV-2, rhinovirus), pediatric meningoencephalitis (enterovirus D68, parechovirus A), severe pediatric diarrhea (rotavirus), *etc.*	

Table 1. List of J-GRID+ Japanese universities with corresponding counterpart institutions and the contents of their research (continued)

Japanese university Representative of the project	Country: counterpart institutions, (year of establishment)
Osaka Metropolitan University Prof. Yasutoshi Kido	Democratic Republic of Congo: National Institute of Biomedical Research (Since: 2020)
Infectious diseases handled: Mpox, Malaria, Covid-19, AMR, NTD, cancer-causing pathogens (HBV, H.pylori)	
Nagasaki University (*15*) Prof. Jiro Yasuda	Brazil: Keizo Asami Institute, Federal University of Pernambuco (Since: 2024)
Infectious diseases handled: Expected diseases include dengue fever, chikungunya fever, Zika fever, influenza, COVID-19, yellow fever, West Nile fever, Oropouche fever, South American hemorrhagic fever, malaria, leishmaniasis, schistosomiasis, and leptospirosis. Current research: Research into emerging viral infectious diseases, research into parasitic diseases such as Chagas disease, genomic and epidemiological research into pathogens, pathological research to clarify the pathological mechanisms of infectious diseases prevalent in Latin America, research into arboviruses.	

Figure 1. Location of overseas research centers and the core centers (J-GRID+).

research initiatives. With this outlook, J-GRID+ strives to be an enduring platform that supports global health security while respecting and strengthening international relationships.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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[#]*Current affiliation*: Japan Institute for Health Security.
**Address correspondence to*:
Miyako Otsuka, Japan Institute for Health Security, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: otsuka.mi@jihs.go.jp

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Key success factors in clinical trial operation of the smallpox vaccine LC16m8 against mpox in Colombia

Naoki Tomotsugu[1,*,#], Maria Jose Amaya-Mahecha[2], Mieko Hamana[1,#], María Del Mar Bautista-Gonzalez[2], Hernando Guillermo Gaitán-Duarte[2], Jorge Alberto Cortés[2], Sohtaro Mine[1,#], Akira Ainai[1,#], Jaime E. Castellanos[2], Daisuke Tokita[1,#], Wataru Sugiura[1,#], Mugen Ujiie[1,#], Carlos Arturo Álvarez-Moreno[2]

[1] National Center for Global Health and Medicine, Tokyo, Japan;
[2] Universidad Nacional de Colombia, Bogotá, Colombia.

Abstract: In 2023, the Japan Institute for Health Security (JIHS) and the Universidad Nacional de Colombia (UNAL) conducted a successful clinical trial of the LC16m8 mpox vaccine in Colombia. The joint Japan-Colombia research team categorized the trial's challenges and success factors into several key operational aspects for analysis. Key success factors were an established database of Colombian human immunodeficiency virus (HIV) patient and pre-exposure prophylaxis (PrEP) population registries, and strong experience with large-scale clinical trials of HIV and COVID-19. In addition, a strong network of infectious disease specialists in Colombia enabled close communication between the study site directors and the research team. This allowed for rapid staffing and training, which was consistent with the study schedule. The outcome of this research identifies key success factors for the immediate implementation of large-scale clinical trials and will contribute to preparedness for future pandemics.

***Keywords*:** pandemic, preparedness, HIV, PrEP

Introduction

Intermittent outbreaks of infectious diseases highlight the need for rapid responses. Following the COVID-19 pandemic, the World Health Organization (WHO) declared mpox (formerly known as monkeypox) a public health emergency of international concern (PHEIC) in July 2022 (*1*), with another declaration in August 2024 (*2*), signaling the risk of recurring pandemics. Furthermore, international organizations have promoted "100 Days Missions" to accelerate vaccine and therapeutic development (*3*). In the U.S., Operation Warp Speed was activated and vaccine development took place at a remarkable pace, but numerous challenges still remain to be overcome to achieve the 100 Days Mission (*4-6*).

