

2013

# The Select Agent Program and dual use research of concern: their effects on the regulatory environment of pandemic influenza studies

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**The Select Agent Program and dual use research of concern: their effects on the  
regulatory environment of pandemic influenza studies**

by

**Matthew House**

A thesis submitted to the graduate faculty  
in partial fulfillment of the requirements for the degree of  
MASTER OF PUBLIC ADMINISTRATION

Major: Public Administration

Program of Study Committee:

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2013

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## NOMENCLATURE

HHS	Health and Human Services
CDC	Centers for Disease Control and Prevention
WAH	work-at-home
USDA	United States Department of Agriculture
CRE	carbapenem-resistant enterobacteriaceae
DHS	United States Department of Homeland Security
AIDS	Acquired Immunodeficiency Syndrome
HIV	Human Immunodeficiency Virus
HPV	Human papillomavirus
HA	hemagglutinin
NA	neuraminidase
WHO	United Nations World Health Organization
ICU	intensive-care unit
HCW	healthcare worker

ACIP	Advisory Committee on Immunization Practices
HPAI	Highly Pathogenic Avian Influenza
DSAT	Division of Select Agents and Toxins
DURC	dual use research of concern
NSABB	National Science Advisory Board for Biosecurity
PHEP	Public Health and Emergency Preparedness
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
RO	responsible officer
PI	principle investigator
SOP	standard operating procedure
EH&S	Environmental Health and Safety
BMBL	Biosafety in Microbiology Biomedical Laboratories
GAO	Government Accountability Office

## ACKNOWLEDGEMENTS

I would like to thank my committee chair, Steffen Schmidt, and my committee members, Kelly Shaw, and Jim Roth, for their guidance and support throughout the course of this research.

I would also like to thank my friends (especially Mitch Owen, Eric Hoffmeyer, and Jeff Fletcher) for talking with me and tolerating my stress-induced difficulties throughout the past two years. I want to also offer my thanks to those who spoke with me on the subject of pandemic influenza; your expertise was crucial for this project.

The largest appreciation goes to mom. Without her endless love, support, and dutiful proof-reading, I would not be where I am today.



## ABSTRACT

The threat of pandemic influenza is one of the largest areas of concern for the 21<sup>st</sup> century, because of population and globalization. The effects of a serious pandemic were clearly seen in 1918 and the world narrowly missed a modern catastrophe when the low-mortality, but highly contagious, H1N1 Influenza circulated the globe.

Currently, H5N1 Avian Influenza represents the largest threat with regards to influenza, but should H1N1 mutate into a more lethal variety or H7N9 continue to spread, the results would be disastrous. There are a variety of factors that are associated with prevention and mitigation of a potentially lethal pandemic. Within the United States, research of deadly influenza is being conducted amid controversy. The two main camps of debate, science and security, both have legitimate points and valid claims for why they are correct. The United States government is tasked with attempting to have the best of both worlds in regards to biosecurity as witnessed with the Select Agent Program. The recent H5N1 study controversy renewed public and government interest for “dual use” research. The government is tasked with trying to permit scientific freedom while simultaneously minimizing risk of dangerous information dissemination. Because of the complexity of the situation, an ideal regulatory environment is extremely difficult, if not outright impossible, to create.

## CHAPTER 1

### INTRODUCTION

There are a large amount of problems afflicting the world. Tensions on the Korean peninsula, nuclear proliferation, financial unease, and a host of others prove to be problematic for government. One recent development has been the outbreak of a novel type of avian influenza, called H7N9. While less than 100 confirmed cases have been reported and only a fraction of them have proven fatal, worldwide health authorities are very concerned. Lethal pandemic influenza is a nightmare scenario for the United States and world community as the repercussions of it would impact every facet of human life.

This paper will begin with a fictional scenario regarding pandemic influenza and then touch on the overall threat of microbial agents. After outlining basic problems regarding pandemic influenza that cannot be solved, the paper will then detail the basic scientific aspects of viruses and influenza specifically, with special focus on H1N1 and H5N1. Two policy areas of influenza regulation within the United States will be focused on: the Select Agent Program and dual use research of concern. This paper will show that while rhetoric regarding the Select Agent Program and dual use research concern strongly favors deregulating and reducing government oversight of scientific research, it is far from simple. The federal government is caught in a very difficult problem: science vs. security. In these two cases, there often does not exist a simple and straightforward solution.

#### Viral Pandemic Scenario

The beginning day or days will be described as fairly innocuous. A large metropolitan hospital or clinic will see an unusually larger number of incoming patients with a variety of

symptoms. Otherwise healthy young adults will demonstrate varying symptoms including the traditional fever, cough, and muscles pains associated with seasonal influenza. Others may present respiratory difficulties ranging from the mild shortness of breath, a more severe case of pneumonia, or even serious respiratory failure. Still even others will present gastrointestinal pain and cramps, diarrhea, and nausea which are symptomatic of the painful but non-threatening “stomach flu.” All these patients with different, but potentially overlapping symptoms may not raise alarm bells in time for physicians to accurately diagnose them as having Highly Pathogenic Avian Influenza (H5N1).<sup>1</sup> As more cases present themselves, especially if they appear in different cities and regions, the pieces of the puzzle may be put together but by this time, containment will be difficult if not impossible.

Within days, the U.S. Department of Health and Human Services (HHS), along with the Centers for Disease Control (CDC), will be actively monitoring the growing situation and reporting to the Executive Branch hourly. The disease is recognized by laboratory results as confirmed human cases of H5N1 Influenza. It appears to have an incubation period of 3-5 days with sporadic reports suggesting an incubation time of upwards to 8-9 days.<sup>2</sup> The news of Avian Influenza is well known throughout the medical community as well as the general public within a week. Within the first week of the outbreak, federal and state employees are receiving reports of hospitals beginning to be inundated with patients due to a variety of reasons. The spread of the virus is accelerating, but many healthy patients are checking into hospitals because of media-inspired hypochondria. A more serious report has surfaced stating that many doctors and nurses are electing to stay home in fear that they will become contaminated and spread it to their

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<sup>1</sup> "Avian Influenza A Virus Infections in Humans," Centers for Disease Control and Prevention, June 21, 2012, <http://www.cdc.gov/flu/avianflu/avian-in-humans.htm>, (Accessed January 19, 2013).

<sup>2</sup> Yang Huai, et. al, "Incubation Period for Human Cases of Avian Influenza A (H5N1) Infection, China," *Emerging Infectious Diseases* 14, no. 11 (November 2008): 1819-821, doi:10.3201/eid1411.080509, 1819.

families. With a growing epidemic and fewer medical personnel, several medical facilities are near the point of collapse.<sup>3</sup>

Early on, the CDC has ascertained that the viral pathogen is being spread by aerosols, which are miniature droplets of contaminated water. These aerosols are spread when infected individuals cough or sneeze and expel them into the air or wipe them on a surface. The ideal measure to halt infection and protect healthy individuals would be through vaccination, but because of the nature of H5N1 influenza, there are no vaccines in existence yet although production has begun. Vaccines will not be ready for many weeks and until then, the only measures available are the use of anti-viral medications, such as the popular Tamiflu, and social distancing. By the end of the first week, mortality numbers are beginning to surface and the results are compounding the fears of the government and medical community; the new strain of H5N1 has a mortality rate of just over 50%, which is shy of the mortality of the pre-outbreak strain of 60%.<sup>4</sup>

At the end of the second week, hospitals and clinics are officially overflowing and in the hardest hit areas, some have virtually collapsed. Many medical facilities cannot treat all the cases of H5N1, much less the other every-day cases that come to medical facilities for relief and/or repair. There are fewer medical supplies by this point, not to mention fewer medical personnel, to treat simple broken bones or bacterial infections. Despite a full release of much needed medical supplies from the Strategic Emergency Stockpile by the U.S. federal government, many hospitals are low on anti-viral medications and every respiratory ventilator is being used. The mortality estimates have caused even the more diligent medical personnel to

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<sup>3</sup> William R. Clark, *Bracing for Armageddon?: The Science and Politics of Bioterrorism in America*, (New York: Oxford University Press, 2008), 5-7.

<sup>4</sup> Clark, 7-8.

forgo their employment and practice isolation as a means of social distancing. At the end of the third week, the viral the epidemic has officially spread beyond U.S. borders and has become a global epidemic, or pandemic. Because the first confirmed cases of H5N1 were reported from the United States, nations around the world are closing their borders to U.S. citizens and cancelling U.S. imports. Global trade is grinding to a halt and markets are feeling the effects. Because of the seriousness of the contagion and scarcity of medical supplies, reports of civil unrest and riots are being reported in the hardest hit areas. Local law enforcement is undermanned and sufficiently overwhelmed. Many states have mobilized their National Guard units to maintain basic law and order.<sup>5</sup>

While certain areas have suffered more than others and some have been almost disease-free, almost all schools and universities around the nation are closed by the third week. The few that are still open are seeing low attendance. Sporting events, both collegiate and professional have been cancelled and many large businesses are closed, or operating via telecommuting. Many high-infection areas are seeing increasing food shortages as drivers are refusing to enter for fear of contracting the avian influenza.<sup>6</sup> Adding to the severity of the situation is the role of the media. The 24-hour-news cycle, with multiple pundits weighing their opinions and large amount of incorrect information on the Internet, stokes the public's fears even further. Clever catchphrases like the "killer flu" and grossly incorrect death rates continue to fuel panic and negate rational actions.<sup>7</sup> Between the lack of medical supplies and care, shortage of food, decreased law enforcement and media fear-spreading, civil disorder grows.

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<sup>5</sup> Ibid., 9.

<sup>6</sup> Ibid., 9-10.

<sup>7</sup> United States of America, National Defense University, *Pandemic Panic in the Media*, By Robert Armstrong, Mary B. Hill-Harmon, and Stephen Prior, July 2005,

The United States' nature of federalism means that health care varies from state to state. Also, despite the resources of the federal government and National Guard, both entities do not have adequate amounts of resources to assist or supplant programs and responsibilities typically controlled by the state governments. Also, despite the severity of the situation, the legal impediments are still in place which create confusion and an inability to respond to certain situations. The U.S. government is also fearful of drastic and illegal state actions to halt the spread of infection. States in lesser hit areas may be inclined to utilize their National Guard and police resources to close state borders, especially if they border disaster-zone states. This action, while illegal, would seriously affect interstate commerce and make transportation of supplies and personnel much more difficult. Federal intervention would be required if this were to occur and by this time, federal resources are spread very thin.<sup>8</sup>

While the infection is leveling off by the end of the first month, the death toll is continuing to rise and the first vaccines are nowhere near ready for release, despite unprecedented waivers of FDA and other federal guidelines. Typical vaccine production, from start to finish under ideal circumstances, is about 5 months.<sup>9</sup> By this time, the virus is appearing in many countries and global trade is crumbling. Foreign investment in American companies halts and foreign possession of U.S. holdings are being liquidated. Banks are closing and other businesses are closing temporarily or going broke.<sup>10</sup> One of the larger reasons a full financial collapse has yet to occur is because of a heavy reliance on e-commerce and the increased ability for many Americans to work from home. Never before has a workforce been able to complete

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<http://www.ndu.edu/CTNSP/docUploaded/Panic%20in%20the%20media%20Paper.pdf>, (Accessed January 19, 2013),” 1-4.

<sup>8</sup> Clark, 12-13.

<sup>9</sup> "Pandemic Influenza Vaccine Manufacturing Process and Timeline," WHO, August 6, 2009, [http://www.who.int/csr/disease/swineflu/notes/h1n1\\_vaccine\\_20090806/en/index.html](http://www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090806/en/index.html), (Accessed January 19, 2013).

<sup>10</sup> Clark, 14.

necessary work without a centralized location. Despite years of resources and business continuity manuals, many businesses are forced to install a WAH (work-at-home) system in an ad hoc manner; those ill-prepared rules and resources are struggling. On top of that, residential Internet bandwidths are not able to meet the highly increased demands of a workforce operating at home and many Internet Service Providers cannot keep up. Because of the variance in digital infrastructure around the nation, certain areas remain operational while others have irregular/disrupted services and it reverberates throughout the economy.<sup>11</sup>

Despite efforts to mitigate the problem by the federal and state governments, citizens in the most severely affected cities are abandoning these hot spots for the countryside and other “safer” areas. While there are still large areas of the country that are yet relatively unaffected with regards to infection rates, the urban evacuees are inadvertently acting as agents to continue the spread of H5N1. Because of this rapid urban flight, which is spreading the disease as well as consuming scarce food and medical supplies, the threat for state border closings gets higher. Because of the growing threat of spreading infection, the federal government would be required to enforce large scale quarantines which have not been seen since the Spanish Influenza of 1918. Certain cities would necessitate complete lockdown with all public gatherings banned and all businesses closed. After a month or more since the first cases appeared, disorder is becoming a regular occurrence in many cities as citizens, some armed, openly clash with law enforcement and National Guard. Especially in the quarantined cities, violence and social breakdown is now occurring daily. Many liken the conditions of several American cities to that of post-Katrina New Orleans, where basic utilities were non-existent and law enforcement thin at best.<sup>12</sup>

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<sup>11</sup> Gartner PowerPoint

<sup>12</sup> Clark, 14.; <http://www.cdc.gov/quarantine/aboutlawsregulationsquarantineisolation.html>; (New Orleans stuff)

Until the first vaccinations are available, the best that government officials can do is hold law and order as intact as possible, keep basic utility services functioning, and practice medical triage with what few resources are available. Pandemics typically come in waves of two or more in temperate climates. In the relative intermission between the first and second wave (normally the summer months), federal and state governments will have the opportunity to repair what needs to be prepared and begin vaccine inoculation if it is ready.

The previous scenario is not out of a fictional novel or Hollywood film, but based on actual government exercises most notably a 2001 federal government exercise called “Dark Winter.”<sup>13</sup> Dark Winter was originally a scenario based on a bioterrorism smallpox virus attack. Many details of the scenario were changed to reflect the current status of H5N1 Avian Influenza, including symptoms, incubation periods, mortality rates, and the vaccine. Unlike the smallpox virus, which already has a vaccine in existence, there is no vaccine for H5N1. In order to manufacture an effective vaccine, H5N1 must first acquire the genetic component for human-to-human transmissibility.<sup>14</sup> Should this happen, it is hoped that the virus will be identified and contained before it spreads, but this hope cannot shape U.S. policy; the worst case scenario must be prepared for. Bioterrorism is a definite threat to U.S. and international security, but a naturally occurring pandemic can prove to be much more dangerous. As Dr. William Clark, states, “Almost everyone now agrees that the threat posed by outbreaks of emerging pathogens is certainly as great as, and probably greater than, that posed by bioterrorism.” He elaborates further in that, “Pandemic influenza... is an event of near certainty, with unimaginable consequences.”<sup>15</sup>

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<sup>13</sup> Clark, 19.

