Biodefense and Emergency Use Authorization: Different Originations, Purposes, and Evolutionary Paths of Institutions in the United States and South Korea

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Research Article

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Abstract

Background:

Historical institutionalism (HI) determines that institutions have been transformed by a pattern of punctuated evolution due to exogenous shocks. Although scholars frequently emphasize the role of agency - endogenous factors – when it comes to institutional changes, but the HI analytic narratives still remain in the meso-level analysis in the context of structure and agency. This article provides domestic and policy-level accounts of where biodefense institutions of the United States and South Korea come from, seeing through emergency-use-authorization (EUA) policy, and how the EUA policies have evolved by employing the policy-learning concepts through the Event-related Policy Change Model.

Results:

By employing the Birkland's model, this article complements the limitation of the meso-level analysis in addressing that the 2001 Amerithrax and the 2015 Middle East Respiratory Syndrome (MERS) outbreak rooted originations and purposes of the biodefense respectively. Since the crisis, a new post-crisis agenda in society contributed to establishing new domestic coalition, which begin to act as endogenous driving forces that institutionalize new biodefense institutions and even reinforce them through path dependent way when the institutions evolved. Therefore, EUA policy cores (Post-Exposure Prophylaxis (PEP) in the United States and Non-Pharmaceutical Intervention (NPI) in South Korea keep strengthened during the policy revisions.

Conclusions:

The United States and South Korea have different originations and purposes of biodefense, which are institutions evolving through self-reinforce dependent way based on the lessons learned from past crises. In sum, under the homeland security biodefense institution, the US EUA focuses on the development of specialized, unlicensed PEP in response to public health emergencies; on the other hand, under the disease containment-centric biodefense institution, the Korean EUA is specialized to conduct NPI missions in response to public health emergencies.

Introduction

The emergency use of unapproved medical countermeasures (MCMs) is an innovative policy enabling the use of MCMs[1] that are not yet licensed by the domestic drug approval system to deal with public health emergencies immediately. Since the COVID-19 pandemic, the emergency use of unapproved MCMs has been continuously cited in the media and academia. Two countries – the United States and South Korea – have developed their own Emergency Use Authorization (EUA) policies to allow the 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 (IVD) kits on 4 February 2020. However, the continued lack of COVID-19 testing in the

United States slowed timely infection intervention, a clear failure when compared to the massive volume of suspected case testing undergone in South Korea [1].

What exactly is different about the EUA policy approaches between the two countries? Expanding on the existing HI literature, this article identifies the focusing events in the United States and South Korea that led to the emergence of different policy domains that shaped the different EUA policy of each country along three dimensions: origin, purpose, and features of the EUA policy. Also, this article determines path dependency that the EUA policies in both countries have gradually expanded in scope to include all possible threats in subsequent legislation. Theoretical debate in the HI school of thought between Hall and Taylor vs. Hay and Wincott provides us deepen insights fully incorporating new institutionalism in the context of the relationship between structure and agency [2][3][4]. Beyond the 'latent structuralism' title, many HI scholars have studied the role of agency – the attributes of power and idea – when it comes to the mutability of institutions. However, the analytical framework of HI still has theoretical limitations to analyze institutional changes at the meso-level only [5]. This article fills the theoretical limitation from the meso-level analysis of historical institutionalism by applying Thomas Birkland's Event-Related Policy Change Model to account for how institutional changes shape political behaviors in domestic and policy levels; for instance, how EUA policy was adopted, revised, and evolved occurred differently in the United States versus South Korea. First, this article determines the emergence of biodefense institutions in the United States and South Korea through the origins and purposes of the EUA policies in each country. 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 Middle East Respiratory Syndrome (MERS) outbreak and radiation exposure was later added to the list of targeted threats. It is worth noting that a homeland security centric biodefense institution in the United States and a disease containment centric biodefense institution in South Korea have been reinforced by subsequent policy revisions, instead of being replaced. Many emerging scholars emphasize the role of endogenous factors (e.g. political behaviors), the agent-centric narratives still remain in meso-level analysis, but have weak descriptive study portraying how institutional changes really worked. Thus, this article reviews the latest discussions dynamics of exogenous or endogenous factors, mutually shaping each other, when it comes to institutional changes. By integrating the HI narratives with Birkland's model, this article provides detail descriptive study illustrating how endogenous factors really worked within the relationship between structure and agency when institutions changed. In the last section, this article includes case studies of the United States and South Korea, which illustrate in detail how institutional change works in reality; in other words, how both countries adopted and revised their biodefense institution in different way.

