Use of Unapproved Medical Countermeasures During Public Health Emergencies: Comparing the United States and South Korea

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LIST OF ABBREVIATIONS

ACF----------	Advocacy Coalition Framework
AVA ----------	Anthrax Vaccine Adsorbed
ASPR----------	Assistant Secretary for Preparedness and Response
CBRN----------	Chemical, Biological, Radiological and Nuclear
CDC ----------	Center for Disease Control and Prevention
COVID-19 ----------	Coronavirus disease caused by SARS-CoV-2 virus
DOD ----------	Department of Defense
EUA ----------	Emergency Use Authorization
EUI ----------	Emergency Use Instruction
DHS ----------	Department of Homeland Security
FBI ----------	Federal Bureau of Investigation
FEMA ----------	Federal Emergency Management Agency
FDA ----------	Food and Drug Administration
GAO ----------	General Accounting Office
HHS ----------	Department of Health and Human Service
IVD ----------	In-Vitro Diagnostic Kits
KCDC ----------	Korean Center for Disease Control and Prevention
LDT ----------	Laboratory Developed Testing
MCM ----------	Medical Countermeasures
MOHW ----------	Ministry of Health and Welfare
NIH ----------	National Institutes of Health
PAHPA----------	Pandemic and All Hazards Preparedness Act
PAHPRA----------	Pandemic and All Hazards Preparedness Reauthorization Act
PEP----------	Post-Exposure Prophylaxis
SNS ----------	Strategic National Stockpile
USPS ----------	U.S. Postal Service

ABSTRACT

USE OF UNAPPROVED MEDICAL COUNTERMEASURES DURING PUBLIC HEALTH EMERGENCY: COMPARING THE UNITED STATES AND SOUTH KOREA

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Biodefense includes the implementation of various activities related to biological warfare, bioterrorism, biosurveillance, emergency preparedness, and medical countermeasure (MCM) development. According to the narratives of historical institutionalism (HI), biodefense is an institution that has transformed by following a pattern of punctuated evolution due to exogenous shocks. However, other scholars criticize the meso-level analysis of the HI school of thought and emphasize the role of agency (endogenous factors) in institutional changes. This dissertation provides domestic-level, detailed accounts of how the biodefense institutions of the United States and South Korea have evolved by employing Thomas Birkland's Event-Related Policy Change Model. According to Birkland's model, the Emergency Use Authorization (EUA) policy, one of the representative biodefense policies, was legislated in the United States based on the lessons learned from Amerithrax in 2001, while Korea's policy was based on the lessons learned from the Middle East Respiratory Syndrome (MERS) outbreak in 2015. Due to

these divergent lessons arising from different focusing events (critical junctures), the US EUA stresses homeland security policy and follows an evolutionary path of strengthening post-exposure prophylaxis (PEP) missions. On the other hand, the Korean EUA pursues disease containment missions and follows an evolutionary path of strengthening diagnostic capabilities. Finally, the different features of the EUA policies in the two countries are the result of different testing outcomes during the early phase of the COVID-19 pandemic. This dissertation examines why the homeland security-centric US EUA struggled to integrate with other public health systems to support large-scale testing missions. Furthermore, policy recommendations for the United States, South Korea, and other countries pursuing an EUA policy are proposed.

CHAPTER 1: Introduction

Introduction

The world faces unprecedented public health threats caused by new and re-emerging microbes that are highly contagious in nature, spread much faster and wider than before, and for which there are no available vaccines or therapeutics. The 2003 Severe Acute Respiratory Syndrome (SARS) outbreak in Asia, the global H1N1 influenza pandemic of 2009, and the 2020 COVID-19 pandemic demonstrate the risks posed by novel emerging infectious disease threats. SARS first appeared in 2003 in China, but it spread worldwide beyond Asia within a few months.[1] The 2009 influenza (H1N1) pandemic spread internationally with unprecedented speed; unlike past influenza pandemic events that often take more than six months to spread internationally, the new H1N1 virus spread worldwide in less than six weeks.[2] In 2015, Middle East Respiratory Syndrome (MERS), for which dromedary camels are suspected to be the primary reservoir, emerged unexpectedly in South Korea in a single passenger and turned into an epidemic within a month.[3] Currently, all media headlines

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[1] The United States Centers for Disease Control and Prevention (CDC), "About Severe Acute Respiratory Syndrome (SARS)," updated in Feb 20, 2013, last access in Dec 20, 2019, available at https://www.cdc.gov/sars/about/index.html.

[2] World Health Organization (WHO), "Changes in reporting requirements for pandemic (H1N1) 2009 virus infection," Pandemic (H1N1) 2009 briefing note 3 (revised), last access on Dec 20, 2019, available at https://www.who.int/csr/disease/swineflu/notes/h1n1_surveillance_20090710/en/.

[3] World Health Organization (WHO), "Middle East respiratory syndrome coronavirus (MERS-CoV) Fact sheet, updated in March 11, 2019, last access on Dec 10, 2019, available at

are covering the ongoing pandemic caused by a new strain of coronavirus, SARS-CoV-2, which first emerged in Wuhan, China, and for which there were initially no pharmaceutical treatments, cures, or vaccines. The extreme measures that the Chinese government resorted to - quarantining an entire city and region - have now been adopted by other countries fighting this disease. As the pandemic continues to wreak havoc, the world is relying on the competition between leading countries such as the United States, Russia, and China to develop a safe and efficacious COVID-19 vaccine.

To counter public health threats, the public health authorities of countries generally seek to obtain new and better medical countermeasures (MCMs). MCMs - consisting of vaccines, therapeutic drugs, diagnostics, and medical devices - are the essential means for protecting the population against infectious disease outbreaks. When facing a new infectious disease outbreak, however, the existing MCMs approval systems cannot provide the most effective way to protect the population in a timely manner. For example, even though the MERS virus was identified for the first time in 2012 and caused an outbreak in South Korea in 2015, a MERS coronavirus vaccine candidate entered a first-in-human trial (phase 1a) in April 2020.[4] Moreover, the therapeutic options for MERS (another species of coronavirus) are not effective in treating the novel coronavirus (SARS-CoV-2). Development of SARS-CoV-2 vaccines remains in progress, the use of a vaccine is likely to become available at least by the fourth quarter of 2020[5]; thus, only supportive and experimental care are available until

https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov).

[4] ScienceDaily.com, "Promising MERS coronavirus vaccine trial in humans," sourced by German Center for Infection Research, April 22, 2020, available at https://www.sciencedaily.com/releases/2020/04/200422132600.htm

[5] McKinsey and Company Report, "On pins and needles: Will COVID19 vaccines 'save the world'?," July 29, 2020, available at https://www.mckinsey.com/~/media/McKinsey/Industries/Pharmaceuticals%20and%20Medical%20Pr

then. On average, in the US, research and development takes approximately 8~10 years given the strict drug approval process.[6] All the stages of MCM development are regulated and each stage must pass the governments' strict pharmaceutical regulations, respectively, from research and development to clinical trials to post-marketing as well as the importation of MCMs created abroad. Such a long and strict drug approval process assures the safety and trust of the public health system, but it also significantly lengthens the time before a population can access an MCM. In other words, we should expect to continue to face new public health threats for which no medical treatments are readily available.

Governments should seek alternative public health emergency plans in order to respond timely to public health threats that emerge unexpectedly and for which no MCMs are available. The emergency use of unapproved MCMs is an innovative policy enabling the use of MCMs that are not yet licensed by the domestic drug approval system to deal with public health emergencies immediately. Two countries – the United States and South Korea – have developed their own Emergency Use Authorization (EUA) policies to allow distribution and employment of investigational MCMs or off-label use of approved MCMs in response to a public health emergency. To respond to the current COVID-19 pandemic, both the United States and South Korea issued EUAs for COVID-19 in-vitro diagnostic kits on 4 February 2020.[7] Both countries approved

oducts/Our%20Insights/On%20pins%20and%20needles%20Will%20COVID%2019%20vaccines%20save%20the%20world/On-pins-and-needles-Will-COVID-19-vaccines-save-the-world-v4.pdf?shouldIndex=false

[6] Chean Yeah Yong et al., "Recent Advances in the Vaccine Development Against Middle East Respiratory Syndrome-Coronavirus," *Front Microbiol*. 2019 Volume 10 Article 1781; also see, Jeremy Puthumanan, et al., "Speed, Evidence, and Safety Characteristics of Vaccine Approvals by the US Food and Drug Administration," *JAMA Intern Med.* Published online November 10, 2020.

[7] South Korea and the United States issued EUA on the same day (Feb 4, 2020), but Korea (GMT+9) announced earlier than the United States (GMT-5), given the different time zone.

emergency use of IVDs for COVID-19 at the same time, but the outcomes of the their COVID-19 testing programs were quite different. The continued lack of COVID-19 testing in the United States slows timely infection intervention, a clear failure when compared to the massive volume of suspected case testing undergone in South Korea.[8] By 25 February, South Korea had conducted over 35,000 coronavirus tests, while the United States, had tested only 425 people, excluding returnees on evacuation flights.[9] By March 11, South Korea had already tested almost 200,000 people and were able to test 15,000 people a day, while the United States took two months to achieve those same numbers.[10] Why was the United States so far behind South Korea in testing and reporting in this crisis?

What exactly is different about the EUA policy approaches between the two countries? There exist a few comparative reviews of the different legal bases and implementation mechanisms of these policies, but, to date, the literature does not address why these countries developed different EUA policies or how these policies have affected their ability to respond to pandemic threats. Expanding on the existing literature, this dissertation identifies the focusing events in the United States and South Korea that led to the emergence of different policy domains that shaped the EUA policy

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[8] Larry Buchanan, K. Rebecca Lai and Allison McCann, "U.S. Lags in Coronavirus Testing After Slow Response to Outbreak," *The New York Times,* March 17, 2020, available at https://www.nytimes.com/interactive/2020/03/17/us/coronavirus-testing-data.html?action=click&module=Top%20Stories&pgtype=Homepage

[9] Carolyn Y. Johnson, Laurie McGinley, and Lena H. Sun, "A faulty CDC coronavirus test delays monitoring of disease's spread," *Washington Post,* Feb. 25, 2020, available at https://www.washingtonpost.com/health/2020/02/25/cdc-coronavirus-test/

[10] See the transcript of the Congressional testimony on March 11, 2020, "Dr. Fauci and Other CDC & NIH Officials Testify on Coronavirus – March 11," *REV.COM,* available at https://www.rev.com/blog/transcripts/dr-fauci-and-other-cdc-nih-officials-testify-on-coronavirus-march-11

of each country along three dimensions: origin, purpose, and features of the policy, presented in Table 1-1.

Table 1-1: Origin, Evolution, and Differences Between EUA Policies in the United States and South Korea

Characteristics		**United States EUA**	**South Korean EUA**
Origin	Focusing Event	2001 Anthrax Attacks	2015 MERS Outbreak
Purpose	Post-Event Policy Domain	Homeland Security	Disease Containment
Features	Threat Assessment	Actual & Potential	Actual
	Objective of the Policy	Preparedness & Response	Detection & Diagnosis
	Target of the Policy	CBRN (later expanded to All-Hazards)	Infectious Diseases (later expanded to Radiation Exposure)

In regard to the threat assessment, this research asserts that actual threats encompass those that a country is currently facing or expects to soon face, and potential threats encompass those that exist by virtue of public health vulnerabilities in a country, but have low probability. Based on Table 1-1, the United States EUA aims to strengthen preparedness and response capabilities against both actual and potential public health threats, while the South Korean EUA aims to strengthen diagnostic capabilities in the event of actual public health threats.

Building upon the basis of different policy approaches, the main question of this dissertation is: why do the EUA policies of the United States and South Korea operate so differently? This dissertation develops two main arguments. First, I argue that the

divergent policy approaches are correlated with different policymaking motivations rooted in external shocks (focusing events) unique to each country. Thomas Birkland's Event-Related Policy Change Model (hereafter, the Birkland model) is the main research framework employed to determine how disparate crises (focusing events) contributed to creating different policy domains in each country. By employing the Birkland model, this dissertation illustrates how each state's unique experience generated by its own focusing event contributed to the emergence of different policy domains in each country.

Second, the different policy domains established by the focusing events created diverging conditions under which each country developed its EUA policy. The 2001 anthrax letter attacks created a homeland security domain in the United States, which laid groundwork for the US EUA policy, while the 2015 MERS outbreak created a disease containment domain in South Korea. The homeland security domain formed the foundation of the US EUA policy, which is a prominent feature of the security-focused biodefense policy that aims to prepare and respond to both all actual and potential public health threats. In contrast, the Korean EUA stems from the disease containment domain and focuses on diagnostic kits for emergency use purposes in order to detect and diagnose specific actual public health threats. The emergency use of novel vaccines or therapeutic drugs is rarely considered in Korea, although the nation has a history of introducing already-in-market vaccines and drugs under emergency measures for the purpose of maintaining a stable supply of medical countermeasures (called an emergency introduction). In other words, the different policy approaches of the two countries are the products of different policy domains. Since the new policy domains emerged, as the Birkland model points out, a new group (e.g. bureaucracy or

organization) involved in the new policy domain was mobilized in each country. The post-event policy domain is important to understand the feature of EUA policy because these newly mobilized groups based on the policy domains are responsible for the legislation, revision, and operation of the EUA policies in each country.

Initially, the US EUA targeted only those chemical, biological, radiological, and nuclear (CBRN) threats listed under the Project Bioshield Act of 2004, which focused on bioterrorism. However, the US EUA has gradually expanded the scope of the policy to include all possible threats such as infectious diseases in subsequent legislation. Instead of legislating new policy covering infectious diseases, the US EUA expands its scope of the policy from CBRN threats to pandemic threats. This policy evolution implies that once a new policy domain is accepted or institutionalized in a society, the society is likely to pile up new emerging domains neatly on the top of the previous one rather than replacing the old with the new. This is called path dependency in historical institutionalism. Echoing the tenets of historical institutionalism, this dissertation asserts that the US EUA has not functioned satisfactorily in the current COVID-19 pandemic, compared to the Korean EUA's performance, due to the different institutions and policy domains between the two countries. In other words, the Korean EUA with the disease containment domain is efficiently integrated into other supportive public health policies and makes synergy effect to maximize the number of corona testing; however, the US EUA with homeland security domain is hardly to do so because the US EUA's primary adherence to a security-oriented objective as a biodefense policy against CBRN threats.

This dissertation does not argue that the ineffectiveness of EUA is solely significant determinant for different testing outcomes (the effectiveness of EUA)

between the two countries during COVID-19 pandemic. In fact, various U.S. media blamed the poor public health responses of the Trump Administration during COVID-19 outbreak.[11] The incompetence and negligence of the top-leadership are, of course, key factors to worsen the pandemic. However, this dissertation argues that if the feature of EUA policy is omitted as an independent variable, then scholars could fall victim to the omitted variable bias.[12] In order to illustrate the effectiveness of EUA during the COVID-19 pandemic – how EUA policy integrates with other supportive public health policies – this dissertation introduces three factors - biosurveillance, lab-partnership, and insurance system. These three factors are deeply involved with the different testing capacities and outcomes (the effectiveness of EUA) of the two countries in the early phase of the COVID-19 pandemic.

This dissertation consists of five chapters. The first chapter details the outline of this dissertation including background, literature review, research design, and methodologies. Chapters two and three are case studies of the United States and South Korea respectively, which describe the story of how the each EUA policy was enacted after a focusing event. The U.S. case study in the chapter two highlights the evolution of the US EUA policy from a focus on CBRN threats to all-hazards including naturally occurring infectious diseases. And the chapter three covers the case of South Korea

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11 Nathaniel Weixel, "Experts warn of worsening pandemic unless Trump takes action," *The Hill,* November 8, 2020, available at https://thehill.com/policy/healthcare/524879-experts-warn-of-worsening-pandemic-unless-trump-takes-action ; also see, Philip Rucker et al., "34 days of pandemic: Inside Trump's desperate attempts to reopen America," *The Washington Post,* May 2, 2020, available at https://www.washingtonpost.com/politics/34-days-of-pandemic-inside-trumps-desperate-attempts-to-reopen-america/2020/05/02/e99911f4-8b54-11ea-9dfd-990f9dcc71fc_story.html ; Stephen Collinson, "Trump's stunning abdication of leadership comes as pandemic worsens," *CNN,* November 12, 2020, available at https://www.cnn.com/2020/11/12/politics/donald-trump-coronavirus-leadership/index.html

12 Gary King, Robert Keohane and Sidney Verba, *Designing Social Inquiry: Scientific Inference in Qualitative Research* (Princeton, NJ: Princeton University Press, 1994), pp. 168–73.

how the Korean EUA was originated and evolved. The chapter four analyzes why South Korean outperformed the US in COVID-19 testing, which was due in part to the degree to which each country's EUA policy was integrated into their broader public health system. The United States failed to fully integrate its EUA policy with public health which led to serious problems in developing and distributing diagnostics for COVID-19 in 2020. In contrast, a key feature of Korea's EUA policy, that diagnostics approved for emergency use are cooperated with the biosurveillance system and are also available for citizens free of charge. Also, the Korean lab-partnership sharing standards and procedures with public and private sectors ensures that the diagnostics deployed by South Korea would be more accessible. Last, chapter five discusses research implications of this dissertation, outlines biodefense policy recommendations for both countries, how to strengthen the utility of EUA in both countries, and best practices that other countries should consider when developing their own EUA policies.

Background on US and Korean EUA Policies

To ensure that MCMs are efficacious, governments establish strict approval regulations covering all the stages of MCM research, development, production, and utilization. The Federal Drug Administration (FDA) is the body that approves all MCMs in the United States. However, there have been many cases where state public health authorities have hesitated the use of investigational MCMs that have yet to complete all official approval process – these are unlicensed MCMs. Many governments have officially or unofficially allowed the use of investigational MCMs and the off-label use of approved MCMs, under the name of "compassionate use," as the last resort treatment for a single or a small-scale group of patients facing life-

threatening illnesses. The compassionate use of unlicensed MCMs is allowed for individual-level requests by patients on the verge of death. For example, an individual or a group of patients who have terminal cancer and for whom licensed anticancer drugs are ineffective can request access to prescribed investigational anticancer drugs as a last resort. Recently, HIV antivirals were first used to treat COVID-19 patients in Thailand, and this experimental use can be a good example of the compassionate use that patients take risks of letting doctors prescribe approved drugs for off-label uses.[13] Another example is President Trump was given the Regeneron's antibody cocktail by the compassionate use request.[14] This use of the investigational dug (Regeneron antibody cocktail) is not approved by drug approval regulations, but individual doctors, patients, and groups of patients can request an exemption that investigational products can be used in the hopes of helping patients as last resort treatments. The exemptions made by individual requests are not designed to be applied in the midst of a large-scale health crisis. The compassionate use is, thus, less likely to be well-suited for addressing threats posed by large-scale public health emergencies.

Beyond the compassionate use, many countries legislate an exceptive provision for state-level use of unlicensed MCMs. This special approval for novel MCMs is usually applied on a case-by-case basis to respond against national exigencies caused by pandemics, catastrophic disasters, or wars. The bottom line of the exceptional use of MCMs is to create a saving clause for crisis management and damage mitigation in

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[13] CNN news, "Thai doctor says new drug combination treated coronavirus patient," posted on February 2, 2020, available at https://www.cnn.com/asia/live-news/coronavirus-outbreak-02-02-20-intl-hnk/h_f9dcabd30a7a19762113ae3aae284742

[14] Lisa Kearns, Alison Bateman-House, and Arthur L. Caplan, "What President Trump's 'compassionate use' of a Covid-19 drug means — and doesn't mean," *STAT,* October 8 2020, available at https://www.statnews.com/2020/10/08/compassionate-use-covid-19-drug-means-and-doesnt-mean/

the case of a national contingency. Because the exceptional use of MCMs is a kind of national contingency plan, a decision for issuing exceptional use is solely made by political leaderships or top authorities. Hence, legal provisions regarding the exceptional use usually exist by one or two legal sentences. For example, the Japanese Pharmaceutical Affair Laws addresses a provision regarding exceptional use of MCMs in Article 69-2 (Emergency Orders) as following;

> When the Minister finds that is it necessary to prevent the occurrence or spread of hazards to public health and hygiene …(skip)… shall be able to order any emergency measures to be taken to prevent the occurrence or spread of hazards to public health and hygiene.[15]

In South Korea, the Minister of National Defense (counterpart to the US Secretary of Defense) can request an exceptional use of MCMs over the domestic pharmaceutical regulations for the purpose of national security under Article 42 (Permission, etc. for Importation of Drugs, etc.) of Pharmaceutical Affairs Act as following;

> (2) the Minister of National Defense …(skip)…may import drugs, etc. without obtaining marketing approval, or filing marketing notification, of each product under paragraph (1) in any of following cases.[16]

In contrast to the exceptional use as an abstract and ambiguous contingency plan, emergency use authorization (EUA) is basically a policy sophisticatedly consisting of various provisions and standard operation procedures, which allows the use of investigational new MCMs. In other words, EUA policy requires a policy mechanism that triggers the implementation of the EUA by determining what

[15] Article 69-2 of the Pharmaceutical Affairs Law. Law No. 145 of 1960. English revisions. Trans by Global Forum LJD. Tokyo: Government of Japan; June 21, 2006.
[16] Article 42 of Pharmaceutical Affairs Act, [Enforcement Date. December 02, 2016.] [Act No.14328, December 02, 2016., Partial Amendment], official translation by National Law Information Center in Ministry of Government Legislation, Republic of Korea, available at http://www.law.go.kr/LSW/eng/engMain.do

constitutes a public health emergency, when a public health emergency can be declared, and who is responsible for the declaration of a public health emergency. For example, since the US Department of Homeland Security (DHS) indicates *Bacillus anthracis* as a material threat against the population of the United States sufficient to affect national security, the US Department of Health and Human Services (HHS) declared a public health emergency on October 2008, authorizing the US Food and Drug Administration (FDA) to issue the EUA of doxycycline hyclate tablets for post-exposure prophylaxis (PEP) and mass-dispensing.[17] Closer scrutiny reveals that the United States and South Korea have different approaches to implementing the emergency use of unlicensed MCMs.

EUA Laws in the US and South Korea

Both the United States and South Korea have developed policies for the approval and broad distribution of investigational new MCMs or the off-label use of approved MCMs in response to a public health emergency. These policies are called Emergency Use Authorizations (EUA). It is reasonable to assume that both EUA policies allow the use of the same or at least similar unlicensed MCMs, given that their respective health security environments are regularly facing public health threats. Bioterrorism and pandemics are common health security threats to both the United States and South Korea. Despite their common threats, the two countries have developed different policies for the emergency use of unlicensed MCMs based on their

[17] The US Food and Drug Administration, "Authorization of Emergency Use of Doxycycline Hyclate Tablet Emergency Kits for Eligible United States Postal Service Participants in the Cities Readiness Initiative and Their Household Members; Availability," *doc: 73 FR 62507*, published on October 21, 2008, available at https://www.federalregister.gov/documents/2008/10/21/E8-25062/authorization-of-emergency-use-of-doxycycline-hyclate-tablet-emergency-kits-for-eligible-united

different past experiences; South Korea was impacted more by SARS and MERS than the United States, while the United States is more afraid of bioterrorism than Korea

This dissertation categorizes three policy features among the two countries, which correlate with new policy domains arising from unique focusing events. These emergency use policies differ based on the timing of the policy, the purpose of the policy, and the target of the policy as following Table 1-2.

Table 1-2: Comparing Key Characteristics of US and Korean EUA Policies

Characteristics	United States EUA	South Korean EUA
Threat Assessment	Actual & Potential	Actual
Purpose of the Policy	Preparedness & Response	Detection & Diagnosis
Target of the Policy	CBRN	Infectious Diseases
Revised Target	All-Hazards	Radiation Exposure

First, the types of threats each EUA focuses on are a critical difference between the two countries. Both EUAs operate proactively before public health threats enter into the country. These countries usually specify eligible unlicensed MCMs when they expect certain public health threats; however, the United States also includes actual emergencies that are ongoing in its EUA. Actual threat means a kind of threats that a country currently facing or expects to face soon, and potential threat means a kind of threat which exists by virtue of public health vulnerabilities in a country. Under the guidance of the Department of Homeland Security (DHS), the United States EUA covers both actual and potential public health threats. Jonathan Tucker points out that

since the announcement of Homeland Security Presidential Directive-10 (HSPD-10) after the September 11th attacks and Amerithrax, DHS has been conducting national risk assessments of new biological threats, and significant resources have been allocated to assess both current and future threats to the United States.[18] For example, although the US Centers for Disease Control and Prevention (CDC) has stated that the risk of a widespread Ebola virus disease (EVD) outbreak in the United States is very low, DHS, in coordination with the CDC and the National Security Council, has taken significant steps to mitigate the spread of EVD and other potential threats to public health in the United States.[19] EVD is one of the most fearful global pandemic threats which has no treatment and a high fatality rate. Despite the United States only having four confirmed cases of Ebola in 2014, the EVD was designated as a potential public health threat and the US public health authority issued an EUA for EVD diagnostic kits. In South Korea, there were no EVD cases, so no EUA regarding EVD was issued in South Korea. Though South Korea confirmed its first Zika virus disease case in March 2016, it did not issue an EUA for Zika virus diagnostic kits until 16 August 2016. The main reason for the issuance of the EUA was the 2016 Olympic Games in Rio, which attracted many Korean tourists and the Korean national Olympic team to Brazil. Thus, the threat of the Zika virus entering the country became an actual threat.

Second, the two countries have different purposes for implementing the emergency use of unlicensed MCMs. The United States EUA focuses on public health preparedness and response in the event of a public health emergency. After the anthrax

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[18] Jonathan B. Tucker, "Biological Threat Assessment: Is the Cure Worse Than the Disease," *Arms Control Today,* Volume 34: October 2004, available at https://www.armscontrol.org/act/2004-10/features/biological-threat-assessment-cure-worse-disease

[19] United States Department of Homeland Security, "Ebola Response," published in June 21, 2016, available at https://www.dhs.gov/archive/ebola-response

letter attacks of 2001, common themes of after-action reports and lessons learned analyses emphasized the need for reinforcing and expanding the benefits of "public health preparedness" and the importance of "rapid response."[20] On 12 June 2002, the Public Health Security and Bioterrorism Preparedness and Response Act was signed into effect. The purpose of this act was to strengthen national preparedness for bioterrorism attacks and other public health emergencies. This law laid the groundwork for the establishment of the Strategic National Stockpile (SNS) of all MCMs and necessary supplies in the event of bioterrorism or other public health emergencies.[21] In 2004, US Congress passed the Project Bioshield Act that introduced the EUA policy as a means of implementing the legislation. The Project Bioshield Act was designed to ensure the authority of the US government to develop, acquire, stockpile, and make available the MCMs needed to protect the US population against weapons of mass destruction.[22]

In contrast to the US approach, which defines MCMs broadly, the South Korean EUA is only applicable to medical devices, such as in-vitro diagnostic (IVD) kits. This is because the legal basis for Korea's EUA is Paragraph 7 of Article 10 and Paragraph 7 of Article 32 in the Enforcement Regulations of the Medical Device Act which was

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[20] See, United States General Accounting Office, "A report to the Honorable Bill Frist, Majority Leader, US Senate, BIOTERRORISM: Public Health Response to Anthrax Incidents of 2001", *GAO-04-152,* Oct 2003; United States General Accounting Office, "Homeland Security: New Department Could Improve Coordination, but Transferring Control of Certain Public Health Programs Raises Concerns," *GAO-02-954T*. Washington, D.C.: July 16, 2002; Bipartisan Commission on Biodefense, "A National Blue Print for Biodefense: Leadership and Major Reform Needed to Optimize Efforts," *the Blue Ribbon Study Panel Report,* October, 2015.

[21] Public Health Security and Bioterrorism Preparedness and Response Act (PUBLIC LAW 107-188-JUNE 12, 2002)

[22] MedicalCountermeasures.gov under the US Department of HHS, "Project Bioshield Overview," last accessed on Dec 10, 2016, available at https://www.medicalcountermeasures.gov/barda/cbrn/project-bioshield-overview/

approved in June 2016.[23] The official full name of the Korean EUA is *The Emergency Use Authorization of In-Vitro Diagnostics for Infectious Disease*. Both clauses provide a legal basis of exemption for the manufacture and import of medical devices to prevent infectious disease outbreaks.[24] Because of the legal parameters of the Medical Device Act, in-vitro diagnostic kits are the only medical devices eligible for emergency use. To achieve this goal, the Korean government integrates the EUA policy with national insurance system. Ministry of Health and Welfare expanded national health insurance coverage to cover the use of products, such as diagnostic kits, with an EUA for free. The free use of diagnostic kits reduces the financial burden on the population, thereby facilitating the testing of a larger percentage of the population in order to diagnose infectious diseases more quickly and easily. Insurance coverage helps maximize the effectiveness of Korea's massive diagnostics practices based on a disease prevention principle: the earlier suspected cases are detected, the more effective a disease prevention campaign works.[25] In short, both EUA policies pursue rapid response, but have different priorities. While the United States EUA prioritizes public health preparedness to ensure the timely access of MCMs to the population on a large scale, the South Korean EUA prioritizes detection and diagnosis of infectious diseases in large-scale to ensure disease control and prevention.

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[23] Both clauses were deleted on December 31, 2018. Instead, Article 46-2, newly inserted a "Medical Device Act" by Act No. 15486, Mar. 13, 2018, which becomes a new legal basis of the Korean EUA

[24] The Article 10 Paragraph 7 and Article 32 Paragraph 7 of Enforcement Regulations of the Medical Device Act [Ordinance of the Prime Minister No. 1284, June 15, 2016], National Law Information Center in Ministry of Government Legislation, Republic of Korea, available at http://www.law.go.kr/LSW/main.html

[25] Park Jae-Sun, Choi Young-sill, Yoo Cheon-Kwon, Division of Laboratory Diagnosis Management, KCDC, "Introduction of Emergency Use Authorization of In-Vitro Diagnostics for Infectious Disease," *Weekly Health and Disease,* Vol.10 No.22, 2017, pp.555-559

Lastly, the targets of the emergency use policies differ between the two countries. In the beginning, the United States EUA under the Project Bioshield Act promised the use of unlicensed MCMs for CBRN threats such as anthrax. Along with the legislation of the Pandemic and All-Hazards Preparedness Act of 2006 (PAHPA) and the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) that reassure EUA policy, the target range of the US EUA broadened from CBRN to naturally occurring diseases. Compared with the US EUA, the initial South Korea EUA only covered infectious diseases, but, in 2019, added radiation exposure as a targeted threat for the EUA policy. To date, no EUA has been issued in Korea for medical devices to detect radiation exposures. These different targeted threats become evident when we review each country's list of eligible unlicensed MCMs for public health emergencies. As of 2019, the United States has approved the use of unlicensed MCMs designed to counter seven public health threats: Anthrax, Ebola, Enterovirus, radiation exposure, H7N9 Influenza, MERS, Zika, and a nerve agent.[26] Based on these seven targets, the United States aims to counter all hazards from naturally occurring diseases to CBRN threats. South Korea had issued the EUA authorizing the use of unlicensed in-vitro diagnostics (IVDs) kits for MERS and Zika.[27]

Different entities and agencies involved in the issuance of EUAs influence these differing lists of targets. In the United States, in order to issue an EUA, one of three criteria of emergency determinations must be met: (1) a public health emergency

[26] The US Food &Drug Administration (FDA), "Emergency Use Authorization," updated on Nov 13, 2019, last accessed on Dec 20, 2019, available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#FrenchFDP

[27] Two EUAs were terminated in 2017, so no EUA items had been available by 2020 when the EUA for COVID-19 issued on Feb 4, 2020. See Korea Center for Diseases Control and Prevention (KCDC) handed out a press release on Aug 4, 2017, available at https://www.mohw.go.kr/react/al/sal0301vw.jsp?PAR_MENU_ID=04&MENU_ID=0403&CONT_SEQ=340898

determined by the Secretary of HHS, (2) a military emergency determined by the Secretary of the Department of Defense (DOD), or (3) a domestic emergency determined by the Secretary of the DHS. Once an emergency has been determined by one of these three agencies, the FDA Commissioner is responsible for issuing the EUA to diagnose, treat, or prevent serious or life-threatening diseases or CBRN threats.[28] In South Korea, a public health emergency sufficient for EUA issuance is defined by the Infectious Disease Control and Prevention Act. In the case of a looming public health emergency, the Korean CDC (KCDC) Commissioner can submit an EUA request to the Minister of Food and Drug Safety (comparable to the US FDA). Such requests for a South Korean EUA are limited to infectious disease responses.

In sum, the United States and South Korea have contrasting policy approaches to the emergency use of unlicensed MCMs. The United States EUA works both proactively to strengthen public health preparedness and reactively to respond to all hazards. However, the South Korea EUA also works reactively only by aiming to strengthen diagnostic capabilities to respond to current diseases threats, not future possible threats.

Literature Review: Theory and Policy

This section describes and evaluates the theoretical literature on policy formulation and implementation which I will use as the framework for analyzing the EUA policies of the United States and South Korea. In addition, this section reviews

[28] Section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), also see FDA website, "Emergency Use Authorization," available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

the handful of academic studies that have examining the development and implementation of EUA policies in the United States and South Korea. This section will also examine literature comparing Japan's policy for emergency use to the US policy since Japan is one of the few other countries which such a policy in place.

Literature Review: EUA Policies in the US, Japan, and South Korea

Presently, there is a limited amount of literature studying the purpose and effectiveness of EUAs as well as thedifferent and unique characteristics of EUA policies in different countries. Although the US EU policy has been in place since 2004, there has not been any scholarly attention to the origin, evolution, and implementation of this policy. There have been a small number of articles comparing the US EUA policy to similar policies adopted by Japan and South Korea, but this literature is highly descriptive, does not seek to explain the conditions that led to the formulation of these policies or their evolution, and is not grounded in any theory. This section of the literature review will first summarize existing research on the US EUA policy and then describe existing literature that compares the different approaches towards EUA policy taken by the United States, Japan, and South Korea.

Two articles by Nightingale et al. (2007) and Kels (2015) describe the unique features of the US EUA policy. Nightingale et al. sheds light on the strategic advantages of the formulation of the EUA policy in the United States. They contend that both the use of unapproved MCMs and the off-label use of FDA approved MCMs under the EUA can provide reliable and timely large-scale treatment for both civilian and military

entities.[29] Kels (2015) insists that the public health strength of the US was improved by the revision of the EUA policy from the PAHPA 2003 to the PAHPRA 2013, which is more efficient in dealing with both actual and potential public health emergencies by eliminating some requirements for the issuance of the EUA. [30] One of the improved features of PAHPRA 2013 is that the US government is granted explicit statutory authorization to stockpile MCMs regardless of their approval status, and it can assess the ability to pre-position MCMs before an actual emergency in order to enable rapid dispensing once an EUA is issued. Both Nightingale et al. (2007) and Kels (2015) emphasize the security benefits of an EUA against public health threats that could potentially inflict catastrophic consequences, even if the probability of that event (e.g., bioterrorism) is low.

It is also instructive to examine two articles, by Urushihara et al. and by Shimazawa and Ikeda, that compare the US EUA policy to an equivalent policy in Japan called Emergency Approval (EA). According to Urushihara et al., the US and Japan have different legal systems regarding public health emergency response; they conclude that the regulatory stances of the two states resulted in different outcomes from the 2009 H1N1 influenza pandemic.[31] The Urushihara et al.'s article started during the 2009 H1N1 pandemic when the US public health authority approved the use of *peramivir,* a novel investigational antiviral drug*,* by the EUA on 23 October 2009, while Japanese approval of using *peramivir* was delayed until late January 2010. As seen in Table 1-3,

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[29] Stuart L. Nightingale, Joanna M. Prasher and Stewart Simonson, "Emergency Use Authorization (EUA) to Enable Use of Needed Products in Civilian and Military Emergencies, United States," *Emerging Infectious Disease* Vol. 12 No.7 July 2007.

[30] Charles G. Kels, "Dispensing Medical Countermeasures: Emergency Use Authorities and Liability Protections," *Health Security.* Vol. 13 No. 2 2015

[31] Hisashi Urushihara et al "Emergency Authorization of Medical Products: Regulatory Challenges from the 2009 H1N1 Influenza Pandemic in Japan," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science,* Vol. 10 No. 4, 2012.

Urushihara et al. contributes to the comparative analysis of both states' legal systems in which the EUA and EA approve the unlicensed MCMs differently in a certain situation.