<sup>14</sup> NEED citation for smallpox vaccine and why we don't have H5N1 now.

<sup>15</sup> Clark, 19.



## Microbial Threats

### **Bacteria (CRE)**

Microbes have long affected mankind. Both viruses and bacteria have been the culprits behind the majority of diseases that have afflicted humans since our species first emerged up until the present day. Bacteria, unlike viruses, are complete, albeit simplified, organisms. Prior to the invention of antibiotic drugs, common infections like staph or syphilis could prove to be fatal. Penicillin was first mass produced during World War II; after the war, bacteria-infections became more of a nuisance instead of life-threatening. Currently in the United States, death from bacterial infections is only 1/20 of the number compared to bacterial mortalities in 1900.<sup>16</sup> The advances made by 20<sup>th</sup> century medicine may be becoming undone as antibiotic-resistance becomes more pronounced.

Recently, the Centers for Disease Control released an emergency bulletin about the rise and dangers associated with a new threat: *carbapenem-resistant enterobacteriaceae* (CRE). CRE is a type of bacteria that lives and reproduces within the gastrointestinal tracts of human beings. The bacterium causes infections when it is accidentally released from the intestines. These infections were normally treated with antibiotics, but within the past ten years, there has been a massive increase, almost quadrupled, in the amount of antibiotic-resistant strains of this bacterium to the point that the CDC is sounding the alarm. As of March 2013, CRE has been confirmed in at least one healthcare facility in 42 states.<sup>17</sup>

Within the CDC surveillance network, there is a dangerously high occurrence rate of CRE within long-term care facilities (17.8%) as opposed to hospitals (4.6%). This is especially

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<sup>16</sup> Robert Fogel, "Penicillin: The First Miracle Drug," Fun Facts About Fungi, December 8, 2006, <http://herbarium.usu.edu/fungi/funfacts/penicillin.htm>, (Accessed March 13, 2013).

<sup>17</sup> Bump, Philip, "The Superbug Scare Is This Bad," The Atlantic Wire, March 11, 2013, <http://www.theatlanticwire.com/global/2013/03/superbug-scare-charts/62962/>, (Accessed March 13, 2013).

worrisome as infections have a greater impact on the elderly and critically-ill and those residing in long-term facilities typically have a weakened immune system as compared to those who may come into a hospital. CRE may be even more widespread than the current CDC estimates; only six states have mandates which require CRE to be reported to federal authorities. Also, there is no designated and structured surveillance system for CRE within the federal government; the resulting evaluation is a product of information gathered from three other surveillance systems. Within the counts of confirmed cases, there are other carbapenem-*resistant* bacteria that were not counted because they are not within the *enterobacteriaceae* family. There is a real fear that medicine may have to return to practices not seen since the early part of the 20<sup>th</sup> century.<sup>18</sup> Antibiotic-resistant bacteria are a growing concern in the medical community and a perfect example of the growing threat microbes possess. While some of the effects may be similar, the causes for disease differ greatly when comparing bacteria and viruses. In order to retain focus, this paper will look at viruses and the ill effects they can have upon society.

### **Viral (1918 Spanish Influenza)**

The fear of a viral pandemic is completely justified. History has shown that influenza pandemics occur every 10-60 years. In the 20<sup>th</sup> century alone, there were three official pandemics occurring in 1918, 1958/59, and in 1968/69. It will be explained in more detail in following sections, but a viral pandemic takes place when there “is a notable genetic change (termed genetic shift) in the circulating strain of influenza, leaving large portions of the human population vulnerable to infection and illness.”<sup>19</sup> The world experienced a viral pandemic in

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<sup>18</sup> Ibid.

<sup>19</sup> I. W. Fong, and Ken Alibek, *Bioterrorism and Infectious Agents: A New Dilemma for the 21st Century* / Edited by I. W. Fong and Ken Alibek, (New York: Springer Verlag, 2009), 241.

2009-10 which will be discussed in-depth later as well. While the medical community was caught off-guard, the 2009 H1N1 Pandemic did not constitute a high mortality rate and the potential crisis was averted. The 2009 strand of H1N1 caused relatively little harm, whereas its predecessor, the 1918 Spanish Influenza constitutes a worthwhile case study of what a lethal viral pandemic can achieve.

The 1918 Pandemic was the first biological outbreak to occur in “modern” times, medically speaking. Divine retribution, bad air, or other false causations for illness were no longer accepted; doctors knew that bacteria and viruses were to blame. Antiseptic observations, sterilization, vaccine inoculations, and other recognizable practices had wide-spread use and so the 1918 Pandemic was the first “modern” outbreak. Despite the name, the emergence of the 1918 Spanish Influenza most likely originated within the United States considering that one of the first lethal versions of the virus was confirmed in Philadelphia.<sup>20</sup>

As the virus spread around the world, there was widespread death, especially among populations that had relative immune naivety to influenza, despite the fact that it was mutating into a milder form. To articulate the impact that this virus had upon world populations, it’s necessary to have a few examples. Guam and the Mexican state of Chiapas both experienced mortality rates of 10% for the entirety of the population, not just those infected. In remote Pacific imperial islands, the numbers were even more appalling. When the influenza virus made landfall on September 30, 1918 in Western Samoa, the island population was 38,302. By the end of 1918, the population was 29,802; the island had experienced a 22% decrease in population

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<sup>20</sup>John M. Barry, *The Great Influenza: The Story of the Deadliest Pandemic in History*, (New York: Penguin Books, 2005), 4.

due to the 1918 Pandemic. There are no accurate estimates for the number of individuals killed in China, but all indications point to an enormous quantity.<sup>21</sup>

The 1918 Pandemic killed more people than any other outbreak in history, even more than the bubonic plague of the Middle Ages. The lowest estimates for worldwide mortalities are around 21 million, but that number is based on records and reports from the times. Modern pathologists estimate that the actual death toll from the pandemic is most likely around 50 million with upper estimates possibly around 100 million. Of those who were killed, half were in their 20s or 30s which is typically the prime of one's life and health. If the upper estimates are to be believed, then roughly 8-10% of all young adults worldwide were killed by influenza. This is one of the hallmarks and tragedies of pandemic influenza as it disproportionately affects those who are in their peak physical prime.<sup>22</sup> History has proven that the world can be suddenly struck by a mutated viral strain, and despite modern medicine, the effect can be severe. This paper will view the threat of viral microbes and how it pertains to the modern 21<sup>st</sup> century.

#### Bioterror/Bioerror

The end of the Cold War did not end the threat of attack, just a change of method. Nuclear war was no longer a credible threat as it had been for the past 40 years. Nuclear war and the mitigation of those effects had been the hallmark of disaster preparedness throughout the latter half of the 20<sup>th</sup> century. When the rise and threat of terrorism was noticed and accepted as a credible threat towards the end of the Cold War, governments began the practice of stockpiling

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<sup>21</sup> Ibid., 362-64.

<sup>22</sup> Ibid., 4-5.

countermeasures to these threats, including medical supplies and vaccines in the case of a biological attack.<sup>23</sup>

Nathan Wolfe, author of *The Viral Storm*, writes on the threat of a biologically-based weapon used for the purposes of bioterror. As technology evolves and globalism increases information diffusion, the prevalence of people who have the abilities to access and utilize detailed biological information will increase exponentially. Thus, people with the will, knowledge, and commitment to manipulate microbes for malicious intent will increase. The technology to engineer a bioweapon outside of a laboratory setting will also become cheaper and more disseminated. In decades prior, the ability to manufacture deadly chemical gases, explosives, or even cook methamphetamine was confined solely to high-end laboratories. This is not the case anymore and Wolfe predicts that the same widespread, high-end, chemical abilities will soon be common place with biological materials.<sup>24</sup>

Proof that bioterror was a legitimate concern was revealed to the world in the last decade of the 20<sup>th</sup> century. In June 1993, an apocalyptic Japanese cult named “Aum Shinrikyo” aerosolized *Bacillus anthracis* (anthrax) and attacked a metropolitan center in Tokyo. The attack itself was a failure in that caused no loss of human life. The particular strain of anthrax used was of poor quality and had very low spore concentrations. Also, the method of aerosol dispersal was inefficient. After the attack and subsequent investigation, it was discovered that Aum Shinrikyo had laboratories where they not only researched anthrax, but also botulinum toxin, Q fever and cholera. The cult had also undertaken a trip under the guise of a “medical mission” to the Democratic Republic of the Congo to acquire the Ebola virus. Bioweapons, like pandemic influenza, are the quintessential weapon for asymmetrical warfare and thus, one of the best

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<sup>23</sup> Fong and Alibek, 237.

<sup>24</sup> Wolfe, 157-58.

methods for a terrorist organization. In today's globalized society, they are relatively easy to acquire and require a low amount of monetary investment (as compared to chemical or nuclear weapons). Biological weapons, especially viruses, spread on their own volition as well. Chemical and nuclear weapons are destructive, but confined to a singular area. A microbial agent has no boundaries or limit in its ability to spread.<sup>25</sup>

Wolfe writes that of equal concern to bioterror is the possibility of "bioerror." Bioerror is the accidental release of a hazardous microbial agent. While not malevolent like a bioterror attack, an accidental bioerror release could have the same disastrous results. In 1977, the U.S.S.R., Hong Kong and parts of Northern China experienced an influenza epidemic. The virus that caused the epidemic was almost genetically identical to an influenza outbreak that had occurred 20 years prior. It will be explained in greater detail further in the paper, but influenza viruses mutate and evolve at a very rapid pace insomuch that one seasonal influenza virus is substantively different enough to warrant a new vaccine from the previous seasons' inoculation. According to Wolfe, to find an almost identical strain to a virus that had not been seen in 20 years suggests that the 1977 outbreak was caused by an accidental laboratory release.<sup>26</sup> The potential for bioerror was one of the primary reasons for the inception of the CDC/USDA Select Agent Program, which will be discussed in detail further on.

Despite the potential for a terrorist attack utilizing biological weapons or the possibility that a hazardous microbe may escape a facility and wreak havoc, Nathan Wolfe states that natural occurrence is presently more likely. The natural mutation and evolution of viruses is occurring 24/7 with no signs of abatement. As it will be explained in the following section, nature and human-derived globalization is doing the most labor for pandemic influenza trial and

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<sup>25</sup> Ibid., 154-56.

<sup>26</sup> Ibid., 156-57.

error. Scientists are constantly discovering completely new genetic strains of viruses on a yearly basis. The natural world, with the assistance of man-based systems like non-stop global travel, is more likely to produce a deadly transmissible form of influenza.<sup>27</sup>

## Problems With No Solution

### **U.S. Federalism and Laws**

Since the foundation of the United States, the government has employed some variance of a “federal” system. Federalism is the principle of the necessary separation and subsequent dispersal of powers between the three branches of government (legislative, executive, and judicial) at the federal, state, and local levels. Unlike a unitary system, where complete power is concentrated in one location, American federalism allows the various states and localities a measure of self-governance which is highly practical given the size and diversity of the United States. In the event of a disaster, U.S. federalism maintains that response is best handled at the local level given the fact that the responders will most likely have intimate knowledge of the area and situation in which the disaster occurs. When a disaster exceeds the abilities of states and localities to manage it sufficiently, the federal government will step in to provide support. The problem with pandemic influenza is that response has to be quick and comprehensive from the first case if there is any hope to contain it. This necessity runs in contrast to U.S. federalism.<sup>28</sup>

There are three main agencies involved with a response to a viral pandemic: the Department of Health and Human Services (HHS), the Centers for Disease Control (CDC), and the Department of Homeland Security (DHS). The Centers for Disease Control operate and

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<sup>27</sup> Ibid., 158.

<sup>28</sup> Richard Weitz, *Federalism and Domestic Disasters: Promoting a Balanced Approach*, Publication, January 6, 2006, [http://www.hudson.org/files/publications/FederalismDomesticDisasters\\_Weitz.pdf](http://www.hudson.org/files/publications/FederalismDomesticDisasters_Weitz.pdf), (Accessed March 19, 2013).

allocate the National Strategic Stockpile, which is an emergency surplus of medicines and medical equipment that are necessary in the event of a public health emergency. Health and Human Services are the main coordinating body during a pandemic. Should an imminent situation occur, HHS can declare a “public health emergency” in a particular state which allows legal authority for federal intervention.<sup>29</sup> Once a state of emergency is established, the *National Strategy for Pandemic Influenza* designates HHS as the coordinator of the entire public health response at the federal, state, and local level. The Department of Homeland Security’s mission is to oversee implementation of the *National Strategy for Pandemic Influenza* as well as other domestically-based national security measures.<sup>30</sup> A viral pandemic forces the federal government to assert full command and coordination of public health which is very atypical. Contrary to the actual total control that the government will assume, the *National Strategy for Pandemic Influenza* states that,

States, localities, and tribal entities across the Nation will each have to address the medical and non-medical impacts of the pandemic with available resources. This means that it is essential for State, local and tribal entities to have plans in place to support the full spectrum of societal needs over the course of weeks or months, and for the Federal Government to provide clear guidance on the manner in which these needs can be met.<sup>31</sup>

Despite the fact that the federal government will administer and coordinate the pandemic public health response, there is clear evidence of ambiguity within the actual framework of the federal government’s own strategic plans. The concept of separated and shared powers between federal

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<sup>29</sup> Ibid., 16.

<sup>30</sup> *National Strategy for Pandemic Influenza: Implementation Plan*, [Washington, D.C.]: Homeland Security Council, 2006, 29.

<sup>31</sup> Ibid., 28.



and local governments works well under normal conditions, but it complicates matters in the event of pandemic influenza.