[1] MCMs (Medical Countermeasures): consists of biologics (vaccines), therapeutic drugs and other medical devices that may be used in public health emergencies.

Background

Biodefense as an Institution

Institution is often defined as an organizational structure of the polity consisting of the formal or informal procedures, routines, norms and conventions, which would shape political behaviors and shape the outcomes of political processes [2][6][7]. In this context, 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 diverse biodefense activities across federal departments and agencies in order to protect American lives from biological threats [8]. Biodefense also includes the implementation of various activities related to counter-bioterrorism and biological warfare, arms control and nonproliferation, biosurveillance, emergency preparedness, and MCM development. Thus, biodefense entails those actions designed to counter biological threats, reduce risks, and prepare for, respond to, and recover from bioincidents [9]. The field of biodefense is thus treated as an institution where US national security concerns awake political leaderships to take actions for adopting, revising, or withdrawing biodefense policies [10].

There are multiple theories and models that seek to explain how policies, especially major policy changes, emerge. Echoing the tenets of historical institutionalism, this article posits that biodefense as an institution governing the behaviors of people and shape unique political objectives. The specific focus of this article is on policy changes (EUA policy) in the field of biodefense. An EUA is policy 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. As seeing Table 1, EUA policy represents the features of biodefense institutions in each country;

Table 1: Comparing Key Characteristics of US and Korean Biodefense

Characteristics	United States	South Korean
Origination of the Policy	2001 anthrax letter attack	2015 MERS outbreak
Purpose of the Policy	Preparedness & Response	Detection & Diagnosis
Target of the Policy	CBRN	Infectious Diseases
Revised Target	All-Hazards	Radiation Exposure

Structure and Agency: Different Origins and Purposes of Biodefense Institutions

Due to the different critical junctures – the 2001 anthrax letter attack and the 2015 MERS outbreak – therefore, institutional outcomes (set of processes – rules, procedures, or policies) of the two country have no choice but to be different; because the US EUA was born for homeland security purpose while the Korean EUA was born for disease containment purpose (Kim, 2021). The US EUA policy was first adopted since the 2001 anthrax letter attack and the Korean EUA policy was first adopted since the 2015 MERS outbreak, and these two crises are exogenous shocks leading the legislation of legal backgrounds for EUA policies in both countries. In general, 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 accounts for institutional origins and changes in the language of *critical juncture*, which is a decisive moment of innovation caused by crises (exogenous shocks) such as a revolution, war, or regime change. Critical juncture is referred to as a period of significant change which typically occurs in distinct ways of shaping the national political arena in different countries [2][6]. In

this view, the 2001 anthrax letter attack and the 2015 MERS outbreak are critical junctures of both countries respectively.

Due to the different critical junctures – the 2001 anthrax letter attack and the 2015 MERS outbreak – therefore, institutional outcomes (set of processes – rules, procedures, or policies) of the two country have no choice but to be different; because the US EUA was born for homeland security purpose while the Korean EUA was born for disease containment purpose [11]. In general, institutional outcomes shaping policy purpose and process are purely a matter of domestic politics deeply involved with political behaviors of agents such as coalitions or interest groups. Many HI literatures point out the limitation of structuralist HI narratives focusing solely on the results of exogenous factors. These scholars understand institutions as the products of agency, rather than constraints. The role of agents in the course of endogenous institutional change becomes central to HI discussions in addressing that human (agencies) enact institutions, and they likewise transform institutions in response to environmental changes, thus, institutional outcomes can change over time [12][13][14].