Table 1-3: Comparison of Emergency Authorization Systems for Unapproved Medicinal Products and Unapproved Indications of Approved Products between Japan and the United States[32]

System Elements	United States	Japan
Applicable Regulation	Emergency Use Authorization (EUA)	Emergency Approvals (EA)
Objective	To permit the US FDA the emergency use of an unapproved medical product or an unapproved use of an approved medical product in certain well-defined emergency situations, including not only public health emergency but also others such as CBRN emergency	In case of public health emergency, expeditiously grant approval of an unapproved product
Legal Basis	Federal Food, Drug, and Cosmetic Act 564; Project Bioshield Act	Pharmaceutical Affairs Law 14-3
Related Documents	Public Health Service Act 319; Guidance – Emergency Use Authorization of Medical Product	Minister of Health, Labour, and Welfare (MHLW) Health Crisis Management Basic Policy Act Concerning the Measures for Protection of the People in Armed Attack Situation
Responsible Authority	Secretary of HHS & FDA commissioner	MHLW

[32] Hisashi Urushihara et al "Emergency Authorization of Medical Products: Regulatory Challenges from the 2009 H1N1 Influenza Pandemic in Japan," Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science, Vol. 10 No. 4, 2012.

Determination of Emergency	One of the 3 Criteria Met: 1. The Secretary of HHS determines a public health emergency involving specified CBRN agent; 2. The Secretary of the DHS determines a potential domestic emergency involving potential risk of attack with specified CBRN agents 3. The Secretary of the DOD determines a military emergency involving risk of attack to military force with specified CBRN agents.	No criteria provided for public health emergency in the Japanese system of law
Emergency Declaration Entity	Secretary of HHS	Cabinet Office
Eligible Products	1. It is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious of life-threatening disease or condition caused by the agents specified in the declaration of emergency, based on the totality of scientific evidence available; 2. The know and potential benefits outweigh the know and potential risks of the products when used; and 3. No alternative is available • Absolutely new medical products that have not been previously approved by any authority •Unapproved products that are approved in countries other than the home country • Unapproved indication of domestically approved products	A product, whose application for emergency approval is intended, is designated by Cabinet Order as satisfying the 2 criteria below: Necessary for use in emergencies to prevent the spread of life-threatening or serious diseases or the enlargement of other health hazards, and for which no other countermeasures are available; and Approved for the applicable indication in foreign countries having a regulatory system for medical products with comparable scientific standards to ensure the quality, efficacy, and safety of the product. Designation of applicable countries should be done by Cabinet Order. Unapproved products that are approved in countries other than the home country

		Unapproved indication of domestically approved products
Authorization	FDA Commissioner may issue the EUA only if it is concluded that the above necessary criteria are met, after consultation with the directors of NIH and CDC	MHLW is able to grant marketing approval for the applicable product, based on the opinion of the Pharmaceutical Affairs and Food Sanitation Council
Conditions for Use	Enforceable at the discretion of the FDACommissioner	Enforceable at the discretion of the Minister of Health, Labour, and Welfare
Termination	Expires 1 year after the Declaration of Emergency, unless previously revoked or renewed	Not provided

Based on their legal comparison, Urushihara et al. illustrate that the Japanese EA is stipulated as a type of "legal authorization status," compared to the "experimental status" of the United States EUA. "Legal authorization status" means that Japanese public health authorities can quickly confer legal status on eligible unapproved MCMs comparable to other MCMs under the formal approval granted according to the routine legal process. The policy mechanism of the Japanese EA is similar to a type of expedited authorization mechanism, in which unapproved MCMs eligible during an emergency should provide clinical trial data that were derived for regulatory review in other advanced countries.[33] On the other hand, the United States EUA is ''a temporary measure for making a product available during an emergency.''[34] Because the EUA is an exceptional measure for an emergency situation, it does not confer any formal

[33] Hisashi Urushihara et al "Emergency Authorization of Medical Products: Regulatory Challenges from the 2009 H1N1 Influenza Pandemic in Japan," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science,* Vol. 10 No. 4, 2012.
[34] Debra Birnkrant and Edward Cox, "The emergency use authorization of peramivir for treatment of 2009 H1N1 influenza," *N Engl J Med* Dec 3, 2009, 361(23) pp. 2204-2207.

marketing authorization nor does it need to meet the high standards of the formal drug approval in the United States, such as data packages of clinical trials required for FDA approval. Therefore, under the experimental status of the EUA, products remain investigational.[35]

Table 1-4: Lists of Counter-CBRN Products in the United States and Japan[36]

CBRN Material		The United States	Japan
Chemical	Organophosphate	Atropine, Pyridostigmine	Atropine, Amyl Nitrite
	Cyanide	Hydroxocobalamin, Na2S2O3	Hydroxocobalamin, Na2S2O3
Biological	Anthrax	Penicillin G, Ciprofloxacin, Doxycycline, Levofloxacin, Minocycline, Raxibacumab	Benzylpenicillin, Ciprofloxacin, Doxycycline, Levofloxacin, Minocycline, Norfloxacin, Tosufloxacin
	Plague	Levofloxacin, Streptomycin	Levofloxacin, Streptomycin
	Botulism	BAT	
Radiological & Nuclear	Pu, Am, Cm	Ca-DTPA/Zn-DTPA	Ca-DTPA/Zn-DTPA
	Radioactive Cs/Tld	Fe4[Fe(CN)6]3 (Prussian blue)	Fe4[Fe(CN)6]3 (Prussian blue)
	Radioactive I	KI	KI

[35] Hisashi Urushihara et al "Emergency Authorization of Medical Products: Regulatory Challenges from the 2009 H1N1 Influenza Pandemic in Japan," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science,* Vol. 10 No. 4, 2012.

[36] Combination of the tables 2 and table 3 in the article. See, Rumiko Shimazawa and Masayuki Ikeda, "Development of Drug-Approval Regulations for Medical Countermeasures against CBRN agents in Japan," *Health Security,* Vol. 13 No. 2 2015.

Finally, Urushihara et al. argue that the experimental status fulfilled all the criteria to approve *peramivir* in addition to the already marketed antivirals *oseltamivir* and *zanamivir*, so they could be used in the 2009 H1N1 pandemic. On the other hand, the legal authorization status only allowed the use of the already-marketed items (*oseltamivir* and *zanamivir)* and delayed permitting the use of the investigation item (*peramivir)* until late January 2010 in Japan.

Shimazawa and Ikeda (2015) found that Japan has three fewer types of MCMs in their stockpile against CBRN threats, compared with the US stockpiles (see Table 1-4). Shimazawa and Ikeda, based on a study of MCM stockpile lists in two countries, also illustrated that the Japanese legal culture for using MCMs is more conservative in terms of safety than that of the United States. Their study examined the use of legally approved MCMs against CBRN threats in each country, and it provides important insight into how the United States and Japan adopted different postures and legal schemes in terms of the use of MCMs. Japan lists 16 therapeutic drugs against seven CBRN threats: two for chemical threats (organophosphate, cyanide), two for biological threats (anthrax, plague), and three for radiological/nuclear threats (plutonium – Pu /americium – Am /curium – Cm; radioactive cesium and thallium - Cs/Tld; and iodine – I).[37] Even though the total number of determined drugs (16) of the United States and Japan is the same, there are three different items between the two countries. The authors emphasized that the Animal Rule in the US allowed three products (pyridostigmine, raxibacumab, and BAT) to be used in the United States, which are unavailable to use in Japan. The Animal Rule is a biodefense policy regulated by the FDA, under which

[37] Each of Pu, Am, Cm in the table means plutonium, americium, and curium. Radioactive Cs/Tld means radioactive cesium and radioactive thallium.

new MCMs can be approved after successful testing in animals only if human efficacy studies are neither ethical nor feasible. Rumiko and Masayuki contend that the Animal Rule expanded the accessibility of investigational MCMs in the United States, so introducing the Animal Rule in Japan could improve the flexibility of the country's emergency response in a CBRN crisis.[38]

Korean scholars have also studied the US EUA policy in order to improve the EUA policy of South Korea. Park Jae-Sun et al. (2017) analyzed the different and unique aspects of the Korean EUA with the United States EUA. Park Jae-Sun et al. explains that after the experience of the 2015 MERS outbreak, the Korean government legislated the EUA (officially referred to as the Emergency Use Authorization of In-Vitro Diagnostics for Infectious Disease) as a new policy tool for timely and practical use of unapproved diagnostic products of some infectious diseases. Unlike the US EUA, the Korean EUA authorizes the use of only unapproved medical diagnostic kits (in-vitro) for rapid detection and response to infectious disease outbreaks. Also, the Korean CDC and Korean FDA require temporary authorization for giving insurance coverage on the EUA items, which provides free medical check-ups for the entire population in a public health emergency. In order to improve the EUA system, they argue that Korea should also strengthen "pre-EUA" activities, emulating the United States. Pre-EUA activity is regarded as a proactive threat assessment in biodefense policy, similar to the way that the military carries out intelligence activities. One of the most basic policy processes that serves as a pre-EUA activity is the US public health authority forming lists of all eligible MCM candidates, based on threat evaluations, that

[38] Rumiko Shimazawa and Masayuki Ikeda, "Development of Drug-Approval Regulations for Medical Countermeasures against CBRN agents in Japan," *Health Security,* Vol. 13 No. 2 2015.

can be timely used in a potential public health emergency.[39] Considering the rapidly changing health security environment as well as the unexpected transition to a response effort, the US FDA encourages the sponsors of potential MCMs that might be considered for an EUA to contact the FDA before submitting a formal request for an EUA. The FDA defines these submissions and related interactions as "pre-EUA" activities.[40]

Overall, the academic literature on EUA policy is quite limited. While the existing literature describes the EUA policies in the United States, Japan, and South Korea, the literature does not explain or analyze the emergence of EUA policy in any of these countries, why these policies have evolved differently in each country, and implications and impacts of these differences on national response to public health emergencies. Indeed, there has been no study about why and how the United States and South Korean EUAs were established and have evolved.

Literature Review: Theories of Policy Formulation and Implementation

There are multiple theories and models that seek to explain how policies, especially major policy changes, emerge. The specific focus of this dissertation is on policy changes in the field of biodefense. Biodefense includes the implementation of various activities related to counter-bioterrorism and biological warfare, arms control and nonproliferation, biosurveillance, emergency preparedness, and MCM

[39] Park Jae-Sun, Choi Young-sill, Yoo Cheon-Kwon, Division of Laboratory Diagnosis Management, KCDC, "Introduction of Emergency Use Authorization of In-Vitro Diagnostics for Infectious Disease," *Weekly Health and Disease,* Vol.10 No.22, 2017, pp.555-559

[40] The United States FDA, Office of Counterterrorism and Emerging Threats, "Emergency Use Authorization of Medical Products and Related Authorities - Guidance for Industry and Other Stakeholders," *Doc Number: FDA-2016-D-1025,* January 2017

development. Thus, biodefense entails those actions designed to counter biological threats, reduce risks, and prepare for, respond to, and recover from bioincidents.[41] For the purpose of this dissertation, the field of biodefense will be treated as an institution defined as "the idea that formal structures would shape behaviors and shape the outcomes of political processes."[42] Hall and Taylor define institutions "the formal or informal procedures, routines, norms and conventions embedded in the organizational structure of the polity or political economy."[43] In other words, biodefense can be considered an institution consisting of various policies and organizations that govern the behaviors of a set of individuals within a given society. For example, the United States has regularly published a National Biodefense Strategy, which provides a framework for orchestrating these diverse activities across federal departments and agencies in order to protect American lives from biological threats.[44] An EUA that allows large-scale distribution of investigational or new MCMs at the national level, regardless of potential adverse effects, to deal with a public health emergency is one of the significant features of biodefense institutions.

Simply put, institutions are believed to as "stable, valued, recurring patterns of behavior";[45] however, scholars of new institutionalism ask, "where do the origins of

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[41] Office of the Assistant Secretary for Preparedness and Response, US Department of Health & Human Services, "Frequently Asked Questions: National Biodefense Strategy," accessed on June 17, available at https://www.phe.gov/Preparedness/biodefense-strategy/Pages/faqs.aspx

[42] This is a conventional definition of institution in political science. See; B. Guy Peters, "Institutionalism," in *The Oxford Handbook of British Politics*, edited by Matthew Flinders, Andrew Gamble, Colin Hay, and Michael Kenny, available at https://www.oxfordhandbooks.com

[43] Peter A. Hall and Rosemary C. R. Taylor, "Political Science and the Three New Institutionalisms," *Political Studies* (1996), p. 938

[44] See, White House, "The purpose of the 2018 National Biodefense Strategy," available at https://www.whitehouse.gov/wp-content/uploads/2018/09/National-Biodefense-Strategy.pdf

[45] Samuel P Huntington, *Political Order in Changing Societies* (Yale University Press 1968), p.9

institutions come from and why do they change?" As discussed in the policy and legal literature reviews regarding the US EUA and the Korean EUA, both policies have undergone adjustments. The US EUA was legislated after the 2001 anthrax letter attacks and underwent multiple revisions over time. The Korean EUA was legislated after the 2015 MERS outbreak and radiation exposure was later added to the list of targeted threats. In the same vein with new institutionalism, this research starts from the question: Why and how they were these authorities for emergency use authorization legislated and revised? Danzig (2012) took the first step toward understanding how US biodefense policy has evolved. Danzig argues that the development of US biodefense policies has followed a pattern of "punctuated evolution," where changes only occur when an exogenous shock forces decision-makers to take action.[46] In the same vein, Musmar (2017) illustrated the evolution of federal biodefense policy and MCM development, particularly in the use of unlicensed MCMs for the pediatric population. For instance, coverage of pediatric populations was strengthened in 2013 PAHPRA legislation following Hurricane Katrina.[47] It is important to note that the Musmar study provides an applied account of the Danzig's punctuated evolution concept within the actual US biodefense policy area using the MCM accessibility to pediatric populations. The "punctuated evolution by exogenous shock" is a typical framework for analyzing institutional changes or evolutions in the context of historical institutionalism. Historical institutionalism is a major camp of new institutionalism that studies the mutability of institutions, but also has theoretical limitations to analyze

[46] Richard Danzig, A decade of countering bioterrorism: Incremental progress, fundamental failings. *Biosecurity and Bioterrorism, 10*(1), 49–54.

[47] Jomana F. Musmar, "The Path to PAHPRA: The Evolution of Pediatric Biodefense Legislation and Medical Countermeasure Development," (PhD diss., George Mason University, 2017)

institutional changes at the meso-level only.[48] Building upon theoretical reviews of historical institutionalism, this dissertation applies Birkland's Event-Related Policy Change Model to account for the adaption and revision of EUA policy in the United States and South Korea.

Critical Juncture & Path Dependency

Historical institutionalism (HI) provides a theoretical lens that focuses on institutional origins and changing patterns under the assumption that institutions come, in a meaningful sense, from the past. Based on structural-functionalist tenants, HI scholars focus on the ways in which different institutional configurations shape interests, strategies, and behaviors to produce distinctive outcomes.[49] In this perspective that an institution shapes and affects behaviors, HI scholars interpret the emergence of a new institution as the product of an interaction between agents resulting from the collapse of the existing institutions due to a crisis. HI accounts for institutional origins and changes in the language of *critical juncture*, which is a decisive moment of innovation caused by crises crisis (exogenous shocks) such as a revolution, war, or regime change. Collier and Collier define *critical juncture* as a period of significant change, which typically occurs "in distinct ways in different countries, and that these differences played a central role in shaping the national political arena in the following decades."[50] At the international level, John Ikenberry emphasizes the historical role of

[48] Yeon-Seob Ha, "Recent Trends in New Institutionalism: Theoretical Innovations and Convergence," *Korean Association of Governmental Studies (KAGOS),* Vol.36 No.4 (2002 Winter), pp.339-359

[49] Peter A. Hall and Rosemary C. R. Taylor, "Political Science and the Three New Institutionalisms," *Political Studies* (1996), pp.937-938

[50] Ruth Berins Collier and David Collier*, Shaping the Political Arena; critical junctures, the labor moment, and regime dynamics in Latin America*, (NJ: Princeton University Press, 1991), pp, 28-29

critical junctures (he refers to them as "historical junctures") where the building and rebuilding of the liberal international order has been periodically established by historical junctures when leading liberal states has been in a position to shape global rules and institutions.[51]

The idea of a critical juncture causing institutional changes contributes to the main narratives of HI that illustrate the trajectory of institutional innovation from critical past moments as constant and predictable. The patterns of institutional innovation often rely on or share the same pathway of development with the previous innovation – this is called *path dependency*. Basically, critical junctures constitute the starting points for many path dependent processes, and path dependence is a crucial causal mechanism for HI scholars.[52] The main logical foundation of path dependence is "self-reinforcement." Irish Economist Brian Arthur insists that an individual's current choices depend on their past ones in a self-reinforcing manner. Along with the same line, he argues social systems tend to converge on a single path, as the product of an arbitrary initial decision or interaction that leads to self-reinforcing patterns.[53] The self-reinforcing manner of institutional innovation is elaborated by the notion of *punctuated equilibria*, which enables prediction about how institutional changes would be under certain parameters.[54] The punctuated equilibria of institutional change asserts

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[51] G. John Ikenberry, *Liberal Leviathan; the Origins, Crisis, and Transformation of the American World Order*, (NJ: Princeton University Press, 2011), p.65

[52] Giovanni Capoccia and R. Daniel Kelemen, "The Study of Critical Junctures: Theory, Narrative, and Counterfactuals in Historical Institutionalism", *World Politics,* Vol. 59, No. 3 (April, 2007), p.342

[53] Brian Arthur, "Self-Reinforcing Mechanisms in Economics," in Chapter 7 of *Increasing Returns and Path Dependence in the Economy*, edited by Arthur, W. Brian, and Kenneth J. Arrow (Ann Arbor: University of Michigan Press, 1994), available at https://www.jstor.org/stable/10.3998/mpub.10029

[54] Stephen Jay Gould and Niles Eldredge, "Punctuated Equilibria: The Tempo and Mode of Evolution Reconsidered," *Paleobiology* Vol. 3, No. 2 (Spring, 1977), pp. 115-151; also see, Stephen D. Krasner, "Approaches to the State: Alternative Conceptions and Historical Dynamics," *Comparative Politics,* Vol. 16, No. 2 (Jan., 1984), pp. 223-246

that brief and sporadic moments, as critical junctures, become triggers of institutional change by collapsing existing institutions or providing actors with the opportunity to select a different path. As Danzig points out, the development of US biodefense policies followed a pattern of "punctuated evolution,"[55] in which institutional change predominantly arose from exogenous shocks that resulted in the emergence of a new pattern or equilibrium. In other words, critical events that awoke US national security concerns (exogenous shock) catalyzed new biodefense policies or revisions of existing policies.

Although the punctuated equilibria framework contributes to the explanatory power of HI – how history has influenced institutional changes or developments - some scholars point out the limitation of HI narratives focusing solely on the results of exogenous factors. They argue that it is important to observe not only exogenous factors, but also endogenous factors. Streeck and Thelen introduce counter-examples of non-sudden and non-sporadic institutional changes that exhibit "gradual institutional transformations that add up to major historical discontinuities."[56] Greif and Laitin suggest that continuous changes of institutions by "self-undermining" powers play significant roles, in addition to the self-reinforcing manner of path dependency.[57] The role of agents in the course of endogenous institutional change becomes central to HI discussions. Conran and Thelen criticize the punctuated equilibrium framework for moving beyond the question of whether agency trumps structure or the role of agency

[55] Richard Danzig, "A decade of countering bioterrorism: Incremental progress, fundamental failings," *Biosecurity and Bioterrorism, 10*(1), 49–54.
[56] Wolfgang Streeck and Kathleen Thelen, *Beyond Continuity: Institutional Change in Advanced Political Economies*, (Oxford, Oxford University Press, 2005)
[57] Avner Grief and David D. Laitin, "A Theory of Endogenous Institutional Change," *American Political Science Review,* Vol. 98, No. 4 November 2004, pp.663-652

in shaping institutional change.[58] These scholars understand institutions as the products of agency, rather than constraints. Humans (agencies) enact institutions, and they likewise transform institutions in response to environmental changes, thus, institutional outcomes (set of processes – rules, procedures, or policies) can change over time. Hacker introduces the concept of *drift* that highlights the role of agents, internal conflicts or contested within or by agents in the course of institutional changes, when explaining the strategies of reforming the US social welfare program.[59] In other words, institutional changes involve the dynamic interactions between endogenous factors such as conflicts and contests between agents (e.g., turf war) and exogenous factors (critical junctures).

The purview and explanatory power of the punctuated equilibria framework long remained in the meta discourse level, which discussed abstract causality between exogenous factors (environmental shifts or shocks) and a pattern of institutional change. This traditional HI framework matured to give more attention to endogenous factors. The dynamic between endogenous and exogenous factors provides us with a better understanding of how institutional changes occur. Therefore, groups of congregated agencies – namely, society or the public - become the centers of institutional change. However, the current theoretical framework of HI is still limited to a detailed account explaining the effectiveness of environmental shifts influencing the role of endogenous factors. To strengthen connectivity between exogenous and endogenous factors, Slater and Simmons highlight the role of the "antecedent condition," which precede a critical

[58] James Conran and Kathleen Thelen, "Institutional Change," in Chapter 3 of *the Oxford Handbook of Historical Institutionalism,* edited by Orfeo Fioretos, Tulia G. Falleti, and Adam Sheingate, (NY: Oxford University Press, 2016) pp.65-66

[59] Jacob S. Hacker, "Privatizing Risk without Privatizing the Welfare State: The Hidden Politics of Social Policy Retrenchment in the United States," *The American Political Science Review*, May, 2004, Vol. 98, No. 2 (May, 2004), pp. 243-260

juncture to determine the precise causal and non-causal status of institutional changes.[60] Soifer also emphasizes a precondition of critical junctures, whether the permissive condition or the productive condition, to precisely analyze a causality of institutional changes.[61] Since the emergence of the role of endogenous factors in HI, the necessity for strong causality of institutional changes arose. To fill the causal weakness of HI, this dissertation borrows the concept of "policy-learning." The concept of 'learning' and 'learning-process' provides a much simpler and clearer way to observe actual connectivity between exogenous and endogenous factors in terms of institutional change – to whom and what kinds of lessons were learned from exogenous shocks.

Policy is one of the institutional outcomes that the introduction, revision, and withdrawal of policy can operationalize as an institutional change. Policy scholars and political scientists focus on the new point of view that policy is based on idea-driven belief systems, rather than the conventional narratives that power and interests are at the center of politics and the policy-making process. Since political and policy decisions are motivated by beliefs, scholars study the learning process by which participants use information and knowledge to develop, test, and refine their beliefs.[62] In other words, beliefs are changed through the learning process, which contributes to policy changes, that is, outcomes of institutional changes. These include notions of "political-learning"

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[60] Dan Slater and Erica Simmons, "Informative Regress: Critical Antecedents in Comparative Politics", *Comparative Political Studies* (2010), volume: 43 issue: 7, pp. 886–917

[61] Hillel David Soifer, "The Causal Logic of Critical Junctures", *Comparative Political Studies* (2012), volume: 45 issue: 12, pp.1572-1597

[62] Paul A. Sabatier, "An Advocacy Coalition Framework of Policy Change and the Role of Policy-Oriented Learning Therein," *Policy Sciences*, Vol. 21, No. 2/3 (1988), pp. 129-168; see, Hank C. Jenkins-Smith and Paul A. Sabatier, "Evaluating the Advocacy Coalition Framework," *Journal of Public Policy,* Vol. 14, No. 2 (Apr. - Jun., 1994), pp. 175-203; John W. Kingdon, *Agendas, alternatives, and public policies*. (2nd ed.) (New York: Longman, 2003)

developed by Heclo[63], "policy-oriented learning" developed by Sabatier[64], "lesson-drawing" analyzed by Rose[65], "social learning" discussed by Hall[66], and "government learning" identified by Etheredge.[67] These concepts highlight that humans and their institutions behave in ways subject to adaptable bounded rationality. Finally, Bennett and Howlett examine various approaches about policy learning and identify three types of learning in terms of who learns, what they learn, and the effects of learning on subsequent policies as seen in Table 1-5.

Table 1-5: Three Types of Learning and Policy Change[68]

Learning Type	Learner	Learns Topic	Learning Effect
Government Learning	State Officials	Process-Related	Organizational Change
Lesson Drawing	Policy Networks	Instruments	Program Change
Social Learning	Policy Communities	Ideas	Paradigm Shift

Moreover, Kingdon uses the metaphor of "streams" to describe how beliefs facilitate policy change though the learning process. Kingdon argues that once a new issue gains enough attention, a "window of opportunity" is opened to set up a new public agenda. Through a window of opportunity, the three types of streams running in

[63] Hugh Heclo. *Modern Social Politics in Britain and Sweden: From Relief to Income Maintenance*, (CT: Yale University Press, 1974)
[64] Paul A. Sabatier, "An Advocacy Coalition Framework of Policy Change and the Role of Policy-Oriented Learning Therein," *Policy Sciences,* Vol. 21, No. 2/3 (1988),
[65] Richard Rose*, "*What Is Lesson-Drawing?" *Journal of Public Policy,* Vol. 11, No. 1 (Jan. - Mar., 1991), pp. 3-30
[66] Peter A. Hall, "Policy Paradigms, Social Learning, and the State: The Case of Economic Policymaking in Britain," *Comparative Politics,* Vol. 25, No. 3 (Apr., 1993), pp. 275-296
[67] Lloyd S. Etheredge. *Government learning: An overview*, edited by Samuel L. Long, *The Handbook of Political Behavior*. vol. 2. (New York: Plenum Press, 1981) pp. 73-161.
[68] Colin J. Bennett and Michael Howlett, "The lessons of learning: Reconciling Theories of Policy Learning and Policy Change," *Policy Sciences* 25/1992, p.289

parallel, but independently, can converge: (1) the state of politics and public opinion (the political stream), (2) the potential solutions to a problem (the policy stream), and (3) the attributes of a problem (the problem stream). These streams converge when an issue gains enough public attention to be placed on the public agenda. In other words, when an issue establishes a new public agenda and a set of new beliefs, society begins to consider alternative solutions and countermeasures, which causes policy changes. [69] Sabatier's Advocacy Coalition Framework (ACF) emphasizes the mobilization of interest groups to change policies. The ACF examines why advocacy coalitions within policy subsystems are the critical vehicle for understanding the role of policy analysis in policy-oriented learning, leading to policy change. [70] Building upon Kingdon's policy stream model and Sabatier's ACF model, Thomas Birkland developed the Event-Related Policy Change Model. The Birkland model provides a more detailed account for how focusing events (exogenous shocks) trigger the emergency of a policy domain that lays a groundwork for policy changes within society. His model contributes to explaining the role of focusing events (exogenous shocks) as facilitators for endogenous dynamics, which can increase public attention to a problem and lead to the emergence of a new policy domain resulting in policy changes.

Birkland's Event-Related Policy Change Model

As seen in Table 1-6, Birkland identifies three types of focusing events: crisis, disaster, and catastrophe. He defines crises as being induced by the actions or inactions of an organization; disasters as the result of natural phenomena or external

[69] John W. Kingdon, *Agendas, alternatives, and public policies*. (2nd ed.). New York: Longman.
[70] Paul A. Sabatier, "An Advocacy Coalition Framework of Policy Change and the Role of Policy-Oriented Learning Therein," *Policy Sciences*, Vol. 21, No. 2/3 (1988), pp. 129-168

human actions to which a single government or organization can respond; and catastrophes as more profound than disasters so that a single local or national government is unable to respond sufficiently.[71]

Table 1-6: Crises, Disasters, and Catastrophes[72]

Scale or Magnitude of the Event 	Crises	Disasters	Natural Catastrophes
	Chernobyl	September 11th Attacks	Hurricane Katrina
	Tylenol Poisoning	PanAm 103	South Asia Tsunami
	Swiss Canyon Incident	Katherine Flood	–

Based on the different roles that vary with each type of focusing event, Birkland illustrates a mechanism of how the impact of a focusing event can construct a policy domain that generates significant post-event policy changes. For example, Birkland explains that in the event of a natural disaster, which is often interpreted as an "act of God," society is less likely to condemn a government, instead focusing on what can be done to help the victims. Conversely, a request for responsibility and accountability emerges when society faces an event resulting from human error or government failure.[73]

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[71] Bill Faulkner, "Towards a framework for tourism disaster management," *Tourism Management* 22: 135-41 (2001) quoted in Thomas A. Birkland, *Lessons of disaster: Policy change after catastrophic events*, (DC: Georgetown University Press, 2006), p.1-3.

[72] Faulkner (2001) quoted in Thomas A. Birkland, *Lessons of Disaster; policy change after catastrophic events*, (DC: Georgetown Univ Press, 2006) p.1-3.

[73] Thomas A. Birkland, *After Disaster; agenda setting, public policy and focusing event*, (DC: Georgetown Univ Press, 1997) p.1-3

Building upon the correlation between a focusing event and a new emerging policy domain, Birkland develops the "Model of Event-Related Policy Learning" in his book, *Lesson of Disaster*.

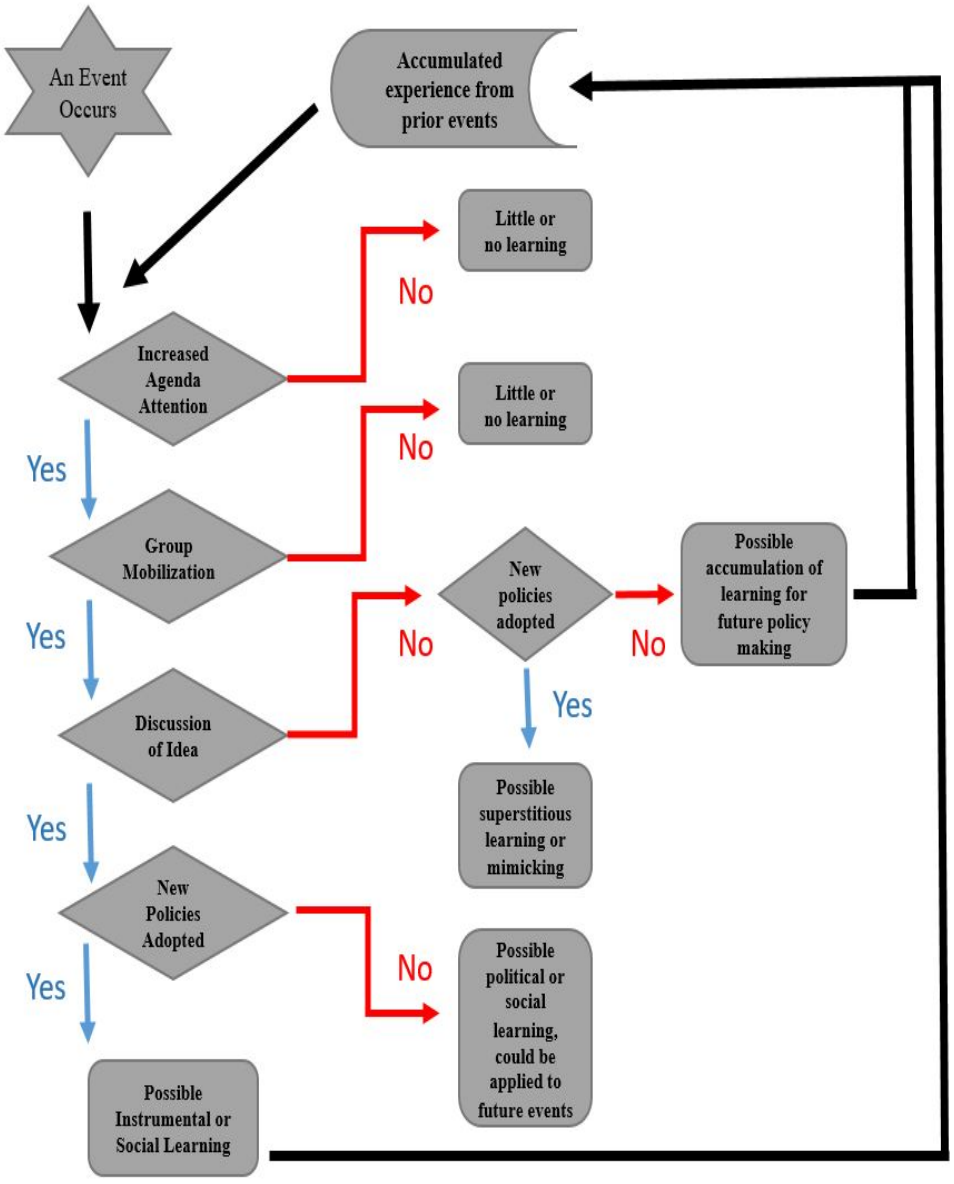

Figure 1-1: A Model of Event-Related Policy Learning[74]

[74] Thomas A. Birkland, *Lessons of Disaster; policy change after catastrophic events*, (DC: Georgetown Univ Press, 2006), p.18

Birkland categorizes and defines the different sorts of potential focusing events that could trigger policy change as the result of different learning processes in the development of a new policy domain. As seeing in Figure 1-1, the experience of a focusing event plays a primary role in the learning process, which leads to either the revision of existing policy domains or the creation of new ones. This model can be used to demonstrate how the September 11th attack, categorized as a disaster, created a policy domain of "homeland security," which evolved from older notions of counterterrorism, national security, and emergency management. This model provides a reasonable and rigorous narrative explaining the legislation of the post-9/11 national security acts such as the Bioshield Act and the Patriot Act.

Research Design and Methods

Based on the Birkland's model, this dissertation examines and illustrate how a focusing event created a new policy domain in terms of the legislation and revision of EUA policy both in the United States and South Korea. In this model, Birkland introduces the categories of evidence as seeing Table 1-7: news media, interest groups, congress, and regulatory and implementing agencies.

Table 1-7: Typical Evidence of Learning in the Policy Process[75]

Organization or Institution Type	Evidence of Learning
News Media	Stories about the problem
	Changes in the nature of news coverage
Interest Groups	Changes in appearances at congressional hearings
	Increased attention from news media (generated by group)
Congress	Legislative change
	Change in the substance of debate
	Change in the topic areas of hearings
Regulatory & Implementing Agencies	Issuance of new & proposed regulation
	Changes in procedures & in the interpretation & implementation of statutes and regulations
	Changes in the nature & substance of the regulations being issued

These evidences lay the groundwork for the Birkland's model to describe events that occurred, how these issues got on the agenda, which groups or coalitions were mobilized, what were the different solutions proposed and debated, and what new policies were adopted or revised in light of lessons learned from the events. This dissertation studies the development of EUA policies in the United States and South Korea based on the four criteria of learning evidence. First, this this dissertation illustrates stories about problems introduced by major news media. One thing different than the Birkland's study is quantitative research for news coverage.

[75] Thomas A. Birkland, Lessons of Disaster, (DC: Georgetown Univ Press, 2006), p.21

Birkland, in his study, selected *The New York Times* as the media outlet used to analyze the change in the occurrences of headlines that use "terrorism" as a key term arranged by *LexisNexis;* [76] however, there does not exist an internet-based platform in South Korea acceptably comparable to *LexisNexis* for legal study purposes. Also, all news is arranged by the numbers of hits and comments through multiple internet searching platforms like google or yahoo, so it is hard to represent the ubiquity or majority of public opinion by one major news media. Therefore, both case studies for the United States and South Korea focus on describing stories and narratives about the problems delivered by major media. After that, this dissertation uses various congressional reports and hearings, laws and official government documents to determine how interest groups in each country was mobilized.

In sum, as in in the Figure 1-2, case studies of both the United States and South Korea illustrate how focusing events – 9/11 and Amerithrax in the United States and the MERS outbreak in South Korea – facilitated mobilization of interest groups and idea discussions, which resulted in the adoption of a new policy – Emergency Use Authorizations (EUA). In addition to the primary source lists for learning evidence above, HSPD-10, the DTRA-CSIS Report, and other GAO reports are used to describe how the anthrax letter attack led to the emergence of the homeland security domain in the United States. In South Korea's case, KCDC reports and post-MERS conferences in academia are used to describe how the MERS outbreak led to the formation of the disease containment domain.