Federalism is not a uniquely American concept and variations of it are used in other developed nations. However, a majority of developed nations main method of governance is unitarily-based; in other words, government is highly centralized. While unitary systems are efficient in other nations, their utility would not be as high in the United States. Because federalism is the prevailing method of governance, certain societal responsibilities, like public health, exude a wide amount of state control. Public health lacks conformity among the 50 states; the public health needs of Massachusetts are not identical to the health needs of Mississippi. Each state has its own system which negatively exacerbates a public health disaster like pandemic influenza. Also, when emergencies require the need to use coercive powers (mandatory medical examinations, forced quarantines, property confiscation, etc.), there exists a large amount of reluctance and hesitation. State infrastructures and personnel will need to be utilized to their fullest extent, but there exists a hesitancy to do what is required if it potentially infringes on civil liberties. States do not want to be overzealous, especially if there are legal ramifications. Pandemic influenza response and mitigation is inherently a collective effort, which conflicts with the notion of American individualism.<sup>32</sup> A full federal response would be necessary and the government has taken steps to utilize and act in concert with state authorities, but friction and miscommunication will naturally take place which, during a pandemic, could exacerbate the problem further.

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<sup>32</sup> Clark, 133-35.

## Globalization

We live in a massively interconnected world and it is constantly becoming more seamless. In the beginning of the century, it was completely possible for the United States to remain relatively unaffected by the outbreak of a World War across the Atlantic. In today's globalized society, even small events have large impacts. On March 18, 2013, global stocks fell because of the financial debacle in the small island nation of Cyprus. The nation, which is heavily involved in the financial sector, is feeling the effects of the previous Greek financial crisis. If Cypriot banks were to fail, it would signify an inherent weakness in the entirety of the Eurozone and have drastic economic consequences for the United States and Asian markets.<sup>33</sup> Globalization is the proliferation of not only markets, but ideas, people, products, and animals to every part of the globe in an accelerated and seamless manner.

Nathan Wolfe's research and publication, *The Viral Storm*, is an authoritative work on the potential for pandemic influenza. He writes in great detail about the impact that globalization is going to have in regards to the potentiality for a deadly pandemic outbreak. On February 21, 2003, a sick man checked into the Metropole Hotel in Hong Kong, completely oblivious to the role he was to play. This man had recently come from the nearby Chinese province of Guangdong and he was infected with the Severe Acute Respiratory Syndrome (SARS) virus. This man, whom investigators three months later identified as patient zero, alone infected 16 other individuals and acted as a "super spreader." A super spreader is "a person (or animal) who plays an outsized role in the spread of an infection disease."<sup>34</sup>

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<sup>33</sup> Cyrus Sanati, "Why Cyprus Matters to U.S. Investors," CNNMoney, March 18, 2013, <http://finance.fortune.cnn.com/2013/03/18/cyprus-bailout/?iid=EL>, (Accessed March 19, 2013).

<sup>34</sup> Nathan Wolfe, *The Viral Storm: The Dawn of a New Pandemic Age*, 1st ed., (New York: Times Books, 2011), 159.

Wolfe states that Hong Kong itself played an important role in the acquisition and subsequent worldwide spread of the SARS virus. Hong Kong has a massive human population density and is a global hub, with hundreds of incoming and outgoing flights per day. Guangdong is very near to Hong Kong and is home to “wet markets,” which are unsanitary bazaars that market and sell non-domesticated animal delicacies as well as live specimens themselves. As Wolfe articulates that the conditions for a microbial outbreak are perfect when there is a high human population, an enormous livestock production market which has easy access to wildlife microbial reservoirs, and a modern human/animal transportation network. Hong Kong is a perfect example of a globalized microbial melting pot, but it is not the only one. Cities in China, Southeast Asia, Africa and Central/South America all have the potential for animal-human microbial mixing because the populated cities are nestled shoulder-to-shoulder with local wildlife populations. Wolfe states that one of the largest predictors of a potential viral outbreak is the rise of urbanization. Over 50% of the world population now resides in an urban environment, which is a first in human history. Experts predict by the year 2050, the number will be closer to 70%.<sup>35</sup> With so much of the world’s population living in conditions that are unregulated and biologically hazardous, the potential for pandemic will only increase as globalization continues.

Wolfe articulates that other diseases, which are correlated to globalization, may play a factor in the likelihood of a microbial public health emergency. When viruses make an animal-human leap, they often are met at a dead end. The virus usually does not have the perfect genetic code to successfully infect and defeat the host organism. The host immune system is often able to successfully win out against the foreign contagion. However, this would not be the case in an

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<sup>35</sup> Ibid., 159-61.

immunosuppressed individual, like someone infected with HIV/AIDS. Human immunodeficiency virus (HIV) does not kill the host; it attacks and effectively decommissions the host's immune system which causes acquired immunodeficiency syndrome (AIDS). AIDS sufferers will die from another infection that their immune system no longer is able to attack. Wolfe states that if a virus were to jump from animal into a human with AIDS, that virus would live where it otherwise should have been halted. The new virus would have extra time to mutate into a more potent and lethal version of itself. With globalization continuing the spread of HIV, the statistical likelihood for a new virus to find a biological beachhead increases ever more.<sup>36</sup> Nathan Wolfe presents a startling case for the problems that globalization can present when attempting to prevent the rise and propagation of pandemic influenza. However, like American federalism, this is a problem that cannot be easily solved.

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<sup>36</sup> Ibid., 164.

## CHAPTER 2

## THE BIOLOGICAL HAZARD

## The Basics

**Virology Overview**

Viruses coat the entirety of our planet; they are in the air, ground and water. They cover our skin, are ingested when we eat or drink and live within our bodies. Viruses are simplistic microbes; they are composed of just a fraction of genetic material surrounded by a protective coat of protein molecules. In order for a virus to replicate, it must imbed and reprogram a susceptible host cell. Once the cell has been successfully occupied, the virus can reprogram the cell's protein production processes to replicate viral progeny. Cells have a finite amount of resources and upon cellular depletion, the matured viral offspring will rupture and release large numbers of viral replicas which then infect new cells.<sup>37</sup>

There are many viruses that can infect the human body, but a majority cause little or no harm to the organism. In fact, humans are immune to a host of viruses that are problematic to other organisms. The viruses that are well-known ones are the slim minority that cause problems. There are two alternatives that a virus can instigate upon infecting a host organism. The first possibility is active spread and reproduction within the host. This alternative replicates the virus and heightens the severity of the infection, but this comes with the risk of being captured and killed by the host's immune system. Many viruses are effectively killed by an immunological response and their sole purpose (survival and reproduction) ends. The other alternative is to survive within the host organism in a dormant state of hibernation. The inactive virus has a much higher probability of evading an immunological response, but latency forgoes

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<sup>37</sup> Michael B.A. Oldstone, *Viruses, Plagues, and History: Past, Present, and Future* (Oxford: Oxford University Press, 2010), 10-12, 14.

the ability to replicate and spread. These two alternatives are not “decided” in the sense of what we would attribute to higher-level organisms. Viral microbes often take their cues from their environment as to when to be active or inactive. For example, the virus *herpes simplex*, which is the cause of oral cold sores, activates when the host organism is undergoing environmental stress. The name “cold sore” is derived from the fact that the virus often activates when the organism’s immune system is already fighting an infection, like the common cold. Other stresses that can cause activation are severe sunburns, emotional/mental stress, or sleep irregularities. *Herpes simplex* rarely activates when the host organism is rested and healthy.<sup>38</sup>

Disease caused by viruses can happen three different ways. The toxicity of the viral proteins can kill the host cell, which is one method by which the viral offspring can be released from their cellular incubator for further spread. Viruses can also engage in alteration of the host cell functions. There are instances when it is advantageous for the virus to keep the host cell alive albeit with reprogramed functionality. The last method by which viruses can cause disease within an organism is through an extreme immunological response. The immune system’s function is to identify, isolate, and destroy viruses and infected cells, but when a virus has spread quickly in a host organism, destroying the infection can cause serious harm to the organism.<sup>39</sup> While the immune system itself aids in the destruction of the host in the last scenario, the best method to treat a viral infection is to naturally or artificially stimulate an immune system response.

The basic definition of “immune” is that an organism is resistant to a disease caused by a microbe. With a potentially infectious disease, the organism possesses antibodies of a recognized microbe that act as a biological surveillance system. Each antibody is specifically

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<sup>38</sup> Wolfe, 28-30.

<sup>39</sup> Oldstone, 14-15.

programmed for detection of one particular hazardous microbe and once contact is made, the immune system attacks and destroys the invasive entity. However, being immune to a particular disease does not mean that the disease is not present within the organism; it can mean that the infection is so mild that the organism does not feel any negative repercussions. There are strains of the human papillomavirus (HPV) that have no signs or symptoms of infection throughout the entirety of the host's lifetime. In order for the body to produce needed antibodies, the body requires exposure to a particular virus. Vaccines of inactivated or partial viruses are administered to produce a safe immune system response that will immunize the host against infection by a live active virus.<sup>40</sup> At the very least, a vaccine will reduce the severity of infection. Many viruses are in a constant state of mutation and evolution, especially influenza. An influenza vaccination will not be the exact same virus that infects an individual, but there will be enough genetic similarities that immune response and recovery will be significantly improved.<sup>41</sup>

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<sup>40</sup> Oldstone, 41.

<sup>41</sup> Mark S. Smolinski, Margaret A. Hamburg, and Joshua Lederberg, eds., *Microbial Threats to Health: Emergence, Detection, and Response* (Washington D.C.: National Academies Press, 2003), 144.

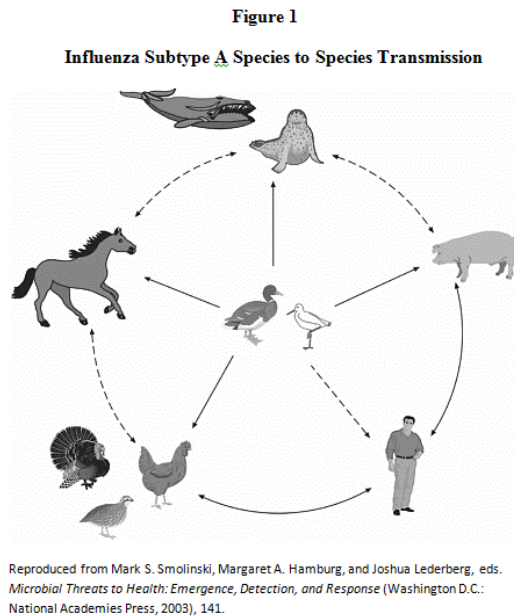
## Influenza

Similar to living organisms, viruses have just as much variation. For the purpose of this paper, influenza viruses that infect *homo sapiens* will be the main focus. While there are multiple subtypes of influenza virus, humans are not susceptible to all of them. There are three main subtypes which affect humans: Influenza virus A, B, and C. Subtypes B and C are limited in their capacity because they are infectious only to humans (with some cases

appearing in seals and pigs, respectively). Because humans are the only practical carriers of subtypes B and C, the ability for drastic genetic diversification is reduced. However, Influenza virus subtype A has been well documented to infect a wide range of different animals, including pigs, domesticated birds, wild birds, sea mammals, horses as well as humans.<sup>42</sup> Figure 1 shows

the versatility of Influenza Subtype A and its ability to infect a wide variety of different avian and mammalian organisms. The solid lines indicates proven vectors of transmission of the virus from one species to another, while the dotted lines indicate theorized, but unproved inter-species transmission. Figure 1 shows that wild birds are the prime reservoir for Influenza Subtype A; the prime mediums for mutation and subsequent human infection are domesticated pigs and birds.<sup>43</sup>

There are two glycoproteins in influenza viruses which act as the main agents for viral success and subsequent mutation, hemagglutinin and neuraminidase. Hemagglutinin (HA) is the



<sup>42</sup> Anna I. Cheh, *Disaster Medicine*, Edited by Gregory R. Ciotto, 3<sup>rd</sup> ed., (Philadelphia: Mosby Elsevier, 2006), 684.

<sup>43</sup> Smolinski et. al., 141.



protein responsible for binding the virus to a host's cell wall and infecting the cell. The neuraminidase (NA) protein allows for viral replication and subsequent release from the host. If any one of these proteins is unable to function properly within a host, then the virus will not be able to infect and replicate.<sup>44</sup>

Constant influenza mutations raise the likelihood a new virus can subvert immune surveillance and out-pace artificial vaccinations. There are two methods by which influenza subtype A mutates and evolves: antigenic drift and antigenic shift. Antigenic drift (mutation) is basically an accelerated version of traditional evolution and natural selection. Small mutations accumulate over time and depending on the amount and type of change, they can produce new viral strains. Antigenic drift is responsible for the new seasonal influenza vaccine that needs to be produced every year. The strain of influenza has changed enough over the course of a year that a new vaccine is necessary.<sup>45</sup> Unlike other viruses, influenza undergoes an extremely high rate of mutation throughout its replication cycle. Although antigenic drift is very common and necessitates new seasonal influenza vaccines, it is unlikely to mutate into a strain that could cause a pandemic.<sup>46</sup>

The other method for viral mutation is antigenic shift, and it is this possibility that has scientists fearful of a possible influenza pandemic. Unlike antigenic drift, antigenic shift incorporates a major change to the viral genetic code. Influenza's structure allows for change to happen very easily; the genetic code is segmented into eight RNA sections.<sup>47</sup> Two different, but genetically-related viruses, can infect the same host and because of the segmented RNA, the

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<sup>44</sup> Cheh, 684.

<sup>45</sup> "How the Flu Virus Can Change: "Drift" and "Shift"," Centers for Disease Control and Prevention, February 08, 2011, <http://www.cdc.gov/flu/about/viruses/change.htm>, (Accessed January 26, 2013).

<sup>46</sup> Smolinski et. al., 139.