Building upon the HI narrative, this article analyzed the originations and purposes of EUA policy in the United States and South Korea. However, it is important to pay attention that both EUA policies had been revised by subsequent issues and events (e.g. Hurricane Katrina or H1N1 influenza in the United States); thus, 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. Although both EUA policies have been expanded, it is observed that policy cores of both EUAs are sustained and even strengthened on the course of policy revisions. For example, post-exposure prophylaxis (PEP) is the policy core of the US EUA policy specialized to the mass-distribution of vaccines in the case of CBRN terrorism (homeland security purpose), while non-pharmaceutical intervention (NPI) is the policy core of the Korean EUA policy specialized to the mass-testing campaign in the case of infectious disease outbreak (disease containment purpose). In theory, these 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 [15]. The main logical foundation of path dependence is “self-reinforcement” that 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 [16]. The self-reinforcing manner of institutional innovation is elaborated by the notion of *punctuated equilibria*, where 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 [17][18]. A distinguished biodefense scholar, Richard Danzig, points out, 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 actions [10]. In the same vein, the US federal biodefense policy and MCM development, particularly coverage of pediatric populations, was strengthened by legislations following Hurricane Katrina [19]. The tenets of punctuated evolution can answer why institutional changes have sustained a policy core of EUA policy in each country as if evolutionary system. 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 atop the previous one rather than replacing old with new, in essence similar to path-dependent innovations. 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 [13][20][21].

The purview and explanatory power of the punctuated equilibria framework long remained in structural-functionalist context, which discussed abstract causality between exogenous factors (environmental shifts or shocks) and a pattern of institutional change. Back into the debate between Hall and Taylor vs. Hay and Wincott, the crux of the matter is how we define and draw the dynamic of structure and agency in terms of institutional changes. Scholars emphasize the role of wider of meta institutional context in addressing agents and structures are mutually shaping over time [22]. 'Meta institutional' analysis examines institutional changes from various angles such as structural context, crises and wider power context or policy context [23]. To strengthen connectivity between exogenous and endogenous factors, moreover, Slater and Simmons (2010) highlight the role of the "antecedent condition," which precede a critical juncture to determine the precise causal and non-causal status of institutional changes [24]. Soifer (2012) also emphasizes a precondition of critical junctures, whether the permissive condition or the productive condition, to precisely analyze a causality of institutional changes [25].

Method

Policy Learning Model: Coherent Explanatory Power to back up Historical Institutionalism

The new HI literatures matured to give more attention to endogenous factors but still remain in the meso-level analysis, which hardly explain "how it actually changed?" To fill the weakness of descriptive power portraying how political behaviors were shaped within the interaction between structure and agency, this article 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. Scholars 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 [26][27][28]. Therefore, the learning process by which participants use information and knowledge to develop, test, and refine their beliefs becomes center of academic debates. These include notions of "political-learning" developed by Heclo [29], "policy-oriented learning" developed by Sabatier [26], "lesson-drawing" analyzed by Rose [30], "social learning" discussed by Hall [31], and "government learning" identified by Etheredge [32].

Building upon the discussion about policy learning process, Thomas Birkland develops a more detailed model for how focusing events (exogenous shocks) trigger the emergency of a policy domain that lays a groundwork for policy changes within society (seeing Figure 1). The policy domain is generally defined and studied as a component of the political system that is organized around substantive issues. Policy domains are largely socially constructed, varying with issues and politics, which leads to legislative enactment of major policy change [33]. Therefore, groups of congregated agencies (namely, society or the public) and the dynamic interactions among agencies such as conflicts and contests between agents (e.g., turf war) become the centers of institutional change. 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 [34].

This model well demonstrates mutuality between structure and agent in addressing that once am exogenous shock triggered the emergence of new political agenda and political behaviors of the agents, these endogenous factors lead institutional changes; but the newly mobilized endogenous factors also perform a vital role of sustaining and reinforcing policy cores. Therefore, since a group was mobilized after a crisis, the group has remained in society and played significant roles in strengthening policy cores (e.g. PEP and NPI) by the self-reinforcing manner. Case study in the next chapter illustrates how homeland security group was mobilized in the United States after the 2001 Amerithrax and why the policy core (PEP) of the US EUA was strengthened by the twice policy revision after Hurricane Katrina (2005) and the H1N1 pandemic (2009). Comparing to the US case, epidemiologists were mobilized in Korea after the 2015 MERS outbreak, and the policy core (NPI) of the Korean EUA was strengthened by a revision as a result of the 2018 trade war with Japan.