Under these circumstances, in 2023, the Japan Institute for Health Security (JIHS) in Japan and the Universidad Nacional de Colombia (UNAL) in Colombia conducted a clinical trial in Colombia to evaluate the LC16m8 mpox vaccine against mpox. Despite challenges such as vaccine expiration, budget constraints, and regulatory hurdles, the Colombian research team successfully completed the trial. That is, we were able to initiate the study under all the restrictions, enrolled more than 500 cases in less than 2 months, and conducted the observations as planned. In the preparation of the study, we could save considerable time in several processes as we described in the following sections.

Given the likelihood of future pandemics requiring rapid, large-scale international clinical trials, this correspondence focuses on operational lessons from our study and identifies key success factors to inform future preparedness. Detailed vaccine background and trial design are beyond our scope and will be presented in other protocol and results publications.

The challenges of the clinical trial

The research team from both countries categorized the challenges of the clinical trials into the following categories: *i*) regulatory aspects (Institutional Review Board (IRB)/regulatory authority), *ii*) administrative aspects (contracts), *iii*) technical aspects (electronic data capture (EDC)/electronic patient-reported outcomes (ePRO)), *iv*) training, *v*) subject recruitment, and *vi*) personnel.

i) Regulatory aspects (IRB/regulatory authority)

Long time for approval by the regulatory authority

Conducting a clinical trial in Colombia requires ethics committee approval and regulatory authority permission, but the strict review process often leads to delays. Recognizing the mpox vaccine's public health importance, the Colombian Ministry of Health (MOH) prioritized the trial under a Japan-Colombia cooperation agreement. The MOH and research team emphasized the study's significance through multiple meetings with regulatory agencies, successfully reducing the regulatory review time. Usually, it takes 6 months to 1 year or more, but through the team's efforts with direct negotiations, we were able to shorten the time to 2 months.

Additional GMP documentation required for extended vaccine expiration

Since the expiration date of the vaccine had been extended from 4 to 10 years, documentation was requested by the Colombian regulatory authorities regarding stability testing of the vaccine against light, temperature, and humidity. Most required documents showing the vaccine stability were already available, but a Good Manufacturing Practice (GMP) certificate was also required. The MOH, Labor and Welfare (MHLW), and vaccine manufacturing companies, the Japanese research team, successfully cooperated to obtain it.

ii) Administrative aspects (contracts)

Short time to make alliances with research sites

Colombia has a strong network of infectious disease specialists, enabling close communication between study site directors and the research team. This facilitated rapid recruitment and training of personnel, ensuring the study timeline. The clinical research centers involved have extensive experience with HIV and pre-exposure prophylaxis (PrEP) populations, and their directors are highly experienced in clinical research. Two centers had also conducted major public health studies on COVID-19, allowing for swift collaboration. Additionally, all principal investigators are members of the Colombian Association of Infectious Diseases (ACIN), which plays a key role in academic events and clinical guidelines for infectious diseases. Normally, in an area where we had no experience or relationships at all, it would have taken us a year or more to gain the understanding of the institution, build relationships, and sign a contract. Thanks to our experience and relationships in the research field, we were able to shorten that period to 2 months.

iii) Technical aspects (EDC/ePRO)

Short period of time to develop the data management system

The Colombian research team selected research electronic data capture (REDCap), a secure and user-friendly electronic data capture (EDC) system, for clinical data management, ensuring privacy and confidentiality standards. For electronic patient-reported outcomes (ePRO), the team developed a cross-platform mobile application using Flutter, integrated with REDCap *via* an application programming interface (API). The app also supports photo uploads for enhanced data entry. Normally, it would take at least 6 months to a year to develop an app that can be used with Apple and Android and allows photo storage and an API to work with REDCap, but with the help of our talented engineers and team, we were able to complete this in just 3 months. These integrated systems were developed efficiently, prioritizing usability and privacy.