<sup>47</sup> Smolinski et. al., 139.

viruses can recombine their genetic material (reassortment) to produce a new and “novel” virus. The novel virus may have different HA or HA/NA proteins which would allow it to perform differently than the parent virus. When the novel virus emerges from the host, it is very different from the equivalent virus that already infects humans. Antigenic shift can create novel viruses for which humans may have little to no immunity against. Luckily, antigenic shift only happens occasionally with comparison to the constant state of mutation that is already occurring.<sup>48</sup>

### **Differences Between Seasonal and Pandemic Influenza**

Influenza is a natural, albeit unfortunate, part of life. Not to be associated with the “stomach flu”, which is a completely separate microbe, seasonal influenza infection typically happens at some point in most human’s lives. Seasonal influenza, as the name implies, is an annual event in temperate climates, coinciding with the winter and spring months. There are more deaths per year associated with seasonal influenza than any other infectious disease in the developed world. About 36,000 people in the United States lose their lives to seasonal influenza yearly, mainly through the secondary complications influenza creates (i.e. pneumonia). A majority of the victims are elderly, but young children are also susceptible. As discussed previously, viral complications often affect those with weaker immune systems and seasonal influenza follows this trend. On average, seasonal flu generates 226,000 hospitalizations yearly. However, the seasonal variety has a relatively low attack rate. An “attack rate” can be defined as the percentage of the population that becomes infected with a viral pathogen. Seasonal flu has an average attack rate of 5-15% in any given year. Because of the relatively low attack rate, less

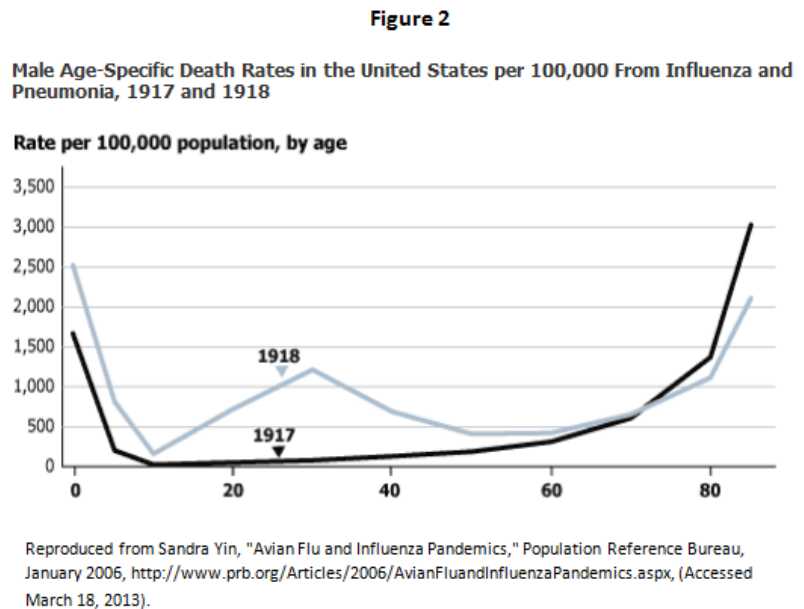
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<sup>48</sup> "How the Flu Virus Can Change: “Drift” and “Shift”," (Accessed January 26, 2013).

than a quarter of the U.S. population will become infected in a given year.<sup>49</sup> Pandemic influenza differs greatly in this aspect.

Pandemics are often characterized when there is a large amount of the population that has no natural immunity to the virus in question, which implies a very high attack rate. Seasonal influenza has a lower attack rate because it is often a mutated form of the previous

season's influenza; large amounts of the public were exposed to a variant of the previous virus allows for some cross-immunity. A pandemic occurs when large portions of the population are susceptible from a previously mentioned novel virus. As the 1918 H1N1 Pandemic shows, younger age groups are more at risk than the elderly age groups during a pandemic, which runs counter to the typical trend seen in seasonal influenza. As explained earlier, viral illness can also be caused by an immunological over-response and it is believed that this may also explain why young adults are affected disproportionately. Figure 2 shows male age-related mortality rates for influenza in 1917 and 1918. Typical for seasonal influenza is that the groups affected most are the very young and elderly as what happened in 1917. The influenza of 1918 was characterized



<sup>49</sup> Jon Stuart Abramson, *Inside the 2009 Influenza Pandemic* (Singapore: World Scientific, 2011), 8-9.

by pandemic influenza and young, healthy adults are heavily affected in an atypical manner not seen with seasonal influenza.<sup>50</sup>

Pandemics are also characterized as having a high transmissibility rate. When the virus easily propagates from person to person via various methods, it is a good indicator that the virus possesses a genetic component suitable for a pandemic. Transmissibility is measured by how many singular infected person infects, or the virus's "reproduction" number (R). Seasonal influenza is characterized by an R value of  $<2$ , which means that on average, an infected individual will spread the disease to less than two others. Pandemics have an R value of  $>2$ , so that on average, one infected person will spread the virus to two or more others. Pandemics often spread throughout a particular community for four to eight weeks and eventually circulate the globe in six to nine months. Pandemics are also classified as generally having two distinct waves, with the first being less extreme as the second, although, up to four waves are possible. The last significant variant between pandemic influenza and seasonal influenza is the attack rate; pandemics often have a 20-50% attack rate, which is significantly higher than seasonal influenza.<sup>51</sup> A serious pandemic influenza requires ease of transmissibility, an attack rate much higher than seasonal influenza, and a high mortality rate. There are many different variants of influenza which cause great concern, and two of the most prominent strains are H1N1 and H5N1.

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<sup>50</sup> Sandra Yin, "Avian Flu and Influenza Pandemics," Population Reference Bureau, January 2006, <http://www.prb.org/Articles/2006/AvianFluandInfluenzaPandemics.aspx>, (Accessed March 18, 2013).

<sup>51</sup> Abramson, 9-12.

## Human Susceptibility

As previously stated, one of the defining characteristics of pandemic influenza is the higher susceptibility of humans over that of seasonal influenza. Seasonal influenza has an attack rate of 5-10% compared to the 20-50% attack rate in pandemics. The causality for higher than average attack rates, as previously discussed, is the antigenic shift that occurs to produce novel influenza viruses. A novel strain implies a drastic genetic variance which allows for immune evasion as compared to the original virus. Because mutation implies an inherent amount of similarities between that of the parent and offspring, some people are liable to have cross-reacting antibodies to a novel virus because of its genetic similarities to a previous virus. This has traditionally been the case in pandemics and because of age, older humans have a higher probability of holding protective antibodies, which was seen in the 2009 Pandemic. The 1918 H1N1 virus evolved and circulated the globe up until 1957.<sup>52</sup> With regards to the 2009 novel H1N1 virus, “many older people had preexisting antibodies that cross-reacted with the novel 2009 pandemic virus, which is antigenically related to, but highly divergent from the 1918 pandemic H1N1 virus.”<sup>53</sup> For pandemic influenza, youth is a detrimental factor in potential susceptibility.

In a concentrated ICU Canadian study, the author states that, “... severe disease and mortality in [H1N1] is concentrated in relatively healthy adolescents and adults between ages 10 and 60 years, a pattern... previously only seen during the H1N1 Spanish pandemic.” While a majority of those in the critical-care study had pre-existing conditions (comorbidities) like chronic lung disease, obesity, or hypertension, they were otherwise healthy and would have

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<sup>52</sup> Ibid., 10-11.

<sup>53</sup> Michael G. Ison and Nelson Lee, “Influenza 2010-2011: Lessons from the 2009 pandemic,” *Cleveland Clinic Journal of Medicine* 77, no. 11 (November 2010): 812-20, doi:10.3949/ccjm.77a.10135, 813.

likely survived a seasonal influenza infection.<sup>54</sup> H1N1, as compared to seasonal influenza, killed a disproportionate amount of young adults to elderly adults. Callousness aside, the amount of years lost with H1N1 pandemic influenza was greater than that of seasonal influenza.<sup>55</sup> The 2009 H1N1 Influenza Pandemic provides a perfect example of the human susceptibility that can be expected in the next pandemic; young adults are at a higher risk.

### **Antiviral Resistance**

The best method to treat and protect individuals from influenza in general is vaccination. Unlike seasonal influenza, which originates through gradual mutation, pandemic influenza has drastic genetic differences because of its novel form. In order for an effective vaccine to be engineered and mass produced, a complete human-human form of the pandemic influenza must exist. Isolating and deactivating the virus for vaccine production will most likely not happen until after patient zero (the first confirmed case) has already begun spreading the disease. The best alternative to vaccination is antiviral therapy.

There are currently two classes of antiviral medications: adamantane and neuraminidase inhibitors. Adamantanes “block the ion channel formed by the influenza matrix (M2) protein.”<sup>56</sup> What this means is that once the virus has successfully inserted itself into the host cell, the adamantane will interfere with the viral proteins as it attempts to reprogram cellular activities. Neuraminidase inhibitors block NA protein activity and prevent viral release from the host cell.

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<sup>54</sup> Anand Kumar, Ryan Zarychanski, and Ruxandra Pinto; et al, "Critically Ill Patients Wit 2009 Influenza A (H1N1) Infection in Canada," *JAMA* 302, no. 14 (November 4, 2009): 1874-876, <http://jama.ama-assn.org/cgi/content/full/302/17/1872>, (Accessed July 11, 2012).

<sup>55</sup> James Gallagher, “Swine-flu Infected ‘fifth of People’,” *BBC News*, January 25, 2013, <http://www.bbc.co.uk/news/health-21194090>, (Accessed January 25, 2013).

<sup>56</sup> Smolinski et. al., 143.

By preventing release, the infection is slowed and the immune system has a higher probability of isolating and destroying infected cells while keeping harm to the organism at a minimum.<sup>57</sup> The 2009 H1N1 Pandemic and subsequent seasonal influenzas have shown an almost universal resistance to adamantine.

A significant rise in adamantine resistance was first discovered in 2004 and subsequently wide-spread during the 2009 H1N1 Pandemic. In May 2009, the CDC reported that high levels of resistance to adamantane were being confirmed in a variety of patients with infected with H1N1. Nick Anthis of *Scienceblogs.com*, writes

Swine flu... has a single mutation (S31N) that makes it resistant to adamantane drugs.

This is actually a relatively common mutation found in flu viruses in general and the main source of all flu adamantane resistance. Over time, widespread use of this relatively older class of drugs has put significant evolutionary pressure on influenza, giving viruses with this mutation a selective advantage, leading to increasing rates of adamantane resistance in recent years.<sup>58</sup>

Adamantane has been a staple pharmaceutical option for influenza treatment for years, but has since become obsolete. For the 2005-06 influenza season, the CDC officially recommended that all health care professionals cease prescriptions of adamantane. A single point mutation within the influenza virus on five different locations can provide effect viral resistance to the medication, while detracting nothing from its ability to reproduce and pass on the evolutionary

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<sup>57</sup> *Ibid.*, 143.

<sup>58</sup> Nick Anthis, "Why Swine Flu Is Resistant to Adamantane Drugs," *The Scientific Activist* (web log), May 1, 2009, <http://scienceblogs.com/scientificactivist/2009/05/01/why-swine-flu-is-resistant-to/>, (Accessed March 1, 2013).

advantage.<sup>59</sup> While adamantane has fallen from the list of applicable antiviral treatments, neuraminidase inhibitors are still widely used. However, this may not last forever.

In the 2009 H1N1 Pandemic as well as cases of confirmed H5N1 Avian Influenza, there were sporadic instances of viral resistance to neuraminidase inhibitors. As previously stated, neuraminidase inhibitors prevent viral release from the infected cells. The most common drugs

in this category are

oseltamivir (Tamiflu)

and zanamivir

(Relenza). These two

medications comprise

the majority of world

dependence in

successful influenza

antiviral treatment since the loss of the adamantane class. The resistance is primarily against

oseltamivir and is caused by the H274Y (sometimes numbered H275Y) mutation in the NA

protein. Oseltamivir is the most widely stockpiled antiviral because of its superior

bioavailability as compared to zanamivir. Oseltamivir can be administered orally whereas

zanamivir's poorer bioavailability demands inhalation for effectiveness.<sup>60</sup> The H274Y mutation

may compromise the integrity of another antiviral medication in treatment of seasonal influenza

as well as pandemic influenza. An Australian study writes that "oseltamivir-resistant A (H5N1)

**Figure 3**

**Antiviral Resistance Among Circulating Influenza Viruses**

VIRUS	RESISTANCE TO ADAMANTANES	RESISTANCE TO NEURAMINIDASE INHIBITORS
Seasonal A/H1N1	Rare	100% (NA mutation H275Y) <sup>a</sup>
Pandemic A/H1N1	99.7% (M2 mutation S31N)	Rare
Seasonal A/H3N2	~100% (M2 mutation S31N)	Rare
A/H5N1 Clade 1	~100% (M2 mutation S31N)	Rare
A/H5N1 Clade 2.1	80%	Rare
A/H5N1 Clade 2.2	Rare	Rare
A/H5N1 Clade 2.3	Rare	Rare

<sup>a</sup>Resistance emerged during the 2007-2008 influenza season; resistance was rarely discovered previously.

Reproduced from Michael G. Ison and Nelson Lee, "Influenza 2010-2011: Lessons from the 2009 pandemic," *Cleveland Clinic Journal of Medicine* 77, no. 11 (November 2010): 812-20, doi:10.3949/ccjm.77a.10135, 817.

<sup>59</sup> "CDC Recommends against the Use of Amantadine and Rimantadine for the Treatment or Prophylaxis of Influenza in the United States during the 2005-06 Influenza Season," *Health Alert Network*, January 14, 2006, <http://emergency.cdc.gov/HAN/han00240.asp>, (Accessed March 1, 2013).

<sup>60</sup>Aeron C. Hurt, Jessica K. Holien, Michael W. Parker, and Ian G. Barr. "Oseltamivir Resistance and the H274Y Neuraminidase Mutation in Seasonal, Pandemic and Highly Pathogenic Influenza Viruses," *Drugs* 69, no. 18 (2009): 2523-531, doi:10.2165/11531450-000000000-00000, 2523-24.



variants with an H274Y neuraminidase mutation have been isolated from treated patients...<sup>61</sup>

Not only has oseltamivir-resistance surfaced in seasonal influenza and H1N1, but it is also appearing in H5N1 Avian influenza. Because of the nature of pandemic influenza, a vaccine will not be available for months post-outbreak. Neuraminidase inhibitor antivirals are the only viable medication ready to be administered should a pandemic occur, but antiviral resistance may deprive the public of this option.

## H1N1 Influenza

### **Biological Characteristics**

There have been many variants of the H1N1 virus that have infected humans. As stated previously, the 1918 Spanish Influenza was a lethal version of the H1N1 virus which caused large amounts of global fatalities in the post-WWI pandemic. H1N1 was also responsible for the 2009 Swine Influenza pandemic. While nowhere near as lethal as its distant relative (1918), the current form of H1N1 has distinctive characteristics. Patients infected with H1N1 can show signs of minor upper respiratory distress to full viral pneumonia. The symptoms of the virus overlap somewhat with that of seasonal influenza with patients reporting a cough, sore throats, and/or fever. H1N1 differs strongly as compared to seasonal influenza in that it can cause painful gastrointestinal complications including nausea, vomiting, and diarrhea<sup>62</sup>.