Case Study of the United States

Twin Focusing Events (9/11 and Amerithrax) and a New Agenda (Counterterrorism)

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 [35]. 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. 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.

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, it was deemed necessary to recognize emerging CBRN terrorism as a potential new type of public health threat. On 12 October 2001, Vice President Dick Cheney stated that it is "reasonable" to assume the anthrax attacks were linked to the 9/11 terrorist attacks, because al-Qaeda-trained operatives know “how to deploy and use these kinds of substances [weaponizable biological and chemical materials]” [36]. 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” [37].

Accompanying the increasingly political narratives concerning CBRN terrorism threats, the majority of the 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

with focuses on 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 [38].

Homeland Security Group Mobilized

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 [39]. 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. 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.

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. On 12 June 2002, the Public Health Security and Bioterrorism Preparedness and Response Act (PL 107-188, 2002; also known as the Bioterrorism Act [40]) was signed into effect. 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 [40].

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. The U.S. General Accounting Office (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 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" [41].

Finally, 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 Homeland Security Act of 2002 was enacted on November 2002, which authorized the establishment of the US Department of Homeland Security (DHS). The homeland security group was deeply involved with the discussion of idea about biodefense as well as the legislation of Project Bioshield Act as seeing the issuance of the Homeland Security Presidential Directive-10 (HSPD-10). The title of the HSPD-10 – *Biodefense for the 21st Century* – 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" [42].

Biodefense and Idea Discussed

After the anthrax 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" against chemical biological, radiological and nuclear (CBRN) threats [41][43][44]. In terms of preparedness and response for national emergencies, particularly bioterrorism events, the mass use of post-exposure prophylaxis (PEP) emerged as key necessity to US biodefense [38]. 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. However, the CDC floundered when making a clear decision about the use of prophylaxis. 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 [45][46][47]. 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 [45].

Moreover, the initial post-exposure prophylaxis (PEP) program recommended 60 days of antimicrobial PEPs (either doxycyclineor ciprofloxacin), but later the CDC issued an extended regimen for 40 additional days [45]. The extension was recommended with or without three doses of anthrax vaccine adsorbed (AVA) under an investigational new drug protocol as an extended PEP program [46]. 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, 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” [48].

Legislation of the Project Bioshield Act & EUA

The prophylaxis-related issues became the center of lessons learned from the 2001 anthrax letter attack. Most 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. Finally, President George W. Bush signed the Project BioShield Act of 2004 into law, which facilitated the development of MCMs against CBRN agents. 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 WMDs [49]. 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 [50]. 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.

Evolution of the EUA: PAHPA and PAHPRA

The Project Bioshield Act has evolved and revised via the Pandemic and All-Hazards Preparedness Act of 2006 (PAHPA) after the Hurricane Katrina (2005) and the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) after the 2009 H1N1 pandemic. The experience of the Hurricane Katrina (2005) provides the United States the significant lessons to adopt the concept of “all-hazard emergency preparedness” integrating biodefense with public health areas [19]. 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 [51]. Due to the different public health and security environments, the Bush’s administration’s biodefense strategy has focused on preparing for and responding to public health threats, the Obama’s biosecurity strategy gives the emphasis on prevention efforts [52]. The homeland security domain made by the Amerithrax began to embrace the concept of “emergency preparedness” by the PAHPA of 2006 after Hurricane Katrina and the concept of “disease control and prevention” by the PAHPRA of 2013 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.

Although the scope of the EUA policy expanded in accordance with the PAHPA of 2006 and the PAHPRA of 2013, these two revisions of the EUA policy shared the same path of development with the policy core – the use of unlicensed MCMs as post exposure prophylaxis (PEP) which has kept in the baseline of the newly expanded EUA policies. Under the PAHPA of 2006, two EUA models for doxycycline – the US Postal Service and City Readiness Initiatives (CRI) – 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. 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 antimicrobials (doxycycline hyclate tablets) in the case of an anthrax attack and its medical instructions to residential households within 48 hours [53]. Therefore, as seeing Figure 2, the EUA for doxycycline hyclate tablets, in conjunction with the CRI program, completed the mission of mass and timely distribution of PEPs.