In-depth training for medical staff at facilities with no EDC experience

A training program was introduced for vaccination-specialist nurses unfamiliar with EDC systems, focusing on accurate data entry. It included regular evaluations, real-time support from a physician, frequent simulations, and instructional videos. The application development team and EDC focal point also provided support during participant visits.

iv) Training

New vaccination method

As multiple puncture vaccinations with bifurcated needles are not common in Colombia, the Japanese research team collaborated to provide the training videos (*https://youtu.be/0Y1F9-E7zks?if=76MZFcr7TzKWSI5o*) and had the vaccinators replicate the procedures demonstrated in the video.

Accelerated training period

We implemented several strategies to rapidly train staff and equip them with the necessary knowledge. Those materials were developed for the investigators, research center coordinators and tech professionals, such as protocol training video (*https://1drv.ms/v/s!AolrGsZiZ0cdhKs1LgMm2SFIrNXwNA?e=5cxbAU*), case report form (CRF) training video (*https://drive.google.com/drive/folders/1n2dN7t1C64ZoCZBDZER1VIaGNJbR3Wx-?usp=sharing*), adverse events video (*https://1drv.ms/v/s!AolrGsZiZ0cdhKs0GmVYc4Ulv8hiUg?e=Ffhdwf*), and also provided the staff with pocket guidelines (*https://1drv.ms/b/s!AolrGsZiZ0cdhK0XSr93wCvK9m34Cg?e=dFgSfg, https://1drv.ms/b/s!AolrGsZiZ0cdhK0YCflQhXc3q4-GYQ?e=AxN0bc*).

Staff lacking experience with diverse populations

The Colombian team observed that some staff members had limited experience working with diverse populations. To address this, they developed diversity guidelines (*https://onedrive.live.com/?authkey=%21ACbLxVnWPgHnU1w&id=1D476762C61A6B89%2171321&cid=1D476762C61A6B89&parId=root&parQt=sharedby*

Table 1. Summary of the key success factors

Category	Challenge	Solution
i) Regulatory aspects (IRB/regulatory authority)	• Long times for approval by the regulatory authority	Conducting a clinical trial in Colombia requires ethics and regulatory approvals, but through direct negotiations and the prioritization of the mpox vaccine under a Japan-Colombia cooperation agreement, the review process was shortened from 6 months to 2 months.
	• Additional GMP documentation required for extended vaccine expiration	The Colombian regulatory authorities requested stability testing documentation for the vaccine, and with successful cooperation between the MOH, MHLW, vaccine manufacturers, and the Japanese research team, a GMP certificate was obtained.
ii) Administrative aspects (Contracts)	• Short time to make alliances w ith research sites	Colombia's strong network of infectious disease specialists and experienced clinical research centers enabled rapid collaboration, recruitment, and contracting — reducing a process that normally takes over a year to just 2 months.
iii) Technical aspects (EDC/ePRO)	• Short period of time to develop the data management system	The Colombian research team efficiently developed an integrated clinical data system using REDCap and a custom cross-platform mobile app with photo upload and API functionality, completing in 3 months what typically takes 6–12 months, while ensuring usability and privacy.
	• In-depth training for medical staff at facilities with no EDC experience	A comprehensive training program was implemented for vaccination-specialist nurses unfamiliar with EDC systems, combining evaluations, simulations, real-time support, and instructional materials to ensure accurate data entry and smooth participant visits.
iv) Training	• New vaccination method	Due to the rarity of multiple puncture vaccination with a bifurcated needle in Colombia, the Japanese research team provided training videos and had vaccinators practice the demonstrated procedures.
	• Accelerated training period	To rapidly train staff, we developed and provided targeted educational materials — including training videos on the protocol, case report forms, and adverse events, as well as pocket guidelines—for investigators, coordinators, and technical professionals.
	• Staff lacking experience with diverse populations	To address limited experience with diverse populations, the Colombian team developed diversity guidelines with visual aids, conducted workshops to enhance understanding of gender diversity, and provided a participant invitation script, ensuring respectful and inclusive trial engagement.
v) Subject recruitment	• Selection of Medical Centers for HIV Patient Recruitment	The participating medical centers were selected for their specialized HIV and PrEP programs and used Colombia's existing HIV patient database to optimize recruitment.
	• Managing Holiday-Related Challenges in a Clinical Trial	A major challenge in the clinical trial was participants traveling to warm regions with swimming pools, which contradicted the vaccination instructions to keep the arm dry for 14 days; the team addressed this by emphasizing vaccination benefits, offering alternatives, and rescheduling vaccinations as needed.
	• Stigma surrounding mpox	To reduce mpox-related stigma, particularly toward LGBTIQA+ individuals, we implemented confidentiality protocols, held focus groups with community leaders supported by PAHO/WHO, and strategically located vaccination centers in private settings to ensure a safe, inclusive, and nonjudgmental environment for all participants.
	• Strengthening Community Partnerships: Collaboration with REDSOMOS	A cooperation agreement with REDSOMOS, a community-based organization promoting sexual and gender diversity, was established to enhance outreach to the LGBTIQA+ community, ensuring confidentiality and strengthening trust and inclusivity within the project.
vi) Personnel	• Maintaining staff motivation during schedule delays	To maintain staff motivation during the study's delay, the team used the extra time for skill enhancement, process refinement, and participant education, while participating centers provided financial support by temporarily covering salaries until reimbursements were processed.