### **2009 Pandemic Overview**

The first wave of the 2009 H1N1 Influenza Pandemic began with an outbreak of influenza-like infection was reported to the World Health Organization (WHO) from Veracruz,

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<sup>61</sup> Ibid., 2527-28.

<sup>62</sup> Ison, Lee, 813.

Mexico on April 12, 2009. Although flu-like symptoms in people had been appearing in Mexico for nearly a month prior, it was quickly discovered that the infection was not a bacterial infection or a case of seasonal influenza. WHO officials were concerned from the onset that this disease could become a full-blown pandemic. For years, most experts had predicted that the next serious pandemic would begin somewhere in Asia. It was shocking to discover a potential threat coming from Mexico. By the end of May, there were 5,337 confirmed cases within Mexico, with 74% of them under the age of 30. Genetic testing revealed that the virus had made the mutation required for human-to-human transmissibility months prior to the first confirmed cases, but disease surveillance systems failed to catch it in time for containment. The 2009 H1N1 virus is a virus that contains genetic material from birds, pigs, and humans. It was discovered the virus that morphed into the 2009 H1N1 had been circulating in pigs for over ten years before it successfully acquired the genetic component to jump from human-to-human.<sup>63</sup>

The first confirmed American patient was diagnosed on April 10, 2009. More cases began to surface soon thereafter, hundreds of miles from the first patient who was located in California. The patients had no connections that would have suggested a root contaminant; CDC surmised at this point that the virus was able to transfer itself via human-to-human contact.<sup>64</sup> On April 24, 2009, the WHO declared this strain to be a phase 5 Pandemic Alert.<sup>65</sup> There are six overall phases to the WHO Pandemic classification system. As shown in Figure 4, phase 5 states that the infection is still in alert-phase, albeit the highest level of alert. The virus, at this point, is in large clusters in more than one nation, but human-to-human spread is still localized. The virus appears to be managing to mutate itself to become better adaptable in transmissibility, but has

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<sup>63</sup> Abramson, 5, 39-41.

<sup>64</sup> "The 2009 H1N1 Pandemic: Summary Highlights, April 2009-April 2010," Centers for Disease Control and Prevention, June 16, 2010, <http://www.cdc.gov/h1n1flu/cdcresponse.htm>, 1-2, (accessed December 3, 2011).

<sup>65</sup> "The 2009 H1N1 Pandemic: Summary Highlights, April 2009-April 2010," 41.

not yet reached that point. The danger for full phase 6 pandemic is the last stage, which means that the infection has reached a sustainable and easily transmissible point which suggests it is able to easily cross multiple national borders.<sup>66</sup>

Shortly before the phase 5 declaration, the CDC was already at work trying to develop a vaccine. Because containment was no longer a viable option, vaccination was the only sure method to protect the population. Prior to the outbreak of H1N1, the United States government had begun pandemic-response preparations. During normal seasonal influenza years, roughly 40% of the vaccines used are manufactured outside of the United States. If a pandemic were to occur, it can be assumed

that the normal supply of foreign vaccines would not be available. In order to bolster U.S. public health defenses, the government had been incentivizing private companies to expand their production facilities domestically.<sup>67</sup> On April 26, 2009, the CDC released 25% of its Strategic

**Figure 4**

WHO Phases		Federal Government Response Stages	
<b>INTER-PANDEMIC PERIOD</b>			
1	No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human disease is considered to be low.	0	New domestic animal outbreak in at-risk country
2	No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.		
<b>PANDEMIC ALERT PERIOD</b>			
3	Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact.	0	New domestic animal outbreak in at-risk country
		1	Suspected human outbreak overseas
4	Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans.	2	Confirmed human outbreak overseas
5	Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk).		
<b>PANDEMIC PERIOD</b>			
6	Pandemic phase: increased and sustained transmission in general population.	3	Widespread human outbreaks in multiple locations overseas
		4	First human case in North America
		5	Spread throughout United States
		6	Recovery and preparation for subsequent waves

Reproduced from "WHO Global Pandemic Phases and the Stages for Federal Government Response," Digital image, Center for Biological Counterterrorism and Emerging Diseases CDC-ED, [http://bepast.org/dataman.pl?c=lib&dir=disease\\_information/Pandemic%20Influenza](http://bepast.org/dataman.pl?c=lib&dir=disease_information/Pandemic%20Influenza), (Accessed July 23, 2012).

<sup>66</sup> *Appendix C: WHO Pandemic Phases*, PDF, (U.S. Department of Health and Human Services, Washington D.C.), (accessed December 3, 2011).

<sup>67</sup> Abramson, 43.

National Stockpile to the states, based on population. The supplies included antivirals (ex. Tamiflu), personal protective supplies (ex. facemasks) and short-supply medical equipment for hospitals and clinics, like ventilators.<sup>68</sup> On June 11, 2009, the WHO officially stated that H1N1 was a phase 6 full pandemic, as confirmed cases were appearing in Europe and Asia. Throughout the First Wave, between 1-10% of those who were infected required hospitalization. Of those hospitalized, 2-9% of the cases were fatal. Also, 7-10% of the hospitalizations were pregnant women. A key trait of the 1918 influenza was the increased susceptibility of pregnant women and the 2009 H1N1 behaved similarly. By the end of July, there were 43,700 confirmed cases of H1N1 in the United States, with the highest rates occurring in the 5-24 years old age bracket. There were 300 deaths directly attributed to H1N1 and pregnant women accounted for 6% of those deaths, even though they only compose roughly 1% of the entire U.S. population at any given time. Also, those pregnant women who perished generally had no comorbidities (chronic preexisting conditions which would have naturally exacerbated the infection), which could have contributed to a weaker immune system.<sup>69</sup>

By the time the first wave ended, the CDC in the United States estimated that between 1.8 and 5.7 million Americans had been infected with 9,000-21,000 requiring hospitalization. Precise statistics do not exist, because after a certain period, only a small number of those complaining of fever and respiratory problems were actually tested for H1N1.<sup>70</sup> Throughout the entirety of the first wave, CDC worked in tandem with state and territorial health agencies to limit the rate of infection and coordinate health care efforts. Recommendations for the uses of stockpiled antivirals, public outreach campaigns (social distancing and hygiene) and surveillance

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<sup>68</sup>"The 2009 H1N1 Pandemic: Summary Highlights, April 2009-April 2010," 3.

<sup>69</sup> Abramson, 48-53.

<sup>70</sup> Abramson, 57.

were the primary concern for CDC at this point, as no vaccine had yet been formulated.

However, the CDC had already begun planning and preparing local health departments in June 2009 for the eventual vaccine campaign.<sup>71</sup> The prevalence of H1N1 infections dropped during the summer of 2009 and the first wave ended.

In September 2009, the United States experienced the beginning of the second wave. Because of the short window between the end of the first wave and the beginning of the second, the health industry in the United States was unprepared for the inundation that was received. Hospitalizations were common with H1N1 and many required special treatment in Intensive-Care Units (ICUs). Hospital beds, especially in ICUs, quickly ran out. Because of the severity of the disease, many people sought medical attention through Emergency Rooms instead of scheduling a time with their general practitioner. Many states' budgets were strained and they did not have adequate resources to deal with the surge in September and October 2009. The second wave had unique characteristics as well, some of which were predicted prior to its eruption. The frequency and ease of transmission were higher, as well as the intensity of the symptoms. During the second wave, a greater percentage became ill than in the first wave and a greater percentage of those requiring hospitalization had few or no previous comorbidities. By mid-October, there had been roughly 21,000 hospitalizations associated from H1N1 in the United States and about 2,400 deaths. The disease still affected younger people disproportionately. The second wave was much more pronounced and harsher than the first wave, but this was expected by authorities.<sup>72</sup>

H1N1 was combated in the United States through a vaccine program coordinated by the CDC. Vaccination was the only method to truly halt the spread of the infection. Quarantine and

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<sup>71</sup> "The 2009 H1N1 Pandemic: Summary Highlights, April 2009-April 2010," 5-6.

<sup>72</sup> Abramson, 92-96.

other methods were impractical due to the prevalence of the disease among the population.

There were two problems with the vaccine strategy; time and growth. The first wave had ended only months prior and the government had decided that the vaccine would be manufactured through unfertilized chicken eggs. Isolating a virus and getting it to grow, but not destroy the host cell, is a notoriously difficult process. H1N1 did not respond as well to mass-production growth. Many vaccines are produced using chicken eggs, but H1N1 killed many of the egg cells and large amounts of the initial batches were unusable. Through a combination of poor growth results and a lack of time, the United States' supplies of H1N1 vaccines were limited when the second wave began. Compounding this problem was the recession. Many state and local communities, due to the economic meltdown, had been forced to cut back on health personnel, which meant fewer hospital resources and fewer qualified to administer vaccines.<sup>73</sup>

Vaccines were unavailable until mid-October when the first quantities were administered. Because of the short supply and large demand, a list of high-priority populations was devised for vaccine inoculation before the public-at-large gained access. In list of importance to the CDC were health care workers (HCWs), pregnant women, people caring for children under the age of six months, people age six months to 24 years of age, and finally people with preexisting high risk conditions age 25 to 64. For months into the second wave, demand was consistently higher than the supply. It was not until the end of 2009 when the second wave finally began to subside that demand for the vaccine decreased. At this point, some states were finding that they had surpluses of the vaccine and opened up vaccination to all. The CDC encouraged the use of the vaccine to all persons because of the potential for a third wave. By the end of February, near the end of the second wave and the H1N1 pandemic in general, it was estimated that roughly 91

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<sup>73</sup> Abramson, 100, 113.

million people in the United States, or 30% of the population, had been vaccinated once, if not twice because it was often required that children had two vaccinations for full immunity.<sup>74</sup>

On February 24, 2010, at the Advisory Committee on Immunization Practices (ACIP) meeting, the CDC gave a report detailing the entirety of H1N1 pandemic to that point. At the time, it was estimated that there had been 57 million cases of H1N1 in the United States or about 20% of the population, with 19 million cases appearing in children (33%). Estimates also included about 257,000 hospitalizations and 11,000 mortalities. Seasonal influenza usually has around 226,000 hospitalizations and about 36,000 mortalities. While the total mortality rate for H1N1 was only about a third of that of seasonal, it is noted that the death rate was three times as high for young adults infected with H1N1 than seasonal flu. Also, African-Americans were disproportionately represented in the mortality rate than in all the other ethnicities. The most likely explanation for this disparity is lack access to quality health care services.<sup>75</sup>

In a concentrated ICU Canadian study, the author states that, "... severe disease and mortality in [H1N1] is concentrated in relatively healthy adolescents and adults between ages 10 and 60 years, a pattern... previously only seen during the H1N1 Spanish pandemic." While a majority of those in the critical-care study had pre-existing conditions (comorbidities) like chronic lung disease, obesity, or hypertension, they were otherwise healthy and would have likely survived a seasonal influenza infection.<sup>76</sup> The fact that H1N1 was able to severely affect reasonably healthy young individuals is the main cause for concern with regards to future

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<sup>74</sup> "The 2009 H1N1 Pandemic: Summary Highlights, April 2009-April 2010," 12-14

<sup>75</sup> Abramson, 97-98.

<sup>76</sup> Anand Kumar, Ryan Zarychanski, and Ruxandra Pinto; et al, "Critically Ill Patients With 2009 Influenza A (H1N1) Infection in Canada," *JAMA* 302, no. 14 (November 4, 2009): 1874-876, <http://jama.ama-assn.org/cgi/content/full/302/17/1872>, (Accessed July 11, 2012).

pandemics. By spring 2010, the H1N1 pandemic was officially over and no third wave ever occurred.

More recent data estimate that H1N1 was more prevalent than initially thought. Worldwide data from 19 different countries indicate that the 2009 H1N1 influenza virus infected roughly 1 in 5 individuals and almost 50% of schoolchildren. Many of the estimates were based on the prevalence of ill individuals, however, H1N1 infection does not always equate into a full symptomatic reaction. A large number may have been infected and showed only slight symptoms of viral infection. Despite the fact that less than two out of every 10,000 died from the virus, it is estimated that roughly 24% of the world population was infected.<sup>77</sup> The United States and the world dodged a proverbial bullet with H1N1. Despite its very high attack rate, the mortality rate was extremely small.

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<sup>77</sup> Gallagher, January 25, 2013.



## Highly Pathogenic Avian Influenza (HPAI) - H5N1

## Biological Characteristics

Figure 5

**Cumulative Number of Confirmed Human Cases for Avian Influenza A  
(H5N1) reported to WHO, 2003-2013**

Country	2003-2009*		2010		2011		2012		2013		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	0	0	2	0	3	0	0	0	6	0
Cambodia	9	7	1	1	8	8	3	3	7	6	28	25
China	38	25	2	1	1	1	2	1	2	0	45	28
Djibouti	1	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	29	13	39	15	11	5	1	1	170	61
Indonesia	162	134	9	7	12	10	9	9	0	0	192	160
Iraq	3	2	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	7	2	0	0	4	2	0	0	123	61
<b>Total</b>	<b>468</b>	<b>282</b>	<b>48</b>	<b>24</b>	<b>62</b>	<b>34</b>	<b>32</b>	<b>20</b>	<b>10</b>	<b>7</b>	<b>620</b>	<b>367</b>

Reproduced from "Cumulative Number of Confirmed Human Cases for Avian Influenza A (H5N1) Reported to WHO, 2003 – 2013," Digital image. World Health Organization, February 15, 2013, [http://www.who.int/influenza/human\\_animal\\_interface/EN\\_GIP\\_20130215CumulativeNumberH5N1cases.pdf](http://www.who.int/influenza/human_animal_interface/EN_GIP_20130215CumulativeNumberH5N1cases.pdf), (Accessed March 13, 2013).