The PAHPA of 2006 was reauthorized by the name of PAHPRA of 2013, and reinforced the mission of mass and timely dispensing of PEPs. The PEP programs for doxycycline such as City Readiness Initiatives are further 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 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" [54]. 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" [54].

Case Study of South Korea

Focusing Events (2015 MERS) and New Agenda (Disease Containment)

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 Middle East Respiratory Syndrome (MERS). The businessman had just returned from a trip to the Middle East; by visiting so many hospitals while the businessman was contagious, he unknowingly infected many healthcare workers and patients with MERS. MERS-CoV, the virus that causes MERS, is a member of the *coronaviridae* family. Same as SARS-CoV-2 causing COVID-19, MERS-CoV features non-specific flu-like symptoms, asymptomatic, and pre-symptomatic transmission, which is hard to identify early. The invisible disease was rapidly spread in Korea by the two amplifiers – nosocomial infection and super-spreader.

First, the MERS outbreak became intensified by nosocomial infection within hospitals [55]. Nosocomial infections, referred to as healthcare-associated infections (HAI), are infections acquired during the process of receiving health care services. In general, hospitals are hubs for sick people who are vulnerable to any kind of infectious diseases. 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. Second, super-spreaders became another disease amplifier of the MERS outbreak. The businessman (patient zero or index patient) started a chain reaction of disease transmission in multiple hospitals, rendering him a "super-spreader" [56]. This chain reaction of MERS infections further

perpetuated transmission as those infected persons sought medical attention at other facilities. 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 [57]. 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. Containment of the invisible disease spread within society was the first priority for the Korean public health authority.

Mobilization of the Public health Group

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 [58][59]. 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 [60]. Based on the Congressional resolution,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."* Based on this plan, Korea Center for Disease Control and Prevention (KCDC)'s capabilities and authorities were expanded, and**24-hour-a-day Emergency Operation Centers staffed by full-time epidemiologists were created in order to lead the initial response to reports of a new disease outbreak [2] [68].

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 [61]. 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.Korea society leaned from the 2015 MERS outbreak thatany delay in diagnosing, treating, and isolating an infected patient could unintentionally and unknowingly allow that patient to become a super-spreader. 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. This legislation effort implies that accurate and timely diagnostic capabilities are key to identify cases who 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 which becomes the foundation of a new policy – 3T practice (testing, tracing, and treatment) – later in the COVID-19 pandemic [62]. 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 [63]. Also, the Korean Academy of Science and Technology held a round-table discussion with medical professionals about the MERS outbreak and future response plans on 1 July 2015. The participants emphasized the adoption of a US-style EUA policy is essential to identify and trace cases as early as possible [64].

EUA Legislation in the Medical Device Act

To solve the super-spreader issue, South Korea public health authority adopted EUA policy, officially entitled *The Emergency Use Authorization of In-Vitro Diagnostics for Infectious Disease*. 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) [3] were added in the "Enforcement Regulations of the Medical Device Act" as a legal basis for the emergency use of in-vitro diagnostic kits. According to this law, by commissioner of KCDC, the commissioner of KFDA issues the exemption of testing kit's examination (authorizing emergency use or called to as EUA) in the case of a public health emergency defined in the Infectious Disease Control and Prevention Act. Because of the legal parameters of the Medical Device Act, the Korean EUA is only applicable to medical devices, such as in-vitro diagnostic (IVD) kits. In contrast to the US approach, which defines MCMs broadly, the Korean EUA cannot issue the use of novel vaccines or therapeutic drugs.[4]

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 [69]. 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.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, as seeing Figure 3. 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 and banned the import of Japanese seafood produced by the eight provinces near Fukushima. In May 2015, Japan filed a lawsuit with the World Trade Organization (WTO), arguing that Korea's import ban was unreasonable [65].

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. 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 [66]. It is worth noting that the Korean EUA was developed along the existing path emphasizing diagnosis (detection), a process of path dependency. 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" [67].

[2] KCDC was promoted to Agency-level organization during the COVID-19 pandemic (September 2020). Now the official name of this organization is Korea Disease Control and Prevention Agency (KDCA)
[3] 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
[4] The Korean EUA policy was revised in March 2021 to open the list of eligible products from diagnostic kits only to all MCMs including all biologics such as vaccines and therapeutic drugs.