&o=OneUp) featuring a mascot illustration explaining the distinctions between sex, gender, gender identity, sexual orientation, *etc*. Through dedicated guidance and workshops, staff gained a deeper understanding of gender diversity, enabling the trial to proceed smoothly with fair and respectful engagement of all participants. Furthermore, the Colombian team provided the team with a script to use when inviting people to participate.

v) Subject recruitment

Selection of Medical Centers for HIV Patient Recruitment
The participating medical centers were selected based on the target population. All three centers, which are *Clínica Universitaria Colombia*, *Infectoclinicos*, and *Hospital Universitario San Ignacio*, have specialized programs for HIV patient care and PrEP. These sites leveraged Colombia's existing HIV patient database to optimize recruitment.

Managing Holiday-Related Challenges in a Clinical Trial
One of the biggest challenges in the clinical trial was the common practice of traveling to warm regions with swimming pools and the sea, as wetting the vaccinated arm was contraindicated for the first 14 days. Being in a tropical country without distinct seasons, such trips are frequent, especially during holidays, because Bogotá is located 2,600 meters above sea level. To address this, the team emphasized the benefits of vaccination, provided alternatives like keeping the vaccinated arm dry while swimming, and highlighted the increased infection risk during holidays (Figure 1). When necessary, vaccinations were rescheduled to accommodate participants' travel plans.

Stigma surrounding mpox
To address the stigma surrounding mpox, particularly the misconception that the infection exclusively affects lesbian, gay, bisexual, transgender, intersex, queer, asexual and other sexually or gender diverse (LGBTIQA+) individuals, we took measures to minimize the risk of stigmatization. It should be noted that a focus group was previously carried out with the leaders of the LGBTIQA+ population with the support of Pan American Health Organization (PAHO)/WHO

Figure 1. Invitation infographics for candidates for the clinical trial.

to understand their feelings and perceptions regarding the possibility of vaccination against mpox. Vaccination centers were strategically placed in private locations to ensure participants could access the study without fear of judgment or discrimination. Additionally, strict confidentiality protocols were implemented to protect the privacy of all participants throughout the process. These measures were essential in fostering a safe and inclusive environment for the study.