Like the H1N1 virus, HPAI exhibits a wide range of symptoms. These can include the typical seasonal influenza symptoms of fever, cough, muscle pain, etc. Respiratory impediments such as shortness of breath to the more serious cases of pneumonia and full respiratory failure have also been documented. Lastly, HPAI can inflict gastrointestinal distress in the form of pain, nausea, diarrhea, and vomiting. Laboratory testing is the only measure to confirm an H5N1 infection<sup>78</sup>. Confirmed cases of HPAI are few and sporadic and thus, inferences upon its current biological characteristics must be made with caution. A study conducted in the latter half of 2008 (when there was only 400+ cases) discovered that the incubation period for avian-human infection was less than seven days. An exact range could not

<sup>78</sup> "Avian Influenza A Virus Infections in Humans," June 21, 2012.

be accurately determined. However, there have been some cases, albeit limited, human-human transmission of HPAI and the approximate incubation period appeared to be three to five days. However, researchers in China discovered one cluster (more on clusters in the following section) where the incubation period appeared to be eight to nine days.<sup>79</sup>

H5N1 has shown to occur more often in people under the age of 40, with mortality rates highest in the 10-19 years old category. As Figure 5 shows, over 600 humans have been infected with HPAI H5N1 since 2004. Of these confirmed cases, approximately 60% of them have died. Despite a mortality rate that is higher than any previously known influenza virus, 60% may be a bit extreme. The majority of confirmed cases have appeared in Asia and many of the infected persons sought medical intervention only when their illness became seriously pronounced. It is highly likely that there are many HPAI H5N1 cases that are mild enough that medical attention is not sought out.<sup>80</sup> Despite this, the mortality rate is still extremely high and constitutes the greatest reason for HPAI H5N1 prevention. As of April 17, 2013, Egypt reported its 3<sup>rd</sup> H5N1 case. The individual, a 26 year old male, did not survive the infection.<sup>81</sup>

## **Emergence and Spread**

As it stands, H5N1 is spreading throughout the globe in birds. There are confirmed cases of domesticated poultry infected with avian influenza throughout Asia, northern Africa and Mexico\*. Migratory birds, the reservoir for avian influenza, have also been confirmed to be

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<sup>79</sup> Yang Huai, et. al, 1819.

<sup>80</sup> "Highly Pathogenic Avian Influenza A (H5N1) in People," Centers for Disease Control and Prevention, June 21, 2012, <http://www.cdc.gov/flu/avianflu/h5n1-people.htmnt.htm>, (Accessed January 19, 2013).

<sup>81</sup> "Egypt Reports 2 Bird Flu Deaths This Year," Aswat Masriya, April 17, 2013, <http://en.aswatmasriya.com/news/view.aspx?id=ce941b4e-3022-431a-ac4d-8ff4c3a20ede>, (Accessed April 18, 2013).

infected recently with confirmed results throughout Asia, the Middle East and Denmark.<sup>82</sup>

H5N1 remains fairly entrenched within many Asian countries for a variety of factors. Poultry is an important commodity in East Asia and demand has skyrocketed. A large amount of poultry production is unregulated and does not meet quality-control standards that are common throughout the developed world. Small-scale and local farms especially are apt to practice free-range farming of their domesticated poultry, which allows the birds to come into contact with wild birds and acquire HPAI. Proper veterinary practices are not conducted because surveillance is highly patchwork and its reporting of potential poultry contamination of HPAI often falls to the producers. The most effective method to neutralize a contaminated population of infected birds is to systematically cull and burn the livestock, which many governments are apt to do. Because of the environmental conditions that are present in Asia, it is highly unlikely that avian influenza will be neutralized in the various nations in which it is currently endemic.<sup>83</sup>

To date, the status of HPAI is labeled as a World Health Organization pandemic alert Phase 3.<sup>84</sup> Referring to Figure 4 in on page 34, phase 3 of the WHO system is defined as “human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact.”<sup>85</sup> HPAI has successfully jumped from avian to human, but the cases are sporadic and fairly limited. There have also been probable human-human transmissions within small clusters in Asia. These infected clusters have been shown to produce

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<sup>82</sup> "Current Avian Influenza (H5N1) Affected Areas," Public Health Agency of Canada, February 26, 2013, <http://www.phac-aspc.gc.ca/h5n1/index-eng.php>, (Accessed March 13, 2013).

<sup>83</sup> Italy. United Nations, Food and Agriculture Organization, *Approaches to Controlling, Preventing and Eliminating H5N1 Highly Pathogenic Avian Influenza in Endemic Countries*, May 24, 2011, <http://www.fao.org/docrep/014/i2150e/i2150e00.htm>, (Accessed March 13, 2013).

<sup>84</sup> "Current WHO Phase of Pandemic Alert (avian Influenza H5N1)," WHO, 2013, <http://www.who.int/influenza/preparedness/pandemic/h5n1phase/en/index.html>, (Accessed January 19, 2013).

\* Avian Influenza A/H7N3

<sup>85</sup> "WHO Global Pandemic Phases and the Stages for Federal Government Response," Digital image, Center for Biological Couterterrorism and Emerging Diseases CDC-ED, [http://bepast.org/dataman.pl?c=lib&dir=disease\\_information/Pandemic%20Influenza](http://bepast.org/dataman.pl?c=lib&dir=disease_information/Pandemic%20Influenza), (Accessed July 23, 2012).

2-8 infected humans per group. While it is highly likely that limited human-human transmission has occurred, it has only happened in these clusters, which are usually composed of a single, blood-related household. Each potential human-human case cannot be successfully confirmed because each individual had contact with a dead and/or sick bird as well; it is possible, although statistically unlikely, that they contracted the virus from the bird and not another family member.<sup>86</sup>

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<sup>86</sup> "Highly Pathogenic Avian Influenza A (H5N1) in People," (Accessed January 19, 2013).

## CHAPTER 3

### POLICY PROBLEMS

#### The Select Agent Program

##### **Origins**

The U.S. government's website for the National Select Agent Registry details the origins for the program. In 1995, a microbiologist was arrested and subsequently convicted for fraud after obtaining samples of bacteria called *Yersinia pestis*. This bacterium is the cause of bubonic plague, more commonly known as the Black Death. By means of fraudulent claims, the bacterium was obtained via mail-order delivery. This incident was a frightening alarm for government officials, as there existed no federal regulations for laboratories and individuals for the possession, usage, and transfer of select agents and toxins within the United States. The phrase "select agents and toxins" can be defined as "biological agents and toxins that could pose a severe threat to public health and plant health, or to animal or plant products."<sup>87</sup>

In order to remedy this lack of oversight, Congress passed Section 511 of the Antiterrorism and Effective Death Penalty Act of 1996. Section 511 instructed the Department of Health and Human Services to: (A) compile a list of select agents that posed a large public health threat, (B) develop standard operating procedures for the transfer of select agents, and (C) to establish training requirements for anyone wishing to work with listed select agents. The potential for bioerror was too great for this issue to be purposefully overlooked. Once the select agent list was established, HHS transferred implementation of the new law to the Centers for

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<sup>87</sup> "About Us," National Select Agent Registry, March 12, 2013, <http://www.selectagents.gov/AboutUS.html>, (Accessed March 20, 2013).

Disease Control. The CDC established the Division of Select Agents and Toxins (DSAT) and founded the Select Agent Program.<sup>88</sup>

The post-September 11<sup>th</sup> anthrax mailings (Amerithrax) saw a substantial increase in regulatory requirements in the Select Agent Program. The U.S. federal government was concerned that another terrorist attack on the United States could be biological in nature and that the terrorists could acquire the bioweapon components from domestic facilities.<sup>89</sup> In addition to the existing Select Agent Program, more stringent rules and regulations were placed on selected agents, pathogens and toxins through the USA Patriot Act of 2001 and the Public Health Security and Bioterrorism Preparedness and Response Act (Bioterrorism Act) of 2002. The Bioterrorism Act mandated a select agent list for animals and plants be implemented in the same fashion and in conjuncture with the CDC's registry. Implementation and regulation of the new select agent plant and animal list was logically ceded to the Department of Agriculture who used their Animal and Plant Health Inspection Service to create the Agricultural Select Agent Program. The human and agricultural select agent registries together comprise the Federal Select Agent Program.<sup>90</sup> The logic behind this comprehensive program was that better security of hazardous microbes would help prevent malicious or accidental release of microbes that could seriously impact public health or domestic agriculture. The prevention of bioterror and bioerror is necessary for domestic security and that demands a strong regulatory system be implemented.<sup>91</sup>

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<sup>88</sup> Ibid., 2013.

<sup>89</sup> Jennifer Gaudioso, Reynolds M. Salerno, and Natalie Barnett, "Developing a Risk Assessment and Management Approach to Laboratory Biosecurity," *Applied Biosafety* 11, no. 1 (2006): 24-31, 24.

<sup>90</sup> "About Us," National Select Agent Registry, 2013.

<sup>91</sup> Jennifer Gaudioso and Reynolds M. Salerno, "SCIENCE AND GOVERNMENT: Biosecurity and Research: Minimizing Adverse Impacts," *Science* 304, no. 5671 (April 30, 2004): 687, doi:10.1126/science.1096911.

## Recent Changes

In July 2010, President Obama signed *Executive Order 13546* which began the process of reform within the entirety of the Federal Select Agent Program. The EO mandated that HHS and the USDA establish a subset of extremely hazardous select agents to be categorized as Tier I select agents. The remaining select agents not chosen will retain the existing regulations as de-facto Tier II agents. The EO also stated that HHS and USDA were to consider select agents to be removed from the list, if deemed practical.<sup>92</sup> The new rules came into effect on April 3, 2013. In order for entities to utilize Tier I agents, they will need to enforce “special rules for screening and physical security, on top of those already required by the Select Agent Program.”<sup>93</sup> Tier I agents were selected on the criteria of how easily the microbes could cause mass casualties and destroy the functionality of societal structures, like infrastructure, service provision, and economic markets. Viral strains associated with a potential pandemic influenza (HPAI H5N1, 2009 H1N1, reconstructed 1918 H1N1) are not classified as Tier I agents so they will not be subjected to the stricter regulatory environment as agents like *Ebola*, foot and mouth, and anthrax.<sup>94</sup>

## Problems

Access to Select Agent pathogens is extremely time-consuming and highly regulated. In order to get clearance, the FBI must run a background check on the individual in question and that can take up to eight weeks. Certain people are not allowed to apply for clearance as well,

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<sup>92</sup> "About Us," National Select Agent Registry, 2013.

<sup>93</sup> Robert Roos, "With New Rules, Few Public Health Labs to Handle Riskiest Agents," CIDRAP, December 13, 2012, <http://www.cidrap.umn.edu/cidrap/content/bt/bioprep/news/dec1312select.html>, (Accessed March 25, 2013).

<sup>94</sup> "Federal Panel Selects Tier 1 Agents," OH&S, June 20, 2011, <http://ohsonline.com/articles/2011/06/20/federal-panel-selects-tier-1-agents.aspx>, (Accessed March 30, 2013).

including convicted criminals, people with recorded mental illness, foreign nationals from officially-recognized terrorist-sponsor nations, and dishonorably discharged military personnel. While many of these exclusions are logically sound, there are definite problems. A researcher with no malcontent could be originally from a nation such as Iran, Syria, or even more remarkably, Cuba. The black or white approach to granting clearance for biological research simplifies the regulatory environment to a certain extent, but it can possibly deny access by top academics in the field. If the FBI's background check comes through satisfactory, there still exists a large amount of federally required training, paperwork and processing which necessitates more time and financial resources.<sup>95</sup>

Select Agent pathogens are highly regulated and limited with regards to transfer procedures. In order to maintain safety protocols and security, all transfers from one facility to another must be approved by federal authorities, even if it is a facility-to-facility transfer on the same campus. At the registered facility itself, there are high levels of physical security including multiple barriers to access and the addition of a designated security officer, all of which are financed through the facility in question. Paperwork and logs of personnel activities must be maintained strictly for federal auditing and inspections and any sort of disposal of the pathogen has to occur in a pre-approved, controlled, disposal facility.<sup>96</sup> Select Agent pathogens are very secure from malicious theft, but they have angered many within the scientific community.

Despite these security regulations, hazardous biological substances can still be acquired. Many dangerous agents are readily available in the natural world if one knows where to look. Acquisition is also easier to achieve in some locations overseas (i.e. Aum Shinrikyo's attempt to

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<sup>95</sup> *Safety and Compliance Program for Select Agents and Toxins and High Consequence Livestock Pathogens*. Report, <http://www.research.northwestern.edu/ors/forms/select-agent-program.pdf>, (Accessed January 15, 2013), 2, 4. ; Gaudio and Salerno, 687.

<sup>96</sup> *Safety and Compliance Program for Select Agents*, 4-7.



acquire the Ebola virus) and it would be relatively easy to smuggle a small amount into the United States. Also, biological technology is becoming more available and inexpensive which means some dangerous microbes/toxins will be able to be artificially synthesized in the near future.<sup>97</sup> Besides the non-inclusive nature of parts of security clearance acquisition, the simple financial and bureaucratic hurdles are having an effect. In a 2004-05 survey, 20% of Select Agent researchers stated that the regulatory laws in place were affecting their ability to coordinate and research with others both domestically and internationally. The same survey also noted that 40% of respondents indicated that they were using federal research grants to implement required security changes to their facilities. Some researchers have also opted away from using funds from the Department of Homeland Security based completely on the necessary requirements associated with conforming to federal compliance standards.<sup>98</sup>

A CDC economic analysis concluded that costs associated with implementation of Select Agent Program regulations ranged anywhere from \$15,000 to \$150,000 dollars annually, depending on the facility. The USDA estimates fell within the range set previously by the CDC; annual costs for regulatory compliance are about \$50,000. The majority of the funds are tied up in three key areas: maintaining physical security measures at the various facilities, inventory accounting, and basic administrative work. The cost estimates listed are those that are needed for ongoing operations and they do not factor in construction costs implementing stricter security measures after passage of the USA PATRIOT Act and Bioterrorism Act.<sup>99</sup> At the USDA

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<sup>97</sup> Gaudio, Salerno, and Barnett," 24.

<sup>98</sup> M. B. Dias, L. Reyes-Gonzalez, F. M. Veloso, and E. A. Casman, "Effects of the USA PATRIOT Act and the 2002 Bioterrorism Preparedness Act on Select Agent Research in the United States," *Proceedings of the National Academy of Sciences* 107, no. 21 (May 10, 2010): 9556-561. doi:10.1073/pnas.0915002107," 1.