Results

The 2001 Amerithrax and the 2015 MERS outbreak were critical junctures that caused significant changes to the biodefense institutions in the United States and South Korea. The US EUA pursued homeland security benefits by focusing on preparedness and response after the 2001 anthrax letter attacks, while the South Korean EUA pursued public health benefits by focusing on disease containment 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. Through the theoretical lens of historical institutionalism, these two critical junctures were decisive moments resulting in institutional innovation in the two countries. The EUA is the most representative case of the post-Amerithrax movement that a new institution – homeland security-oriented biodefense – was established in the United States. The Korean EUA was also created as part of a broader biodefense strategy to contain infectious diseases based on the country's experience with the 2015 MERS outbreak.

In addition to the role of exogenous shocks as critical junctures, these case studies demonstrate the actual role of endogenous factors when it comes to institutional change. Especially, the path-dependency narrative explains the unique evolutionary paths of the US and Korean EUA. The emergence of the new policy domains in these two countries marks a key linkage between exogenous and endogenous factors when institutionalizing biodefense systems. The homeland security group in the United States and the epidemiology group in South Korea were mobilized aftermath of the focusing events. As a result, the US 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. On the other hand, 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." Due to path dependency, institutional innovations in the two countries share the same pathway of development as their previous innovation, and EUA policy in each country followed this pattern. Therefore, the US biodefense

PEP core has strengthened in a “self-reinforcing” manner, despite subsequent policy revisions by other focusing events, under the homeland security domain. In the same vein, the Korean biodefense NPI core has strengthened under the disease containment domain.

Discussion

This study examined how the US and South Korea biodefense institutions are differently evolved in the light of the EUA policy. The homeland security-oriented biodefense institution of the United States and the public health centric biodefense institution of South Korea have developed unique features of biodefense capacities specialized to their security environments. 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. South Korea’s use of new diagnostic kits by EUA policy 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.

Conclusion

This paper 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.

Abbreviations

EUA
Emergency Use Authorization
MCMs
Medical Countermeasures
COVID-19
New Coronavirus caused by SARS-CoV-2 virus

PEP
Post Exposure Prophylaxis
NPI
Non Pharmaceutica Intervention
MERS
Middle East Respiratory Syndrome
CDC
Center for Disease Control and Prevention
FDA
Food & Drug Administration

Declarations

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The author declare that he has no conflicts of interest.