[76] Thomas A. Birkland, *Lessons of Disaster* (DC: Georgetown Univ Press, 2006), p.25

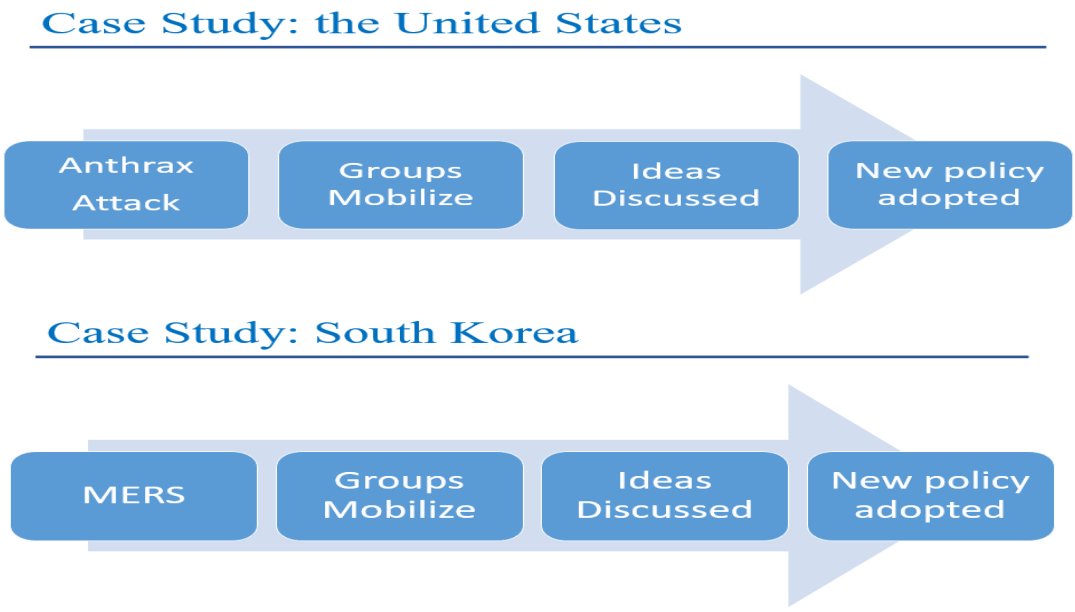

Figure 1-2: Case Study Process

CHAPTER 2: Case Study of the United States EUA Policy

Introduction

Due to the 11 September 2001 terrorist attacks (9/11), the United States had already begun to quickly establish a new policy domain - homeland security - in response to the increasing threat of terrorism.[77] The 2001 anthrax letter attacks (Amerithrax) was the first confirmed use of *Bacillus anthracis* for bioterrorism, which caused unprecedented social chaos in the United States. Breaking news and special reports from all news media flooded the public during the crisis. Along with the increasing concerns of conventional terrorism threats emerging from 9/11, the 2001 anthrax letter attacks added a new concern of terrorists exploiting weapons of mass destruction (WMDs), especially with regards to biological weapons. Counterterrorism and WMD nonproliferation became the top priority for US policy agendas following 9/11 and Amerithrax in 2001. To protect the US homeland and population from the emerging chemical, biological, radiological, and nuclear (CBRN) terrorism threats, it was deemed necessary to recognize CBRN terrorism as a potential new type of public health threat in the United States.

As a consequence of these terror events, homeland security emerged as the new leading domestic policy domain, which embraces political, military, law enforcement,

[77] Thomas A. Birkland, *Lessons of disaster: Policy change after catastrophic events*, (Washington DC: Georgetown University Press, 2006)

and public health areas to deal with these newly emerging threats. In Homeland Security Presidential Directive-10 (HSPD-10), President George W. Bush stated, "the United States will continue to use all means necessary to prevent, protect against, and mitigate biological weapons attacks perpetrated against our homeland and our global interests."[78] The homeland security domain embraces not only a mission to secure the nation from conventional terrorism threats, but also to protect its citizens and interests from CBRN terrorism, particularly in bioterrorism. Therefore, since the anthrax letter attacks, public health preparedness in response to bioterrorism became a new policy objective, which is subordinated to the homeland security domain. The EUA policy was enacted as a part of the new public health objective to develop public health preparedness and response to CBRN threats.

This chapter determines that the features of the US EUA policy have generated by lessons learned from Amerithrax. Along with the post-9/11 homeland security movement, the Amerithrax investigations and evaluations provided a new public health goal: public health preparedness and response to CBRN threats. As a result, the US EUA emphasizes post-exposure countermeasures to protect public health. Moreover, this chapter illustrates that the US EUA has evolved from a policy targeting only CBRN threats to a policy targeting more broad threats including infectious diseases. Even though the US EUA broadly expanded its scope of policy regarding threats to public health, the US EUA follows a path of development for strengthening homeland security. Therefore, this chapter shows that the US EUA was born as a homeland

[78] White House, Homeland Security Presidential Directive -10 (HSPD-10), "Biodefense for the 21st Century," Office of the Press Secretary, released April 28, 2004, available at https://fas.org/irp/offdocs/nspd/hspd-10.html

security policy, and has evolved into a biodefense policy pursuing public health objectives, as a defensive measure against low-probability/high-consequence events.

Twin Focusing Events: September 11th Terrorist Attacks & the 2001 Anthrax Letter Attacks

The September 11th attacks (hereafter referred to as 9/11) were a historical nightmare for the United States. On that day in 2001, the Islamic terrorist group, al-Qaeda, conducted a series of four suicide attacks by hijacked airplanes that were crashed into the North and South Towers of the World Trade Center in New York City and the Pentagon. Another hijacked aircraft believed to be targeted at the US Capitol Building crashed into a field in Pennsylvania after crewmembers and passengers attempted to retake control of the plane. This deadly incident resulted in more than 2,000 people died and at least $10 billion in losses of infrastructure and property damages.[79] The impact of 9/11 resulted in huge changes in many aspects of the United States including politics, foreign policy, and society, in the era referred to as post-9/11. Unfortunately, one week after the 9/11, on 18 September 2001, letters laced with anthrax were dispersed in the United States. The 2001 anthrax letter attacks comprise the first deliberate use of anthrax as a bioweapon in the United States. The causative agent of anthrax is *Bacillus anthracis*, which is a rod-shaped, gram-positive bacteria. *Bacillus anthracis* is widely assumed to be the most likely agent of biowarfare or bioterrorism, because the bacteria are in the form of spores, making them extremely tolerant to environmental degradation. The rod-shaped bacteria can infect humans through three different routes: cutaneous, gastrointestinal and inhalational routes.

[79] Institute for the Analysis of Global Security, "how much did the September 11 terrorist attack cost America?" accessed in August 15, 2020, available at http://www.iags.org/costof911.html

Among the three forms of anthrax, inhalational form is the most lethal course of anthrax infection.

Amerithrax resulted in 22 confirmed cases anthrax among those who came in contact with the seven contaminated letters. Eleven of these cases were of the cutaneous form, while the other 11 suffered from the inhalation form of the disease; five victims died. On 2 October 2001, an infectious disease physician initially recognized a possible case of anthrax in a man hospitalized in Palm Beach County, Florida. The next day, on 4 October, the diagnostic testing through the Florida Department of Health and the CDC confirmed an infection with *B. anthracis*.[80] At this point, there were already seven more patients with cutaneous anthrax in the northeastern areas of the United States. The CDC and other state and local public health authorities initiated epidemiologic and environmental investigations to determine the source of these anthrax exposures. Finally, CDC surmised that these simultaneous localized outbreaks of anthrax infections were linked with the "intentional delivery of *B. anthracis* spores through mailed letters or packages."[81]

The United States public health and law enforcement authorities led by the CDC and FBI uncovered the truth of how the anthrax letter attacks were conducted. The seven letters containing anthrax spores were sent to seven different destinations using the US Postal Service (USPS). Targets included five new media centers: AMI in Florida as well as NBC, ABC, CBS, and the NY Post in New York. The remaining two letters were sent to Senator Daschle and Senator Leahy's offices in Washington, DC.

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[80] The U.S. Center for Disease Control and Prevention. "Notice to Readers: Ongoing Investigation of Anthrax – Florida, October 2001," *Morbidity and Mortality Weekly Report,* Oct 12, 2001, 50(40)

[81] The U.S. Center for Disease Control and Prevention., "Investigation of Anthrax Associated with Intentional Exposure and Interim Public Health Guidelines, October 2001," *Morbidity and Mortality Weekly Report, 2001; (50):889-893*

Despite knowing the targets and travel method (mailing), there is a black box that cannot explain the infection routes of some cases. Four cases of unexpected inhalational anthrax infections occurred in postal workers in a Washington, D.C. It is curious that these cases, mostly contracted within postal facilities, presented as the inhalation form of anthrax instead if the cutaneous form. Powdered anthrax spores contained within envelops should be less likely to cause inhalational anthrax infection. In order to infect via inhalation, particles of agents should be aerosolized and one to five nanometers in size.[82] The envelope may act as a sieve by which highly-compressed air produced by a mail sorting machine can aerosolize *B. anthracis* spores, which may have occurred at both the Hamilton (New Jersey) and Brentwood (Washington, DC) facilities.[83] Indeed, environmental sampling showed diffuse contamination of the postal facility in D.C., which the CDC should suggest that prophylaxis is necessary for all employees.[84]

Impacts of the 2001 Anthrax Letter Attack

The consequences of bioterrorism can be quite horrific. In addition to the direct casualties (11 illnesses and 5 deaths), the attacks led to more than 30,000 people including postal workers to receive antibiotic treatment and the expensive decontamination of buildings. The economic cost of the anthrax letter attacks was exorbitant: total cost associated with decontamination was about $320 million,[85] and

[82] Kevin P Fennelly et al. "Airborne infection with Bacillus anthracis--from mills to mail." *Emerging Infectious Diseases,* vol. 10, 6 (2004), pp. 996-1002
[83] Daniel B. Jernigan, et al. "Investigation of Bioterrorism-Related Anthrax, United States, 2001: Epidemiologic Findings," *Emerging Infectious Diseases,* Vol. 8, No. 10 (October 2002). p. 1023
[84] Puneet K. Dewan et al., "Inhalational Anthrax Outbreak among Postal Workers, Washington, D.C., 2001," *Emerging Infectious Diseases,* Volume 8, Number 10, October 2002
[85] Ketra Schmitt and Nicholas A. Zacchia, "Total decontamination cost of the anthrax letter attacks," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* Vol. 10, No. 1, pp. 98-107

medical expenditures totaled approximately $177 million.[86] In addition to the economy damages and casualties, the 2001 anthrax letter attacks devastated the United States by revealing vulnerabilities of the public health emergency system. Various vulnerabilities and weaknesses of the US public health emergency system were revealed during the course of emergency response actions against the anthrax letter attacks.

The primary deficiencies that most post-event evaluations point out are the lack of risk communication during emergency and an uncertain decision-making apparatus. Gursky, Inglesby, and O'Toole found that the lack of clear risk communication networks resulted in unnecessary crosstalk and time delays, which led to ineffective emergency response actions during the crisis. For example, although many people working in DC live in Maryland and Virginia, the three different state health departments (DC, MD, and VA failed to cooperate when they issued their respective jurisdictional reports for public health emergency response.[87] Heatherley also emphasized the insufficient risk-communication within public health network. Thompson, Armstrong, and Thompson also argue that inter-agency coordination was a major challenge in the response. The CDC and Department of Defense (DOD) did not share the same information about the dispersal ability of the weaponized anthrax used in the attacks.[88]

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[86] Nicholas A Zacchia and Ketra Schmitt, "Medical Spending for the 2001 Anthrax Letter Attacks," *Disaster Medicine and Public Health Preparedness,* Volume 13, Issue 3June 2019 , pp. 539-546

[87] Elin Gursky, Thomas V. Inglesby, and Tara O'Toole, "Anthrax 2001: Observations on the Medical and Public Health Response", *Biosecurity and Bioterrorism: Biodefense, Strategy, Practice, and Science,* Volume1, Number2, 2003, p.103-105

[88] Richard Preston, *The Demon in the Freezer* (New York, NY: Random House, 2002): 1-26. See; Kimberly M. Thompson, Robert E. Armstrong, and Donald F. Thompson, "Bayes, Bugs, and Bioterrorists; Lessons Learned from the Anthrax Attack," *Center for Technology and National Security Policy,* National Defense University, April 2005.

Another big issue in post-event investigations is the designation of what individual or entity is tasked with making decisions in a public health emergency, particularly in regard to recommending antibiotic prophylaxis with uncertain efficacy. There were no specific vaccines nor therapeutic drugs for the inhalation form of anthrax that had been officially approved by public health authorities. The CDC was the only federal agency that can give the scientific guidance to local-level practices. To whom we should provide drugs? What is the recommended dosage of the selected drug? The CDC should mandate specific public health actions, particularly for administration of antibiotic prophylaxis, but there were huge confusions and time-delays surrounding the CDC's recommendations.[89] In fact, the initial post-exposure prophylaxis (PEP) program recommended 60 days of antimicrobial PEPs (either doxycycline or ciprofloxacin)[90], but later the CDC issued an extended regimen (40 additional days). The extension was recommended with or without three doses of anthrax vaccine adsorbed (AVA) under an investigational new drug (IND) protocol (extended PEP program).[91] The CDC, as the central federal agency for public health, failed to make timely and appropriate decisions about the use of antibiotic prophylaxis, which caused massive confusion for local-level public health practices during the emergency. Gursky,

[89] Editorial board of the journal, "Lessons learned from the CDC's post-exposure prophylaxis program following the anthrax attacks of 2001," *Pharmacoepidemiology and Drug Safety,* 2005; 14: pp. 389–391 See; The U.S. Centers for Disease Control and Prevention. *"Update: investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax." Morbidity and Mortality Weekly Report (MMWR)* 2001; 50: pp. 941–948. Also see; The U.S. Centers for Disease Control and Prevention. "Notice to readers: additional options for preventive treatment for persons exposed to inhalational anthrax," *Morbidity and Mortality Weekly Report (MMWR),* 2001; 50: p. 1142

[90] The U.S. Centers for Disease Control and Prevention, "Update: investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax," *Morbidity and Mortality Weekly Report (MMWR),* 2001; 50: 941–948.

[91] The U.S. Centers for Disease Control and Prevention, "Notice to readers: additional options for preventive treatment for persons exposed to inhalational anthrax," *Morbidity and Mortality Weekly Report (MMWR),* 2001; 50: 1142

Inglesby, and O'Toole also point out that it was hard for the CDC as such a research organization to make timely and decisive operational actions at the local level under scientific uncertainties. The key uncertainty in this crisis was the use of post-exposure chemoprophylaxis, for which the CDC struggled to address because it is "a research-based organization, far removed from how public health is delivered."[92]

In sum, the 2001 anthrax letter attack is a focusing event devastating the United States, which revealed vulnerabilities of the public health emergency system as well as created catastrophic results such as the casualties and the economy damages. There was no central agency that was authorized to make timely decisions under such uncertainty conditions. All governments, regardless of level, did not perform adequately in terms of public health emergency response, because of the lack of risk communication during emergency. Therefore, many post-event evaluations emphasize that the inefficient coordination between governmental levels resulted in delayed and inappropriate response actions. Particularly, the necessity of a central agency that can perform risk versus benefit-based decision making emerged with the issues relating to the use of prophylaxis. The prophylaxis-related issues became the center of lessons learned from the 2001 anthrax letter attack.

Lessons Learned from the Focusing Events

Mobilization of the Homeland Security Group

The anthrax letter attacks were bundled with September 11th attacks as a collective focusing event for the United States that catalyzed the creation of the

[92] Elin Gursky, Thomas V. Inglesby, and Tara O'Toole, "Anthrax 2001: Observations on the Medical and Public Health Response", *Biosecurity and Bioterrorism: Biodefense, Strategy, Practice, and Science,* Volume1, Number2, 2003, p.103-105

homeland security policy domain. The adoption of the homeland security policy domain dominated all areas and fields of the post-9/11 movement in the United States. The former Secretary of DHS under the Obama administration, Janet Napolitano, views, in retrospect, that Americans in 2001 - including both ordinary citizens and those in the highest levels of the US government - were seized by a national sense of paranoia and dread of terrorism.[93] For example, the use of the term – "terrorism" – in headlines *of The New York Times* skyrocketed from September 11, 2001 until 2004.[94]

Along with increasing counterterrorism efforts and information sharing about September 11th, the National Commission on Terrorist Attacks Upon the United States (also known as the 9/11 Commission) was established on November 27, 2002 by Public Law 107-306. The law directed the 9/11 Commission to investigate "facts and circumstances relating to the terrorist attacks of September 11, 2001," including those relating to intelligence agencies, law enforcement agencies, diplomacy, immigration issues and border control, the flow of assets to terrorist organizations commercial aviation, the role of congressional oversight and resource allocation and other areas determined relevant by the Commission.[95] The extent of the Commission's activities was not limited to specific security issues directly involved with September 11th such as intelligence, law enforcement, or aviation. Rather, the Commission's investigation extended to all areas that should or may involve September 11th under the objective of protecting the homeland; Birkland explains this is because 9/11 is a focusing event in

[93] Janet Napolitano, *How Safe Are We?* (NY: PublicAffairs, 2009)
[94] Thomas A. Birkland, *Lessons of Disaster; policy change after catastrophic events,* (Washington DC.; Georgetown Univ. Press, 2006) p.48
[95] The 9/11 Commission Report: *Final Report of the National Commission on Terrorist Attacks Upon the United States,* authorized edition, (NY: Norton & Company, 2004), Preface xv

the United States.[96] In fact, Birkland shows that there were 26 new public laws related to terrorism, which serve as evidence of instrumental learning in the post-9/11 movement: five laws for "War on Terrorism", two for "Intelligence," three for "Law Enforcement," three for "Diplomacy and Foreign Aid," and thirteen for "Homeland Defense."[97] The post-9/11counterterrorism efforts expanded in scope to include the non-traditional counter-terrorism disciplines and began to consolidate them to one name : homeland security.

The emergence of the homeland security domain in parallel with expanding counter-terrorism efforts mobilized the homeland security group. President G.W. Bush issued Executive Order 13228 on 8 October 2001, which established the Office of Homeland Security within the Executive Office of the President. The Assistant to the President for Homeland Security is positioned as the head of the Office of Homeland Security. The mission of the Office of Homeland Security is to develop a comprehensive "national strategy to secure the United States from terrorist threats" and coordinate "the Executive Branch's efforts to detect, prepare for, prevent, protect against, respond to, and recover from terrorist attacks" within the US territory.[98] Also, the Executive Order 13228 also establishes a Homeland Security Council consisting of various high-ranking officers, which is responsible for advising and assisting the President with respect to all aspects of homeland security. The membership of the Council shows that high-ranking officers, chiefs, and directors from various federal

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[96] Thomas A. Birkland, *Lessons of Disaster; policy change after catastrophic events,* (Washington DC.; Georgetown Univ. Press, 2006) PP.44-45

[97] Thomas A. Birkland, *Lessons of Disaster; policy change after catastrophic events,* (Washington DC.; Georgetown Univ. Press, 2006) pp.51-53

[98] The White House, "Establishing the Office of Homeland Security and the Homeland Security Council," Executive Order 13228, issued on October 8, 2001, available at *https://fas.org/irp/offdocs/eo/eo-13228.htm*

agencies and departments rallied around the flag, namely Homeland Security Council.[99] Executive Order 13228 called for the coordination of US national efforts against terrorism threats and, consequently, contributed to the mobilization of the homeland security group.

Finally, the Homeland Security Act of 2002 was enacted on 25 November 2002, which authorized the establishment of the US Department of Homeland Security (DHS). The Homeland Security Act is a historical milestone of US national security that mobilized resources and efforts across all levels of government to deal with terrorism threats. The Homeland Security Act of 2002 brought many responsibilities for public health preparedness and response within one department (DHS), which was composed of 180,000 personnel from twenty-two federal organizations.[100] As a federal department consisting of diverse specialties, the DHS adheres to the concept of homeland security by integrated an all-encompassing approach to counterterrorism. When the Federal Emergency Management Agency (FEMA) organization was absorbed under the growing behemoth that was DHS, the new department assumed FEMA's "all-hazards" approach for responses to threats ranging from of chemical or biological agents to disasters to damage of critical infrastructures and even disease spread.[101] For example, Title III of the Homeland Security Act of 2002, *"Science and Technology In Support of Homeland Security,"* describes national plans to develop countermeasures for terrorism exploiting CBRN materials. Title V of it, *"Emergency*

[99] The White House, *Ibid.,* Executive Order 13228, October 8, 2001
[100] Janet Napolitano describes the DHS was a the third-largest cabinet agency in the US government, consist of 18,000 employees, and now reaches at the size of 246,000 employees in 2019. See; Janet Napolitano, *How Safe Are We?* (NY: Public Affairs, 2009), p.9
[101] Janet Napolitano, *How Safe Are We?* (NY: Public Affairs, 2009), pp.17-18

Preparedness and Response," describes national plans to ensure response and preparedness for emergencies including terrorist attacks and natural disasters.[102]

The newly formed homeland security group embraced biodefense topics since its origin following Amerithrax. In other words, biodefense became one of core subjects of counterterrorism through homeland security efforts. Indeed, there was no a single word of *"anthrax letter"* issues in a Congressional Research Service report regarding management and organization of DHS; the only mentioned is Civilian Biodefense Research Programs (HHS) as one of the primary components transferred to the Department of Homeland Security.[103] As a result, key figures of the homeland security group hold positions in the biodefense group. For example, the Bipartisan Commission on Biodefense, formerly known as the Blue Ribbon Study Panel on Biodefense, was established in 2014 to assess gaps in US biodefense. The Blue Ribbon Panel analyzes comprehensive US biodefense capabilities against biological threats and provides recommendations to foster the improvement of biodefense capabilities. The Bipartisan Commission on Biodefense currently co-chaired by former Senator Joe Lieberman and former Governor Tom Ridge, consists of various former high-ranking government officers and former Congress members, most of whom have strong ties to the homeland security domain. Indeed, Joe Lieberman was the first to propose creation of a cabinet-level Department of Homeland Security when he was a Senator.[104] Moreover, Tom Ridge was appointed as the Assistant to the President for Homeland Security by

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[102] Public Law 107-296, An Act to establish the Department of Homeland Security, and for other purposes (called to as the Homeland Security Act (HSA) of 2002

[103] Harold C. Relyea, "Homeland Security: Department Organization and Management," Report for Congress, *Congressional Research Service*, Order Code RL31493, August 7, 2002

[104] The U.S. Senate Committee on Homeland Security & Governmental Affairs, "Lieberman, Specter Offer Homeland Defense Legislation Proposals Will Be Reviewed At Friday Hearing," October 11, 2001, available at https://www.hsgac.senate.gov/media/majority-media/lieberman-specter-offer-homeland-defense-legislation-proposals-will-be-reviewed-at-friday-hearing

President George W. Bush after September 11th and served in that position from 2001 to 2003. Later, he became the first US Secretary of Homeland Security when President Bush established DHS in 2003. Other members include are former Senate Majority Leader Tom Daschle, former Representative Jim Greenwood, former Homeland Security Advisor Kenneth Wainstein, and former Homeland Security and Counter Terrorism Advisor Lisa Monaco.[105] Based on its objective and membership, it seems obvious that the terminology – biodefense – in its namesake is rooted in the pursuit of homeland security, rather than general public health. Though the Bipartisan Commission on Biodefense is a privately-funded commission that does represent all the United States biodefense efforts, the significance of this Commission cannot be overlooked. Given the huge influence of its annual publications as well as bipartisan activities testifying before Congress and meeting with officials at the White House, the characteristics and purposes (homeland security and counterterrorism) of the Bipartisan Commission on Biodefense's activities have significant implications for the post-9/11 and post-Amerithrax biodefense era.

Of course, there were skeptics warning against such a rapid expansion of DHS responsibilities and authorities. The United States General Accounting Office (GAO) cautioned rapidly centralizing authorities for public health preparedness and response under the current homeland security movement. The GAO called attention to the Homeland Security Act that transfers specific public health preparedness and response programs once housed in HHS to DHS, such as research and development on chemical,

[105] Also see the other past and current member organization in the Blue Ribbon Study Panel on Biodefense, available at https://biodefensecommission.org/mission-our-team/

biological, radiological, and nuclear threats.[106] Also, other GAO report warned of potential inefficiencies if the Laboratory Registration/Select Agent Program authorized by the Public Health Security and Bioterrorism Preparedness and Response Act were transferred from CDC to DHS.[107] As the GAO papers point out, the growing homeland security domain was snowballing to all areas of government, including public health preparedness and response.

The newly mobilized homeland security group was strengthened, disseminated, and institutionalized by education. Homeland security is an evolving interdisciplinary area of study and practice; thus, US academic institutions have steadily developed certificate, Bachelor's degree, and Master's degree programs related to the homeland security issues.[108] For example, the US Naval Postgraduate School in Monterey, California established the Center for Homeland Defense and Security (CHDS) in April 2002. Since CHDS offers a Master of Homeland Security, other academic institutions competitively developed similar homeland security-related programs at various levels of academic degrees. Countless numbers of students graduating from such academic programs become homeland security professionals and contribute to the consolidation of the homeland security group.

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[106] The United States General Accounting Office, "Homeland Security: New Department Could Improve Coordination, but Transferring Control of Certain Public Health Programs Raises Concerns," GAO-02-954T. Washington, D.C.: July 16, 2002.

[107] The United States General Accounting Office, "Homeland Security: New Department Could Improve Biomedical R&D Coordination but May Disrupt Dual-Purpose Efforts," GAO-02-924T. Washington, D.C.: July 9, 2002.

[108] Dale Jones and Austen Givens, "Public Administration: The Central Discipline in Homeland Security," in Chapter of *The Future of Public Administration, Public Management, and Public Service Around the World: the Minnowbrook perspective*, edited by Rosemary O'Leary, David M. Van Slyke, and Soonhee Kim, (Washington DC., Georgetown Univ. Press, 2010), pp.72-73

Emergence of Biodefense for Homeland Security

Prompted by the rapid post-9/11 homeland security movement, Amerithrax added to America's deep concerns about CBRN threats as WMDs for terrorists. The common myth that biological weapons are "the poor man's atomic bomb" stimulated public fears that advanced biotechnology lowers the technological threshold, thereby facilitating easier and cheaper development of biological weapons.[109] It is often believed that a few rogue scientists operating in shabby laboratory facilities, even in container boxes, are capable of developing dangerous biological materials. However, this CBRN terrorism narrative does not account for the fact that organizational and institutional barriers impede the transfer of "tacit knowledges" that is essential to successfully develop weaponizable biological agents.[110] This was a point of origin for misunderstanding of the nature of biological weapons lumped terrorism and WMD together into a new emerging threat – CBRN terrorism. Koblentz points out that although al-Qaeda began pursuing biological warfare capabilities in 1999, the perception of the threat posed by do-it-yourself (DIY) jihadi bioterrorism was exaggerated, because it is technically difficult hard to weaponize anthrax spores as high-quality dry powders that are easily aerosolized.[111] Nevertheless, on 12 October 2001, Vice President Dick Cheney stated that it is "reasonable" to assume the anthrax attacks are linked to the 9/11 terrorist attacks, because al-Qaeda-trained operatives

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[109] Richard K Bett, "The New Threat of Mass Destruction," *Foreign Affairs,* vol. 77, no.1 1988, pp. 26-41. Also see; The United States Congress, Office of Technology Assessment, "Technologies Underlying Weapon of Mass Destruction," OTA-BP-ISC-115, Washington DC., U.S. Government Printing Office, 1993; Jonathan Tucker and Raymond Zilinskas, "The Promise and Perils of Synthetic Biology," *New Atlantis,* no.12 2006, pp.25-45; The Commission on the Prevention of WMD Proliferation and Terrorism, *World at Risk,* (NY: Vintage, 2008)

[110] Sonia Ben Ouagrham-Gormley, *Barriers to Bioweapons; the Challenges to Expertise and Organization for Weapon Development,* (NY: Cornell Univ. Press, 2014)

[111] Gregory D. Koblentz, *Living Weapons; Biological Warfare and International Security,* (NY: Cornell Univ. Press, 2009), pp. 220-224

know "how to deploy and use these kinds of substances [weaponizable biological and chemical materials]."[112] At a 15 October 2001 press conference, President George W. Bush stated that "there may be some possible link" between the anthrax-contained envelopes and Osama bin Laden, adding "I wouldn't put it past him."[113]

In company with the increasingly political narratives concerning CBRN terrorism threats, the majority of post-Amerithrax evaluations and investigations held critical reviews for all levels of the US public health emergency system, and made policy recommendations for what should be done in such future scenarios – preparedness and response. For example, the US Defense Threat Reduction Agency (DTRA) and Center for Strategic and International Studies (CSIS) published a joint post-event analysis report. The US DTRA-CSIS report concludes that the 2001 anthrax letter attacks, along with the September 11th attacks, forced the United States to confront new threats –terrorism within the homeland and the proliferation of WMDs, thus assigning public health as a key element to US defense.[114] This report emphasizes that the United States should ensure adequate preparedness and strengthen its response capabilities. Policy recommendations include the recapitalization of public health infrastructures, the development of forensic and diagnostic capabilities, the improvement of inter-governments communication as well as the preparedness of mass-medication and treatment delivery strategies. In terms of preparedness and response for

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[112] CNN news, "Cheney: 'Reasonable' to assume anthrax cases linked to terrorists," posted on October, 12, 2001, available at https://www.cnn.com/2001/US/10/12/gen.cheney/index.html

[113] The Washington Post, "Text: Bush Meets with Italian Prime Minister," posted on October 15, 2001, available at https://www.washingtonpost.com/wp-srv/nation/specials/attacked/transcripts/bushtext_101501.html

[114] David Heymart, "Lessons from the Anthrax Attacks –Implications for US. Bioterrorism Preparedness", organized by the Center for Strategic and International Studies (CSIS) and the Defense Threat Reduction Agency (DTRA), published April 2002, p.28, available at https://biotech.law.lsu.edu/blaw/anthrax/dtra02.pdf

national emergencies, particularly bioterrorism events, the mass use of post-exposure prophylaxis (PEP) emerged as key necessity to US biodefense. [115]

Vaccines and PEP have quite different medical purposes. A vaccine is an *ex-ante* biological preparation administered before an actual infection in order to provide active acquired immunity to a particular infectious disease, while a PEP is an *ex-post* preventive medical treatment administered after expected exposure to a particular infectious disease in order to prevent becoming infected. During the anthrax letter attacks, an estimated 10,000 individuals, including postal workers, were potentially exposed to *B. anthracis* and advised to take PEPs to prevent inhalational anthrax. As previously mentioned, the CDC floundered when making a decision about the use of prophylaxis. The United States did not develop emergency response and preparedness measures that strengthen the effectiveness and timeliness of dispensing antimicrobials and vaccines for PEP. Early on, the CDC recommended two antimicrobial prophylaxes – doxycycline and ciprofloxacin – as the post-event countermeasures. However, CDC later selected only doxycycline as a single MCM due to issues regarding efficacy, resistance, side effects, and cost. [116] Moreover, the CDC added a third option for PEP that suggests "40 additional days of anti-microbial prophylaxis plus three doses of anthrax vaccine (AVA) administered over a 4-week period."[117]

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[115] David Heymart, "Lessons from the Anthrax Attacks –Implications for US. Bioterrorism Preparedness," organized by the Center for Strategic and International Studies (CSIS) and the Defense Threat Reduction Agency (DTRA), published April 2002, available at https://biotech.law.lsu.edu/blaw/anthrax/dtra02.pdf

[116] Centers for Disease Control and Prevention, "Update: investigation of bioterrorism-related anthrax and interim guideline for clinical evaluation of persons with possible anthrax," *Morbidity and Mortality Weekly Report (MMWR),* 2001; 50: 941-948

[117] Centers for Disease Control and Prevention, "Notice to readers: additional options for preventive treatment for persons exposed to inhalational anthrax," *Morbidity and Mortality Weekly Report (MMWR),* 2001;50: 1142

Finally, on 12 June 2002, the Public Health Security and Bioterrorism Preparedness and Response Act (PL 177-188, also known as the Bioterrorism Act) was signed into effect. It is worth noting that the Bioterrorism Act served as the groundwork for public health securitization becoming categorized as 'Homeland Defense' against bioterrorism, which impacted the birth of the US Biodefense. The purpose of this law was to strengthen national preparedness for bioterrorism and other public health emergencies, giving much more weigh to security benefits over public health benefits. One of the most notable biodefense inventions created by the Bioterrorism Act was the concept of "Select Agents" to tighten control and restrict access to certain dangerous biological agents and toxins. Also, it established the Strategic National Stockpile (SNS) to maintain a stockpile of medical countermeasures and necessary supplies in the event of bioterrorism or another public health emergency.[118]

Both the Public Health Security and Bioterrorism Preparedness and Response Act and Homeland Security Act of 2002 solidified the urgency of CBRN terrorism threats as the post-9/11 and post-Amerithrax homeland security domain overtook public health domains. The United States government immediately reacted to the September 11th and the anthrax letter attacks as one event, which lumped public health issues into homeland security benefits. GAO released a post-Amerithrax evaluation report. written for the US Senate, that emphasized the need to reinforce and expand the benefits of public health preparedness and rapid response. On the first page, the GAO report clearly

[118] Public Health Security and Bioterrorism Preparedness and Response Act (Public Law 107-188-June 12, 2002)

states its purpose: "Because of [the Senate's] interest in bioterrorism preparedness, you asked GAO to review the public health response to the anthrax incidents."[119]

Legislation of the Project Bioshield Act & EUA

With the rise of the homeland security policy domain, "preparedness and response" against bioterrorism emerges as a new policy buzzword for US public health emergencies. As a result, President George W. Bush introduced homeland security as the new agenda of the United States government by issuing the Homeland Security Presidential Directive-10 (HSPD-10, or often called to Biodefense for the 21st Century) in April 2004. The tile of the HSPD-10 clearly signs that biodefense was initially subordinate to the homeland security domain. The overall tone of the HSPD-10 is, as the title of the document hints, a security-oriented narrative about defending the US territory and population against biological threats. The main sentence of the HSPD-10 announces that "the United States will continue to use all means necessary to prevent, protect against, and mitigate biological weapons attacks perpetrated against our homeland and our global interests."[120] The HSPD-10 prioritized the potential use of harmful biological agents exploited by terrorists or terrorism-sponsoring states as the new emerging threat to the United States. However, the HSPD-10 also indicated that the United States government began to subordinate the pursuit of general public health as a subcomponent of homeland security. In addition to the increasing threat of man-made biological threats, the outbreak of Severe Acute Respiratory Syndromes (SARS)

[119] United States General Accounting Office, "A report to the Honorable Bill Frist, Majority Leader, U.S. Senate, BIOTERRORISM: Public Health Response to Anthrax Incidents of 2001," GAO-04-152, Oct 2003

[120] The White House, Homeland Security Presidential Directive -10 (HSPD-10), "Biodefense for the 21st Century," Office of the Press Secretary, released April 28, 2004, available at https://fas.org/irp/offdocs/nspd/hspd-10.html

H5N1 avian influenza in 2003 further alerted the world to the threat of naturally-occurring infectious diseases. However, the HSPD-10 did not seriously consider the need for US public health response capabilities against global pandemic threats, instead it interpreted such global health threats as part of the US homeland security perspective. Focus on biodefence (measures to prepare for and respond to the intentional use of disease as a weapon) is the Bush's administration's main approach to biological threats.[121] It highlights the justification of biodefense through the homeland security prism in addressing that "disease outbreaks, whether natural or deliberate, respect no geographic or political borders," and "we must guard against the spread of potentially infectious agents from beyond our borders."[122] These sentences emphasizing "border" imply that biodefense is a type of policy tool designed to prevent and block the introduction or inflow of harmful biological agents into the US. In other words, the agenda set by HSPD-10 is the pursuit of security benefits to protect the borders of the homeland through public health benefits.

In the stream activities related to the homeland security domain, President George W. Bush signed the Project BioShield Act of 2004 into law, which facilitated the development of MCMs against CBRN agents (see Table 2-1). The Project BioShield Act was designed to strengthen public health emergency preparedness and response by ensuring the authority of the US government to develop, acquire, stockpile, and make available the medical countermeasures needed to protect the population against

[121] Gregory D. Koblentz, "From biodefence to biosecurity: the Obama administration's strategy for countering biological threats," *International Affairs,* Volume 88, Issue 1, January 2012, Pages 131–148,

[122] Homeland Security Presidential Directive -10 (HSPD-10), Ibid.

WMDs.[123]." The implementation of Project Bioshield consists of three major duties: funding needed countermeasures, facilitating research and development, and facilitating the use of MCMs in an emergency; the Emergency Use Authorization (EUA) is one of three main pillars of this Project Bioshield.[124]

Table 2-1: Summary of the US EUA[125]

Elements	United States Emergency Use Authorization
Responsible Authority	Secretary of HHS; delegated in part to FDA commissioner
Object	Specifically allowing the use of unapproved products or the unapproved use of approved products
Determination of Emergency	One of the following 3 criteria must be satisfied: 1. Secretary of HHS determines a public health emergency involving specified CBRN agent 2. Secretary of the DHS determines a potential domestic emergency involving potential risk of attack with specified CBRN agents 3. Secretary of the DOD determines a military emergency involving risk of attack to military force with specified CBRN agents
Declaration of Emergency	Secretary of HHS declares an emergency justifying an EUA

[123] MedicalCountermeasures.gov under the US Department of HHS, "Project BioShield Overview," last accessed on Dec 10, 2016, available at https://www.medicalcountermeasures.gov/barda/cbrn/project-bioshield-overview/

[124] "Fact Sheet of Project Bioshield Act," Association of State and Territorial Health Officials (ASTHO), available at https://www.astho.org/Programs/Preparedness/Public-Health-Emergency-Law/Emergency-Use-Authorization-Toolkit/Project-BioShield-Act-Fact-Sheet/

[125] Hisashi Urushihara et al "Emergency Authorization of Medical Products: Regulatory Challenges from the 2009 H1N1 Influenza Pandemic in Japan," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science,* Vol. 10 No. 4, 2012. Also see; The United States Congress, "Summary: S.15 — 108th Congress (2003-2004), Project BioShield Act of 2004," sponsored Senate Gregg Judd [R-NH], introduced March 11, 2003, available at https://www.congress.gov/bill/108th-congress/senate-bill/15; The US Food and Drug Administration, "Questions and answers for public health preparedness and response stakeholders," updated on January 2014, last accessed on Nov 7, 2016

Eligible Products	1. It is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious of life-threatening disease or condition caused by the agents specified in the declaration of emergency, based on the totality of scientific evidence available 2. The know and potential benefits outweigh the know and potential risks of the products when used 3. No alternative is available • Absolutely new medical products that have not been previously approved by any authority •Unapproved products that are approved in countries other than the home country • Unapproved indication of domestically approved products
Authorization	FDA commissioner may issue the EUA only if it is concluded that the above necessary criteria are met, after consultation with the directors of NIH and CDC
Termination	Expires 1 year after the declaration of emergency, unless previously revoked or renewed

Issuance of an EUA comes into force under Section 564 of the Federal Food, Drug, and Cosmetic (FD&C) Act in accordance with the passing of the Project BioShield Act of 2004. The US EUA became a legal framework in which the Food and Drug Administration (FDA) is allowed to approve the use of unapproved new MCMs or new off-label indications for previously approved MCMs during a declared emergency.