<sup>99</sup> Robin J. Kastenmayer, Rashida M. Moore, Allison L. Bright, Raphael Torres-Cruz, and William R. Elkins, "Select Agent and Toxin Regulations: Beyond the Eighth Edition of the Guide for the Care and Use of Laboratory Animals." *Journal of the American Association for Laboratory Animal Science* 51, no. 3 (May 01, 2012), 336.

National Veterinary Services Laboratory in Ames, Iowa, the construction costs to upgrade the facility to meet the requirements set forth in the aforementioned legislation exceeded \$500,000 dollars in 2002. Select Agent Program requirements are noticeably more expensive than for similar labs who do not house select agents. Requirements such as security guards, biometric scanners, card readers, specialized safety cabinets and lockers, decontamination showers, specialized HVAC units (heating, ventilation and air-conditioning), and many more requirements that are expensive to construct and maintain.<sup>100</sup>

A 2009 study proposed that if the 2002 security regulations were having a drastic impact on the ability and likelihood that scientists will research Select Agent pathogens, there would be a noticeable difference in the amount of published findings pre and post 2002. The researchers used *Bacillus anthracis* (anthrax) and the Ebola virus as the experimental variables and *Klebsiella pneumonia* (a common bacterium which often causes bronchitis) as the control variable. The researchers discovered that annual peer-reviewed papers for the Select Agent pathogens increased, but the number of papers per million dollars of federal funding decreased significantly, unlike the control variable. The data indicates that the efficiency of funding spent towards research has changed since 2002. A survey of prominent scientists in the chosen select agent fields gave some useful qualitative information. It was noted that while more scientists were entering and researching Select Agent pathogens, many were not staying in the fields for long. They also reported that collaboration between different facilities both domestically and internationally were made noticeably slower. The last point of prominent complaint was that the increased amount of administrative paperwork slowed down many projects insomuch that some

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<sup>100</sup> National Research Council, "Responsible Research with Biological Select Agents and Toxins," National Academy of Sciences. 2009, [http://www.nap.edu/catalog.php?record\\_id=12774](http://www.nap.edu/catalog.php?record_id=12774), (Accessed March 16, 2013), 130-33.

take twice as long to complete and because of the required FBI background checks, researchers could no longer efficiently hire students or technicians. While collaboration between domestic and international entities provided mixed results, the major outcome from this research is that the federal regulations regarding the Select Agent Program produced inefficiencies. The researchers do note that the study could only analyze available data and that there may be select agent research that is classified. They also state that some externalities unaccounted for may explain the incongruity between the statements from scientists and the papers published. From the research provided, it can be surmised that research of select agents is contingent on federal grants, despite the inefficiencies.<sup>101</sup>

The Select Agent regulations require mandatory, up-to-date, inventory accounting practices be conducted in order to ascertain the validity of samples. Inventories of select agents require complete labels for identification and total documentation of their presence within the facility. This type of inventory accounting system is logical for hazardous substances like nuclear materials, but does not fit well for biological agents, because of their ability to self-replicate. A “full” inventory of agents could be accounted for, but that does not take into account their reproductive potential. The current system is apt to lull the regulatory agencies into a false sense of security.<sup>102</sup>

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<sup>101</sup> Ibid., 2-5.

<sup>102</sup> National Research Council, 113, 115.

## Dual Use Research of Concern (DURC)

### Overview

Dissemination of scientific knowledge is a cornerstone of scientific principles. Robert Oppenheimer, the lead scientist associated with the United States' deployment of nuclear weapons, advocated in favor of wide dissemination of nuclear physics. As he stated, "It is not possible to be a scientist unless you think that it is of the highest value to share your knowledge, to share it with everyone that is interested."<sup>103</sup> Nuclear technology and knowledge is still a contentious topic today; it has the potential to produce large amounts of electrical energy, but it also has the potential to obliterate large tracts of land and kill millions. These potentials for good or ill are the encompassing notion behind dual-use research of concern (DURC) and biology, like physics, is no different. Biological weapons, unlike nuclear weapons, are relatively easy to produce and cost-effective as compared to nuclear arms.<sup>104</sup> Microbiological knowledge and techniques can artificially enhance microbes for greater lethality as well as manufacture a vaccine for greater societal good; duality of application is the fundamental problem concerning dual use issues. In most cases, the actual research is meant for the greater benefit of the scientific community and society as a whole. However, because techniques and knowledge have implicit applications for malicious use, they become double-edged swords. Dual use refers to the potential that knowledge may be used inappropriately, but dual use research of concern implies a real threat, not an implied one. There has to exist substantial proof that a technique or

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<sup>103</sup> K. Satyanarayana, "Dual dual-use research of concern: Publish and perish?", 1.

<sup>104</sup> Ibid., 1-2.

knowledge-base can be readily applied for harmful effects; dual use research of concern makes the leap from theoretical/perceived threats to legitimized and established threats.<sup>105</sup>

The United States has a justifiable reason to fear bioterrorism as the Amerithrax case proves. Independent scientific studies compose the majority of microbiological research conducted in the United States and it is difficult for the government to justify regulation for limited research scope. In order to gain credibility within the scientific community, experimental methodologies and results must be published in peer-reviewed journals. One of the goals of science is to attempt to reproduce new research in order to validate previously published results. However, by conducting research and publishing results on Select Agent pathogens, such as H5N1 Avian Influenza, it can provide a set of instructions to repeat the experiment and artificially engineer a lethal pathogen for malicious purposes. The independent laboratories and universities around the nation research bacteria and viruses that the federal government does not have resources to conduct on their own. When the results of such an experiment prove to be dangerous, the federal government finds itself in an uncomfortable situation. Basic civil liberties and the open-access nature of science afford protections against censorship, but in the event of a national security event, those protections can be overruled. However, if a precedent towards censorship becomes evident, many researchers will choose not to engage in critical areas of research.

### **NSABB Establishment**

In 2004, the Department of Health and Human Services (HHS) established the National Science Advisory Board for Biosecurity (NSABB) for the explicit purpose of developing criteria

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<sup>105</sup> *Dual Use Research*, Office of Biotechnology Activities- National Institutes of Health, <http://oba.od.nih.gov/biosecurity/biosecurity.html>, (Accessed March 30, 2013).

for DURC dissemination.<sup>106</sup> As defined on the National Institutes of Health website, NSABB “is a federal advisory committee chartered to provide advice, guidance, and leadership regarding biosecurity oversight of dual use research, defined as biological research with legitimate scientific purpose that may be misused to pose a biologic threat to public health and/or national security.”<sup>107</sup> Should an issue arise, HHS must consult this revolving board to determine whether research results should or should not be published. Such an issue presented itself with regards to H5N1 quite recently.

### **2012 H5N1 Research Controversy**

Many aspects of H5N1 are still not well understood by science. Given the statistical mortality rate of ~60% for confirmed cases, this virus demands extensive research because of its potential for large-scale mortality. Researchers in the Netherlands and at the University of Wisconsin-Madison artificially engineered H5N1 to be easily transmissible between ferrets. Ferret immunology is similar to human and extrapolations could be conferred that if certain genetic mutations were to occur naturally or artificially within H5N1, it would acquire the genetic sequence for easy human-human transmissibility. This study, completed in 2011, is arguably the largest biology-related DURC to date. The study, including methodologies, was scheduled to be published in the highly regarded journals *Science* and *Nature*. The NSABB stepped in and on December 20, 2011 declared that the scientific benefits did not outweigh the

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<sup>106</sup> K. Satyanarayana, 2-3.

<sup>107</sup> "OBA - About NSABB," Office of Biotechnology Activities- National Institutes of Health, [http://oba.od.nih.gov/biosecurity/about\\_nsabb.html](http://oba.od.nih.gov/biosecurity/about_nsabb.html), (Accessed April 04, 2013).

security risks involved. Because they do not have the legal authority to enforce censorship, the NSABB asked *Science* and *Nature* to withhold publishing the experimental methodologies.<sup>108</sup>

A recommendation to withhold publication of the American and Dutch research results had never happened before and the world took note. The WHO conveyed highly concerned statements that December and scheduled an international meeting to discuss the issue. On January 20, 2012, researchers associated with both the American and Dutch projects voluntarily upheld the NSABB recommendation and placed a moratorium on publishing the results for 60 days. However, the lead researcher at UW-Madison, Dr. Kawaoka, stated that while results would not be published, the research had to continue on. The WHO international meeting convened on February 16 & 17, 2012 and subsequently stated that there was general disagreement regarding the NSABB's recommendation. While there were large amounts of disagreement, fueled by the alarming nature of the topic, the WHO recommended that the results be published at a later date rather than never at all/or in redacted format.<sup>109</sup>

On March 30, 2012, NSABB revised their previous decisions. Dr. Kawaoka submitted a revised manuscript detailing new information about viral influenza hemagglutinin. Because this new research was deemed a definite benefit for public health, NSABB unanimously approved the revised submission. Dr. Ron Fouchier, the lead author of the Dutch study, submitted a revised manuscript as well. The NSABB ruling was 12-6 in favor of publishing because of two key considerations. First, the revision did not include the exact mutations needed in order for the ferret H5N1 virus to become transmissible via aerosols. The lack of detail is a critical part of the

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<sup>108</sup> Michael Tu, "Between Publishing and Perishing? H5N1 Research Unleashes Unprecedented Dual-Use Research Controversy," May 3, 2012.

<sup>109</sup> Jaclyn Schiff, "Bird Flu Flap: The Controversy Over H5N1," Bird Flu Flap: The Controversy Over H5N1, <http://www.tiki-toki.com/timeline/entry/24992/Bird-Flu-Flap-The-Controversy-Over-H5N1/>, (Accessed March 30, 2013).

potential roadmap to recreate the virulence of the microbe. Also, many on the NSABB board realized that because oversight and regulation between the United States and Holland was not the same, any attempt to censor the information would be an exercise in futility. The potential that the research results would be leaked were too high; it was easier to give approval for publication than try to contain something that the NSABB had no jurisdiction over.<sup>110</sup> The research results from UW-Madison were published in *Nature* journal.<sup>111</sup> Work recently resumed in the latter part of January 2013 on H5N1 Avian Influenza after almost a year hiatus. The controversy still exists and many scientists and government officials believe that the research is a danger.<sup>112</sup> The British Royal Society states that censorship is ineffective and that research has a way of getting released in some fashion. Having a third category between ‘classified’ and ‘unclassified’ is also highly impractical as there does not exist a system to disseminate the material to those who need to know<sup>113</sup>

Throughout the 2012 H5N1 Avian Influenza controversy, there were often questions regarding why the information wasn’t made classified. Governments can share confidential information with one another without the greater population knowing. This makes sense, but there was one reason why this would not work: export controls.

Export controls are rules enacted by various agencies of the U.S. federal government. They are meant to curtail the dissemination of high end and dual use technologies to a variety of nations. Be it for political or national security reasons, the rules list specific technologies, materials, and information that are verboten from leaving the United States (unless a federal license is granted ahead of time). Within academia, the “Fundamental Research Exclusion” allows a lot of traditional academic research to go on

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<sup>110</sup> Nicholas G. Evans, "Great Expectations--ethics, Avian Flu and the Value of Progress," *Journal of Medical Ethics* 39, no. 4 (October 30, 2012): 209-13, doi:10.1136/medethics-2012-100712, (Accessed April 3, 2013), 210.

<sup>111</sup> Tu, 2012.

<sup>112</sup> James Gallagher, BBC News, January 23, 2013.

<sup>113</sup> K. Satyanarayana, 3. ; Michael Tu, 2012.



where it would be otherwise controlled. Fundamental Research allows for exemption for a needed license, but it no longer applies if the research involves the participation of foreign persons or if there exists restrictions on free/open publishing<sup>114</sup>. This was the snag that the research fell into when the controversy erupted. Because the research had been done at a public university under the Fundamental Research Exemption, it needed to be openly published.

### **Dual Use Debate: Science vs. Security**

In the dual use research of concern debate, there is not total disagreement. In fact, for the most part, scientists and policy makers agree on many items. It is generally acknowledged among prominent individuals in this topical area that the federal government needs to have a say in regards to dual use and DURC issues/conduct, especially if the project is being funded with federal dollars. It is also generally accepted that scientists need to play a pivotal role in the generation of new procedures and regulations. Scientists know the ins and outs of a particular topic and their detailed and professional knowledge is required in order to avoid nonsensical blanket policies. There is almost unanimous consensus that research involving select agents needs to continue, despite their dual use applicability. The only way to respond to and mitigate against a serious public health hazard is to know the “enemy.” The more technical knowledge that is generated on hazardous microbes, the easier it is to respond to them.<sup>115</sup>

The main point(s) of contention in the dual use debate are related to the types and scopes of acceptable research and the control mechanisms (or lack thereof) on the research/results. Proponents of the American and Dutch studies argue that the research methodologies used are fairly wide known and well understood. Even if the results of the research were not published,

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<sup>114</sup> “Export Controls,” Office for Responsible Research, <http://www.compliance.iastate.edu/control.html>, (Accessed July 20,2013).

<sup>115</sup> *Dual Use Research*, National Institutes of Health.

the same hypothesis and method to achieve the results could be generated somewhere else by a knowledgeable individual with the proper experience and equipment. Censorship of the results will not make the world any safer, but only delay someone else from doing the same experiment in a different part of the world. Opponents of the study claim that the science and methodologies behind the research constitute a public hazard as it allows would-be terrorists, or their sponsors, to build off of existing data to artificially enhance a lethal influenza virus for easy transmissibility. Opponents also argue that the study was completely unnecessary and that is boiled down to fear mongering. The media does a remarkable job at hyping up and even creating controversy and fear. This fear translates to Congressional action and appropriations which the researchers of the study are taking advantage of.<sup>116</sup>

Notable proponents of the H5N1 studies, Peter Palese and Taia Wang, state that censorship of the study is completely unfounded and unjustified. As stated before, the work performed at UW-Madison and in Holland extrapolated HPAI H5N1 from the ferret test model. While ferrets provide a good model for the human immune system, they are different organisms. The immunological response and detrimental effects seen in ferrets may stay within that species; it need not foretell what would happen in humans. Palese and Wang also go on to state that despite repeated, long-term contact with H5 influenza virus strains, there has never been an epidemic outbreak because the H5 strain has never acquired any human-human transmissibility. For all the recorded epidemics and pandemics of the 20<sup>th</sup> century, the only causal strains were H1, H1, and H3. The H1 viral family was the cause for the 1918 and 2009 pandemics.<sup>117</sup>

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<sup>116</sup> Tom Paulson, "Bird Flu Cockfight: Secrecy vs Science," *Humanosphere*, February 15, 2012, <http://www.humanosphere.org/2012/02/bird-flu-cockfight-secrecy-vs-science/>, (Accessed March 28, 2013).