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Figures

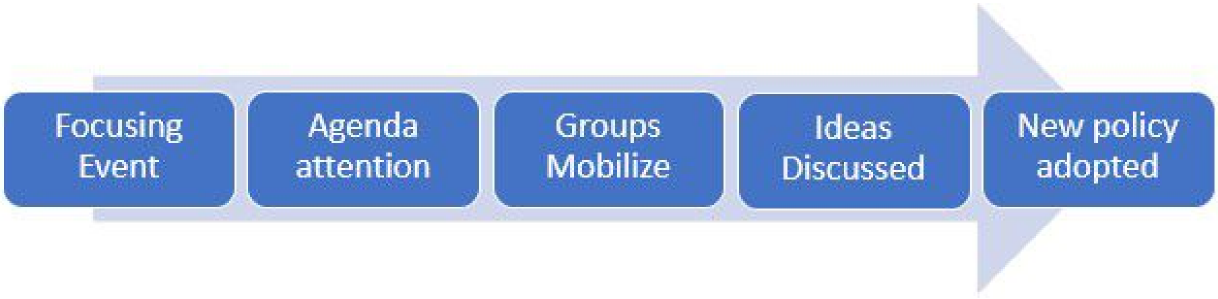

Figure 1

Event-Related Policy Adopting/Changing Process

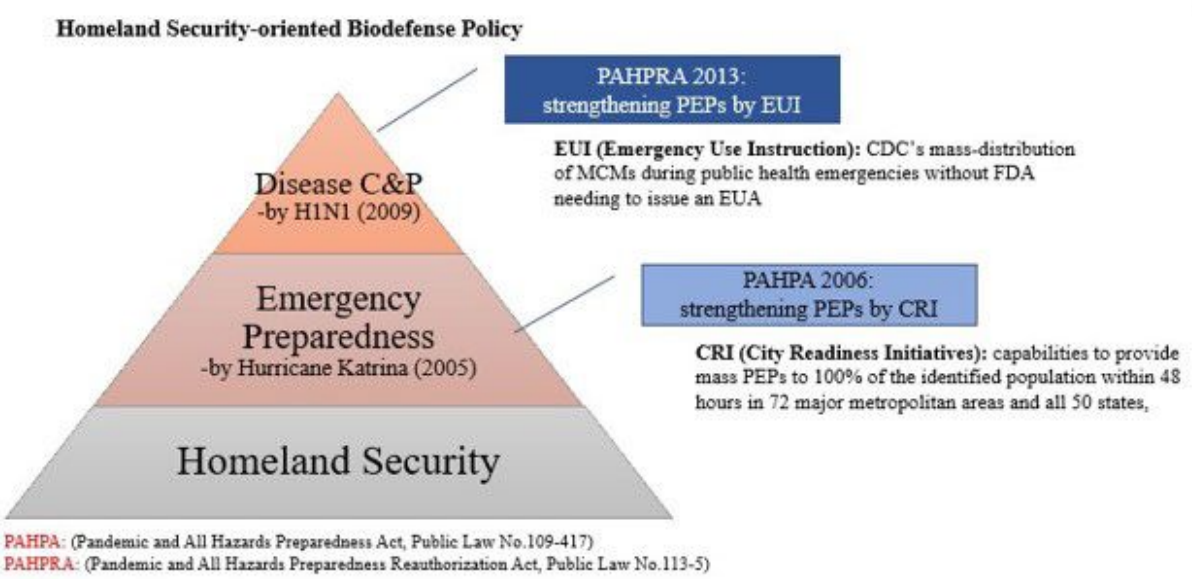

Figure 2

A Structure of the US Biodefense Institutions

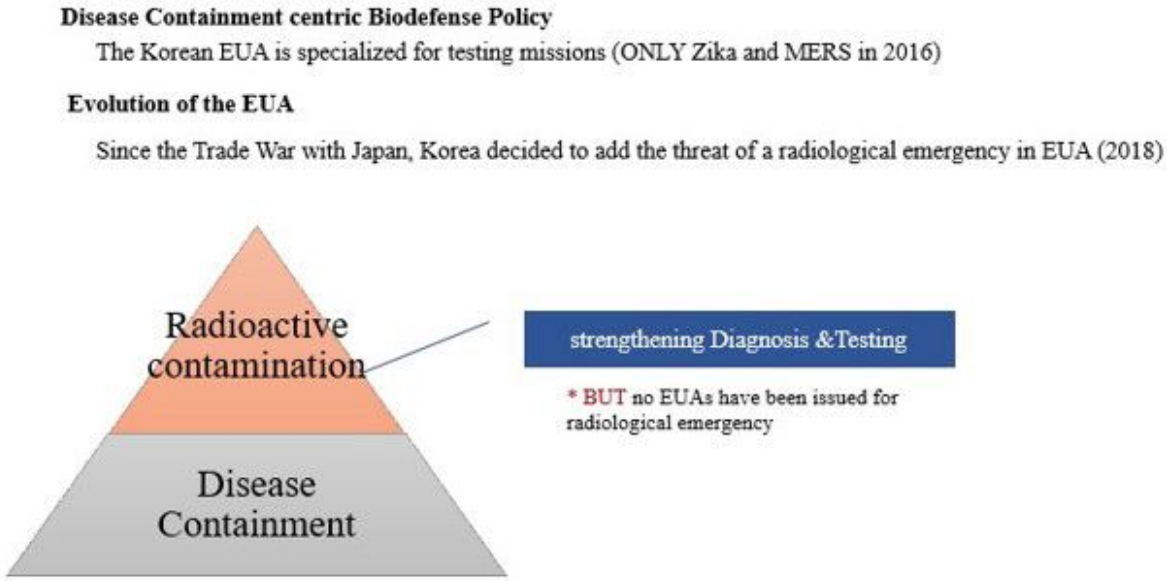

Figure 3

A Structure of the South Korea Biodefense Institutions