Inaugural Use of EUA: Anthrax Vaccine Absorbed (AVA) in 2005

Based on the EUA authority provided by the Project Bioshield Act, the US FDA approved the emergency use of an anthrax vaccine, Anthrax Vaccine Absorbed (AVA), on January 14, 2005 to protect against inhalation anthrax. On 10 December 2004, the Deputy Secretary of Defense determined that there was significant potential for a

military emergency in the form of an anthrax attack on US military forces, and Secretary of Health and Human Services declared an emergency justifying the authorization of the emergency use of AVA on the basis of the DoD's emergency determination.[126] In fact, AVA was neither a novel nor an investigational vaccine, but was already licensed by NIH in November 1970.

Under the Anthrax Vaccine Immunization Program (AVIP) of DoD, since 1998, AVA shots had been mandatory for 1.25 million US military personnel serving in high risk areas for an anthrax attack.[127] However, this program was suspended in October 2004 when a federal judge in DC ruled that the FDA did not follow appropriate procedures in approving and administrating the AVA for inhalational anthrax. The Court found that the main clinical trial of AVA did not conduct vaccine efficacy and safety tests for use against inhalational anthrax, but specifically for mill workers handling goat hair who may be exposed to the cutaneous form of anthrax.[128] Finally, US District Judge Emmet G. Sullivan ordered DoD to stop requiring AVA shots, because the vaccine was not specifically approved or labeled for use against inhalational anthrax. Based on the Court's decision, DoD asked HHS for emergency authority to resume their vaccination program under the Project Bioshield Act of 2004,

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[126] The U.S. Food and Drug Administration (FDA), "Authorization of Emergency Use of Anthrax Vaccine Adsorbed for Prevention of Inhalation Anthrax by Individuals at Heightened Risk of Exposure Due to Attack With Anthrax; Availability," doc cit: 70 FR 5452, published on Feb 2, 2005, available at https://www.federalregister.gov/documents/2005/02/02/05-2028/authorization-of-emergency-use-of-anthrax-vaccine-adsorbed-for-prevention-of-inhalation-anthrax-by

[127] Robert Roos, "FDA seeks comments on controversial anthrax vaccine," *CIDRAP*, Jan 13, 2005, available at https://www.cidrap.umn.edu/news-perspective/2005/01/fda-seeks-comments-controversial-anthrax-vaccine

[128] Roos, Robert. "Judge orders DoD to stop requiring anthrax shots," *CIDRAP,* Dec 23, 2003, available at https://www.cidrap.umn.edu/news-perspective/2003/12/judge-orders-dod-stop-requiring-anthrax-shots

and the FDA issued the emergency authorization on January 2005 under the condition that the shots must be voluntary.[129]

Evolution of the EUA: PAHPA and PAHPRA

Since the US EUA was born from the homeland security policy domain against CBRN threats, AVA was only item approved under the EUA policy. However, the scope of the EUA policy was expanded beyond CBRN threats to other kinds of public health threats in accordance with the revisions of biodefense policy. The Project Bioshield Act has evolved and revised by the Pandemic and All-Hazards Preparedness Act of 2006 (PAHPA) and the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA). EUA policy as one of the three main pillars of Project Bioshield Act has also been revised in response to the issues highlighted by new focusing events. Instead of creating a new separate policy domain related to public health emergencies, however, both the PAHPA of 2006 and the PAHPRA of 2013 authorized EUA policies as an extension of EUA from the Project Bioshield Act.

Although the scope of the EUA policy was expanded in accordance with the PAHPA of 2006 and the PAHPRA of 2013, the use of unlicensed MCMs as post-exposure prophylaxis (PEP) has kept in the bottom line of the newly expanded EUA policies.

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[129] Center for Infectious Disease Research and Policy (CIDRAP), "DoD to resume giving anthrax shots," May 4, 2005, available at https://www.cidrap.umn.edu/news-perspective/2005/05/dod-resume-giving-anthrax-shots

Table 2-2: EUA Items Under Biodefense Policies, 2004-2019

	Project Bioshield Act of 2004	PAHPA of 2006	PAHPRA of 2013
EUA Items	• Anthrax Vaccine Absorbed (AVA)	• Doxycycline mass dispensing for Anthrax, 2008 • H1N1 IVD / Antivirals, 2009	• MERS IVDs, 2013 • H7N9 IVDs, 2013 • Ebola IVDs, 2014 • EV-D68 IVDs, 2015 • Zika IVDs, 2016 • Atropine Auto-Injector, 2017 • Freeze Dried Plasma, 2018

In other words, these two revisions of the EUA policy shares the same path of development with its predecessor (the Project Bioshield Act of 2004), which HI scholars call *path dependency* – the patterns of institutional innovation often rely on or share the same pathway of development with the previous innovation. Under the PAHPA and PAHPRA, different types of MCMs can be granted EUA status by FDA as seen Table 2-2.

After Hurricane Katrina, another critical focusing event in the US, the existing homeland security domain from the Project Bioshield Act expanded its scope of policy from CBRN to all-hazards public health threats through the PAHPA of 2006. Also, the 2009 H1N1 global pandemic provided lessons that the US public health preparedness faces a lack of available testing tools as well as countermeasures for emerging infectious diseases.[130] Since the first EUA for IVD was granted during the H1N1

[130] Office of the Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services, "the National Health Security Strategy and Implementation Plan 2015-2018," page 1 available at https://www.phe.gov/Preparedness/planning/authority/nhss/Documents/nhss-ip.pdf

influenza pandemic, various IVD items have granted EUA status under the PAHPRA of 2013. The homeland security domain made by the Amerithrax began to embrace the concept of "emergency preparedness" after Hurricane Katrina and the concept of "disease control and prevention" after the H1N1 influenza pandemic. Together with these two revisions, the scope of EUA policy broadened from CBRN terrorism threats to other types of threats such as naturally-occurring and accidental events.

No wonder that multiple incidents have influenced the revisions of the EUA policy. The first paragraph of the National Health Security Strategy of the United States mentions about multiple incidents such as the September 11, 2001, attacks and the 2001 anthrax attacks; the outbreak of Severe Acute Respiratory Syndrome (SARS); multiple hurricanes; and the 2009 H1N1 influenza outbreak which provides valuable lessons to facilitate the United States to develop its biodefense strategy.[131] Indeed, lessons learned from Hurricane Katrina and 2009 H1N1 pandemic have affected the revision of EUA policy leading the PAHPA of 2006 and the PAHPRA of 2013 respectively. The catastrophic outcomes from Hurricane Katrina revealed that the current MCM policy under the Project Bioshield Act cannot be met with stable and appropriate medical supplies during public health emergency situations. Because the scope of Project Bioshield Act was limited to CBRN threats only, the EUA under the Project Bioshield Act could not fulfil the function of MCM supplies for victims of natural disasters as well as children. Musmar (2017) points out that there was a severe shortage of medical supplies dedicated to children during public health responses against Hurricane Katrina and Rita in 2005, which led to discuss 'emergency preparedness'

[131]Office of the Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services "the National Health Security Strategy of the United States," December 2009.

issues including emergency pediatric MCM policies. As Danzig describes, the development of US biodefense policies has followed a pattern of "punctuated evolution,"[132] in that certain exogenous shocks have brought out new biodefense policies or revisions of existing policies correspondingly. Along with Hurricane Katrina as a focusing event leading the revision of the 2006 PAHPA, Musmar illustrates that the 2009 H1N1 influenza pandemic played a role of another focusing event leading the revision of the 2013 PAHPRA in terms of the pediatric MCM policies. [133]

PAHPA and emergency preparedness domain

The US FDA indicates that PAHPA was enacted "to improve the nation's public health and medical preparedness and response capabilities for emergencies, whether deliberate, accidental, or natural."[134] To implement this new all-hazards approach, the 2006 PAHPA amended the Public Health Service Act to create the Assistant Secretary for Preparedness and Response (ASPR), a new position, within HHS. The main mission of the ASPR is to strengthen the nation's public health and medical infrastructure and capabilities, which are necessary to quickly mobilize a coordinated national response to disasters and emergencies vital to US national security.[135] The establishment of Biomedical Advanced Research and Development Authority (BARDA) was another

[132] Richard Danzig, "A decade of countering bioterrorism: Incremental progress, fundamental failings," *Biosecurity and Bioterrorism, 10*(1), 49–54.
[133] Jomana F. Musmar, "The Path to PAHPRA: The Evolution of Pediatric Biodefense Legislation and Medical Countermeasure Development," (PhD diss., George Mason University, 2017)
[134] The US Food &Drug Administration (FDA), "MCM-Related Counterterrorism Legislation," accessed on April 10, 2020, available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/mcm-related-counterterrorism-legislation
[135] Office of the Assistant Secretary for Preparedness and Response (ASPR), US Department of Health & Human Services, Mission and Key Priorities, webpage last reviewed on April 3, 2019, available at https://www.phe.gov/about/aspr/Pages/default.aspx

key feature of the PAHPA facilitating the nation's MCM-oriented preparedness and response capabilities for emergencies.

The list of EUA items under the PAHPA illustrates that PAHPA is an extension of the Project Bioshield Act. The FDA authorized EUAs for doxycycline (anthrax) and peramivir (H1N1) under the PAHPA. The EUA for doxycycline implies the PAHPA holds the same homeland security policy domain as the Project Bioshield Act, and the EUA for peramivir shows that the PAHPA extended its scope beyond CBRN threats to public health threats. During the H1N1 pandemic, the FDA authorized an EUA for the novel H1N1 antiviral (peramivir) for the first situation of a non-CBRN threat. Along with the EUA issuance for peramivir, two EUA models for doxycycline (the US Postal Service and City Readiness Initiatives) were granted. The EUA for doxycycline was combined with mass dispensing models through the US Postal Service and City Readiness Initiatives. These two doxycycline EUA models illustrated that the US biodefense community finally reached an important conclusion from the 2001 anthrax letter attacks: the need to strengthen mass dispensing of PEPs.

In 2008, the Secretary of DHS determined, pursuant to section 564(b)(1)(A) of the FD&C Act, that there is significant potential for a domestic emergency involving a heightened risk of an attack with *B. anthracis*.[136] Under the PAHPA of 2006, FDA issued anthrax PEP models for mass dispensing doxycycline in 2008. On 1 October 2008, pursuant to section 564(b) of the Act and on the basis of the DHS's determination, the Secretary of HHS declared an emergency justifying the authorization of the

[136] The U.S. Department of Homeland Security (DHS), Memorandum from Michael Chertoff to Michael O. Leavitt, Determination Pursuant to §564 of the Federal Food, Drug, and Cosmetic Act. September 23, 2008

emergency use of doxycycline hyclate tablets.[137] On the same day (1 October), BARDA requested an EUA for doxycycline hyclate tablet emergency kits for eligible USPS participants in City Readiness Initiatives (CRI) and their household members. CRI involves 72 major metropolitan areas and all 50 states, and primarily aims to develop the mass capabilities to provide PEP to 100% of the identified population within 48 hours of notification to do so. The United States Postal Service (USPS) is one of the key players in the CRI plan because USPS can deliver antimirobials - doxycycline hyclate tablets, in the case of an anthrax attack - and its medical instructions to residential households within 48 hours. However, doxycycline hyclate tablets were not approved with the allowance provide by written information, including emergency use instructions, which are authorized under this EUA.[138] Therefore, the EUA for doxycycline hyclate tablets, in conjunction with the CRI program, completed the mission of mass and timely distribution of PEPs.

PAHPRA and disease control and prevention domain

As the 2009 National Health Security Strategy addresses, the experiences with 2009 H1N1 influenza not only reveals gaps and shortfalls in emergency preparedness and response capabilities of the United States, but also gives a warning that the outbreak of an infectious disease in one area of the world will often very quickly affect distant areas of the globe.[139] At the peak of the H1N1 influenza pandemic, Obama

[137] The US Food and Drug Administration, "a Letter from FDA commissioner to CDC Director," July 21, 2011, available at https://www.fda.gov/media/81453/download Also, see; Declaration of Emergency Pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 360 bbb-3(b) (Oct. 1, 2008).

[138] The US Food &Drug Administration (FDA), *doc:* 73 FR 62507, Ibid. 2008

[139] Office of the Assistant Secretary for Preparedness and Response (ASPR) U.S. Department of Health and Human Services, "the National Health Security Strategy of the United States," December 2009.

administration announced its first biosecurity strategy, entitled "the National Strategy for Countering Biological Threats," which is different from preceding strategy based on the concept of biodefense. While the existing biodefense strategy has focused on preparing for and responding to public health threats, the Obama's biosecurity strategy gives the emphasis on prevention efforts.[140] As a result. the PAHPA of 2006 was reauthorized by the name of PAHPRA of 2013, which aims to extend, fund, and improve several programs designed to prepare for any public health emergency by the preceding act. Indeed, the PAHPRA of 2013 reinforced the mission of mass and timely dispensing of PEPs, and it extended its scope of policy beyond that of the PAHPA of 2006.

The list of EUA items under the PAHRPA also illustrates that PAHPRA is an extension of the Project Bioshield Act and the PAHPA of 2006. Beyond the PAHPA of 2006's scope that aims to cover natural occurring threats, one notable change is that the PAHPRA of 2013 attempts to cover a much broader range of threats including infectious disease threats (pandemic and epidemic). Of course, the term of 'natural occurring' is more general and contains broader public health threats such as tornado or flood, this approach is limited to respond against disasters causing public health threats. The 2009 National Health Security Strategy clearly indicates that "PAHPA addresses their concern about a possible influenza pandemic, which subsequently emerged in 2009."[141] In order to fill the gap revealed by the 2009 Influenza outbreak, it is necessary for the US public health authority to consider effective measures against

[140] Gregory D. Koblentz, "From biodefence to biosecurity: the Obama administration's strategy for countering biological threats," *International Affairs,* Volume 88, Issue 1, January 2012, Pages 131–148,

[141] Office of the Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services, "the National Health Security Strategy of the United States," December 2009

the immediate public health and medical consequences of anticipated and actual public health threats from infectious disease outbreaks. In 2012, a year before the 2013 PAHPRA passed, HHS announced the 2012 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy that clearly illustrate the change of medical countermeasure landscape in addressing that the 2009 H1N1 influenza pandemic demonstrated continuing needs to accelerate and improve disease detection capabilities. [142] Along with the emphasis on disease detection capabilities for prevention efforts, the agenda of disease control and prevention was emerged. It is interesting to note that many unapproved in-vitro diagnostic kits (IVDs) related to pandemic and infectious diseases prevention purposes have been authorized for emergency use as seen Table 9: MERS IVD in 2013, H7N9 IVDs in 2013, Ebola IVDs in 2014, EV-D68 IVD in 2015, and Zika IVDs in 2016.

Although the US EUA began to embrace the disease control and prevention domain by the PAHPRA, the United States did not fully integrate the EUA policy with its public health systems. Since the legislation of the PAHPRA, IVD's are listed as EUA-items to deal with public health emergency. However, the 2016 Zika outbreak in the United States demonstrated that the EUA for Zika IVDs could not play a significant role in the Zika control and prevention practices in the United States. The US Government Accountability Office pointed out three main factors resulting in the failure of the US Zika surveillance and response: first, the mildness and asymptomatic features of Zika disease led people not to seek medical care and diagnostic testing; second, the limited Zika

[142] The U.S. Department of Health and Human Services, "2012 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy," p.9-10, available at https://www.phe.gov/Preparedness/mcm/phemce/Documents/2012-PHEMCE-Strategy.pdf

virus diagnostic testing capacity affected the accuracy of the number of the Zika cases; and third, surveillance was incomplete due to the low availability of diagnostic facilities.[143] As a result, the United States was unable to conduct the large- scale use of the Zika IVDs and hardly integrated these tests with the US public health surveillance systems, even though the Zika IVDs were developed and granted the EUA status in a timely manner. Later, during the COVID-19 pandemic in 2020, SARS-CoV-2 exhibited a similar epidemiology, with non-specific symptoms as well as asymptomatic and pre-symptomatic transmission, but the United States repeated its past mistake of ignoring large-scale testing practices. Chapter 4 will provide a detailed account for how and why the United States failed to conduct mass-testing in the early phase of the COVID-19 pandemic.

Homeland Security centric Biodefense Policy

The United States had conducted some National Exercises which involve simulated CBRN-terrorist events; TOPOFF 1~3, and Dark Winter. The Top Officials exercise (TOPOFF) that DHS tested how key government officials respond to simulated terrorist attacks, which aims to strengthen the Nation's capacity to prepare for, prevent, respond to, and recover from large-scale terrorist acts.[144] Dark Winter was an exercise that tested strategic level responses (the National Security Council) to a simulated smallpox attack on the United States. During the first exercise (TOPOFF 1 in May

[143] The United States Government Accountability Office, "Report to Congressional Requesters, - Emerging Infectious Diseases; Actions Needed to Address the Challenges of Responding to Zika Virus Disease Outbreaks," GAO-17-445, May 2017, p.25-26

[144] Office of Inspector General, DHS, "DHS Efforts to Address Lessons Learned in the Aftermath of Top Officials Exercises," OIG-09-53, April 2009

2000, Denver, before the 2001 anthrax letter attack), the United States learned rapid and accurate laboratory diagnostics capabilities are significant to accomplish disease identification mission prerequisite to treatment options and prediction of the disease spread.[145] Although all lessons learned from these exercises highlight the importance of MCM distribution for treatment mission, no cases address the need for large-scale testing practices.

Rather, quick and accurate identification of a pathogenic organism used for bioterrorism is much essential. Many experts also highlight that laboratories are a key component in bioterrorism preparedness to determine bioterrorism agents. [146] Laboratory diagnostics plays a role of early warning and detecting in the case of public health emergency (particularly, CBRN threats), which facilitates timely response by treatment or prophylaxis.[147] Although the PAHPRA of 2013 expands the scope of EUA policy to infectious diseases, the homeland security tradition of EUA policy – that is PEP – keeps strengthened.

Later, the PEP programs for doxycycline such as City Readiness Initiatives are reinforced by the emergency dispensing order and emergency use instruction (EUI) granted by the PAHPRA of 2013. Both the emergency dispensing order and EUI are advanced forms of the biodefense policy. The FDA explained that the emergency

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[145] Lt Col Tasha L. Pravecek, USAF, BSC, "Lest We Forget: A Critical Analysis of Bioterrorist Incidents, National Exercises, and U.S. Prevention, Response and Recovery Strategies," *US Air Force Counterproliferation Center Future Warfare Series* No. 50

[146] Congress of the United States, House of Representatives, "Memorandum to Members of the Subcommittee on National Security, Veterans Affairs, and International Relations," in Congress Hearing *"Briefing memorandum for the hearing, Combating Terrorism: Federal Response to a Biological Weapons Attack."* July 23, 2001

[147] Congressional testimony, James M. Hughes, M.D., a Director in National Center for Infectious Diseases, "Briefing memorandum for the hearing, Combating Terrorism: Federal Response to a Biological Weapons Attack." Congress Hearing for Committee on Government Reform, U.S. House of Representatives, July 23, 2001

dispensing order authority can "strengthen the nation's public health protections against CBRN threats by facilitating the availability and use of eligible, approved MCMs needed during public health emergencies without FDA needing to issue an Emergency Use Authorization."[148] And, the EUI authority allows the CDC director to facilitate "the availability of streamlined information about the use of eligible, approved MCMs needed during public health emergencies without FDA needing to issue an Emergency Use Authorization."[149] Therefore, on 13 April 2016, the issuance of an Emergency Dispensing Order for doxycycline in support of the EUI for doxycycline, which replaced the previous EUA for doxycycline mass dispensing for post-exposure prophylaxis to inhalational anthrax. Moreover, on the same day, the Emergency Dispensing Order and EUI for ciprofloxacin mass dispensing as a PEP for inhalational anthrax were authorized.[150]

Along with the US biodefense has emerged from the homeland security domain, the US FDA and CDC become primary federal agencies holding exclusive public health authority. For example, issuing EUA for dispensing unapproved MCMs for PEP is an exclusive federal authority in response to public health emergency. However, the exclusive EUA authority reveals weaknesses in EUA for diagnostic kits. In the United States, the FDA basically ruled out state and commercial labs and private companies

[148] The US Food and Drug Administration (FDA), "Emergency Dispensing Orders," website content current as of April 30 ,2019, available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-dispensing-orders

[149]The US Food and Drug Administration (FDA), "Emergency Dispensing Orders," website content current as of April 30 ,2019, available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-dispensing-orders

[150] See: Letter for issuing EUI, "RE: Order Permitting Emergency Dispensing of Oral Formulations of Doxycycline and Waiver of CGMP Requirements during an Anthrax Emergency," April 13, 2016, available at https://www.fda.gov/media/97089/download and also see; Letter for issuing EUI, "RE: Order Permitting Emergency Dispensing of Oral Formulations of Ciprofloxacin and Waiver of CGMP Requirements during an Anthrax Emergency," April 13, 2016, available at https://www.fda.gov/media/97098/download

from developing and manufacturing their own testing kits when it issued the EUA policy. As a main research body of the FDA, the CDC is in charge of researching and analyzing pathogens/agents causing public health emergency. Unlike the Korean CDC, however, the US CDC is the primary federal agency of developing diagnostic kits in response to public health emergency. Therefore, the US EUA policy is for the emergency use of CDC-made kits to distribute to other US laboratories in local, rather than stimulating private sectors for developing and mass-production of diagnostic kits. During the Zika virus case, indeed, a CDC's media statement clearly announced that "EUA will potentially allow CDC to more rapidly perform testing to detect acute Zika virus infection."[151]

The FDA is the primary federal agency that verifies and evaluates the efficacy and effectiveness of new diagnostic kits. Since CDC-made kits received EUA status, private sectors submit EUA applications for their own new items. To verify and evaluate the new items developed by private sectors before issuing EUAs, the FDA adopts CDC's research results (CDC-made diagnostic kit) as a baseline of testing protocols for the development of new testing kits from private sectors. In other words, a method of a CDC-made diagnostic kit first developed in the United States becomes a standard FDA verification and evaluation protocols for developing diagnostic kits. In the case of Zika virus, for example, the first CDC-made kit used S1 and S2 as reference materials.[152] The FDA clearly describes a guideline for developers in addressing that "IVD developers as part of their EUA conditions are required to test an FDA Reference

[151] The US CDC, "CDC Laboratory Test for Zika Virus Authorized for Emergency Use by FDA," media released on March 18, 2016, available at https://www.cdc.gov/media/releases/2016/s0318-zika-lab-test.html

[152] The US CDC, "Instruction For Use (IFU) for "Trioplex Real-time RT-PCR Assay," uploaded in the FDA website, available at https://www.fda.gov/media/123606/download

Material Panel that includes two different Zika virus strains from the Asian lineage (S1 and S2), using an FDA protocol that included a sensitivity evaluation."[153]

Due to the exclusive testing authority of the US CDC, EUAs have been always firstly granted to CDC-made kits; only except the Ebola virus case that the FDA issued an EUA to authorize the emergency use of the U.S. Department of Defense (DoD) EZ1 Real-time RT-PCR Assay for the presumptive detection of Ebola Zaire virus. For example, CDC-made kits have earned EUA status first in every public health emergency case (2009 H1N1, 2013 H7N9, 2013 MERS, 2015 EV-D68, and 2016 Zika).[154] Given the fact that FDA-clearance is required to submit EUA applications, manufacturers and labs should meet FDA requirements and follow FDA protocols developed by the CDC. As a result, private sectors are basically ruled out when establishing standards for verification and evaluation of diagnostic kits, and should follow FDA protocols made by CDC. This exclusive authority of CDC hampers timely public health response if CDC makes mistakes, thus causing the shortfall of testing during the COVID-19 pandemic later.

Conclusion

The terrorist attacks on September 11th led to the formation of a new policy domain the United States called homeland security. As a result of the anthrax letter

[153] The US FDA, "Zika Virus Emergency Use Authorization," content current as of March 1, 2021, available at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices

[154] Lists of EUA items (diagnostic kits) are available at the FDA Archive website; see, the US FDA, "Emergency Use Authorizations for Medical Devices," content current as of March 1, 2021, available at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices

attacks which occurred shortly thereafter in the context of the "global war on terror," biodefense was incorporated into the homeland security domain. Through the theoretical lens of historical institutionalism, the 2001 anthrax letter attack is obviously a critical juncture that was a decisive moment resulting in institutional innovation. The EUA is the most representative case of the post-Amerithrax movement that a new institution – biodefense – was established based on the concept of homeland security. In addition to the role of the exogenous shock (Amerithrax), Birkland's model contributes to explaining how endogenous factors (DHS) relevant to the exogenous shock worked for the post-event institutional changes (EUA). The emergence of the homeland security domain marks a key linkage between exogenous and endogenous factors when institutionalizing the US biodefense system. As a result, biodefense policies (e.g. EUA) that would once have been considered public health priorities were developed and implemented primarily in the context of homeland security and broader efforts to prepare for and respond to the threat of CBRN terrorism.

Moreover, path-dependency in historical institutionalism narratives explains the evolutionary path of the US EUA. New policy domains and goals by PAHPA and PAHPRA did not replace the existing homeland security domain; rather, these two converged and strengthened the previous homeland security domain in a 'self-reinforcing' manner. Although the US EUA policy was eventually expanded under PAHPA and the PAHPRA to cover all-hazards, from CBRN threats to infectious diseases, the implementation of the EUA policy still gave more weight to counter-CBRN activities and goals. Consequently, the homeland security domain embraced much of the public health benefits that protect the population from CBRN and infectious disease threats in order to protect the US and its people.

Given that the EUA is primarily homeland security policy with public health objectives, US policymakers and public health authorities perceive the use of unlicensed MCMs as a defensive measure against low-probability/high-consequence events. In other words, the US EUA policy was the outcome of the US homeland security efforts that pursued public health benefits by countering CBRN terrorism. This perception is underscored by the phrase "preparedness and response," which was used frequently after Amerithrax and emphasizes the use of unlicensed MCMs for treatment purposes, as post-exposure prophylaxis (PEPs).

CHAPTER 3: Case Study of the South Korea EUA Policy

Introduction

In May 2015, the Middle East Respiratory Syndrome (MERS) which had been causing sporadic outbreaks in Saudi Arabia and other Gulf Arab states arrived in South Korea. A businessman returning from Bahrain on May 4, 2015 felt sick, but his diagnosis as the first Korean case of MERS was not confirmed by the Korea Center for Disease Control and Prevention (KCDC) until May 20. The sixteen days between the onset of the businessman's illness and his diagnosis caused an unprecedent disease outbreak and social chaos in South Korea. Seven cases of MERS in South Korea were confirmed on May 20, thirteen cases were more confirmed on May 29, and the number of cases continued to grow exponentially. By the end of the MERS outbreak in South Korea, 186 total cases were confirmed, 38 people died, and more than 16,000 individuals were quarantined.

The scale of this outbreak, the largest outside of the Middle East, was in part a result of the time it took for one businessman to be diagnosed and isolated after he became symptomatic with a high fever and other flu-like symptoms. As a result, the businessman (patient zero) infected 82 people across three different hospitals during

those sixteen days with no disease prevention responses.[155] This chapter underscores several issues that contributed to this outbreak including nosocomial infection, super spreader, and the lack of epidemic information. Due to these issues during the MERS outbreak, a new agenda - disease containment – had raised in the Korea society. As a result, the Korea National Assembly revised the Infectious Disease Control and Prevention Act to better foster disease containment practices. These revisions stem from the lessons learned during the MERS outbreak. For example, one of the most prominent features of the newly revised Act is the strengthening of epidemiological investigation capabilities and the expansion of KCDC's authorities.

This chapter determines that the features of the Korean EUA policy have generated by lessons learned from the MERS outbreak. While the post-Amerithrax movement of the United States developed a new public health goal for homeland security benefits (public health preparedness and response to CBRN threats), Korea developed a new public health goal for disease containment benefits during the MERS outbreak, that is detection and diagnosis of infectious disease. Accordingly, the US EUA features the use of post-exposure countermeasures to protect population as the previous chapter determines, and thus this chapter illustrates the Korean EUA specializes the use of in-vitro diagnostic kits to detect and diagnose infectious diseases. Moreover, the Korean EUA has evolved from a policy targeting only infectious disease to radioactive threats. In other words, the Korean EUA expands its detecting and diagnosing range from infectious disease to radioactive threats. Therefore, this chapter shows that the Korean EUA was born as a general public health policy with disease

[155] Kate Kelland, "Study of South Korean MERS outbreak finds 'super-spreader' patient," *Reuters,* posted on July 8, 2016, available at https://www.reuters.com/article/us-health-southkorea-mers-idUSKCN0ZO2JU

control and prevention objectives. This Korean EUA has evolved into a surveillance policy for disease containment not only against emerging infectious disease but also against radioactive threats.

Focusing Event: Middle East Respiratory Syndrome (MERS) of 2015

A businessman returning from Bahrain on May 4, 2015 felt sick. Although the businessman visited three different hospitals, no medical professionals suspected that he may have been infected with MERS. The businessman had just returned from a trip to the Middle East; but he had been in Bahrain, not Saudi Arabia or other countries considered to be at high risk of MERS. In 2015, South Korea relied on the WHO's Global Public Health Intelligence Network (GPHIN) for early warning of foreign disease outbreaks.[156] Based on the GPHIN sources, Bahrain was not on the WHO's list of countries with high risk of MERS, because no cases had been reported in the nation despite of its geographic proximity to Saudi Arabia, the largest MERS outbreak country. Therefore, the South Korean government did not include Bahrain as a MERS high risk country. The first case of MERS infection would not be reported in Bahrain until April 10, 2016.[157]

By visiting so many hospitals while the businessman was contagious as seeing Figure 3-1, he unknowingly infected many healthcare workers and patients with MERS. MERS-CoV, the virus that causes MERS, is a member of the *coronaviridae* family,

[156] World Health Organization (WHO), "2020 Epidemic intelligence - systematic event detection," accessed on Feb 28, 2020, available at https://www.who.int/csr/alertresponse/epidemicintelligence/en/
[157] World Health Organization (WHO), "Middle East respiratory syndrome coronavirus (MERS-CoV) – Bahrain," April 25, 2016, available at https://www.who.int/csr/don/25-april-2016-mers-bahrain/en/

which amplified nosocomial infection within hospitals.[158] In general, hospitals are hubs for sick people who are vulnerable to any kind of infectious diseases. The unique healthcare culture of Korea is a sociological factor that contributed to be the disease multiplication in hospitals.[159]

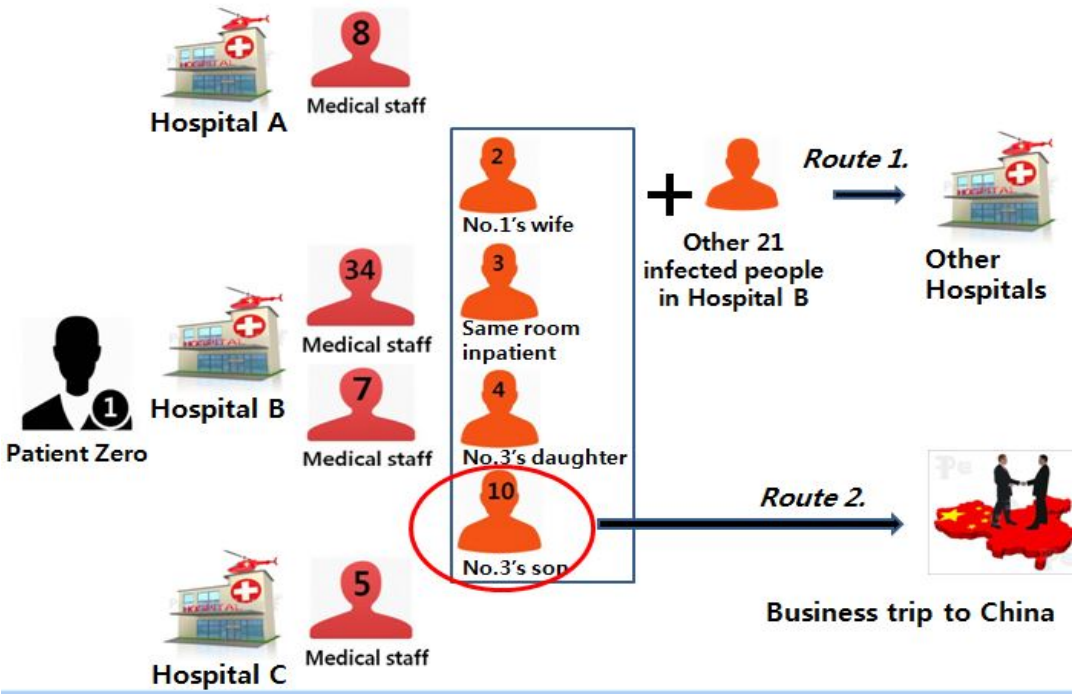

Figure 3-1: Flow Chart of MERS infections in South Korea.[160]

[158] Maimuna S. Majumder, et al. (2017), "Nosocomial amplification of MERS-coronavirus in South Korea 2015," *Trans R Soc Trop Med Hyg.* 2017 Jun; 111(6): 261–269. Published online 2017 Oct 16, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6257029/

[159] Eun-Sung Kim, "A Social Analysis of the Limitation of Governmental MERS Risk Communication," *Crisis and Emergency Management: Theory and Praxis*, 2015, 11(10), pp.91-109

[160] The Figure 3-1 is based on the official patient numbering by KCDC and press released information. Also see, 조선일보, [메르스와의 전쟁] 1 호 환자·2 차 감염자의 병원 이동 경로 따라 메르스 환자 발생 in English, [Chosun Ilbo, "Battle with MERS", the MERS infections in accordance with the routes of visiting hospitals by patient zero and secondary infections], Final updated on June 5, 2015, available at http://news.chosun.com/site/data/html_dir/2015/06/05/2015060500255.html

Instead of managing health with a family doctor, for example, Koreans usually seek and visit various doctors specific to their symptoms or needs, a process called "Doctor Shopping." Also, single-occupied rooms in a hospital are limited and expensive, so many patients (usually four to six people) share an in-patient room. Korea has a unique family nursing culture in which either at least one family member or a residential care worker hired by the family stays with patients 24/7 in the hospital room. Therefore, the population density of hospital rooms is usually high as a result of multiple patients, their families, residential care workers, and medical staff. Hospitals unwittingly became the major routes or places of transmission for the 2015 MERS outbreak in South Korea. For example, 85 of the 186 confirmed MERS cases occurred among healthcare workers at Samsung Hospital, the largest general hospital in South Korea. Also, St. Mary's Hospital in Pyeongtaek, one of the three hospitals visited by patient zero, became the most notorious virus breeding spot infecting 28 people.

In addition to the nosocomial infection spreading within hospitals, the businessman (patient zero or index patient) started a chain reaction of disease transmission in multiple hospitals, rendering him a "super-spreader."[161] This chain reaction of MERS infections further perpetuated transmission as those infected persons sought medical attention at other facilities (see Figure 3-1). Route 1 in Figure 3-1 demonstrates that some MERS patients became new super-spreaders, causing an exponential increase in MERS infections. When patient zero visited three hospitals, he infected four medical staff members, case 8 in hospital A, cases 7 and 34 in hospital B, and case 5 in hospital C. When patient zero was in hospital B, he infected other admitted

[161] Kate Kelland, "Study of South Korean MERS outbreak finds 'super-spreader' patient," *Reuters,* posted on July 8, 2016, available at https://www.reuters.com/article/us-health-southkorea-mers-idUSKCN0ZO2JU

patients and their family members in a hospital room. All of these infected people were moved to other hospitals and the chain reaction of MERS transmission began again.

As route 2 demonstrates, it was possible to stop transmission of MERS if infected and exposed individuals were identified early enough and properly quarantined and isolated. Patient 10 went on a business trip to China despite medical professionals discouraging travel. The KCDC warned the Chinese government which quarantined all passengers, including patient 10, at the airport. This international cooperation provided a significant lesson that quick identification of patients can contribute to the successful prevention of chain reaction of disease transmission.