Strengthening Community Partnerships: Collaboration with REDSOMOS

A cooperation agreement was established with REDSOMOS, a community-based organization promoting sexual and gender diversity, sexual health, and community empowerment since 2007 (*https://www.redsomos.org/*). Given that the study centers already had experience managing participants with HIV and had prior conversations with REDSOMOS, the partnership was strengthened to ensure effective outreach to the LGTBIQA+ community. Furthermore, a legal agreement was established to guarantee the confidentiality of all sensitive data, preventing any risk of information leaks. This collaboration improved the project's visibility and reinforced trust and inclusivity within the targeted population.

vi) Personnel

Maintaining staff motivation during schedule delays

To maintain staff motivation during the study's delay, we reframed it as an opportunity for further preparation. The extra time was used to enhance team skills, refine the vaccination process, practice inclusive language, and improve participant education on mpox infection. This proactive approach kept staff engaged and better prepared for the study's launch.

Conclusion and suggestions

In 2023, JIHS and UNAL conducted a successful clinical trial of LC16m8 mpox vaccine against mpox in Colombia. Key success factors identified from this trial include having an established HIV patient/PrEP registry and extensive prior experience with large-scale clinical trials (*e.g.*, in HIV or COVID-19). Additionally, Colombia's strong network of infectious disease specialists enabled close communication between sites and researchers, allowing for rapid staff recruitment and training in line with the study schedule. Importantly, establishing such disease-specific participant databases and cultivating trial experience ahead of time are critical steps for any country to prepare for future pandemics.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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[#]*Current affiliation*: Japan Institute for Health Security.
**Address correspondence to*:*
Naoki Tomotsugu, Japan Institute for Health Security, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: tomotsugu.n@jihs.go.jp

Global Health & Medicine

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Types of Articles	Words in length (excluding references)	Figures and/or Tables	References
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Communications	~2,000	~2	~20
Perspectives			
Comments			
Correspondence			
Editorials	~1,000	~1	~10
Letters	~1,000	~1	~10
News	~800	~1	~5

Abstract: ~250 words (Original Articles, Brief Reports, Reviews, Policy Forum); ~150 words (Communications, Editorials, Letters, and News).
Keywords: 3~6 words

Brief Reports definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Brief Reports are not intended for publication of incomplete or preliminary findings. Brief Reports should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 30 references. Brief Reports should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results and Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate.

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Manuscripts should be written in clear, grammatically correct English and submitted as a Microsoft Word file in a single-column format. Manuscripts must be paginated and typed in 12-point Times New Roman font with 24-point line spacing. Please do not embed figures in the text. Technical terms should be defined. Abbreviations should be used as little as possible and should be explained at first mention unless the term is a well-known abbreviation (*e.g.* DNA). Single words should not be abbreviated. Please include page numbers in your submitted file. We also encourage use of line numbers.

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2. Main manuscript
3. Figures
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The main manuscripts should be assembled in the following order:

1. Title page
2. Abstract
3. Main Text
4. Acknowledgments
5. References
6. Tables
7. Figure Legend
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Title page: The title page must include 1) the title of the paper (Please note the title should be short, informative, and contain the major key words); 2) full name(s) and affiliation(s) of the author(s), 3) abbreviated names of the author(s), 4) full name, mailing address, telephone/fax numbers, and e-mail address of the corresponding author; and 5) conflicts of interest (if you have an actual or potential conflict of interest to disclose, it must be included as a footnote on the title page of the manuscript; if no conflict of interest exists for each author, please state "There is no conflict of interest to disclose").

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Materials/Patients and Methods: The description should be brief but with sufficient detail to enable others to reproduce the experiments. Procedures that have been published previously should not be described in detail but appropriate references should simply be cited. Only new and significant modifications of previously published procedures require complete description. Names of products and manufacturers with their locations (city and state/country) should be given and sources of animals and cell lines should always be indicated. All clinical investigations must have been conducted in accordance with the Declaration of Helsinki (as revised in 2013, *https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki*). All human and animal studies must have been approved by the appropriate institutional review board(s) and a specific declaration of approval must be made within this section.

Results: The description of the experimental results should be succinct but in sufficient detail to allow the experiments to be analyzed and interpreted by an independent reader. If necessary, subheadings may be used for an orderly presentation. Two levels of subheadings may be used if warranted, please distinguish them clearly. All Figures and Tables should be cited in order, including those in the Supplementary Data.

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