Impacts of the 2015 MERS outbreak

Due to nosocomial infections and super-spreader issues, Korean society descended into chaos; no one knew which hospitals were safe and no one knew who are infected and spread the disease. In a state of chaos, countless volumes of fake news circulated via the Internet and rumors snowballed. Information from unidentified sources designated one hospital as a place that a MERS patient visited, or a person who intentionally ignored the government's quarantine order, thereby spreading the disease.[162] The government warned that it would penalize distributers of fake news and rumors, but struggled to assuage public anxiety and social chaos. Without accurate

[162] 김정균 " 메르스 공포 부추기는 유언비어 급속확산" 서울경제, in English [Jeong-gyun Kim, "Rapid Spread of rumor inciting the fear of MERS," *Seoul Economic Daily*], May 29, 2015, last accessed on June 15, 2020, available at https://news.naver.com/main/read.nhn?mode=LSD&mid=sec&sid1=102&oid=011&aid=0002690012 ; also see, Jeyup S. Kwaak, "MERS, Rumors Spread in South Korea," *The Wall Street Journal*, June 5, 2015, last accessed on June 15, 2020, available at https://www.wsj.com/articles/mers-rumors-spread-in-south-korea-1433484078 ;or see, 한지훈, "국민 겁주는 메르스괴담 처벌 가능할까?" 연합뉴스, in English [Ji-hoon Han, "Rumors of the MERS scaring people can be punishable?" *Yonhap News Agency*] June 1, 2015, last accessed on June 15, 2020, available at https://www.yna.co.kr/view/AKR20150601086600017

information about the MERS epidemic situation including hospital information, sick people who should meet doctors hesitated to go hospitals. As a result, Ministry of Health and Welfare announced a new policy designating some hospitals as "MERS-Free hospitals" which establish a triage system separating patients with flu-like symptoms with other types of patients.[163]

To calm public concern down, moreover, Korean government began disclose epidemic information such as hospital names and movement history of patients. Seoul, the capital city of South Korea, where the Samsung Medical Center is located, suffered the most serious MERS outbreak. Samsung Medical Center was at the heart of the controversy, but official references to the name of the hospital was restricted because of privacy issues. The mayor of Seoul, Won-sun Park, made several requests to the Ministry of Health and Welfare to share on-going MERS epidemic information, but these requests were denied. As the epidemic situation got worsen, the mayor Park decided to take special measures. At midnight on 4 June, the mayor Park held an emergency press conference inviting all major news media. Based on the Seoul government's investigation results, the mayor presented the movement history of patient 35 (a medical staff member at the Samsung Medical Center) and issued an executive order for self-quarantine of 1,565 people who participated in a same event with patient 35.[164] As a result of the information disclosure by the Seoul government and public pressure, the Ministry of Health and Welfare released information about hospitals with MERS cases on 7 June. On the same day, the director of the Samsung

[163] MBC, 보건복지부, 메르스 진료 국민안심병원 오늘 발표, 2015.06.12, in English, [MBC, "Ministry of Health and Welfare announces MERS-Free hospitals today," June 12, 2015], available at https://news.naver.com/main/read.nhn?mode=LPOD&mid=tvh&oid=214&aid=0000506240

[164] Movement history between May 29-31 – from a day that the patient may be exposed to the MERS virus to a day that the patient entered self-quarantine.

Medical Center held a press conference and presented the current state of affairs as well as its countermeasure plans. Interestingly, once information on the extent of the epidemic was shared with the public, the MERS epidemic began to subside. The government announced the *de facto* end of the MERS outbreak in Korea on July 28. Figure 3-2 below shows the epidemic curve of MERS cases in Korea.

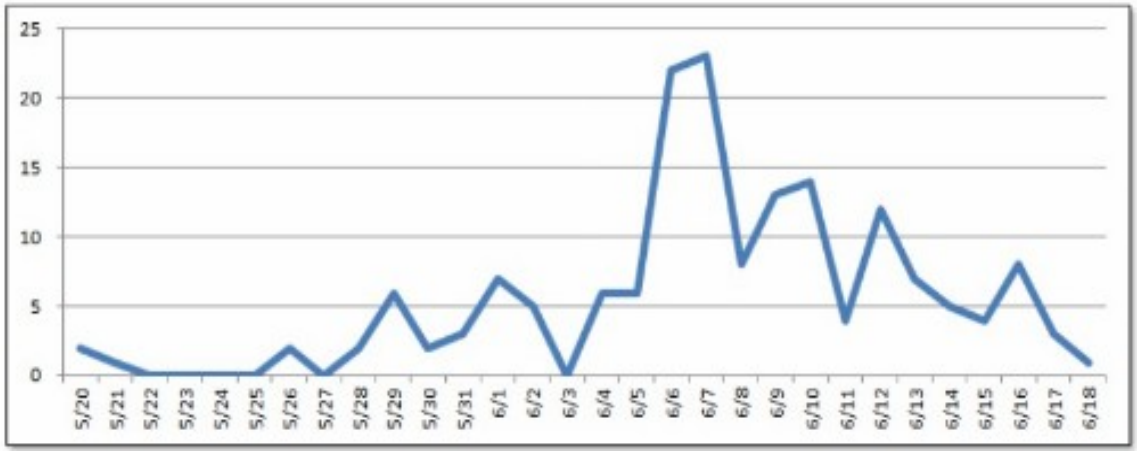

Figure 3-2: The Epidemic Curve of the MERS in Korea[165]

Despite the three months outbreak, the 2015 MERS inflicted huge damages on the Korean society. According to a report that KCDC submitted to National Assembly, overall economic cost made by the 2015 MERS outbreak is estimated 10.8 trillion won (USD 10.8 billion).[166] This cost includes not only direct cost caused by the disease (e.g. income loss or medical cost), but also indirect cost to Korean economy (e.g.

[165] Data retrieved from Ministry of Health and Welfare; seehttp://www.mdtoday.co.kr/mdtoday/index.html?no=255662

[166] Simply calculated by an exchange rate of $1 for 1,000 won. Exchange rate usually ranges from $1 for 1,000 won to $1 for 1,200 won.

restaurant business or hotel industry), and 70,000 jobs were lost during 3 months of the epidemic outbreak.[167]

Lessons Learned from the MERS Outbreak

The most important lesson learned from the MERS outbreak was the super-spreader risk associated with delayed communication and action. When, as is the case with MERS, no medical treatments are available, quick detection (diagnosis) and timely response (quarantine or isolation) are the most important public health practices to prevent the emergence of super-spreaders. Any delay in diagnosing, treating, and isolating an infected patient could unintentionally and unknowingly allow that patient to become a super-spreader. Missing a super-spreader makes it much harder to identify and cut a transmission chain.

Mobilization of the Public health Group

As seen in Figure 3-3, the Korea Society of Infectious Disease emphasized the role of five super-spreaders during the MERS outbreak. Case 1 (or patient zero) infected 28 people, case 14 infected 85 people, case 15 infected 6 people, case 16 infected 23 people, and case 76 infected 11 people. These five super-spreaders created 82.3% of the total confirmed cases (153 cases of 186 total cases).

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[167] 신종 감염병으로 인한 사회경제적 피해 비용 추계 및 신종 감염병 대응 사회투자의 영향 연구` 결과 보고서 (질병관리본부, 2020), 인용 김연주 "확진자 186 명이던 2015 년 메르스 피해약 11 조…코로나 19 는?" 매일경제, 2020.06.07 , in English ["Socio-Economic damage costs caused by new pandemic and research for the impact of social investments in response to new pandemic" (Korea Center for Disease Control and Prevention, 2020) cited in Yeonju Kim, "11 trillion won cost during the 2015 MERS outbreak with 186 cases…how about COVID-19?" *Maeil Business,* June 7, 2020, available at https://www.mk.co.kr/news/economy/view/2020/06/581978/

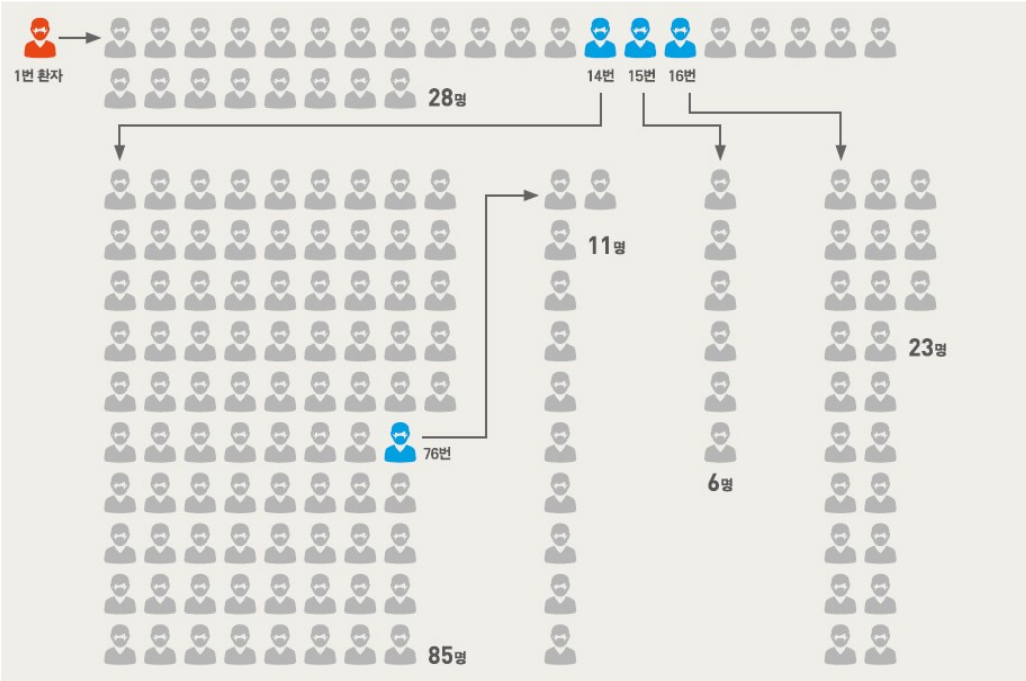


Figure 3-3: Route of MERS transmission[168]

The Korea National Assembly established a Special Committee for MERS Prevention in July 2015, which held congressional hearings nine times during the MERS outbreak. The main purpose of the Special Committee was to determine why mass infections were occurring in hospitals and what the ministries responsible for the MERS outbreak did to contain the outbreak. Directors and physicians at the hospitals where the MERS infection had occurred were summoned for hearings where they were asked about the results of epidemiological investigation into mass-infections at their hospitals.[169] Also, many higher

[168] 대한감염학회, "대한감염학회 백서; 메르스연대기," in English [Korea Society of Infectious Disease (KSID), "KSID White Paper on Chronicles of MERS,"] p.25

[169] 제 335 회 국회, 제 5 차 중동호흡기증후군대책 특별위원회 회의록, 2015 년 7 월 10 일 in Eng [335th National Assembly of the Republic of Korea, Transcript of the 5th meeting of MERS Special Committee, July 10, 2015]; also see, 제 335 회 국회, 제 6 차 중동호흡기 증후군 대책 특별위원회

officers in the ministries responsible for the MERS outbreak, such as Minister of Health and Welfare and Minister of Public Safety and Security, were questioned about their failures to trace disease transmissions.[170] Finally, the Special Committee passed a resolution for "reforming national infection prevention and control system" and requested an investigation by the Board of Audit and Inspection (counterpart to the US General Accounting Office) **in** the Assembly plenary session in August.[171]

Based on the Congressional resolution - "reforming national infection prevention and control system," the Korean government introduced a policy plan, ***"****Measures to Reform National Infection Prevention and Control System for the Purpose of Immediate Response to Emerging Infectious Diseases."* This policy promises to develop four systems to prevent the emergence of infectious diseases, end them quickly, and minimize damage resulting from them**:** (1) first response system, (2) a specialized diagnosis and treatment system, along with quarantine facilities**,** (3) preventing nosocomial infection, and (4) governance arrangements for emerging infectious diseases.[172]

회의록, 2015 년 7 월 14 일 in Eng [335th National Assembly of the Republic of Korea, Transcript of the 6th meeting of MERS Special Committee, July 14, 2015]

[170] 제 335 회 국회, 제 7 차 중동호흡기증후군대책 특별위원회 회의록, 2015 년 7 월 16 일 in Eng [335th National Assembly of the Republic of Korea, Transcript of the 7th meeting of MERS Special Committee, July 16, 2015]; also see, 제 335 회 국회, 제 8 차 중동호흡기 증후군 대책 특별위원회 회의록, 2015 년 7 월 22 일 in Eng [335th National Assembly of the Republic of Korea, Transcript of the 8th meeting of MERS Special Committee, July 22, 2015]

[171] 제 336 회 국회, 국회본회의 회의록, 2015 년 8 월 11 일 in Eng [336th National Assembly of the Republic of Korea, Transcript of Assembly plenary session, August 11, 2015]

[172] Ministry of Health and Welfare of South Korea, "[9.1.] Measures to Reform National Infection Prevention and Control System for the Purpose of Immediate Response to Emerging Infectious Disease," Press released on September 1, 2015, available at https://www.mohw.go.kr/eng/nw/nw0101vw.jsp?PAR_MENU_ID=1007&MENU_ID=100701&page=1&CONT_SEQ=326060

To achieve these four missions, KCDC's capabilities and authorities were expanded, the organization was enlarged, and enlarged KCDC organization, and creation of a new Emergency Operation Center (EOC) which included public health experts, such as epidemiologists (Figure 3-4). In order to strengthen immediate response capabilities against infectious disease outbreaks, the Korean government established a 24-hour-a-day EOC as seen.

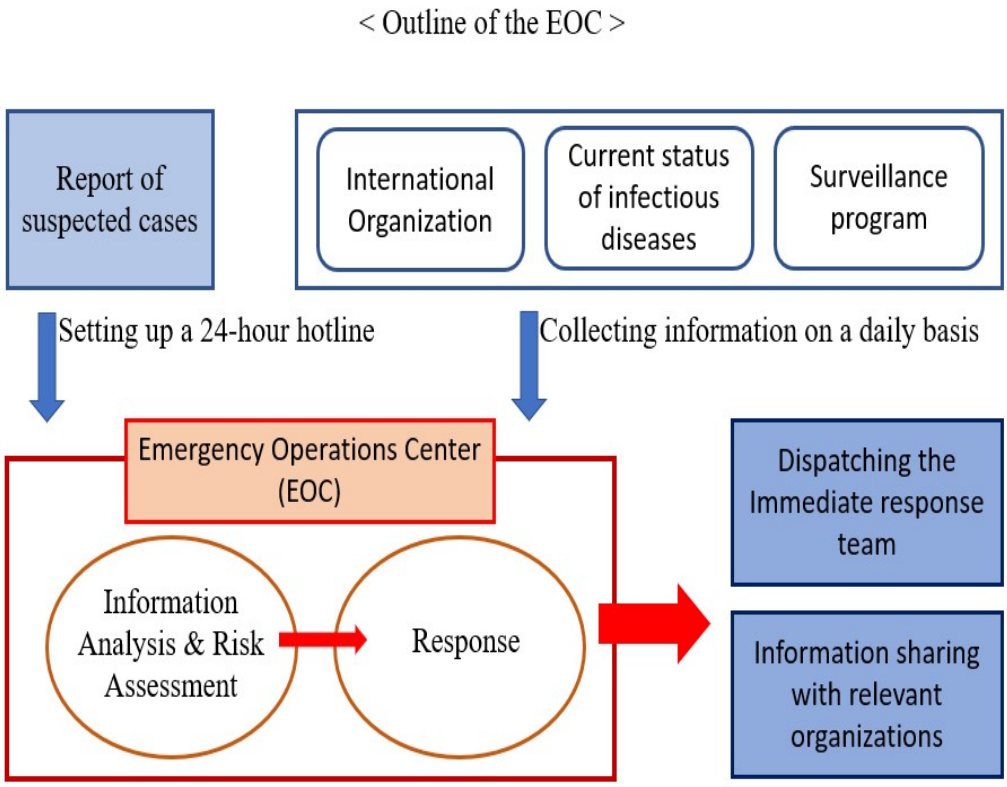


Figure 3-4: Outline of the Emergency Operation Center (EOC)[173]

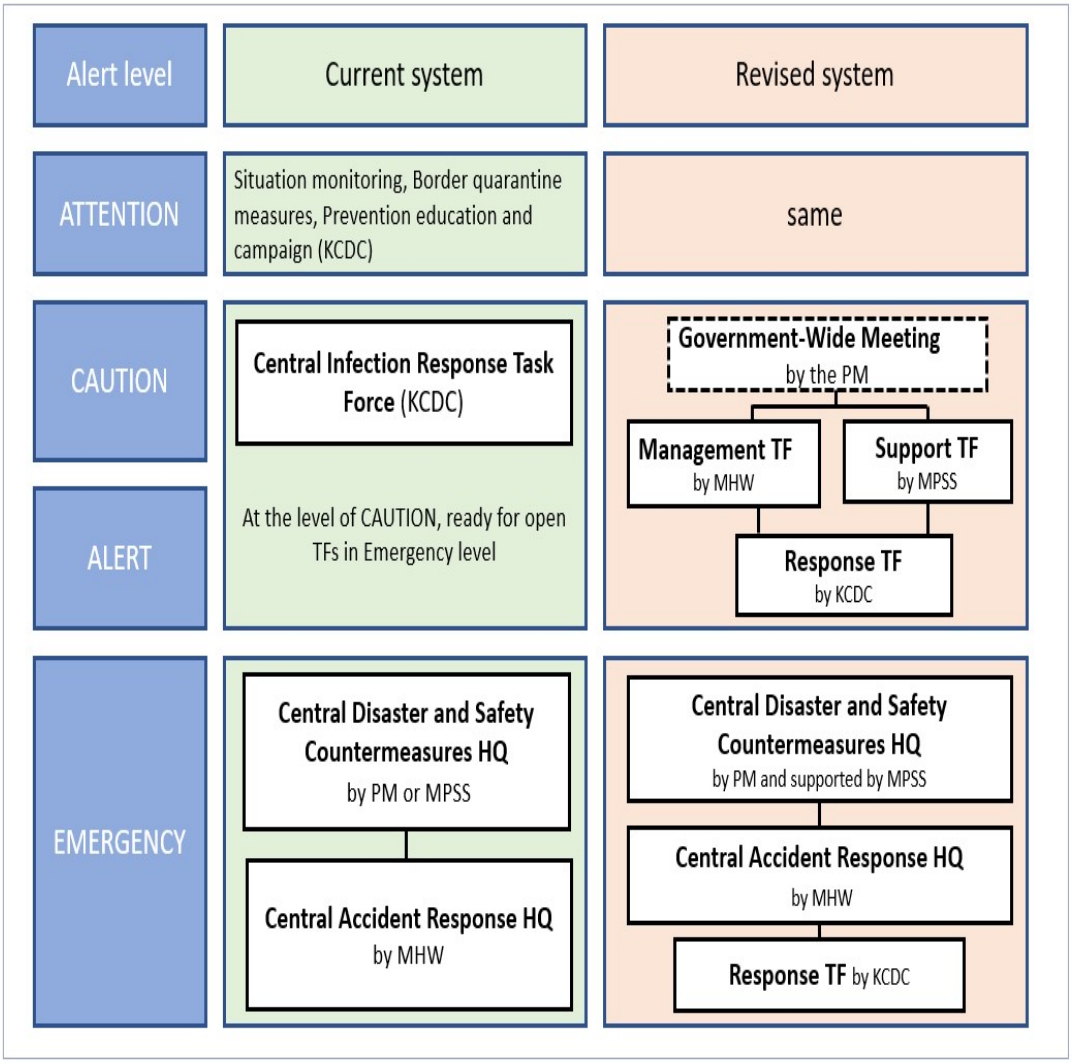
[173] Retrieved from the Korean version (original) translated by the English version. See; original version 질병관리본부, 신종감염병 대응 24 시간 긴급상황실 철치 등 국가방역체계 개편, 2015-09-01; the Korean version available at https://www.cdc.go.kr/board/board.es?mid=&bid=0015&act=view&list_no=65273&tag=&nPage=164 . Also see, English version [the Korean Center for Disease Control and Prevention, "Measures to Reform National Infection Prevention and Control System for the Purpose of Immediate Response to Emerging Infectious Diseases," press released on September 1, 2015], available at

The 24-hour-a-day EOC was established by the Korean government with the goal of always being ready for any public health emergency crisis at any time. The "Immediate Response Team," led by the Division of Infectious Disease Control under KCDC and staffed by full-time epidemiologists, would lead the initial response to reports of a new disease outbreak.

To supervise infection prevention and control practices more effectively, KCDC was also granted wider autonomy and special authorities for disease prevention practices. As a result of KCDC's elevated authority, the KCDC director position was ranked up to the vice minister level in the Ministry of Health and Welfare, and KCDC became the principal organization for preventing and controlling diseases at all stages of an outbreak.[174] As seeing Figure 3-5, moreover, KCDC began to play an essential role in response against epidemic and pandemic outbreaks. Unlike the current public health response system (pre-MERS system), the revised system (post-MERS system) supports the KCDC's role of primary response to public health emergency. In detail, from the phases of "Caution" and "Alert," KCDC organizes the leading Response Task Force with government-wide supports such as the Management Task Force led by the Ministry of Health and Welfare and the Support Task Force led by the Ministry of Public Safety and Security. Once the nation enters the "Emergency" phase, the Response Task Force of KCDC takes the helm of the public health emergency response, which is directly controlled by central authorities such as the Central Disaster and Safety Countermeasure Head-Quarter or the Central Accident Response Head-Quarter.

https://www.mohw.go.kr/eng/nw/nw0101vw.jsp?PAR_MENU_ID=1007&MENU_ID=100701&page=1&CONT_SEQ=326060

[174] During the COVID-19 pandemic (on September 14, 2020), the Korea Center for Disease Control and Prevention (KCDC) raised to the agency-level organization, and renamed Korea Disease Control and Prevention Agency (KDCA). Therefore, the head of this organization is promoted from Director to Commissioner.



*__PM__: Prime Minister; **MPSS:** Ministry of Public Safety and Security; **MHW:** Ministry of Health and Welfare; **KCDC:** the Korea Center for Disease Control and Prevention.

Figure 3-5: Revised Response System According to Alert Level [175]

[175] Retrieved from the Korean version (original) translated by the English version. See; original version 질병관리본부, 신종감염병 대응 24 시간 긴급상황실 철치 등 국가방역체계 개편, 2015-09-01; the Korean version available at https://www.cdc.go.kr/board/board.es?mid=&bid=0015&act=view&list_no=65273&tag=&nPage=164 . Also see, English version [the Korean Center for Disease Control and Prevention, "Measures to Reform National Infection Prevention and Control System for the Purpose of Immediate Response to Emerging Infectious Diseases," press released on September 1, 2015], available at https://www.mohw.go.kr/eng/nw/nw0101vw.jsp?PAR_MENU_ID=1007&MENU_ID=100701&page=1&CONT_SEQ=326060

Idea Discussed and Emergence of Disease Containment

In 2016, the Ministry of Health and Welfare published the *2015 MERS Outbreak in the Republic of Korea: Learning From MERS*, or simply the "2015 MERS White Paper." According to this report, the 2015 MERS outbreak was terminated, not by new biomedical technologies, but by traditional disease prevention practices such as epidemiological investigations that identified sick patients who were isolated and exposed individuals who were quarantined.[176] In the absence of medical countermeasures for the treatment or prevention of MERS, non-pharmaceutical interventions (NPIs), such as contact tracing, isolation, and quarantine, became the foundation of South Korea's public health response. As discussed in previous paragraphs, during the MERS outbreak, Korean society was in social chaos that no one knew who was infected. To avoid such a social chaos, the significance of contact tracing practices by timely sharing epidemic information raised. As a result, the Korea National Assembly concluded to add Article 34-2 (Disclosure of Information during Infectious Disease Emergency) of the Infectious Disease Control and Prevention Act;

> "When an infectious disease harmful to citizens' health is spreading, the Minister of Health and Welfare shall promptly disclose information with which citizens are required to be acquainted for preventing the infectious disease, such as the movement paths, transportation means, medical treatment institutions, and contacts of patients of the infectious disease."[177]
> Article 34-2 (Disclosure of Information during Infectious Disease Emergency)

implies that accurate and timely diagnostic capabilities are key to identify cases who

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[176] 보건복지부, 2015 메르스 백서: 메르스로부터 교훈을 얻다, 발간등록번호 11-1352000-001644-01, 2016 년 7 월 29 일, p.429 in Eng [Ministry of Health and Welfare of South Korea, "the 2015 MERS Outbreak in the Republic of Korea: Learning From MERS," Pub Num. 11-1352000-001644-01, July 29, 2016, p.429]

[177] The newest version is "Article 34-2 of Infectious Disease Control and Prevention Act, [Enforcement Date. September 05, 2020.] [Act No.17067, March 04, 2020., Partial Amendment]", official translation by National Law Information Center in Ministry of Government Legislation, Republic of Korea, available at http://www.law.go.kr/LSW/eng/engMain.do

were infected and who need to be epidemiologically investigated. In other words, diagnostic capabilities are paired with epidemic investigation efforts and epidemic information disclosure policy. Therefore, Korean society led by public health community discussed an idea and need for strengthening diagnostic capabilities for the purpose of disease containment during infectious disease outbreak. This revising effort to collaborate diagnosis, epidemiological investigation and epidemic information disclosure is evolved to a new policy – 3T practice (testing, tracing, and treatment) – later in the COVID-19 pandemic.

The Infectious Disease Control and Prevention Act that Article 34-2 was inserted functions as the foundation for epidemiological investigation, quarantine, isolation, laboratory diagnosis, vaccination, and treatment. At the same time, the Act is expected to function as a framework act to control and treat infectious diseases as social disasters.[178] The experience of the disastrous MERS outbreak highlighted the importance of disease containment in Korea, which leads to revise particularly epidemiological investigation, quarantine, isolation and laboratory diagnosis, instead of pharmaceutical intervention practices such as vaccination and treatment.

The main objective of disease containment efforts is to prevent the spread of a disease. To do so, early detection of disease infection is essential to curtail the chain reaction of disease transmission. Disease containment, practiced by epidemiologists with the goal of preventing chains reaction of disease transmission in the community, become an essential part of Korea's new disease prevention strategy.[179] Disease

[178] Mijeong Park, "Infectious disease-related laws: prevention and control measures," *Epidemiol Health* 2017; Volume: 39, Article ID: e2017033

[179] Walensky RP, del Rio C., "From Mitigation to Containment of the COVID-19 Pandemic: Putting the SARS-CoV-2 Genie Back in the Bottle," *JAMA,* 2020;323(19):1889–1890.

containment practices pursues four missions: (1) identifying affected patients; (2) ensuring appropriate control measures are promptly implemented to contain further spread; (3) determining if transmission and dissemination is occurring; and (4) characterizing the organism or mechanism in order to guide further response actions, patient management, and future responses.[180]

The Health and Welfare Committee of the National Assembly held a panel discussion on 27 August 2015 on how to reform the public health system to respond more effectively to pandemics. Panelists from government, academia, and private sectors discussed six topics, most of which were related to Korea's diagnostic capabilities.[181] Also, the Korean Academy of Science and Technology also held a round-table discussion with medical professionals about the MERS outbreak and future response plans on 1 July 2015. The participants emphasized the vulnerabilities in the Korean public health system such as the lack of epidemiologic capabilities necessary to activate a rapid response against an infectious disease outbreak. Professor Lee of Catholic Kwandong University Medical School pointed out that although there were at least two domestic companies developing MERS diagnostic kits, Korea could not use them because of the KFDA approval processes authorized by the Medical Product Law.

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[180] The Center for Disease Control and Prevention of the United States, "Interim Guidance for a Public Health Response to Contain Novel or Targeted Multidrug-resistance Organisms (MDROs), undated January 2019," p.1 available at https://www.cdc.gov/hai/pdfs/containment/Health-Response-Contain-MDRO-H.pdf

[181] A news introduces the brochure for the panel discussion in National Assembly. See; 대유행병의 효율적 대응을 위한 제도개선 토론회, 국회보건복지위원회, 고려대학교 생명과학대학 공동주관, 의료기기뉴스라인, 2015 년 8 월 27 일, 참고 in Eng [Panel Discussion for institutional revision for efficient response against pandemic, co-sponsored by National Assembly Health and Welfare Committee and Korea University College of Life Science & Biotechnology, Korea Medical Device News, August 2, 2015], available at http://www.kmdianews.com/news/articleView.html?idxno=3756 ,

Finally, Lee suggested the introduction of the United States Emergency Use Authorization (EUA) policy.[182]

Legislative efforts of EUA for diagnostic kits began in earnest by the post-MERS disease containment movement to strengthen diagnostic capabilities. In fact, diagnostic reagents that categorized as industrial products were reassigned to the category of medical devices after the 2009 H1N1 influenza pandemic. Also, the Department of Medical Device Examination was created within the KFDA in January 2015 to be responsible for approval of in-vitro diagnostic kits and reagents.[183] Shortly after the Department of Medical Devices Examination was established, the MERS outbreak began. Despite this new department, it was hard to use in-vitro diagnostic kits in a timely fashion in the field to fight the outbreak. In the wake of the MERS outbreak, therefore, the development of new diagnostic kits and policy for using testing kits was at the forefront of consideration for rapid disease detection. According to an interview with Hyun-ju Oh, the head of Medical Devices Examination Department in KFDA, the need for rapid approval of new in-vitro diagnostic kits, such as the U.S. EUA policy, emerged with the MERS outbreak.[184]

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[182] 이혁민 (가톨릭관동의대 진단검사의학과), 메르스 현황 및 종합대책-메르스 바이러스 검사, 제 91 회 한림원탁토론회 요약문, pp.68-70. In Eng [Hyuk-Min Lee M.D., "MERS Situation, Comprehensive Countermeasures – Virus Diagnosis," the 91th Round-Table Discussion in *The Korean Academy of Science and Technology*, summary paper, pp.68-70]

[183] 이탁순, "전세계호평 'K-진단키트', 긴급승인 있기에 가능," 데일리팜뉴스, 2020 년 5 월 14 일, http://www.dailypharm.com/Users/News/NewsView.html?ID=264543&REFERER=NP In Eng. News Media Interview, [Tak-Soon Lee, "the World favorable 'K-diagnostic kits' due to EUA," *Daily-Pharm News,* May 14, 2020]

[184] 이탁순, "전세계호평 'K-진단키트', 긴급승인 있기에 가능," 데일리팜뉴스, 2020 년 5 월 14 일, http://www.dailypharm.com/Users/News/NewsView.html?ID=264543&REFERER=NP In Eng. News Media Interview, [Tak-Soon Lee, "the World favorable 'K-diagnostic kits' due to EUA," *Daily-Pharm News,* May 14, 2020]

EUA Legislation in the Medical Device Act and Inaugural Use of EUA

Public health and medical communities proposed the adoption of a US-style EUA policy to strengthen Korea's disease containment capabilities. Finally, the South Korea government added two clauses regarding the emergency use of diagnostics within "Enforcement Regulations of the Medical Device Act." Unlike the US EUA legislated in a stand-along Bill (the Project Bioshield Act), the two clauses (Paragraph 7 of Article 10 and Paragraph 7 of Article 32) were added in the "Enforcement Regulations of the Medical Device Act" as a legal basis only for exemption of the manufacturing and the importation of medical devices in a public health emergency:

> "If Minister of Health and Welfare or KCDC commissioner request for prevention of infectious disease and pandemic, manufacture and import of medical devises that commissioner of Ministry of Food and Drug Safety (Korea FDA) indicates emergency use are exempted from examination."[185]

As seen the sentences of the Medical Device Act, there is no specific term of "Emergency Use Authorization." However, these clauses mean that public health authority will authorize the use of an item by exempting examination (approval) processes of the item for emergency – simply being expressed as 'authorizing for emergency use'. [186] According to this law, by commissioner of KCDC, the commissioner of KFDA issues the exemption of testing kit's examination (authorizing

[185] This clause was added on the Article 10 Paragraph 7 and Article 32 Paragraph 7 of "Enforcement Regulations of the Medical Device Act" [Ordinance of the Prime Minister No. 1284, June 15, 2016], National Law Information Center in Ministry of Government Legislation, Republic of Korea, available at http://www.law.go.kr/LSW/main.html

[186] In Korean text, "Emergency Use Authorization" of the United States is translated into one word – 긴급사용승인. However, the Korean EUA policy is said by two words – 긴급사용(space)승인 – that means Authorizing Emergency Use. However, these two terms are used in much the same sense because of the similar policy functions.

emergency use or called to as EUA) in the case of a public health emergency defined in the Infectious Disease Control and Prevention Act.

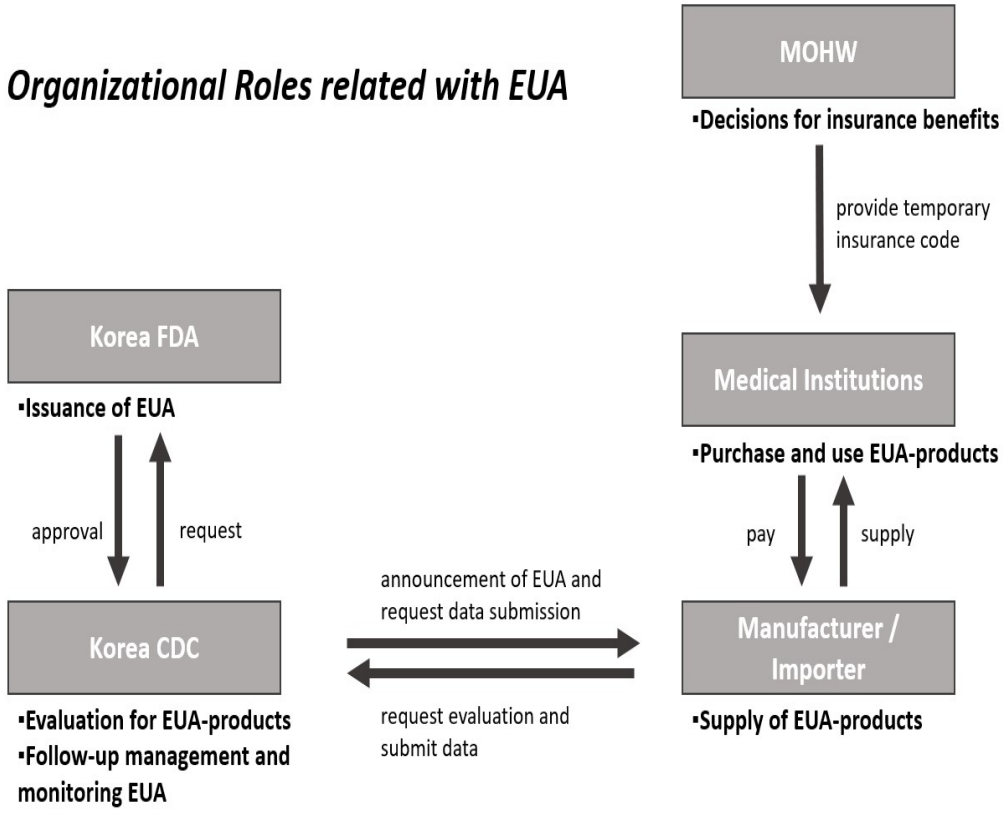

Figure 3-6: Organizational Roles of the EUA process[187]

The Ministry of Health and Welfare (MOHW) explains the process of the EUA and roles of the EUA-related organizations as following Figure 3-6. Figure 3-6 shows that since KCDC advertises for EUA-items (in-vitro diagnostic kits) to deal with public health emergency, manufacturers/importers request evaluation and submit data of their

[187]보건복지부, 메르스 및 지카바이러스 검사 일반병원에서도 가능, 보도자료 2016 년 8 월 12 일, 참고; in Eng. [Ministry of Health and Welfare of South Korea, MERS and Zika Virus Diagnosis, enable in general hospitals, Press Released on August 12, 2016], available at http://www.mohw.go.kr/upload/viewer/skin/doc.html?fn=1470961683463_20160812092804.hwp&rs=/upload/viewer/result/202102/

candidate items to KCDC. Based on KCDC's review of these candidate items, KCDC requests EUAs for items to KFDA. Since KFDA decides to issue EUA for an item (or items), Ministry of Health and Welfare (MOHW) provides a temporary insurance code to the EUA-item. MOHW is a principle authority of managing national health insurance service that is mandatory for all Korean citizen and green-card holders. Therefore, manufacturers/importers can supply the item to medical institutions by insurance-covered price.

The Korean EUA system works similar to the US EUA, but prominent feature of the Korean EUA is the insurance coverage. Under the post-MERS disease containment agenda, the Korean government expanded national health insurance coverage to include the EUA-products, such as diagnostic kits, for free. Therefore, the MOHW determines the range of insurance benefits and provides the terms of using EUA-products when issuing EUA. The insurance coverage for EUA-items contributes to maximizing the effectiveness of Korea's disease containment practices based on a basic disease prevention principle – the earlier suspected cases are detected, the more effective a disease prevention campaign works.[188] The free use of diagnostic kits can reduce financial burdens on the population, which facilitates testing a larger percentage of the population and diagnosing infectious diseases quicker and easier. During the COVID-19 pandemic, the free-testing practice was expanded to all citizens, foreign residents, visitors, and aliens.

[188] Park Jae-Sun, Choi Young-sill, Yoo Cheon-Kwon, Division of Laboratory Diagnosis Management, KCDC, "Introduction of Emergency Use Authorization of In-Vitro Diagnostics for Infectious Disease," *Weekly Health and Disease,* Vol.10 No.22, 2017, pp.555-559

Evolution of the EUA: Zika and MERS in 2016, and Radioactive Contamination

Korea's new EUA policy was first tested in 2016 following the emergence of Zika in South Korea. Among the 14 cases of ZIKV (Zika virus) infection in total from March to October 2016, 9 cases were confirmed by July (1 in March, 3 in April, 1 in May, 1 in June, and 3 in July).[189] On 12 August 2016, the KCDC announced the first issuance of an EUA, which was for MERS diagnostic kits and Zika diagnostic kits. Based on lessons from the 2015 MERS outbreak about the importance of large-scale testing, the Korean public health authority encouraged the private sector to actively participate in testing practice. First, the MOHW provided detailed self-diagnosis criteria for MERS or Zika infections. Those who met these criteria could use a MERS or Zika test at any designated institution for free. The free testing policy was generous to avoid abuse. For example, all pregnant women were allowed free Zika testing without qualification.

Second, the Korean public health authority promptly expanded testing authority to the private sectors. 35 medical institutions (24 medical centers and 11 contract research organizations) certified by Korean academia associations (the Korean Society for Laboratory Medicine, the Korean Association of External Quality Assessment Service) were authorized as testing centers by the director of KCDC, which can use the EUA items (MERS and Zika diagnostic kits) for disease diagnosis purposes. By June 2017, 21 private medical institutions and 12 public clinical laboratories had conducted a total of 3,365 molecular tests for Zika and 30 molecular tests for MERS.[190] To expand

[189] Dora Yoon et al., "Epidemiology and Clinical Characteristics of Zika Virus Infections Imported into Korea from March to October 2016," *Journal of Korean Medical Science,* 32(9): pp.1440-1444, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5546962/

[190] 보건복지부 보도자료, 메르스 지카 검사시약 긴급사용 종료, 허가제품통해 민간의료기관에서 검사 가능, 2017.08.04; in Eng [Ministry of Health and Welfare Media Brief, "MERS and Zika EUAs

the testing authority for using new EUA-items to the private sector, it was necessary to establish standards for diagnostic testing methods for all clinical laboratories in the public and private sectors. Therefore, since the 2015 MERS outbreak, academia (the Korean Society for Laboratory Medicine and the Korean Association of External Quality Assessment Service) becomes main organizer conducting a third-party evaluation and certification for all public and private clinical laboratories. [191] Due to a transparent external quality assessment and certification processes by a third-party authority (academia), all Korean clinical laboratories can share common standard operation procedures, which contributes to the immediate expansion of testing capacities by using EUA-items.

Same as the purview of the US EUA expanded from bioterrorism to all-hazards, the purview of the Korean EUA also expanded; from infectious diseases to radioactive contamination along with a nuclear crisis in the neighboring country – Japan. When a tsunami created a nuclear crisis at Fukushima, Japan in 2011, the world was reminded of the radioactive nightmare of the 1986 Chernobyl disaster. South Korea, as a neighboring country of Japan, paid highest attention to potential radioactivity-related issues. To respond the Fukushima crisis, South Korea banned the import of Japanese seafood produced by the eight provinces near Fukushima, due to concerns about potential radioactive contaminations from the site. In May 2015, Japan filed a lawsuit

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are terminated, now enable to test in private medical institutions by KFDA approved items," August 4, 2017], available at http://www.mohw.go.kr/react/al/sal0301vw.jsp?PAR_MENU_ID=04&MENU_ID=0403&CONT_SEQ=340898&page=1

[191] 대한임상검사정도관리협회, 메르스 및 지카 바이러스 유전자검사참여 민간의료기관 외부정도평가, 정책연구용역사업, 발간등록번호 11-1352159-000837-01, in Eng ["the Korean Association of External Quality Assessment Service, External Quality Assessment to Evaluate MERS Coronavirus and Zika Virus Molecular Tests Performed by Nongovernmental Clinical Laboratories," *Policy Research and Service* Num. 11-1352159-000837-01], available at https://scienceon.kisti.re.kr/commons/util/originalView.do?cn=TRKO201700005167&dbt=TRKO&rn

with the World Trade Organization (WTO), arguing that Korea's import ban was unreasonable.[192] As a result, in February 2018, the WTO upheld a Japanese complaint against the South Korean import bans. However, South Korea decided to appeal the ruling and maintain the ban.

As the conflict escalated, however, South Korea decided to appeal the ruling and maintain the ban. Also, the Medical Device Act was revised in 2018 to include the threat of a radiological emergency. Instead of legislating a new policy for radiation exposures medications such as iodine or anti-cancer drugs, the purview of the Korean EUA was expanded to include radioactive contamination under the Medical Device Act. It is worth noting that the Korean EUA was developed along the existing path emphasizing diagnosis (detection), a process of path dependency. Two clauses - Paragraph 7 of Article 10 and Paragraph 7 of Article 32 - in the "Enforcement Regulations of the Medical Device Act" (mentioned in previous parts) – were deleted, and Article 46-2 was inserted by Act No. 15486, Mar. 13, 2018. Article 46-2 (Special Cases concerning Medical Devices in Cases of Infectious Disease Pandemic) clearly addresses its component of EUA policy that "respond[s] to [an] infectious disease pandemic under the Infectious Disease Control and Prevention Act or radiological emergencies under the Act on Physical Protection and Radiological Emergency."[193]

Finally, in April 2019, the Appellate Body of the WTO upheld South Korean's ban on seafood, overturning a lower panel's ruling in February 2018. In July 2019, a historical dispute between Korean and Japan expanded into a trade-war, with tensions

[192] Yuka Obayashi and Jane Chung, "Japan wins WTO dispute over Fukushima-related food," *Reuters,* February 22, 2018, available at https://www.reuters.com/article/us-japan-southkorea-wto/japan-wins-wto-dispute-over-fukushima-related-food-idUSKCN1G621Z

[193] Article 46-2 of Medical Device Act by Act No. 15486, Mar. 13, 2018

between the two countries deteriorating. Japan halted the export of strategic materials, such as semiconductor components, to Korea. While the relationship between the two countries fell to its worst, South Korea doubled the volume of radiation testing practices for all imported foods from Japan due to potential contamination from the tsunami-damaged Fukushima nuclear plant.[194] Although the newly revised EUA policy covers testing practice for radiological contamination, the Korean government did not really issue any EUA for radiation check; rather increased the number of radioactive inspections by using the existing radiation check products. The South Korean media raised suspicion that the Korean government aimed to exercise stricter rules for radioactive inspections to all importing products from Japan, as a countermeasure to the Japanese export restrictions.[195]

Conclusion

The Korean EUA was created as part of a broader strategy to contain infectious diseases based on the country's experience with the MERS outbreak in 2015. The experiences of nosocomial infections, super-spreader issues and unknown routes of infection from the 2015 MERS outbreak taught Korea unforgettable lessons. The disease containment domain primarily focusing on how to cut the chain reaction of

[194] *Reuter,* "South Korea to increase radiation testing of Japanese food," August 21, 2019, available at https://www.reuters.com/article/us-southkorea-japan-food-radiation/south-korea-to-increase-radiation-testing-of-japanese-food-idUSKCN1VB094

[195] 한재영, 日 방사능 급소 겨냥?, 서울경제, in Eng. [Jae-Young Han, "Targeting the Japanese vulnerable spot – radioactive issues," *Seoul Economy,* August 14, 2019] available at https://www.sedaily.com/NewsView/1VMYU1VSN9

disease transmission was built into Korea based on these lessons, which laid the groundwork for the emergence of the Korean EUA policy.

Same as the US case study, the 2015 MERS outbreak is definitely a critical juncture, a decisive moment resulting in major institutional changes in Korea. EUA is also the most representative case demonstrating the post-MERS movement of South Korea; instead of creating new institution (e.g. biodefense in the United States), Korea strengthened the conventional disease control and prevention institution. Along with the exogenous shock (the 2015 MERS outbreak), the Birkland's model can account for the role of endogenous factors (KCDC) in the Korea's domestic level. Due to the newly emerged disease containment domain, the higher organizational status and authorities were empowered to KCDC to practice mass-testing campaign. The Korean public health authorities learned from the 2015 MERS outbreak that the large-scale testing is the most effective disease control and prevention practice to contain infectious disease outbreaks. Therefore, the provisions of the Korean EUA were legislated in the Medical Device Act, which allows the emergency use of diagnostic kits to inform efforts at disease containment to cut the chain reaction of disease transmission.

As seeing the Zika cases in 2016, the domain of the Korean EUA – disease containment – has developed along the existing path. Besides, Korea embraces radiological emergency within the scope of its EUA policy, as of the 2018 revision of the Medical Device Act, due to the escalating tensions between Korea and Japan. Although the purview of the Korean EUA expand from infectious disease to radiological exposure, the primary mission of the Korean EUA – containment practice– is remained and reinforced to detect and trace the inflow of radiological contamination from Japan, as path dependency demonstrates.

In contrast to the United States with its EUA serving as a primarily security-oriented biodefense policy, the EUA in Korea emerged as a general public health policy with disease control and prevention objectives. Therefore, Korean policymakers and public health authorities perceive the EUA as a tool for disease containment against emerging infectious diseases and radiological contaminations. This perception is underscored by the phrase "detection and diagnosis," which was used frequently after the MERS outbreak, and emphasizes the emergency use of unlicensed MCMs as disease containment.

CHAPTER 4: EUAs during the COVID-19 pandemic

Introduction

Previous chapters explored how different past experiences have affected the emergence of difference policy domains in the United States and South Korea. The homeland security domain emerged in the United States based on the lessons learned from the 2001 Anthrax letter attack, and the disease containment domain emerged in South Korea based on the lessons learned from the 2015 MERS outbreak. The case studies illustrated how these different policy domains laid the groundwork for the emergence of different EUA policies in the United States and South Korea.

Building upon the case studies, this chapter examines how the different EUA policies in the United States and South Korea affected their responses to the COVID-19 pandemic. As explained in the previous chapters, the US EUA focuses on the development of specialized, unlicensed PEP (Post-Exposure Prophylaxis) in response to public health emergencies. In contrast, the Korean EUA focuses on diagnosis and detection efforts in response to public health emergency which results in an emphasis on the development and deployment of diagnostic kits for disease containment. Even though both countries issued their first EUA for testing kits on the same day, February 4, 2020, Korea was able to ramp up its testing much more quickly than the United States in the crucial early days of the pandemic. The Korean EUA was used effectively as a tool to promote early and rapid diagnostics once the COVID-19 pandemic emerged. In

contrast, the US performance in testing for COVID-19 lagged far behind South Korea in the early phase of the COVID-19 pandemic.

As predicted by Birkland's model, the U.S. EUA, which was specialized for treatment of disease outbreaks due to the homeland security domain, was less effective in facilitating large-scale testing than the South Korea EUA which was designed as part of a disease containment policy domain. Concretely, this chapter illustrates that the US EUA under the homeland security domain specialized for PEP efforts was less capable to integrate with other public health policies necessary to support large-scale testing practices. Compared to the U.S. EUA, the Korean EUA under the disease containment domain specialized for diagnosis and detecting infectious diseases was well coordinated with other supportive public health policies to rapidly deploy large-scale testing practice shortly after the pandemic began. Finally, the number of tests conducted in the United States skyrocketed after mid-March 2020 when the United States revised public health policies to circumvent the US EUA policy.

This chapter emphasizes three main EUA-supporting public health systems – public health surveillance, laboratory partnership, and the insurance – that affected the testing capacities and outcomes of the two countries in the early phases of the COVID-19 pandemic (from 4 February to mid-March). Not only EUA but also these three EUA-supporting systems in the two countries have been influenced by the emergence of each policy domains, which led to the dissimilar efficacies of COVID-19 testing practices in the two countries.

This chapter does not argue that these three EUA-supporting public health systems are the only and the most important determinants for the effectiveness of an EUA on testing outcomes. Rather, this chapter argues that if these three factors are

omitted as independent variables, then scholars could fall victim to omitted variable bias.[196] Of course, there are a plethora of factors that may contribute to the lack of COVID-19 testing in the United States compared to South Korea. For example, the absence of political leadership in the United States in response to the pandemic outbreak has been widely cited as an important reason for early missteps and problems.[197] According to interviews with more than 50 current and former public health officials, administration officials, senior scientists, and company executives, factors such as technical flaws, regulatory hurdles, business-as-usual bureaucracies, and the lack of leadership at multiple levels have played a role in the lack of testing in the United States.[198]

This chapter provides a more detailed account of the effectiveness of the EUAs of the two countries in regards to the expansion of testing capacities during the early stages of the COVID-19 pandemic. The Korean EUA with its focus on the disease containment domain had a multiplicative effect on the mass-testing practice by integrating with these three EUA-supporting policies under that domain. On the other

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[196] Gary King, Robert Keohane and Sidney Verba, *Designing Social Inquiry: Scientific Inference in Qualitative Research* (Princeton, NJ: Princeton University Press, 1994), pp. 168–73..

[197] Joe Lockhart, "Trump is failing the leadership test on Coronavirus," *CNN* February 29, 2020, last accessed on Feb 11, 2021, available at https://www.cnn.com/2020/02/29/opinions/trump-failing-leadership-test-coronavirus-opinion-lockhart/index.html. Also see; Seth Cohen, "Trump's Message Is Wrong – Real Leaders Should Be Afraid of Covid-19," *Forbes,* Oct 5, 2020, last accessed on Feb 11, 2021, available at https://www.forbes.com/sites/sethcohen/2020/10/05/trumps-tweet-is-wrong---real-leaders-should-be-afraid-of-covid-19/?sh=3db26a324b2a See; Sten h. Vermund, Ahmed Mushfiq Mobarak, and Howard P. Forman, "We could tackle COVID under an effective leader. Trump is not that leader," *Fortune,* November 2. 2020, last accessed on Feb 11, 2021, available at https://fortune.com/2020/11/02/covid-trump-leadership-failure-2020-election-biden-coronavirus-pandemic/. See; Michael D. Shear, Noah Weiland, Eric Lipton, Maggie Haberman and David E. Sanger, "Inside Trump's Failure: The Rush to Abandon Leadership Role on the Virus," *The New York Times,* July 18, 2020, updated Sept 15, 2020, last accessed on Feb 11, 2021, available at https://www.nytimes.com/2020/07/18/us/politics/trump-coronavirus-response-failure-leadership.html.

[198] Michael D. Shear, Abby Goodnough, Sheila Kaplan, Sheri Fink, Katie Thomas and Noah Weiland, "The Lost Month: How a Failure to Test Blinded the US to Covid-19," *The New York Times,* updated April 1, 2020, last accessed on Feb 11. 2021, available at https://www.nytimes.com/2020/03/28/us/testing-coronavirus-pandemic.html

hand, the U.S. EUA, with its focus on the homeland security domain, was incapable of stimulating the immediate synergy effect with these three EUA-supporting policies and was less effective through mid-March 2020.

Mid-March 2020 was a major turning point in the U.S. response to COVID-19 since this was the point at which US testing capacities skyrocketed. A comparative study between the United States and South Korea clearly shows how the Korean EUA was more effective than the US EUA in rolling out the large-scale testing capabilities that were so essential in the early stages of the pandemic. Of course, in theory, the US EUA was optimized for the development and the use of MCMs, particularly PEP and vaccines. In reality, the United States did perform much better when developing treatments and vaccines and operating a mass-vaccination campaign beginning in late 2020. On the other hand, South Korea hesitated to use new COVID-19 vaccines and began to use vaccines since March 2021 when they revised their EUA policy. Due to the timeline of this dissertation, however, which focuses on the first three months of the pandemic, the role of the US and Korean EUAs for developing PEP and vaccines against COVID-19 will remain for further research.

Early Phase of the COVID-19 Pandemic: The US versus South Korea

COVID-19 Outbreak Becomes a Global Pandemic

Beginning December 2019, patients with an unknown sickness people reported to hospitals in the city of Wuhan, China. Many scientists and public health experts determined that this mysterious illness was caused by a new coronavirus, named SARS-

CoV-2.[199] By the 28 January 2020, this virus had spread to more than 17 countries beyond mainland China, where at least 131 people had already died and more than 4,600 cases were confirmed.[200] As a result, on 30 January 2020, the WHO declared the coronavirus outbreak a Public Health Emergency of International Concern (PHEIC).[201] One year later, as of 30 December 2020, the global confirmed case reached 81.6 million and global death toll was at 1.8 million.[202]

The disease outbreak caused by SARS-CoV-2 has several prominent features. First, COVID-19 is a disease caused by a novel coronavirus, for which no effective MCMs are available to treat and prevent. In the beginning of the pandemic, therefore, only supportive care were available for the treatment of COVID-19 patients. As seen in chapter 1, it usually takes 10 years or more to develop a new MCM. Since the COVID-19 outbreak, many scientist and medical professionals sought alternative ways to treat and prevent COVID-19 infection by off-label use of already-licensed MCMs. For example, HIV antivirals were first used to treat COVID-19 patients in Thailand, and it was claimed that this experiment showed that the HIV antivirals blocked the enzymes that the virus needed for replication, effectively curing the patients.[203]

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[199] This virus was called 2019 novel coronavirus (2019-nCoV) but renamed as "SARS-CoV-2" by the International Committee on Taxonomy of Viruses. See; Coronaviridae Study Group of the International Committee on Taxonomy of Viruses., Gorbalenya, A.E., Baker, S.C. *et al.* "The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2," *Nat Microbiol* 5, 536–544 (2020), available at https://www.nature.com/articles/s41564-020-0695-z#citeas

[200] James Griffiths and Amy Woodyatt, "Death toll from Wuhan coronavirus tops 100 as infection rate accelerates," *CNN,* updated Jan 28m 2020, last accessed on Feb 11, 2021, available at https://www.cnn.com/2020/01/28/asia/wuhan-coronavirus-update-intl-hnk/index.html

[201] World Health Organization (WHO), "WHO Director-General's statement on IHR Emergency Committee on Novel Coronavirus (2019-nCoV)," posted on 30 January 2020, available at https://www.who.int/director-general/speeches/detail/who-director-general-s-statement-on-ihr-emergency-committee-on-novel-coronavirus-(2019-ncov)

[202] All daily weekly or cumulative data about COVID-19 reported cases are available; see WHO Coronavirus Disease (COVID-19) Dashboard. https://COVID-19.who.int/

[203] CNN news, "Thai doctor says new drug combination treated coronavirus patient," posted on February 2, 2020, available at https://www.cnn.com/asia/live-news/coronavirus-outbreak-02-02-20-intl-hnk/h_f9dcabd30a7a19762113ae3aae284742

However, it was concluded that there is no scientific evidence that any medicines used to treat HIV are effective against COVID-19.[204] On 1 May, 2020, the U.S. Food and Drug Administration (FDA) issued an EUA for Veklury (remdesivir) for the treatment of hospitalized patients with severe COVID-19.[205] In other words, before May 2020, there was no medical interventions available to treat COVID-19 patients.

A second important feature of SARS-CoV-2 was the need for large-scale testing practices due to non-specific symptoms, asymptomatic, and pre-symptomatic transmission of the novel coronavirus. Basically, COVID-19 patients present with flu-like symptoms like fever, chills, fatigue, and sore throat, which are hard to distinguish from other common diseases. Despite the similar symptoms, COVID-19 is reported to have stronger contagiousness and causes more serious illness compared to influenza.[206] In addition to the non-specific symptoms of coronavirus infection, asymptomatic spread is one of the most troubling aspect of COVID-19 outbreak. Studies have shown that at least 40-to-50% of people who test positive for COVID-19 have no symptoms.[207] Also, about 15% of confirmed cases are asymptomatic.[208] These high figures of asymptomatic coronavirus cases can pose public health threat, because asymptomatic

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[204] The Centers for Disease Control and Prevention (CDC), "What to Know About HIV and COVID-19," updated on February 1 2021, available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/hiv.html#:~:text=Currently%2C%20treatment%20for%20COVID,treat%20COVID%2D19

[205] On May 1, 2020, the US Food and Drug Administration (FDA) issued an EUA for Veklury (remdesivir) for the treatment of hospitalized patients with severe COVID-19. See, the US FDA, "Velkury EUA Letter of Approval, reissued October 22, 2020," available at https://www.fda.gov/media/137564/download

[206] The Centers for Disease Control and Prevention (CDC), "Symptoms of Coronavirus, updated Dec 22, 2020," last accessed on Feb 11, 2021, available at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

[207] Katie Kerwin McCrimmon, *The truth about COVID-19 and asymptomatic spread: It's common, so wear a mask and avoid large gatherings,* November 5 2020, UChealth.ORG, available at https://www.uchealth.org/today/the-truth-about-asymptomatic-spread-of-covid-19/

[208] Jingjing He et al., "Proportion of asymptomatic coronavirus disease 2019: A systematic review and meta-analysis," *Journal of Medical Virology,* 93(2) February 2021, available at https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.26326

COVID-19 patients unwittingly spread the disease and start a chain reaction of disease transmission.

Diverging Consequences Between the United States and South Korea

The COVID-19 pandemic posed a different public health threat than other types of disease outbreaks: no medical interventions were available against the virus; non-specific flu-like symptoms of COVID-19 infection are hard to distinguish from other common seasonal flus or colds; and asymptomatic and pre-symptomatic cases can unwittingly spread the disease in their communities. Therefore, it is necessary to test most population on a large-scale to detect hidden cases, rather selective testing only for those who have symptoms.

To conduct large-scale testing practices, a stable supply of accurate COVID-19 diagnostic kits is essential. Both the United States and South Korea issued EUAs for COVID-19 *in vitro* diagnostic kits on February 4, 2020, early in the pandemic.[209] However, the two countries experienced very different levels of success in developing and deploying COVID diagnostics on a large-scale to support public health efforts to contain the pandemic. By 25 February, South Korea had tested over 35,000 cases, while the United States had tested only 425 cases.[210]

[209] South Korea and the United States issued EUA on the same day (Feb 4, 2020), but Korea (GMT+9) announced earlier than the United States (GMT-5), given the different time zone.
[210] Carolyn Y. Johnson, Laurie McGinley, and Lena H. Sun, "A faulty CDC coronavirus test delays monitoring of disease's spread," *Washington Post,* Feb. 25, 2020, available at https://www.washingtonpost.com/health/2020/02/25/cdc-coronavirus-test/

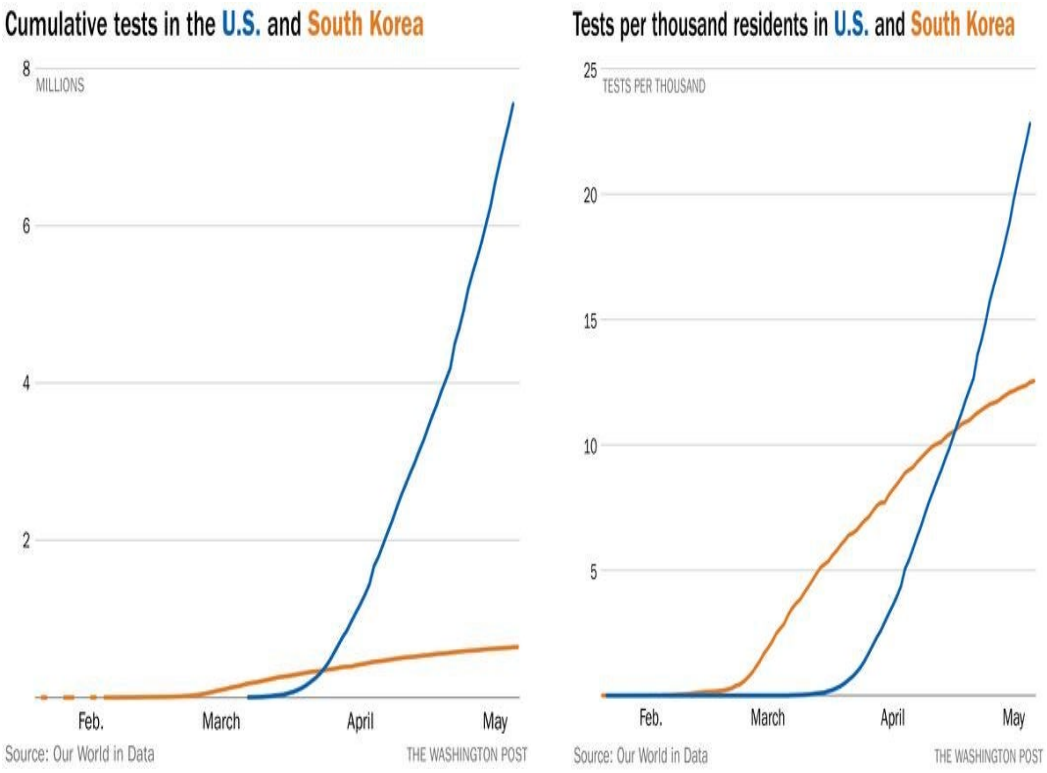

Figure 4-1: Comparing Testing Capacities of the United States and South Korea[211]

On 11 March 2020, U.S. House Oversight Committee Chairwoman Carolyn Maloney raised a question during a hearing: Why are we [the United States] so far behind South Korea in testing and reporting this crisis? Maloney emphasized that South Korea had already tested nearly 200,000 people and were able to test 15,000 people a day, the same figure that took the United States over two months to reach.[212]

[211] Philip Bump, "Comparisons with South Korea tell the opposite story of the one Trump wants," *The Washington Post,* May 7, 2020, available at https://www.washingtonpost.com/politics/2020/05/07/comparisons-with-south-korea-tell-opposite-story-one-trump-wants/

[212] See the transcript of the Congressional testimony on March 11, 2020, "Dr. Fauci and Other CDC & NIH Officials Testify on Coronavirus – March 11," *REV.COM,* available at https://www.rev.com/blog/transcripts/dr-fauci-and-other-cdc-nih-officials-testify-on-coronavirus-march-11

Although both the United States and South Korea issued EUAs for diagnostic kits on the same day (4 February 2020), the success of their national COVID testing programs by mid-March were quite different. data in the Figure 4-1 also shows that the U.S. testing capacities began to expand rapidly from mid-March.

Why did US COVID-19 testing lag so far behind South Korea at the beginning of the pandemic, from February to mid-March 2020? This dissertation argues that the Korean EUA, developed under the disease containment policy domain inspired by the 2015 MERS outbreak, was well-suited for facilitating the emergency use of diagnostic kits for mass-testing purposes. On the other hand, the U.S. EUA, developed under the homeland security domain from the experience of 9/11 and the 2001 Anthrax letter attack, was much more focused on the emergency use of PEP (e.g. medical treatments and vaccinations). This chapter provides more detail account for how both EUAs worked differently in reality in the beginning of the COVID-19 pandemic. Since new diagnostic kits were used by EUA in Korea, the Korean EUA policy was well integrated with other public health systems supportive to conducting large-scale testing practice. Particularly, the Korean public health surveillance system, laboratory-partnership system, and insurance system were promptly coordinating with the EUA policy which contributed to the timey expansion of testing capacities in South Korea. On the other hand, the US public health surveillance system, lab-partnership system, and insurance system could not achieve synergy with the emergency use of testing kits at the beginning of the pandemic. Interestingly, once the United States began to look at the issue of its testing deficiency and revise these public health systems associated with testing capacities, the number of the US COVID-19 testing skyrocketed in mid-March.

Responses Differences in a Public Health Emergency

Three different public health systems – public health surveillance, lab partnership, and insurance –influenced the effectiveness of the use of the EUA items (diagnostic kits). Due to the post-MERS disease containment policy domain, the Korean EUA policy was intimately integrated into these public health systems that supported large-scale testing. The large-scale use of diagnostic kits is the key feature of the Korean surveillance system called the 3T strategy. Also, based on the lessons learned from the MERS outbreak, Korea established a private sector-led laboratory partnership to induce active participation when rapid expansion of testing capacities is required. Free testing through insurance coverage allowed more people to get tested without financial worry.

On the other hand, the US EUA arising from the post-Amerithrax homeland security policy domain had not been integrated with these public health systems. The US public health surveillance system, called the Laboratory Response Network (LRN), specialized in the detection of highly pathogenic and infectious agents, rendering it less effective to find and trace coronavirus contagions. The CDC-led lab partnership regarding the EUA impeded private sector's active participations in coronavirus testing practices. Finally, the uncertain and high prices for testing in the United States likely increased COVID-19 testing hesitancy in the population.

Public Health Surveillance Differences – 3T versus LRN

First, both countries have developed different platform of surveillance system. The Korean surveillance system focuses on epidemiological investigation missions tracing the spread of disease in a community, while the US surveillance system gives

more weigh on laboratory confirmation capabilities to identify pathogens. No wonder South Korea has allocated huge budgets for strengthening local epidemiological capabilities since the 2015 MERS outbreak, while the US lost lots of local public health workers and employees after 2009 recession.[213]

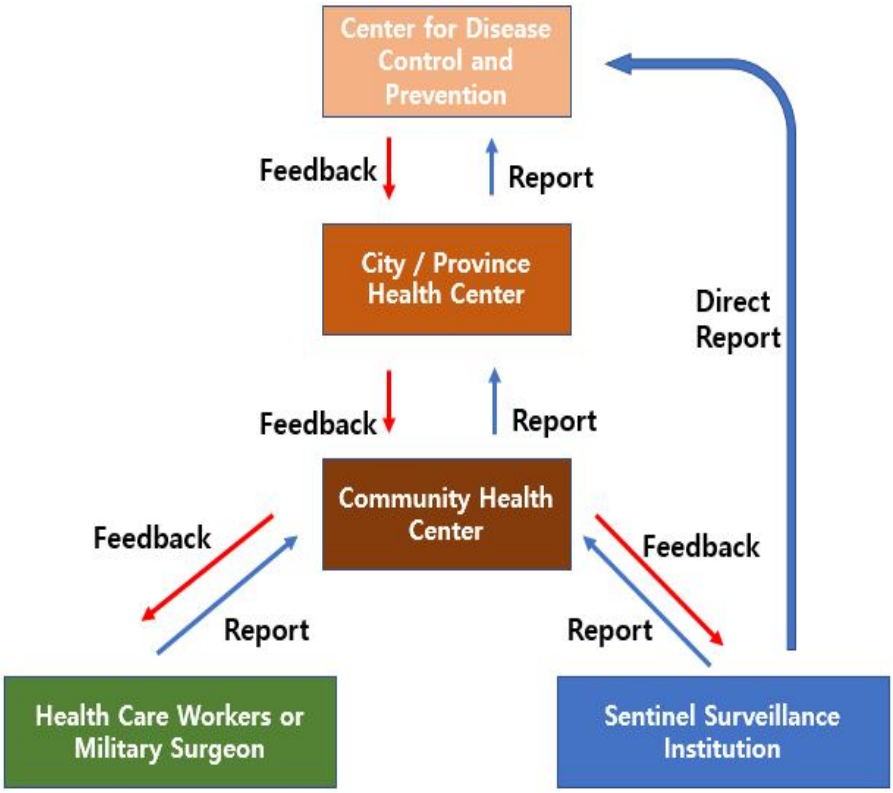

Figure 4-2: The Korean Public Health Surveillance and Reporting System[214]

[213] Adriane Casalotti, "Health department workforce has shrunk 23 percent since 2008," *National Association of Counties,* April 16, 2019, available at https://www.naco.org/articles/health-department-workforce-has-shrunk-23-percent-2008 also see; Robin Taylor Wilson, Catherine L. Troisi, and Tiffany L. Gary-Webb, "A deficit of more than 250,000 public health workers is no way to fight Covid-19," *STAT*, April 5, 2020 available at https://www.statnews.com/2020/04/05/deficit-public-health-workers-no-way-to-fight-covid-19/

[214] Figure 4-2 is translated by the author; sources from Korea Center for Disease Control and Prevention, "Infectious Disease Surveillance", published on May 14 2019, last revised on April 8 2021, last accessed on May 1 2021, available at https://www.kdca.go.kr/contents.es?mid=a20301110100

In Korea, as seeing Figure 4-2, community public health centers play the most central role of public health surveillance and reporting system. This system presents a typical type of the traditional indicator-based surveillance model that reports specific diseases from health care providers to public health officials. However, since the 2015 MERS outbreak, as described in chapter 3, public health expertise teams for epidemiological investigation missions are based in Emergency Operation Centers (EOC) in every local government. Therefore, based on reported data in community public health center, local governments can immediately respond to an infectious disease outbreak in their communities, and upper divisions (e.g. city/province level health centers or KCDC) receive reports for administrative and policy affairs to support local-level practices.

To conduct epidemiological investigation practices in local and community-levels, the use of testing kits is essential in the field operations to timely identify confirmed cases and actively search suspected cases. Based on the lessons learned from the 2015 MERS outbreak, South Korea developed a new disease prevention and control strategy – Trace, Test and Treat (3T) – that laid the groundwork for successful COVID-19 response practices. Active searching efforts to find hidden (suspected) cases are the most significant feature of the Korean 3T practices, which contributes to breaking the chain reaction of disease transmission.[215] To strengthen active search capabilities, the 3T practices give more weigh to preventive testing missions as seen in Figure 4-3. Preemptive testing is defined as a strategy of conducting complete testing on all cluster-

[215] HyunJung Kim, "What Lessons Can the US Learn from Japan and South Korea for Combating Coronavirus?," *Global Biodefense,* March 16, 2020, available at https://globalbiodefense.com/2020/03/16/united-states-lessons-learned-covid-19-pandemic-response-south-korea-japan-observations-hyunjung-kim-gmu-biodefense/

associated patients under investigation who are working, living, or visiting in the confined environment where the cluster was found with an unknown source of infection including asymptomatic cases. [216]

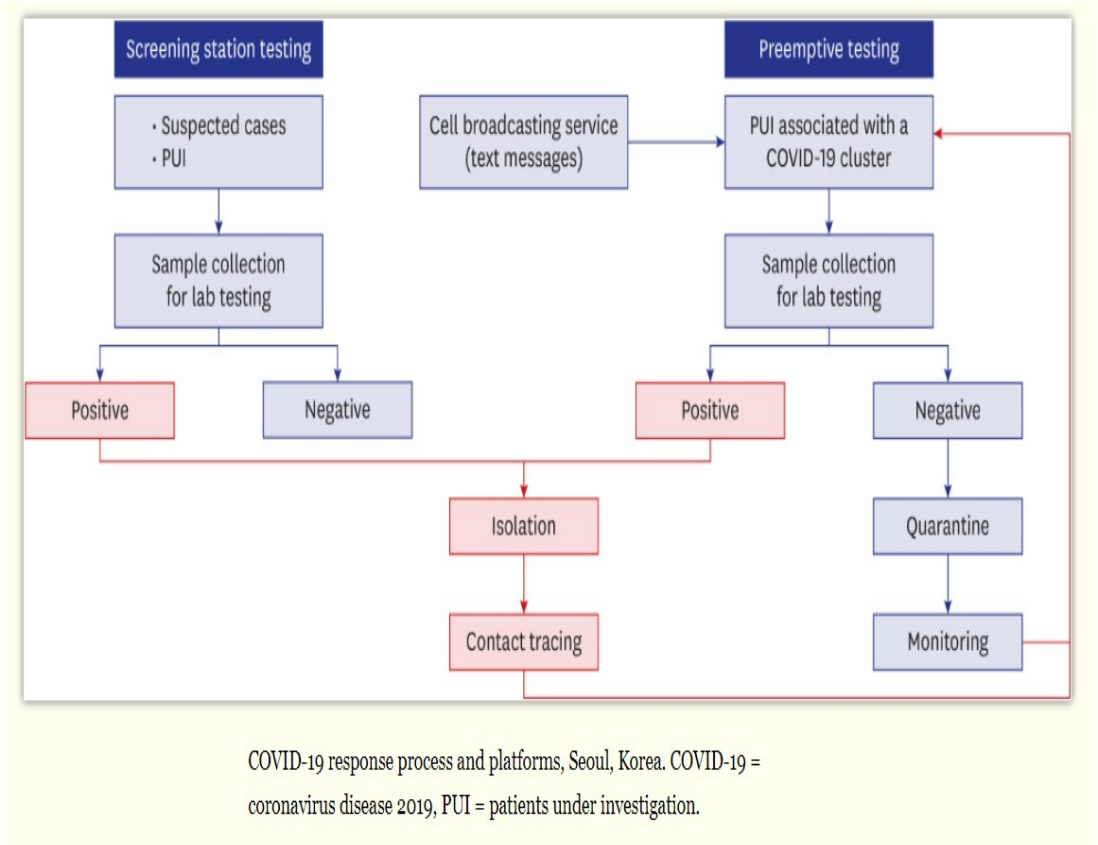

Figure 4-3: Flowchart of the Korean 3T practices [217]

As a result, timely approval for accurate testing kits by EUA is necessary to operate the 3T practices. Since identifying cases by EUA-items (in-vitro diagnostic

[216] Yoojin Park et al., "Application of Testing-Tracing-Treatment Strategy in Response to the COVID-19 Outbreak in Seoul, Korea," *Journal of Korean Medical Science*, 2020 Nov;35(45):e396. English, Published online Nov 06, available at https://jkms.org/search.php?where=aview&id=10.3346/jkms.2020.35.e396&code=0063JKMS&vmode=PUBREADER#!po=68.7500

[217] Yoojin Park et al., Ibid, *Journal of Korean Medical Science*, 2020.

kits), the Korean public health authority and local governments collaborated to document the movement history of patients down to the minute based on a comprehensive epidemiological investigation through interviews with the patient, closed-circuit television (CCTV), smartphone GPS tracking, and credit card transactions. Then all of this collected epidemic information such as where they went, when they were there, and how they got there, are shared with the public. All suspected cases who may have a close contact with confirmed cases or patients under investigation (PUI) associated with a COVID-19 cluster are encouraged to get tested. All confirmed cases are isolated, their contact history is traced by epidemiological investigation teams, and serious cases are provided with medical treatment in negative pressure isolation rooms in government-designated hospitals.

The 3T practices show that Korea developed its own disease containment strategy based on the availability of large-scale testing capabilities that were authorized for emergency use. Together with the EUA, new information and digital technologies were also actively used as part of the 3T practices, and the digital-based public health surveillance system is now regarded as the new pandemic response model for democratic countries.[218]

In contrast to the South Korea's response to COVID-19 by large-scale testing to detect and trace the spread of disease in communities, the United States has a developed public health surveillance system primarily focusing on laboratory capabilities to identify and confirm biological threats which were less effectively integrated with the EUA. The backbone of the US public health surveillance system is

[218] Bicker, Laura., "Coronavirus in South Korea: How 'trace, test and treat' may be saving lives," *BBC News,* March 12, 2020, available at https://www.bbc.com/news/world-asia-51836898

the Laboratory Response Network (LRN) developed by the U.S. CDC in partnership with FBI and the Association of Public Health Laboratory (APHL). The legal basis for the creation of the LRN was Presidential Decision Directive-39 (PDD-39) which was issued in 1999 to deal with terrorist threats.[219] The counterterrorism foundation of LRN was further strengthened by the emergence of the homeland security domain post-Amerithrax, and later the LRN mission expanded to include other public health emergency threats, such as severe acute respiratory syndrome (SARS), H1N1 (2009 pandemic influenza) MERS, and Ebola virus as well as chemical threats. [220] Although the purview of the LRN missions has been extended to cover all-hazard threats, the primary mission of the laboratory-network is to make rapid and high-confidence results supporting critical public health decision-making against biological and chemical terrorism.[221]

To achieve rapid and high-confidence lab confirmation, the LRN consists of three stage of a network system: national laboratories, reference laboratories, and sentinel laboratories (see Figure 4-4). Sentinel laboratories provide routine diagnostic services that can play a key role in the early detection of biological agents; reference laboratories, often called LRN member laboratories, are responsible for investigation and/or referral of specimens sent from the sentinel level; and national laboratories are the top-tier labs responsible for specialized characterization of organisms, bioforensics,

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[219] The White House. Presidential Decision Directive/NSC-39: U.S. Policy on Counterterrorism. June 21, 1995. http://www.fas.org/irp/offdocs/pdd/pdd-39.pdf accessed May2, 2021

[220] Chris N. Mangal and Lucy Maryogo-Robinson, "Leveraging the Laboratory Response Network Model for the Global HEALTH Security Agenda," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science,* 2014 September 1; 12(5): pp274-283, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171117/

[221] US Center for Disease Control and Prevention, "The Laboratory Response Network Partner in Preparedness," website last reviewed on April 10 2019, last accessed on May 1 2021, available at https://emergency.cdc.gov/lrn/

select agent activity (Federal Select Agent Program), and handling highly infectious biological agents.[222]

Figure 4-4: The Structure of Laboratory Response Network for Biological Threats (LRN-B)[223]

Reference labs in Laboratory Response Network for Biological Threats (LRN-B) have taken a leading role in diagnostic testing for infectious disease outbreaks and are responsible for rapid distribution of diagnostic tests and reliable communication of testing results back to the US CDC.

[222] US Center for Disease Control and Prevention, "Laboratory Response Network for Biological Threats (LRN-B)," website last reviewed on April 10 2019, last accessed on May 1 2021, available at https://emergency.cdc.gov/lrn/biological.asp
[223] US Center for Disease Control and Prevention, "Laboratory Response Network for Biological Threats (LRN-B)," website last reviewed on April 10 2019, last accessed on May 1 2021, available at https://emergency.cdc.gov/lrn/biological.asp

While the Korean public health surveillance system necessitates EUAs for in-vitro diagnostic kits to conduct epidemiological investigation missions, the US public health surveillance system primarily focusing on laboratory confirmation missions is less effectively integrated with EUA policy. In other words, the US public health surveillance relies on laboratories (LRN-B) highly capable of detecting and identifying specimen timely and accurately, but less considers how to deal with a high-volume of testing needs in the case of public health emergency.

Based on the direct and indirect experiences of from H1N1 Influenza to Zika, CDC's LRN-B program has learned various lessons and improved response capabilities against infectious disease outbreak.[224] As discussed in Chapter 2, due to the 2009 H1N1 influenza, the US biodefense system embraced the 'disease control and prevention' domain which led to revise and reauthorized PAHPA of 2006. During the H1N1 pandemic, the US public health authority issues not only an EUA for antiviral (*peramivir*), but also in-vitro diagnostic kits (IVDs) for the first time.

Although the United States issued EUAs for IVDs for the first time to deal with infectious disease outbreak, the EUAs were not center of the US public health surveillance system during the 2009 H1N1 Influenza pandemic. The US public health authority struggled to develop and introduce FDA-cleared assays, and later issued EUA status to one of the FDA-cleared assays. Due to some technical issues on the item, however, the first EUA for IVD was delayed by October 2009, despite public health emergency that the Secretary of HHS declared on 26 April 2009.

[224] Julie Villanueva et al., "Detecting Emerging Infectious Diseases: An Overview of the Laboratory Response Network for Biological Threats," *Pubic Health Reports*, 2019, Vol. 134, 16S-21S.

Moreover, there was a gap between public health and private clinical laboratories in the LRN-B network that many private laboratories do not have the expertise to launch FDA-cleared molecular assays, thus laboratory-developed assays made by private laboratories filled the influenza testing gap and significantly contributed to the disease control and prevention during the H1N1 pandemic; EUA was only very useful options for laboratories which has no expertise to develop their own assays.[225] In other words, EUA is an auxiliary to the LRN-B network in terms of public health surveillance.

The H1N1 Influenza case clearly shows the limitation of the LRN-B network as a principle axis of the US public health surveillance system. The LRN-B, laboratory-based surveillance system, was hard to deal with a high-volume of testing needs. Dr. Martin Meltzer, a Senior Health Economist & Distinguished Consultant Division of Emerging Infections and Surveillance Services in the US CDC, pointed out the US LRN network reveals limited surge capacity in addressing that how many samples could be delivered to public health labs in the middle of an epidemic.[226] To cover the testing gap, the US public health authority had no choice but to recommend restrictive testing guidelines to the public. The CDC limited the subject of influenza testing to 1) people who are hospitalized with suspected flu and 2) people such as pregnant women or

[225] Swati Kumar and Kelly J. Henrickson, "Update on Influenza Diagnostics: Lessons from the Novel H1N1 Influenza A Pandemic," *Clinical Microbiology Reviews,* April 2012 25(2):244-261, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3346302/

[226] National Biodefense Science Board (NBSB) Pandemic Influenza Working Group, "Appendix B, H1N1 Countermeasures Strategy and Decision-Making Forum," detailed report, July 2009, p.63, available at https://www.phe.gov/Preparedness/legal/boards/nbsb/meetings/Documents/060718-h1n1-forum.pdf

people with weakened immune system, for whom a diagnosis of flu will help their doctor make decisions about their care.[227]

The Zika outbreak case also demonstrate that US public health surveillance system paid attention to the LRN-B capacities to identify public health threats timely and accurately, but less considers how to conduct actual diagnostic practices in large-scale. Reports show that the United States has barely conducted large-scale diagnostic testing. According to Julie Villanueva et al., the Zika outbreak challenged the US LRN-B systems to take the high-volume of testing practices; the LRN-B tested 1,097 cases during the 2014 MERS outbreak, 180 cases during the 2014-2015 Ebola outbreak, and 92,686 cases during the 2016-2017 Zika virus outbreak.[228] However, the figure of 92,686 Zika tests in a year can be reversely calculated that U.S. testing capacities were 7,700 cases per month, or 250 cases per day. It is hard to say the figure of 250 testing per day is high-volume comparing to the testing capabilities that South Korea achieved during the 2015 MERS outbreak (1,200~1,400 cases per day).[229]

Since the COVID-19 outbreak began, the United States faced the lack of testing capacities again. As U.S. House Oversight Committee Chairwoman Carolyn Maloney pointed out, the United States had tested only 425 cases by 25 February, while South Korea had tested over 35,000 cases.[230] However, the limited surge capacity of the

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[227] The U.S. Center for Disease Control and Prevention, "Influenza Diagnostic Testing During the 2009-2010 Flu Season," website last updated on September 29, 2009, available at https://www.cdc.gov/h1n1flu/diagnostic_testing_public_qa.htm

[228] Julie Villanueva et al, Ibid. 16S-21S

[229] JTBC News,"보건당국 "메르스 검사, 하루 1400 건→800 건 감소" 2015/6/30 in English [JTBC News, Public Health Authority MERS testing decreased from 1400 per day → 800 per day], last accessed on May 1 2021, available at https://mnews.jtbc.joins.com/News/Article.aspx?news_id=NB10945849

[230] Carolyn Y. Johnson, Laurie McGinley, and Lena H. Sun, "A faulty CDC coronavirus test delays monitoring of disease's spread," *Washington Post,* Feb. 25, 2020, available at https://www.washingtonpost.com/health/2020/02/25/cdc-coronavirus-test/

LRN-B network was covered by various efforts; one is EUA that could share the overwhelming surge capacity of the LRN-B. Since the first EUA attempt (4 February 2020) for the CDC diagnostic kit was failed due to technical issues, new EUA for IVD was firstly granted on 15 March, 2020. Next section will cover a detail account for the first EUA issuance. As of 16 March 2020, the U.S. COVID-19 testing capacities reached 15,000 cases per day, equivalent to the South Korea's capacities, and skyrocketed to the capacities of near 2 million per day by the end of 2020.[231]

In sum, LRN-B is a laboratory-based public health surveillance system for rapid, high-confidence results to inform critical public health decisions about biological threats. Although LRN-B system has been extended to be able to address infectious diseases outbreak, it paid lower attention to the need of a large-scale testing mission. Because the LRN-B system consisting of various laboratories is at the center of the US public health surveillance system, EUA policy cannot be fully integrated in the public health surveillance system. The COVID-19 pandemic clearly illustrates what happen if the needs for testing overwhelmingly exceed the LRN-B network's surge capacities. One the other hand, Korea gives more weigh on epidemiological investigation missions. To carry out epidemiological investigation mission, EUA-items (IVDs) are necessary. The Korean case shows EUA policy fully integrated with public health surveillance system can contribute to operating large-scale testing practices in the early phase of the pandemic.

[231] Data retrieved from Statista website; see Statista, "Number of COVID-19 tests performed daily in the U.S. from March 1 to November 26, 2020," available at https://www.statista.com/statistics/1111601/covid-19-tests-carried-out-daily-in-the-us/ last accessed on April 20, 2021.

Laboratory Partnership Differences – Private-Led versus Public-Led

When authorizing the use of new testing kits, it is necessary to establish a coherent partnership between the public health authority in charge of issuing the EUA and the private sector that will manufacture and administer the test. However, the two countries showed different features of the partnership when issuing EUAs – private sector leading partnership in Korea and public authority leading partnership in the United States – which lead to differences in testing capacities in the early phase of the pandemic.

From the 2015 MERS outbreak experiences, as discussed in chapter 3, the Korean public health authority learned the importance of timely expansion of testing capacities in response to infectious disease outbreak. To do so, when issuing an EUA for new diagnostic kits, private sectors were actively involved in the process and verification of the EUA while the Korean public health authority served as a moderator. On the other hand, the emergence of the post-Amerithrax homeland security domain strengthened the exclusivity of the US CDC's authority to handle and deal with public health emergency. When the new coronavirus began spreading, the US CDC unilaterally developed a new COVID-19 diagnostic kits for EUA without any partnership with the private sector. Unfortunately, the CDC efforts to develop new diagnostic kits failed, thus leading to a serious deficit in the US testing program in the early phase of the pandemic.

Private Sector-leading Partnership in Korea

Since the COVID-19 outbreak arose in China, KCDC, the central public health authority of Korea, along with academia and the private sector began to develop

COVID-19 diagnosis kits. The Korean case study about the expansion of testing capacities emphasizes the importance of public-private partnerships. Shortly after the COVID-19 outbreak, KCDC initiated the delegation of the COVID-19 testing authorities for developing testing kits and conducting testing practices with various partners in local, academia, and the private sector. These partnership efforts were feasible because since the 2015 MERS outbreak, all of these partners had already participated in and even played leading roles in the verification, confirmation, evaluation, and issuance of the EUA for the testing kits. Meanwhile, KCDC served as the facilitator and mediator among these various partners.

KCDC supported academia and the private sector when selecting testing kits for EUA and appointing centers for testing practices. Centers for testing practice (also called test centers) are medical and biological science research institutions that KCDC designates as centers to conduct diagnostic testing. The Korean Society for Laboratory Medicine, the Korean Association of External Quality Assessment Service, and other research institutions and firms collaborated to assess and verify the quality of the newly developed reagents, and finally a product - PowerChek 2019-nCoV Real-time PCR Kit – made by KOGENE BioTech, which was first granted EUA by the KFDA on February 4, 2020.[232]

As a favorable outcome of the public-private partnership, all testing standards and procedures regarding the use of these testing kits were commonly shared across all partners. Before the first EUA was issued on February 4, 2020, KCDC and academia

[232] 보건복지부, 신종 코로나바이러스 진단시약 긴급사용 승인, 의료기관까지 검사 확대, In English [Ministry of Health and Welfare (MOHW), Emergency Use of COVID-19 test kit authorized, COVID-19 tests also extend to medical institutions, Feb 4, 2020], available at http://ncov.mohw.go.kr/upload/140/202002/1580792390483_20200204135950.pdf

conducted additional test-related training courses on common laboratory standards and procedures for all medical institutions willing to open a test center. On 4 February when issuing the first EUA, the Director of KCDC announced that 50 private medical institutions had been certified by the Korea Society for Laboratory Medicine and the Korean Association of External Quality Assessment Service as official test centers. These test centers could open after lab personnel took additional test-related training courses and accuracy evaluations proctored by the Korea Society for Laboratory Medicine and the Korean Association of External Quality Assessment Service, which ensure the highest trust for testing.

In particular, academia played a significant role in active participation of private sectors. A coalition of seven academic associations, including the Korea Society for Laboratory Medicine and the Korean Association of External Quality Assessment Service, evaluated blinded tests by sending a package with three positive and four negative agents to all test center applicants.[233] The 46 medical institutions (38 public/private medical centers and 8 contract research organizations) passed this examination and were appointed as official test centers. KCDC approved another 31 institutions later to serve as test centers; these facilities passed the second examinations by the associations.

The efforts to promptly expand the number of test centers and establish common standards and procedures through the public-private partnership contributed to quickly increasing testing capacities in the early phase of the pandemic. Since 7 February, a

[233] Interview with the Chairman of the Korea Society for Laboratory Medicine; see 박선혜, "코로나 19, 검사기관 확대…하루 최대 만오천건 가능, 약업신문, in English [SunHye Park, "COVID-19, Expansion of test centers….15,000 test available at most a day," *Yakup News*, Feb 25, 2020, available at https://www.yakup.com/news/index.html?mode=view&nid=241009

total of 170 testing facilities completed additional test-related training courses, and were ready to conduct COVID-19 tests: 124 local public health centers for collecting samples and 46 medical institutions both collected and diagnosed the collected samples). Before February 7, only the KCDC head-quarter and public health and environment research institutions (18 facilities in city and province-level jurisdictions) were available to conduct COVID-19 test.[234] Based on these continuous efforts, as of the mid-March, four more EUAs were issued for COVID-19 diagnostic kits as seeing Table 4-1, allowing the production of 14,000 test kits per week and the capacity for 15,000 tests per day.[235]

Table 4-1: The List of the Korean EUA for diagnostic kits by mid-March, 2020 [236]

CompanyName (Korean)	Item Name (English)	EUA date
㈜코젠바이오텍	PowerChek 2019-nCoV Real-time PCR Kit	Feb 4, 2020
㈜씨젠	Allplex 2019-nCoV Assay	Feb 12, 2020
솔젠트 ㈜	DiaPlexQ N Coronavirus Detection (2019-nCoV) kit	Feb 27, 2020
에스디바이오센서 ㈜	STANDARD M n-CoV Real-Time Detection kit	Feb 27, 2020
㈜바이오세움	Real-Q 2019 n-CoV Detection Kit	Mar 13, 2020

[234] 동아일보, 신종코로나 검사 수행 민간의료기관 46 곳명단공개됐다. 2020.02.07, in English [Dong-A Ilbo, "a List of private medical institutions for COVID-19 test is opened," February 7, 2020], available at https://www.donga.com/news/article/all/20200207/99586463/1

[235] 김형은, 코로나 19: 한국은 어떻게 이렇게 빨리, 많은 양의 검사를 할 수 있었나, BBC 코리아, In English [Hyung-Eun Kim, "COVID-19: how South Korea enable to conduct such fast and large volumes of testing," *BBC Korea,* March 11 2020]

[236] Data are retrieved from a news media; see, 한아름" 긴급사용승인 진단키트 앞으로 못쓴다….정식허가 받은 업체는? Money S news, 2021.02.04, in English [A Han, "EUA testing kits will stop using …who have official approval?" *Money S News*, Feb 4, 2021] available at https://news.naver.com/main/read.nhn?oid=417&aid=0000654083

Public Authority-leading Partnership in the United States

As illustrated in the previous section on surveillance, the U.S. CDC is positioned at the top of the three-levels of the LRN system and is responsible for developing and distributing diagnostic kits. In contrast to the Korean laboratory-partnership, therefore, the US CDC maintained the centralized authority of developing and distributing diagnostic kits. Since SARS-CoV-2 appeared in China, the US CDC remained the solitary agency to develop a COVID-19 diagnostic kit for nation-wide use. The first batch of the CDC-made kits were shipped to state and local laboratories on 5 February. Before using the CDC-developed tests on actual patients, each state and local laboratory conducted a verification process for the test kits, and many of the laboratories received inconclusive results from one of the reagents. The failure of laboratory verifications due to the faulty CDC-developed diagnostic kit was a major cause of the delayed disease monitoring capabilities in the United States. On 12 February 2020, Nancy Messonnier, the director of the National Center for Immunization and Respiratory Diseases at CDC, acknowledged this situation as a problem. However, she described the problem of the inconclusive results on the reagent as a fairly ordinary technical hiccup, which was not critical so much as a potential issue resulting in false positives or false negatives.[237]

[237] The US CDC, Transcript for CDC Telebriefing: CDC Update on Novel Coronavirus, Feb 12, 2020, available at https://www.cdc.gov/media/releases/2020/t0212-cdc-telebriefing-transcript.html

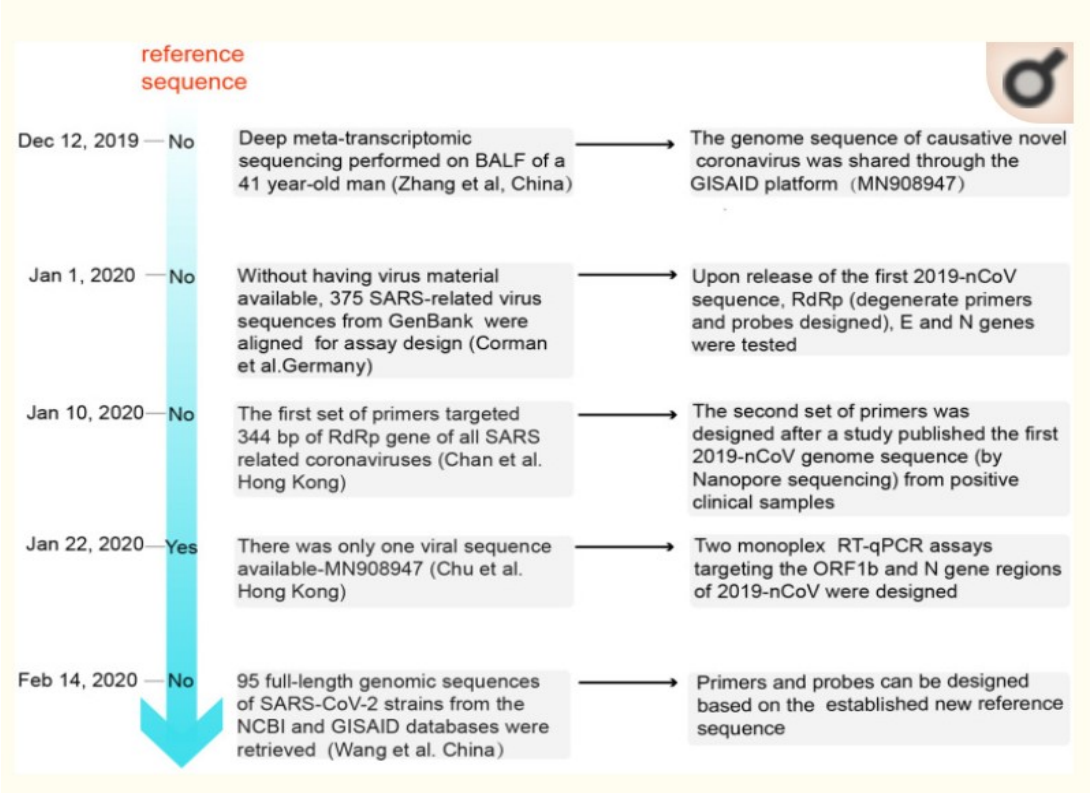

Figure 4-5: The analysis process of primer and probe design for SARS-CoV-2 in chronological order. BALF: bronchoalveolar lavage fluid; GISAID: Global Initiative on Sharing All Influenza Data.[238]

At the start of the new coronavirus outbreak, scientists from across the world struggled to determine the specific viral features (e.g. DNA reference sequence) of the new coronavirus. The findings of a DNA reference sequence for the new coronavirus are necessary to design new primers/probes sets, which lays the groundwork for the development of diagnostic kits. As seen in Figure 4-5, RdRp, E, N, and ORF1b genes of the new coronavirus were identified as eligible for targeted genes to develop diagnostic kits at the very beginning of the COVID-19 pandemic.[239] Based on evidence

[238] Dandan Li, Jiawei Zhang and Jinming Li, Ibid. 2020
[239] Dandan Li, Jiawei Zhang and Jinming Li, "Primer design for quantitative real-time PCR for the emerging Coronavirus SARS-CoV-2," *Theranostics,* 2020 10(16): pp.7150-7162, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7330846/

that these genes demonstrate specific features of the SARS-CoV-2 virus, scientists designed primers and probes for use in SARS-CoV-2 diagnostic kits.

On January 1, German scientists (Corman et al) released sequences of the RdRp, E, and N genes of the SCV-2 virus, but recommended RdRp and E genes rather than N genes due to a sensitivity issue with the N genes.[240] Based on the German research, the Korean public health authority recommended that manufacturers include at least two specific genes (RdRp and E genes) as a baseline when developing diagnostic kits. Thus, the first Korean kit (EUA authorized on February 4) - PowerChek 2019-nCoV Real-time PCR Kit – targeted RdRp and E genes and the second kit (EUA authorized on February 12) - Allplex 2019-nCoV Assay – targeted RdRp, E, and N genes.[241]

Typically, each laboratory usually selects two or more different types of specific genes to target in their diagnostic kit. Unlike the global standard to select two or more different genes for cross-checking, the US CDC selected three N genes (N1, N2, and N3 genes) for developing their COVID-19 diagnostic kits. Unfortunately, a CDC-made reagent targeting N3 gene had problems that resulted in false positive outcomes. On February 26, the US CDC released a new instruction that labs could use the CDC-made kit by analyzing only the N1 and N2 genes of the virus and ignoring the faulty N3 component.[242] However, laboratories in New York argued that the N1 component of

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[240] Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DKW. et al. "Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR," *Euro Surveill.* 2020; 25:2000045

[241] 옥유정, 코로나 19 진단 정확도 논란…유전자검출방식 따져보니, KBS News, 03.22.2020, in English [Yujung Ok, "Controversy of Accuracy of COVID19 Diagnosis…Seeing Ways of Genes Detection*," KBS News,* March 22, 2020] available at https://news.kbs.co.kr/news/view.do?ncd=4407243

[242] The US CDC, "Revision to Test Instructions CDC 2019 Novel Coronavirus (nCoV) Real-Time RT-PCR Diagnostic Panel (EUA200001)," February 26, 2020, available at https://www.aphl.org/Materials/Signed_CDC_Letter_to_PHLs-N3_Removal_Instructions_26Feb2020.pdf

the CDC-made kit was also flawed.[243] Rob J. Dekker et al. also discovered that the false-positive signals from the CDC-made kits resulted from a poorly designed primer and probe.[244] The inconclusive results of the CDC-made testing kits were unsolved until June 12, 2020,[245] thus costing the United States much-needed time to respond to the unprecedented pandemic virus.

Why the US CDC had stuck to using the N genes for so long still remains unknown. However, it is worth noting that the failure of the CDC-made kit was not simply a technical hiccup, but rather the consequence of an institutional loophole. The primary cause of the shortfall in the US COVID-19 testing was not only the CDC's faulty kits, but also the CDC's exclusive authority for developing such tests. In the United States, the FDA basically ruled out state and commercial labs and private companies from developing and manufacturing their own COVID-19 testing kits when it issued the EUA policy. In other words, there were no developers immediately able to offer an alternative test as a back-up when the CDC-made kit ran into problems. In the very beginning of the pandemic, the US CDC spent three weeks trying to fix the faulty kit by persisting in its initial flawed method—relying only on N genes—while other labs were blocked from developing their own diagnostic kits. Meanwhile, South Korea introduced multiple diagnostic kits with various methods – mixing RdRp, E, N, and Orf1a genes – developed by various private companies.

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[243] Julie Steenhuysen and Jonathan Allen, "New York scrambles to replace U.S. government's faulty coronavirus test kit," *Reuters,* Feb 28, 2020, available at https://www.reuters.com/article/us-china-health-usa-testing/new-york-scrambles-to-replace-u-s-governments-faulty-coronavirus-test-kits-idUSKCN20N00J

[244] Rob J. Dekker et al., "Overhauling a faulty control in the CDC-recommended SARS-CoV-2 RT-PCR test," *BioRxiv, Cold Spring Harbor Laboratory*, available at https://www.biorxiv.org/content/10.1101/2020.06.12.147819v1

[245] The US CDC, "CDC Diagnostic Tests for COVID-19," Updated Aug. 5, 2020, available at https://www.cdc.gov/coronavirus/2019-ncov/lab/testing.html

In order to fill the shortfall in testing caused by the faulty CDC-made kit, the United States sought alternative options outside of the CDC. However, another regulation, CLIA, interfered with that alternative. The Clinical Laboratory Improvement Amendments of 1988 (CLIA) is a set of regulations including federal standards applicable to all U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease. The objective of the CLIA program is to ensure quality laboratory testing, and 260,000 laboratory entities are guided by CLIA.[246] Under CLIA, the Centers for Medicare and Medicaid Services (CMS) is a main body to regulate all laboratory testing in the United States. In other words, laboratory-developed testing (LDT) is regulated by CMS under the authority of CLIA.

IVD under the FDA and LDT under the CLIA clashed during the early phase of the pandemic. In-vitro diagnostic (IVD) kit is often referred to as 'commercially developed and distributed' kit, while laboratory-developed test (LDT) is developed and manufactured for individual laboratory by themselves. For instance, a hospital lab may run its own vitamin D assay (LDT), even though there is an FDA-cleared test for vitamin D currently on the market.[247] Traditionally, FDA has exercised enforcement discretion over LDTs but controlled by CLIA, which means LDTs do not need to receive FDA-clearance status. However, Congressional Research Service points out that during the COVID-19 pandemic, all LDTs must either be approved, cleared or authorized under an EUA to be legally used.[248] However, most laboratories and expertise are not familiar with

[246] Centers for Medicare and Medicaid Service, "Clinical Laboratory Improvement Amendments (CLIA)," accessed on June 13, 2020, available at https://www.cms.gov/regulations-and-guidance/legislation/clia

[247] The US FDA, "Laboratory Developed Tests", website on https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests last accessed on May 1, 2021

[248] Amanda J. Sarata, "Development and Regulation of Domestic Diagnostic Testing for Novel Coronavirus (COVID-19): Frequently Asked Questions," *Congressional Research Service,* R46261, March 9, 2020

the EUA processes and requirements, thus they asked FDA to allow laboratories to use LDTs to diagnose SARS-CoV-2 virus.[249] In order to get EUA status, LDT should satisfy premarket approval requirements for IVDs that are usually waived through enforcement discretion by FDA. The US General Accounting Office had previously expressed concerns about the difficulty in developing diagnostic tests that met the FDA requirements for EUA.[250]

Due to the lack of coronavirus testing caused by the CDC-faulty kit, on February 29, the FDA finally shifted its position and issued a new policy that allows laboratories to use and develop in-house diagnostic kits for COVID-19 testing, if the laboratories had previously met federal quality standards.[251] This policy allows "High-Complexity Testing Laboratories" certified under the Clinical Laboratory Improvement Amendments (CLIA) to make and use their own tests, which contributed to increasing the testing numbers in the United States.

On February 29, 2020 when the FDA issued the new testing policy, the first emergency use for COVID-19 testing kits (New York SARS-CoV-2 RT-PCR Diagnostic Panel), made by the New York State Department of Public Health's Wadsworth Center, was issued. However, this first EUA limited testing to the Wadsworth Center and the New York City Department of Health and Mental Hygiene, Public Health Laboratories. However, this assay made by the Wadsworth Center was not designed for high-throughput testing; it was capable of processing approximately 50 to 60 specimens per day per platform with a turnaround time of 4 to 6 hours from

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[249] Robert P. Baird, "What Went Wrong with Coronavirus Testing in the U.S.," *The New Yorker,* March 16, 2020, available at https://www.newyorker.com/news/news-desk/what-went-wrong-with-coronavirus-testing-in-the-us

[250] The US General Accounting Office, "Actions Needed to Address the Challenges of Responding to Zika Virus Disease Outbreaks," GAO-17-445, available at https://www.gao.gov/products/gao-17-445

[251] Jon Cohen, "In bid to rapidly expand coronavirus testing, US agency abruptly changes rules," *Science,* Feb 29, 2020, available at https://www.sciencemag.org/news/2020/02/bid-rapidly-expand-coronavirus-testing-us-agency-abruptly-changes-rules

sample to answer.[252] The EUA for the Wadsworth's assay was also unable, until March 10, to extend the use of this test to other laboratories in the United States qualified by CLIA.[253] Thanks to the February 29 announcement, however, manufacturers and laboratories in the private sector did not need to adhere to the CDC's obsession with the use of N-genes only, but had the flexibility to develop new primers and probes for coronavirus testing. As seen in Table 4-2, since the February 29 announcement, most manufacturers developed new primers and probes targeting different genes.

Along with the February 29 announcement, on March 11, the first driving-thru testing site was opened in Seattle, the state with the second largest COVID-19 cases in the United States after New York. New York and other cities opened driving-thru sites shortly thereafter. However, testing capacities of these two cities (Seattle and NY) were quite different. The UW Medical in North Seattle could test 40 to 50 people per day via the new drive-thru system.[254] New York's drive-thru test site was initially capable of testing up to 200 people a day and eventually expanded to test 500 a day.[255] This demonstrates that although both cities adopted drive-through testing at approximately the same time, New York had a much great capacity to process and analyze the collected samples due to the EUA granted the Wadsworth Center.

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[252] Marie C. Smithgall, Susan Whittier, and Helen Fernandes, "Laboratory Testing of Severe Acute Respiratory Virus Coronavirus 2, A New York Institutional Experience," *Advances in Molecular Pathology,* Nov 3, 2020, PMCID: PMC736806 13-19

[253] The US FDA, EUA letter for New York SARS-CoV-2 RT-PCR Diagnostic Panel to Jill Taylor, Ph.D. Director Wadsworth Center, March 10 2020, available at https://www.fda.gov/media/135661/download

[254] Sophie Lewis, "First drive-thru coronavirus testing facility in the U.S. opens in Seattle," *CBS News,* March 10, available at https://www.cbsnews.com/news/drive-thru-coronavirus-testing-facility-us-seattle-washington/

[255] Elizabeth Chuck, "Cities turn to a new model of coronavirus testing: Drive-thru," *NBC News,* March 13, 2020, available at https://www.nbcnews.com/health/health-news/cities-turn-new-model-coronavirus-testing-drive-throughs-n1158256

Table 4-2: List of the US EUA-item (in-vitro diagnostic kits) by March 2020 [256]

EUA issued Date	Manufacturer	Type of Entity	Diagnostics	Targeted gene
02/29/2020	Wadsworth Center, New York State Department of Public Health's (CDC)	Public health lab	New York SARS-CoV-2 Real-time Reverse Transcriptase (RT)-PCR Diagnostic Panel	N1 and N2
03/04/2020	Abbott Molecular Inc.	Company	Alinity m Resp-4-Plex	RdRp, N, and others
03/05/2020	Clinical Research Sequencing Platform (CRSP), LLC at the Broad Institute of MIT and Harvard	Academic	CRSP SARS-CoV-2 Real-time Reverse Transcriptase (RT)-PCR Diagnostic Assay	N1, N2, and RNase P
03/12/2020	Roche Molecular Systems, Inc. (RMS	Company	cobas SARS-CoV-2	ORF1ab and E
03/13/2020	Thermo Fisher Scientific, Inc.	Company	TaqPath COVID-19 Combo Kit	ORF1ab, N and S
03/16/2020	Hologic, Inc.	Company	Panther Fusion SARS-CoV-2 assay	ORF1ab
03/16/2020	Laboratory Corporation of America (Labcorp)	Company	COVID-19 RT-PCR Test	N1, N2, and RNase P
3/17/2020	Quidel Corporation	Company	Lyra SARS-CoV-2 Assay	pp1ab
03/17/2020	Quest Diagnostics Infectious Disease, Inc.	Company	SARS-CoV-2 RNA, Qualitative Real-Time RT-PCR	N1 and N3
03/18/2020	Abbott Molecular	Company	Abbott RealTime SARS-CoV-2 assay	RdRp and N
03/19/2020	GenMark Diagnostics, Inc.	Company	ePlex SARS-CoV-2 Test	N/A
03/19/2020	DiaSorin Molecular LLC	Company	Simplexa COVID-19 Direct assay	ORF1ab and S
03/20/2020	Primerdesign Ltd.	Company	Primerdesign Ltd COVID-19 genesig Real-Time PCR assay.	N/A
03/20/2020	Cepheid	Company	Xpert Xpress SARS-CoV-2	N2 and E
03/23/2020	BioFire Defense, LLC	Company	BioFire COVID-19 Test	ORF1ab and ORF8
03/23/020	Mesa Biotech Inc	Company	Accula SARS-CoV-2 Test	N-genes

[256] "N/A" means it cannot find information about targeted genes in Instruction For Use (IFU) uploaded in the FDA website. See, the US FDA, "In Vitro Diagnostics EUAs - Molecular Diagnostic Tests for SARS-CoV-2," last accessed on May 1, 2021, available at https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-molecular-diagnostic-tests-sars-cov-2

03/24/2020	PerkinElmer, Inc.	Company	PerkinElmer New Coronavirus Nucleic Acid Detection Kit	ORF1b and N
03/25/2020	Avellino Lab USA, Inc	Company	AvellinoCoV2 test	RNP and E
03/26/2020	BGI Genomics Co. Ltd	Company	Real-Time Fluorescent RT-PCR Kit for Detecting SARS-CoV-2	ORF1ab and β-Actin
03/27/2020	Abbott Diagnostics Scarborough, Inc.	Company	ID NOW COVID-19	RDRP
03.27/2020	Luminex Molecular Diagnostics, Inc.	Company	NxTAG CoV Extended Panel Assay	ORF1ab, E and N
03/30/2020	NeuMoDx Molecular, Inc.	Company	NeuMoDx SARS-CoV-2 Assay	Nsp2 and N
03/30/2020	QIAGEN GmbH	Company	QIAstat-Dx Respiratory SARS-CoV-2 Panel	RdRp and E

Despite the February 29 announcement and following efforts to adopt drive-thru systems, the US testing capacities remained at a minimum until mid-March 2020, when fully automated real-time IVDs were authorized under EUA and became commercially available. As of March 13, CDC labs had tested some 3,900 specimens of the virus, while U.S. public health labs had tested over 12,000 specimens.[257]The FDA introduced a new detailed COVID-19 testing guideline on March 16 that delegated the centralized authority of approving diagnostic tests to local laboratories (under CLIA). The most prominent features of this new guideline were 1) authorities for tests developed and used by laboratories are devolved on state authority instead of federal authority (FDA), and 2) the relaxed regulations (issued February 29) to laboratories under the CLIA were extended to commercial diagnostic test

[257] Matt Gutman,Christina Carrega, andSony Salzman, "What to know about coronavirus testing, including drive-thru clinics, as COVID-19 spreads in US", *ABC News,* March 19, 2020, available at https://abcnews.go.com/US/coronavirus-testing-including-drive-clinics-covid-19-spreads/story?id=69584513

manufacturers.[258] Most EUAs for IVDs began to be granted after March 16, 2020 as seen in Table 4-2.

Table 4-3: Authorized Molecular-Based Laboratory Developed Tests (LDTs) for Detection of Nucleic Acid from SARS-CoV-2

EUA issued Date	Manufacturer	Type of Entity
03/31/2020	Yale New Haven Hospital, Clinical Virology Laboratory	Medical Laboratory
04/02/2020	Diagnostic Molecular Laboratory - Northwestern Medicine	Medical Laboratory
04/02/2020	Infectious Disease Diagnostics Laboratory - Children's Hospital of Philadelphia	Medical Laboratory
04/03/2020	Massachusetts General Hospital	Medical Laboratory
04/10/2020	Orig3n, Inc.	Company
04/10/2020	Specialty Diagnostic (SDI) Laboratories	Company
04/13/2020	Integrity Laboratories	Company
04/14/2020	Exact Sciences Laboratories	Company
04/23/2020	Southwest Regional PCR Laboratory LLC. dba MicroGen DX	Company
04/24/2020	Ultimate Dx Laboratory	Company

In addition to the March 16 announcement, the FDA issued another new policy on March 31, 2020, referred to as 'Umbrella EUA.' The umbrella EUA is an EUA for laboratory-developed tests (LDTs) for the detection of SARS-CoV-2 that meet certain criteria for eligibility described in the EUA. Under this EUA, authorized tests are authorized for use in the single laboratory that developed the authorized test and that is

[258]The US FDA, "Statement: Coronavirus (COVID-19) Update: FDA Provides More Regulatory Relief During Outbreak, Continues to Help Expedite Availability of Diagnostics," March 16, 2020, available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-provides-more-regulatory-relief-during-outbreak-continues-help

certified under CLIA.[259] Therefore, as seen in Table 4-3, nine LDTs from nine different laboratories received Umbrella EUA status during April.

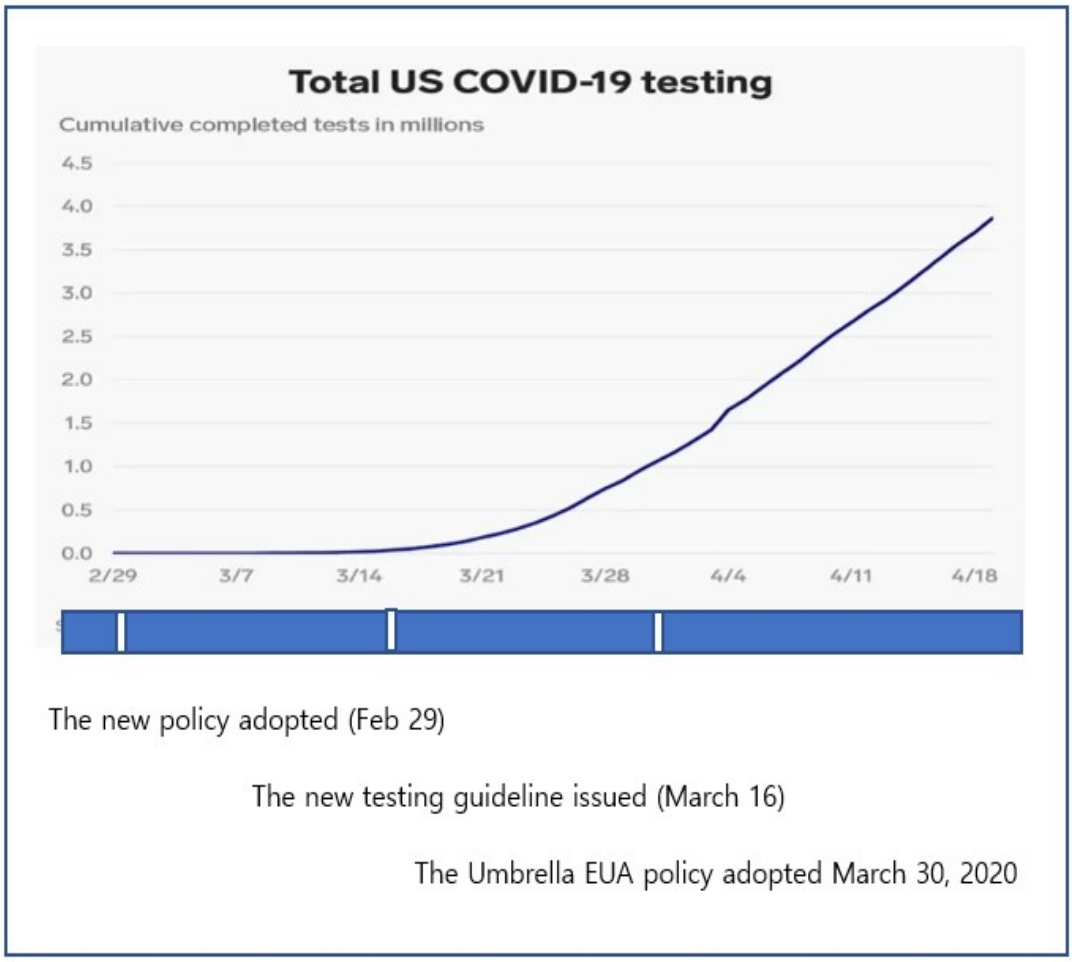

Figure 4-6: Total US COVID-19 Testing [260]

[259] The US FDA, "Umbrella EUA" on March 31 2020, available at https://www.fda.gov/media/136598/download

[260] Adding timeline on the Business Insider's graph; see, Andy Kiersz, "The US has now tested more than 4 million people for the coronavirus, but the number of tests being done per day is plateauing," *Business Insider,* April 20, 2020, available at https://www.businessinsider.com/coronavirus-tests-us-total-daily-counts-over-time-2020-4

Along with the increasing number of EUA issuances, the number of COVID-19 tests in the United States skyrocketed as seen in Figure 4-6. However, the rapid increase in US COVID testing numbers since mid-March seems a red-flag that the US EUA did not work effectively in the early phase of the COVID-19 pandemic. Rather, the decentralizing public health authority of development and distribution of coronavirus testing kits to local and private laboratories (under CLIA) contributed to the rapid increase of the US testing numbers.

In sum, South Korea and the United States have different laboratory partnership in terms of issuing EUAs for diagnostic kits; the former is inclusive and the latter is exclusive. In Korea, the Korean academia associations played a leading role in verification and certification of the private sector (manufacturers, laboratories, and medical centers) with common standards and procedures while public health authorities (KFDA and KCDC) served as moderators. Due to the academia leadership, it was easy to share standard operation procedures (SOP) for newly issued EUA-item widely in all public and private medical institutions and labs. Therefore, mass-production of various diagnostic kits enabled the private sector to make these kits commercially available. On the other hand, the US public health authority (FDA and CDC) were exclusive when issuing the first EUA-item. Since the CDC's exclusive decision to use N-genes alone when developing the new coronavirus testing kit turned into failure, there were no alternatives in the private sector due to the clash between the CLIA and EUA requirements. The CLIA did not demonstrate an effective leadership to bridge private sectors (labs) with public health authority (the EUA issuance). Instead of sharing SOPs or knowhows, CLIA clashed with EUA. Laboratories under CLIA were used to develop their own LDTs, but they were unfamiliar with the complex process of the EUA

submission as well as FDA's oversight on their activities. As a result, the US testing capacities expanded only after the FDA decided to decentralize testing authorities to private and academic labs under the CLIA.

Accessibility Differences – Free Testing versus Insurance Providers

Insurance is one of key factors for health service accessibility. The United States and South Korea have different insurance systems which had an impact on their ability to maximize utilization of the diagnostic tests that were authorized for emergency use. South Korea has a national insurance system run by the government, while the United States has a complicated insurance system with various insurance providers. The Korean EUA is integrated with the national insurance system which lowered the price of in-vitro diagnostic kits authorized for emergency use at the beginning of the pandemic. In contrast, the U.S. EUA did not play a role in adjusting the price of diagnostic tests for consumers and patients and supplementary policies and subsidies had to be implemented instead in a piecemeal and patchwork fashion.

As discussed in Chapter 3, diagnostic tests authorized for emergency use in Korea are automatically covered by the country's national health insurance system The Ministry of Health and Welfare (MOHW) decided to cover all medical expenses involved with COVID-19, from diagnosis to quarantine to treatment. Especially with regards to diagnosis, the MOHW announced that the national health insurance would cover of the price of an EUA item (diagnostic kits), and then medical institutions can purchase and use an authorized item (diagnostic kit) at the insurance-covered price. On February 7, 2020, the MOHW released a code of insurance claims for COVID-19 testing and set the price for testing at $200 (160,000 won in Korean currency); $100

each for upper and lower respiratory samples. The test is free if the person is deemed a close contact to an infected person under investigation (PUI) under the 3T strategy or if a doctor recommends the test for medical reasons. The national health insurance covered 100% of testing expenses if patients met these two guidelines. On the other hand, patients paid 100% of the testing expense ($200) if they obtained testing for self-care purposes. This was a prominent feature of the Korean EUA that aims to maximize the number of tests by lowering the price.

Some public health experts argue that the testing price should be even lower to further increase the number of people getting tested; however, the Director of the KCDC stated that it is difficult to cover people getting tested for unnecessary or self-care purposes. Korean public health authorities were concerned that unlimited, free testing for all people could disrupt the effective allocation of resources, given the fact that the world faced a shortage of diagnostic kits. The Korean public health authority believed that free testing for those with medical reasons for a test and a $200 charge for those seeking self-care was the appropriate guideline for maximizing the number of tests while minimizing waste. The number of people tested and the prices in Korea, the United States, China, Japan, and Singapore can be seen in Table 4-4. As the epicenter of the COVID-19 pandemic, China provided diagnostic testing, including computed tomography (CT) scans, for less than US$100. Due to the shortage of testing kits, the Chinese public health authority recommended running CT scanning first, and then conducting a free diagnostic test if signs of COVID infection were detected by the CT

scan. Japan and Singapore provided free testing, but the subjects eligible to receive the tests was quite limited by strict rules due to the shortage of testing kits.[261]

Table 4-4: Comparison of Price and Testing Volume in Five Countries[262]
(All data is as of March 2, except Singapore (Feb 25)

	S. Korea	U.S.	China	Japan	Singapore
Test price ($USD)	$200	$1,400	Less $100	Free but limited availability	Free but limited availability
Number tested	109,591	472	Unknown	2,517	1,364
Number infected	4,212	85	80,026	256	106

Unlike in the South Korean case, the test price of COVID-19 testing became a hot issue in the United States. Not only was there a shortage of diagnostic testing capabilities but also concerns that the high price of the test could cause people to hesitate to get tested. A survey from the Commonwealth Fund and NBC News on 20 March 2020, showed that found 68% of Americans say the potential out-of-pocket costs associated with tests or treatment would be either very or somewhat important in their decision to seek care.[263] In the United States, 28 million people are uninsured, lowering

[261] Dailymedi New, *Ibid.* March 2, 2020.

[262] 데일리메디, 코로나 19 검사비, 韓 16 만원·美 170 만원·中 10 만원 In English [Dailymedi News, "COVID-19 Testing Price, Korea $20, the US $1,400, China $10"], March 2, 2020, available at http://www.dailymedi.com/detail.php?number=853488

[263] Paige Minemyer, "As number of COVID-19 cases rises, many Americans fear costs of care, testing," *FiereHealthcare.com,* March 23, 2020, available at https://www.fiercehealthcare.com/payer/as-number-covid-19-cases-rises-many-americans-fear-costs-care-testing ; original survey data is retrieved from NBC News and Commonwealth Fund Health Care Poll, "What Are Americans' Views on the Coronavirus Pandemic?, *The Commonwealth Fund*, surveyed on March 20, 2020, available at https://www.commonwealthfund.org/publications/surveys/2020/mar/what-are-americans-views-coronavirus-pandemic

the possibility of these Americans to seek testing due to the cost. Many experts warned that the US pandemic prevention efforts would be fruitless if COVID-19 testing was not made free for all Americans.[264]

As a result, two major legislative efforts passed in March 2020 to finance free testing for uninsured people: the Families First Coronavirus Response Act (FFCRA) passed on March 18 and the Coronavirus Aid, Relief, and Economic Security (CARES) Act passed on March 27.[265] The FFCRA provides employees with paid sick leave or expanded family and medical leave for COVID-19 related reasons.[266] The CARES Act also provides fast and direct economic assistance for American workers, families, and small businesses.[267] Both new policies cover and reimburse COVID-19 diagnostic testing.[268]

By December 2020, public concern about the cost of getting tested seemed to be relieved. According to a survey, the primary reason Americans chose not to get a COVID-19 test was concern about exposure to the virus (30 percent); with others believing that it was very unlikely they had COVID-19 (21 percent); concerns over having to quarantine while waiting for results or if they were positive (15 percent); and

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[264] Gavin Yamey, "Why Coronavirus Testing Should Be Free for All Americans," *Time*, March 5, 2020, available at https://time.com/5797295/coronavirus-testing-free-all-americans/

[265] Wage and Hour Division, US Department of Labor, "Paid Leave Under the Families First Coronavirus Response Act, Federal Register," Doc cite: 85 FR 19326, Doc Num: 2020-07237, available at https://www.federalregister.gov/documents/2020/04/06/2020-07237/paid-leave-under-the-families-first-coronavirus-response-act

[266] US Department of Labor, "Families First Coronavirus Response Act: Employee Paid Leave Rights," last accessed on March 1, 2021, available at https://www.dol.gov/agencies/whd/pandemic/ffcra-employee-paid-leave

[267] US Department of the Treasury, "The Treasury Department is Delivering COVID-19 Relief for All Americans," last accessed on March 1, 2021, available at https://home.treasury.gov/policy-issues/cares

[268] Centers for Medicare & Medicaid Services, "*FAQS ABOUT FAMILIES FIRST CORONAVIRUS RESPONSE ACT AND CORONAVIRUS AID, RELIEF, AND ECONOMIC SECURITY ACT IMPLEMENTATION PART 42*," April 11, 2020, available at https://www.cms.gov/files/document/FFCRA-Part-42-FAQs.pdf

cost (15 percent).[269] However, for cost to remain a primary barrier to getting tested for 15% of the population is still a considerable figure for public health policy-makers. A low reimbursement rate with an uncertain definition of "complete" reimbursement from insurers left the price of testing only partially covered, leading to increased out-of-pocket expenses for patients.[270] A survey on July 2020 also demonstrated that the COVID-19 testing prices exceeded the insurance coverages for COVID testing by either $51 or $100, depending on the test; that the median price for a COVID-19 was $127, with about half of hospitals pricing their tests between $100 and $199; and about one in five price their tests at more than $200.[271] Overall, testing prices varied across the largest hospitals in each state and whether hospitals were in-network or out-of-network for an individuals' insurance plan.[272]Therefore, although the FFCRA and the CARES Act contributed to reducing the financial burden of COVID-19 testing, testing prices for individuals remained unpredictable and not free.

[269] Healthcare Purchasing News, "Survey reveals three of four Americans avoided getting a COVID-19 test when they believed they needed one," December 11, 2020, available at https://www.hpnonline.com/patient-satisfaction/population-health-care-continuum/article/21202072/survey-reveals-three-of-four-americans-avoided-getting-a-covid19-test-when-they-believed-they-needed-one

[270] Sarah Kliff, "Burned by Low Reimbursements, Some Doctors Stop Testing for Covid," *New York Times,* Feb 3, 2021, last accessed on Feb 11, 2021, available at https://www.nytimes.com/2021/02/03/upshot/covid-testing-children-pediatricians.html

[271] The Kaiser Family Foundation, "Analysis Finds List Prices for COVID-19 Tests Range from $20 to $850 At Large Hospitals Nationwide," published on July 15 2020, available at https://www.kff.org/health-costs/press-release/analysis-finds-list-prices-for-covid-19-tests-range-from-20-to-850-at-large-hospitals-nationwide/

[272] Nisha Kurani, Karen Pollitz, Dustin Cotliar, Nicolas Shanosky, and Cynthia Cox, "COVID-19 Test Prices and Payment Policy," *Health System Tracker, Peterson-KFF,* July 15, 2020, available at https://www.healthsystemtracker.org/brief/covid-19-test-prices-and-payment-policy/

Conclusion

This chapter demonstrated that the effectiveness of the EUAs for in-vitro diagnostic kits during the early phase of the pandemic depended on their by integration with other supporting policies such as the public health surveillance system, partnerships between the government and academia and the private sector, , and financial support for patients who sought testing. In South Korea, the EUA contributed to South Korea's disease containment efforts, which used the EUA to optimize the effectiveness of initiating large-scale testing practices in the early phase of the pandemic. Korea's 3T disease containment strategy was facilitated by large-scale testing, well-defined and preplanned laboratory standards paired with active participation from the private sector contributed to the timely expansion of testing capacities, and free or cheap testing. All these three factors were based on the lessons learned from the 2015 MERS outbreak.

On the other hand, the homeland security-based approach to the EUA in the United States played a less effective role in its mass testing operations. As seen in the Korean case, a mass-testing strategy is an effective to respond to an infectious disease outbreak caused by a pathogen (such as SARS-CoV-2) that features non-specific symptoms and asymptomatic and pre-symptomatic transmission. However, the public health surveillance system (LRN-B) in the United States is specialized to detect and confirm biological threats, but is not designed to conduct \ high-volume testing. Also, the CDC, as centralized testing authority of the United States did not collaborate with the private sector and it even hampered the private sector's ability to quickly expand its testing capabilities to cover more of the population. Moreover, the complicated insurance system in the United States increased the financial burden on people who

wanted to get tested, reducing access to the tests. Consequently, the COVID-19 pandemic demonstrates that the US EUA with homeland security features was poorly integrated with other public health policies necessary for an effective rapid response to the COVID-19 pandemic.

There is strong evidence that the COVID-19 pandemic began in the United States as early as December 2019, a week before the first officially documented case. A NIH study demonstrated that seven cases emerged in five states (Illinois, Massachusetts, Wisconsin, Pennsylvania and Mississippi), weeks prior to the first documented cases in the United States.[273] Evidence of sporadic emergence of Sars-CoV-2 infections in New York were also discovered a full month before the first official case of New York.[274] These findings make it clear that the United States would have saved hundreds of thousands of lives if the pandemic response had been faster and more robust in the beginning of the pandemic, empowered by large-scale testing of both cases and contacts.[275] This chapter demonstrated that the United States was unable to set up large-scale testing practices until mid-March 2020. If the United States had set up an effective, large-scale testing system in the early phase of the pandemic, it could have saved hundreds of thousands of lives as well as minimized the economic impact of the

[273] Keri N Althoff et al., "Antibodies to SARS-CoV-2 in All of Us Research Program Participants," January 2-March 18, 2020, *Clinical Infectious Diseases*, 2021;, ciab519

[274] Matthew M. Hernandez et al., "Molecular evidence of SARS-CoV-2 in New York before the first pandemic wave," *Nature Communication*, 2021(12): 3463

[275] Philip Bump, "A better pandemic response might have saved hundreds of thousands of lives- and Trump's presidency", *The Washington Post*, March 25, 2021, available at https://www.washingtonpost.com/politics/2021/03/25/better-pandemic-response-might-have-saved-hundreds-thousands-lives-trumps-presidency/ ; also see, Bill Chappell, "U.S. Could Have Saved 36,000 Lives If Social Distancing Started 1 Week Earlier: Study," *NPR,* May 21, 2020, available at https://www.npr.org/sections/coronavirus-live-updates/2020/05/21/860077940/u-s-could-have-saved-36-000-lives-if-social-distancing-started-1-week-earlier-st

pandemic. To do so in next pandemic, the United States should rebuild its EUA policy and better integrate it with the rest of public health system.

CHAPTER 5: Significance and Recommendations

Conclusion

This dissertation explores the culmination of events and efforts that were necessary for the formulation and implementation of policies that allow for the emergency use of unapproved medical countermeasures (MCMs) – the Emergency Use Authorization (EUA) policies - in the United States and South Korea. As the life sciences and technology progress, the contemporary world is increasingly capable of overcoming many infectious diseases that have plagued humanity for years. However, there are many other diseases that remain unconquered or unknown as new diseases emerge, for which no MCMs are available. If effective MCMs to detect, treat, and prevent these diseases are unavailable, it is necessary to adopt alternative measures – the use of MCMs that are yet approved or have different approved uses than needed. EUA (Emergency Use Authorization) is a policy that allows the use of unlicensed MCMs or the off-label use of licensed MCMs to respond to a public health emergency for which no licensed MCMs are available.

This dissertation regards EUA policy as a key policy that characterizes each country's biodefense institution based on the policy's scale, objectives, and direct impact on the population. Reviewing the emergence and evolution of EUA policies,

allows an examination of the processes that led from a focusing event to the adoption of new policies and the further revision of the policies as informed by historical narratives and contemporary events. This dissertation shows that the US EUA pursued homeland security benefits by focusing on preparedness and response missions after the 2001 anthrax letter attack, while the South Korean EUA pursued public health benefits by focusing on disease containment missions after the 2015 MERS outbreak. As a result, the US EUA was specialized for mass-treatment practices while the Korean EUA was optimized for mass-diagnosis practices.

Biodefense and Historical Institutionalism

Historical institutionalism (HI) is a major camp of new institutionalism that studies the mutability of institutions and institutional changes at the meso-level. Many HI scholars have discussed the role of various endogenous factors and exogenous factors as the major driving forces for institutional change or evolution. Some scholars emphasizing endogenous factors frequently focus on the role of agent and internal conflicts while others emphasize exogenous factors that focus on the impact of environmental shifts or shocks as a critical juncture. Recently, scholars have tended to give more weight on the interaction of endogenous factors and exogenous factors. Scholars such as Slater and Simmons and Soifer highlight the role of precondition or 'antecedent condition' before a critical juncture in order to explain the dynamic of endogenous and exogenous factors resulting in institutional changes.[276]

[276] Dan Slater and Erica Simmons, *"Informative Regress: Critical Antecedents in Comparative Politics"*, Comparative Political Studies (2010), volume: 43 issue: 7, pp. 886–917; also see, Hillel

To understand in greater detail the process of policy changes that fill a gap in the meso-level analysis of historical institutionalism, this dissertation adopted a policy-level analysis using the Event-Related Policy Change Model formulated by Thomas Birkland. The meso-level theoretical discussions of historical institutionalism cannot account for how both endogenous and exogenous factors actually work when an institution begins to change. This dissertation explains the dynamic of endogenous and exogenous factors more detail in policy-level by adopting the Birkland's model, which backups the HI narratives for institutional changes.

From the HI perspective, this dissertation posits that biodefense as an institution consists of various policies and organizations that govern the behaviors of people and shape political objectives. The 2001 anthrax letter attacks and the 2015 MERS outbreak were critical junctures that caused significant changes to the biodefense institutions in the United States and South Korea. These critical junctures became focusing events that contributed to the emergence of a new policy domain in each country: homeland security in the United States and disease containment in South Korea. This dissertation demonstrates that the newly emerged policy domains played a key role in explaining how the impact of exogenous shocks interacted with the role of endogenous factors to change the biodefense institution in each country. The emergence of new policy domains accounts for how lessons from the focusing event were mobilized by different groups and new ideas were discussed within stakeholder communities.

Ultimately, a homeland security-oriented EUA policy was adopted in the United States and a disease containment-oriented EUA policy was adopted in South Korea.

David Soifer, *"The Causal Logic of Critical Junctures"*, Comparative Political Studies (2012), volume: 45 issue: 12, pp.1572-1597

Due to path dependency, institutional innovation often shares the same pathway of development as the previous innovation, and EUA policy in each country followed this pattern. The US EUA for treatment with its homeland security objectives has evolved into an all-hazards preparedness to respond to all potential and actual biological threats to US homeland security. On the other hand, the Korean EUA for diagnosis with its disease containment objectives has evolved to strengthen its detection and diagnosis capacities by adding the mission of radiation detecting for radiological containment.

EUA and COVID-19 pandemic

These different characteristics of each country's EUA policy, developed within different policy domains, was evident in the role they played in US and Korean disease prevention and control practices during the COVID-19 pandemic. Given effective integration of an EUA policy with the EUA-supporting policies (such as public health surveillance, laboratory partnership, and insurance policy), South Korea's use of new diagnostic kits was optimally utilized in disease prevention and control practices. In contrast, the US EUA's homeland security objectives were specialized to deal with highly pathogenic biological agents that could be exploited for bioterrorism, but was less likely to be effective against naturally-emerging diseases that cause a pandemic. Particularly for new infectious disease like the novel coronavirus SARS-CoV-2 that has asymptomatic and pre-symptomatic transmission and non-specific symptoms, large-scale testing is the only way to effectively contain the disease outbreak. However, unlike the South Korea case, homeland security-oriented US EUA did not allow the United States to expand its testing capacities immediately. Especially, the US EUA revealed limitations to its integration with public health surveillance, laboratory-

partnership, and testing accessibility, which hampered the rapid expansion of testing capacities in the beginning of the pandemic. Thereafter, once the limitations of the EUA were circumvented, the testing capacity of the United States began to catch up to that of South Korea, and later skyrocketed after solving these issues.

Implications and Limitations

The primary research methodology used in this dissertation was case studies. As with any qualitative research method, case studies have limitations and pitfalls.[277] This research had no choice but to select the two cases – the United States and South Korea – for comparative study. Prior to the COVID-19 pandemic, the United States and South Korea were only two countries with EUA policies established by legislation. In response to the COVID-19 pandemic, many other countries have adopted EUA or EUA-like policies.[278] For example, United Kingdom has legislated an EUA-like policy for using COVID-19 vaccines, which grants a temporary authorization of the supply of unlicensed vaccines.[279] Further research is needed on how EUA policies in the other countries are formulated and evolve.

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[277] Alexander L. George and Andrew Bennett, *Case Studies and Theory Development in the Social Sciences,* (MA: MIT Press, 2005) pp. 22-25

[278] Clare Dyer, "Covid-19: Government poised to amend regulations to allow use of unlicensed vaccine," *the BMJ,* 2020; 370:M3757, September 28, 2020, available at https://www.bmj.com/content/370/bmj.m3757 ; also see, Aljazeera News, "UAE announces emergency approval for use of coronavirus vaccine," September 19, 2020, available at https://www.aljazeera.com/news/2020/9/15/uae-announces-emergency-approval-for-use-of-coronavirus-vaccine

[279] United Kingdom, Department of Health and Social Care, "Consultation document: Changes to Human Medicine Regulations to support the rollout of COVID-19 vaccines," Aug 28 2020, available at https://www.gov.uk/government/consultations/distributing-vaccines-and-treatments-for-covid-19-and-flu/consultation-document-changes-to-human-medicine-regulations-to-support-the-rollout-of-covid-19-vaccines.

Moreover, COVID-19 is an on-going event as of the writing of this dissertation. Therefore, this dissertation aimed to explore the relationship between EUA policies in the United States and South Korea and the testing capacities in those countries during the early phase of the pandemic. This parameter led the timeline of chapter 4 to extend only to mid-March of 2020. The dissertation demonstrates that during this timeframe the Korean EUA under the disease containment domain performed well while the US EUA under the homeland security domain faced huge challenges in expanding testing capacities. As expected based on theory, the US EUA performed much better in the development of therapeutic drugs and vaccines. The United States issued EUAs for COVID-19 vaccines (produced by Pfizer and Moderna) for the first time in the December 2020, and effectively launched a mass-vaccination campaign. However, South Korea hesitated to use these new COVID-19 vaccines. South Korea did not begin to conduct a COVID-19 mass-vaccination campaign until new legislation was approved in March 2021 that extended Korea's EUA policy to cover therapeutic drugs and vaccines. Further research should compare how the US EUA performed in terms of developing medical countermeasures and enabling mass-vaccination, while South Korea public health authority hesitated in decide whether to authorize new medical countermeasures for emergency use in response to the pandemic.

Policy Recommendations

The findings of this dissertation provide the basis for policy recommendations for the United States, South Korea, and other countries that have recently adopted or are thinking of adopting an EUA policy, that should help these countries design biodefense policies optimized to their public health and security environments.

For the United States:

The US EUA gives more weight to counter-CBRN activities and goals because the US EUA was legislated under homeland security domain based on the experience of the 2001 Amerithrax. Although the US EUA policy evolves to cover all-hazards from CBRN threats to infectious diseases, the US EUA is originated from the post-Amerithrax homeland security movements. In the light of the pandemic response during the early phase of the COVID-19, the US public health authority overlooked the features of a highly contagious disease, that limited the effectiveness of the US EUA policy integrating with other supportive disease control and prevention policies.

1. During the pandemic, the United States circumvented EUA to avoid the clash with CLIA. Thus, the legislative efforts to coordinate EUA issuance with CLIA is needed. The US EUA should be extended to include coverage of LDTs under CLIA. In order to embrace LDTs and commercial IVDs, the US public health authority is better to provide private sectors with guidelines (recommendations) for the development of testing assay, not have the CDC be the sole authority for the design of primers & probes.
2. The United States should allocate more resources to rebuilding epidemiological investigation capabilities at the state and local level. Increasing the number of epidemiology expertise is important, but also EUA for diagnostic kits is one of the effective tools to timely support epidemiological investigation missions to test and trace disease spread.
3. The United States is encouraged to set national-wide standards of verification and validation for IVDs to share various entities such as private laboratory, manufacturer as well as public health laboratory.

4. Timely financial aid to cover the use of EUA items is needed, rather than *ex post* financial support such as the Economic Impact Payments (EIPs). Lessons learned from the COVID-19 pandemic is that lowing the price of diagnostics is significant to encouraging people to get tested.

For South Korea:

The South Korean EUA focuses on diagnostic capabilities, enabling superlative disease prevention and control during the initial phases COVID-19 pandemic. However, the disease containment-centric approach of the South Korean EUA may not be ideal to prevent and respond to other kinds of public health emergencies, such as attacks with biological weapons. Also, the Korean EUA under disease containment domain revealed the weakness for practicing treatment and vaccination campaign, comparing to the US EUA. Lessons learned from the weakness should be covered in further researches.

1. South Korea should strengthen individual laboratory's capabilities to identify and detect highly pathogenic biological agents, given the security environments surrounding Korea Peninsula.
2. The Korean EUA policy was revised in March 2021 to open the list of eligible products from diagnostic kits only to all MCMs including vaccines and drugs. However, the new Korean EUA has a provision like the Japanese Emergency Approval policy - "when importing investigational drug/vaccine, it should be used or authorized at least one foreign country equivalent to or more developed than South Korea." This provision will hamper the development of Korea's biopharma industry by encouraging the Korean government to import MCMs from abroad instead of investing in innovation at home by small and medium-

sized biotech companies.[280] Therefore, South Korea is encouraged to delete this provision.

For Countries that have recently adopted or seeking an EUA policy:

COVID-19 pandemic is an unprecedented pandemic that all countries have suffered from. It is not surprising that many countries are developing or adopting their own EUA policies during the pandemic. However, countries adopting and seeking EUA policy from the experience of COVID-19, as s focusing event, may develop a similar EUA policy with South Korea. These countries should make sure that:

1. EUA is not a political maneuver that political leadership decides to use new MCMs on impulse in the case of public health emergency. Rather EUA is a legal-based system that clearly determines what constitutes a public health emergency, when a public health emergency can be declared, who is responsible for the declaration of a public health emergency, and which types of MCMs are eligible for EUA issuance.
2. The Korean-like EUA policy under disease containment shows great performance for mass-testing practices to cut the chain reaction of disease transmission; but the Korean EUA also has a vulnerable point when investigational MCMs are used for treatment and vaccination missions.
3. Countries facing a low-risk of bioterrorism or biowarfare are not necessary to adopt the US-like EUA policy for homeland security purposes, but should make

[280] 김현중, "긴급사용승인과 대한민국 바이오산업의 미래," 월간조선, 2021.06.13, in English [HyunJung Kim, "Emergency Use Authorization and the Future of Korea's Biopharma Industry," *Monthy Chosun,* June 13, 2021], available at http://monthly.chosun.com/client/mdaily/daily_view.asp?idx=12695&Newsnumb=20210612695 th

sure that treatment and vaccination practices are key to terminating a disease outbreak.

Appendix – Additional Information

1. EUA law of the United States

The US Food and Drug Administration, *Questions and answers for public heal th preparedness and response stakeholders*, updated on January 2014, last acces sed on Nov 7, 2016.

MCM Emergency Preparedness and Response Provisions	***MCM Category***	***FD&C Act Section***
Amendments to the Emergency Use Authorization (EUA) Authority	* Unapproved MCMs * Unapproved uses of approved MCMs	§ 564
Determinations for EUA issuance		§§ 564(b)(1)(A)-(D)
Duration of HHS EUA declaration		§ 564(b)(2)
EUAs issued for preparedness purposes		§ 564(b)(1)
Data collection time period		§ 564(e)(1)(B)(iii)
Categorization of in vitro diagnostics (IVDs)		§ 564(m)

Summary of PAHPRA Amendments to the EUA Authority

2. EUA law of South Korea

Article 42 of Pharmaceutical Affairs Act, which was inserted on Pharmaceutical Affairs Act by Act No. 4852 on December 31, 1994. It was originally Article 34 in 1994, but it has pushed back to Article 42 as the size of the Act becomes larger.[281]

Pharmaceutical Affairs Act No.14328, December 02, 2016.
Article 42 (Permission, etc. for Importation of Drugs, etc.)

(1) Each person, who intends to engage in the business of importing drugs, etc., shall file a report on importation business with the Minister of Food and Drug Safety, as prescribed by Ordinance of the Prime Minister, and obtain marketing approval from, or file marketing notification with, the Minister of Food and Drug Safety for each product, as prescribed by Ordinance of the Prime Minister. The same shall also apply where he/she intends to modify the matters approved or notified.
(2) Notwithstanding paragraph (1), the Minister of National Defense or a person who has filed a report on importation business pursuant to the former part of paragraph (1) (hereinafter referred to as "importer") may import drugs, etc. without obtaining marketing approval, or filing marketing notification, of each product under paragraph (1) in any of following cases:
    1. Where the Minister of National Defense intends to import drugs, etc, not produced domestically for any urgent military purpose, following consultation with the Minister of Food and Drug Safety on the items and quantity of the drugs, etc.

Medical Device Act by Act No. 15486, Mar. 13, 2018
Article 46-2 (Special Cases concerning Medical Devices in Cases of Infectious Disease Pandemic, etc.)

(1) At the request of a relevant central administrative agency (including the Centers for Disease Control and Prevention), the Minister of Food and Drug Safety may

[281] Pharmaceutical Affairs Act, [Enforcement Date. December 31, 1994] [Act No. 4852, December 31, 1994, Partial Amendment], National Law Information Center in Ministry of Government Legislation, Seoul; Republic of Korea

engage in the following activities to adequately respond to infectious disease pandemic (including an outbreak of an infectious disease that could turn into a pandemic) under the Infectious Disease Control and Prevention Act or radiological emergencies under Article 2 (1) 7 of the Act on Physical Protection and Radiological Emergency:

1. Notwithstanding Article 6 (2), an act of having manufacturers who have not been granted manufacturing permission or manufacturing certification or who have not filed a manufacturing notification with respect to medical devices engage in manufacturing;
2. Notwithstanding Article 15 (2), an act of having importers who have not been granted import permission or import certification or who have not filed an import notification with respect to medical devices engage in importing.

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Article 34-2 of Infectious Disease Control and Prevention Act, [Enforcement Date. September 05, 2020.] [Act No.17067, March 04, 2020., Partial Amendment]", official translation by National Law Information Center in Ministry of Government Legislation, Republic of Korea, available at http://www.law.go.kr/LSW/eng/engMain.do

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