<sup>117</sup> Peter Palese and Taia T. Wang, "H5N1 Influenza Viruses: Facts, Not Fear," *Proceedings of the National Academy of Sciences*, Published Online before Print (January 25, 2012): 1-3. doi:10.1073/pnas.1121297109, (Accessed March 30, 2013), 1.

Palese and Wang go on to describe that the mortality rate of about 60% is most likely greatly overestimated. The epicenter for H5N1 is in rural Southeast Asia and the majority of those afflicted with H5N1 have had very low socioeconomic standing. Also, this is relying on self-reporting in that the farmers and laborers infected have to become sick enough to seek medical attention. While dreadful, Palese and Wang argue that the current total most likely represents the most severe cases of H5N1 infection. They state that there are probably many undiagnosed cases of H5N1 infection that are either mild or asymptomatic. By this reckoning, the case fatality rate is most likely much lower than the current 60%.<sup>118</sup>

Palese and Wang conclude that H5N1 studies need to be published in a timely manner and should not be subjected to any measure of censorship or redaction. The complete genetic sequence of the vicious 1918 H1N1 Influenza strain was published in 2005 in *Nature* without any problems from NSABB (four years before the outbreak of the 2009 H1N1 pandemic). They state that is also highly unrealistic that this science will be used for bioterrorism. The necessities to reproduce the experiment and use it for ill purposes would require state of the art bio-facilities, relevant experience working with influenza viruses, a high manner of scientific proficiency, and a large amount of time. *Nature*, Palese and Wang state, is replicating new viruses on a grand scale, 24/7. They propose that natural selection will produce another pandemic before one is generated artificially in a laboratory. In order to be ready for that future pandemic, scientific progress must not allow itself to be halted.<sup>119</sup>

Proponents of the H5N1 influenza studies and unrestricted science in general, are met by an equally convincing argument on the opposite end. A lot of the evidence that is cited has already been explained substantially in prior sections of this paper. The threat and appeal of

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<sup>118</sup> Ibid., 2.

<sup>119</sup> Ibid., 1-2.

bioterrorism in the 21<sup>st</sup> century is not something that can be ignored. The Amerithrax situation thankfully caused minimal damage, as did the 90's bioterror attacks via Aum Shinrikyo.

Advancements in the field of biotechnology may allow a catastrophic event to occur that may not have had the information not been researched and subsequently published. While new regulations have been enacted for federally funded research with DURC implications, they do not cover privately-funded research or research conducted outside of the United States. Prior to the controversy, all research (and non-federal presently) was reliant on self-policing in the scientific community. While the implications for this honor system have been recently reduced, opponents state that the status quo is unacceptable. Reporting unethical research in the scientific community has no incentive process; the accuser is levied with the burden of proof. Even if justifiable accusations are made, but the case is not solid, the accuser could face libel or slander charges in return.<sup>120</sup>

The debate over dual use research of concern was made apparent in some contentious responses to the arguments made by Palese and Wang. Michael Osterholm and Nicholas Kelley responded to the Palese and Wang article with their own follow-up, which pointed out numerous problems from their point of view. The ten cited studies that Palese and Wang utilized have to be taken into context and not cited outright. Osterholm and Kelley state that Palese and Wang's evidence is inconclusive at best. There isn't any evidence to support the assertions of asymptomatic H5N1 infections are very common. Since the evidence is inconclusive, statements regarding the mortality rate of H5N1 may not be overestimated to the extent that Palese and Wang make it to be. Osterholm and Kelley also state that mortality is not the most important factor in the H5N1 dual use debate. There needs to be continued focus on the nature of the

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<sup>120</sup> Sutton, 308.

science vs. security conundrum. Until that's solved in the best possible manner available, the U.S. will not be able to sufficiently meet the threat of a future pandemic influenza.<sup>121</sup>

Nicholas Evans writes concisely and authoritatively in support of potential censorship of scientific research. He states that to appeal to the value of scientific freedom as the fundamental basis for any measure of research is not enough to warrant the research not be fully, or partially, censored. While censorship has been historically supported as detrimental to the betterment of society, it does hold validity in some instances. Scientific freedom, as defined by "the freedom to publish scientific information without interference"<sup>122</sup> is an intrinsic societal good but Evans argues that it is too flimsy of a rationale to validate H5N1 research on its own. Opponents of censorship argue that scientific freedom allows for three key points in dual use H5N1 research: A) confirmation and replication of the research results, B) continual building of scientific knowledge so that research can progress and new knowledge can be generated, and C) proprietary claims on the discovery. To invalidate these claims, Evans states that scientific confirmation and replication can be done without resorting to open access. Respected and well known scientists can be given classified authorization to review and confirm the results. Given the danger of this particular viral strain, Evans states that multiple replications of the study exacerbate and increase the likelihood for a bioterror or bioerror incident. Open access to information does not inherently imply that there will be less scientific advancement or progress either. Secrecy does not necessarily deprive projects of innovative thought. Evans uses the Manhattan Project as an example; the innovative and creative drive to create the world's first fully functioning nuclear weapon in a matter of years was done completely in secret with select

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<sup>121</sup>Michael T. Osterholm and Nicholas S. Kelley, "H5N1 Influenza Virus Seroepidemiological Studies: The Facts Revisited," *Proceedings of the National Academy of Sciences* 109, no. 21 (May 22, 2012): 1332, doi:10.1073/pnas.1203949109, (Accessed April 1, 2013).

<sup>122</sup> Evans, 209-10.

personnel. Proprietary claim over a discovery is important to scientists, but Evans asks whether the credit of discovery is worth the risk that it will be used for malevolent purposes. If a particular study or line of research is found to be implicit in the formulation and use of a biological weapon, the researchers will receive a large amount of blame and their credibility will be sufficiently ruined.<sup>123</sup>

Evans goes on to detract from other arguments made in favor of H5N1 research in general. The benefits of studying the virus, in his opinion, do not outweigh the risk. The benefits of studying H5N1 have been cited as the research will alert the public and scientific community to the dangerous nature of H5N1 and that research will assist in avian influenza surveillance and vaccine production. Evans responds to the first argument in that the controversy that the H5N1 DURC has stirred up has done more to warn the public of the dire potential of H5N1 than any public service announcement ever could. Even before the general public was aware of the danger, the wider scientific community was already quite knowledgeable. The government has been aware of the threat of pandemic influenza in so much that outlays for biodefense in fiscal year 2012 totaled 6.42 billion dollars. This was significantly more spending than the 5 billion dollars spent two years prior in fiscal year 2010. Even in the midst of a massive recession, the government saw the necessity to allocate more money for biodefense measures. Research, for the sake of drumming up support, is unnecessary and not a solid validation. Research to aid in disease surveillance is also not acceptable. There is no guarantee that a possible H5N1 virus that evolves in the natural world will be anything like the engineered viruses made in the laboratory. The argument applies to the vaccine justification as well. While many vaccines provide cross-immunity, or at least some measure of protection, a

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<sup>123</sup> Ibid., 210-11.

virus that evolves naturally may be sufficiently different enough from a vaccine produced from an enhanced laboratory virus that the vaccine is not applicable. Both issues of surveillance and vaccination are much more heavily reliant on other factors such as politics, financing, health infrastructure, etc. To make a case for H5N1 research because it will afford information for vaccine product and surveillance or for public awareness is weak, according to Evans.<sup>124</sup>

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<sup>124</sup> Ibid., 211-12.

## CHAPTER 4

## POLICY IMPLICATIONS

## Conflicting Testimony for Select Agent Regulations

**Change is Required****Figure 6****Total Number of Entities Registered with CDC, by Calendar Year**

	2004	2005	2006	2007	2008	2009	2010	2011	2012
<b>Number of Entities</b>	320	333	336	327	326	319	321	315	309

Reproduced from Lori Bane, "Entities Registered," E-mail message to author, January 30, 2013.

If one were to take a qualitative approach to the statements from many leading scientists, there does appear to be a loss of much needed efficiency after 2002. In 2004, the CDC expected 817 entities to register in the Selective Agent Program, but only 323 chose to do so. Stanford University, a historical leader in clinical research, was one of the entities that opted out.<sup>125</sup> Despite rhetoric that the Select Agent Program regulations were having a negative impact on registered entities, official CDC data for 2004-12 shows that entities remained fairly level (following the initial surprise in 2004). While notable institutions may have decided not to pursue research on select agents, the overall number of entities registered is indicative that research continues. However, this does not alleviate the problem with institutional research efficiency, which has been overcome (so far) by continued support from the federal government. The National Research Council recommends that all entities engaged in select agent research need a separate and stable federal fund for facility upgrades, security subsidization, and administrative support. They state,

<sup>125</sup> Gaudio and Salerno, 687.



Although this type of funding structure may be unusual for biomedical research laboratories, it is not uncommon for funding those areas of science where central infrastructure plays an important role. Primate research centers, telescopes, and the academic research fleet all have funding models in which operating costs are broken out as a separate direct expense, often from a separate account so that operations do not compete directly with science funding.<sup>126</sup>

The likelihood of federal funds for research security and administration, not to mention actual R&D grants, is not secure given the current partisan-fueled fiscal climate. On March 1, 2013, automatic spending cuts across the entirety of the federal government occurred. Prior to this “sequester,” Sen. Tom Harkin released a report in July 2012 stating that the CDC’s Public Health and Emergency Preparedness (PHEP) grants would be severely affected by the reduction to the effect of \$48 million dollars (7.8%).<sup>127</sup> As the CDC site states, the PHEP is “a critical source of funding for state, local, tribal, and territorial public health departments.”<sup>128</sup> As of April 10, 2013, the Obama administration proposed a 2014 budget which has a \$240 million dollar reduction in biodefense and emergency preparedness programs. While this is not finalized, it doesn’t present a confident view in the future of federal biohazard preparedness. In the administration’s defense, there was a proposed increase in federal funding for pandemic preparedness. If enacted, this would be the first pandemic funding increase since 2009. The increased funds would be administered to a variety of programs including research and production of next generation antivirals and new vaccines to combat the recent outbreak of

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<sup>126</sup> National Research Council, 133.

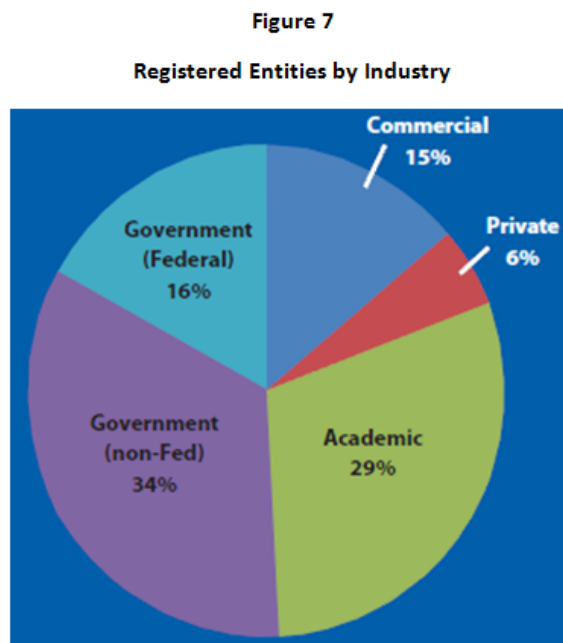
<sup>127</sup> Lisa Schnirring, “Fiscal Cliff Agreement Protects Preparedness Funds--for Now,” CIDRAP, January 2, 2013, <http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/news/jan0213fiscal.html>, (Accessed March 23, 2013).

<sup>128</sup> “Office of Public Health Preparedness and Response,” Centers for Disease Control and Prevention, October 15, 2012, <http://www.cdc.gov/phpr/coopagreement.htm>, (Accessed March 26, 2013).

H7N9 in China.<sup>129</sup> Despite this increase, emergency preparedness and management funding is going to be affected for the near future. With the current fiscal crisis, federal grants for select agent research cannot be counted upon. Until a budget is passed and the United States federal government ceases jumping from one manufactured fiscal crisis to the next, it is the recommendation of this author that non-federal select agent entities (see Figure 7) need to assess their fiscal resources and plan to be able to manage regulatory compliance without necessitating federal funds. This is a worst-case scenario as federal funding will not completely retract, but conservative budgeting could prove beneficial.

The National Research Council presents a variety of recommendation in their report, but the remainders of the recommendations that relate directly to previously mentioned topics are as follows:

1. The Select Agent Program requires more versatility and qualitative authorizations for the various registered entities. The diversity of the various entities ranges from academic institutions, private companies and up



Reproduced from Office of Public Health Preparedness and Response, *CDC Select Agent Program*, Washington D.C.: Centers for Disease Control and Prevention, 2011, [http://www.cdc.gov/phpr/documents/DSAT\\_brochure\\_July2011.pdf](http://www.cdc.gov/phpr/documents/DSAT_brochure_July2011.pdf), (Accessed May 26, 2013).

<sup>129</sup> Robert Roos, "CDC Preparedness Funds Take Hit in Proposed 2014 Budget," CIDRAP, April 10, 2013, <http://www.cidrap.umn.edu/cidrap/content/influenza/biz-plan/news/apr1013budget.html>, (Accessed April 17, 2013).

to federal laboratories. While certain protocols are followed in any environment, organizational size, scope and purpose varies dramatically. A one-size-fits-all approach is not conducive and will cause regulatory friction.<sup>130</sup>

2. The current nuclear-material based inventory system is detrimental. Instead of a “tally the vials” approach, an accountability system should be put in as a replacement. This system would not count the amount of select agents within a registered facility, but account for the people who get access to them. The details would include the types of select agents the entity retains, where the agents are stored. In regards to personnel, the ledger would state who has access, when do the researchers access the materials and why do they do so.<sup>131</sup>
3. There needs to be a separate and dedicated funding source for all registered entities in the Select Agent Program. This fund would not go to research, but to regulatory safety and compliance funding. When dealing with hazardous materials such as the select agents, safety and facility security are critical. The research needs to continue and ought not to be compromised by financial setbacks.<sup>132</sup>

Another author takes a different approach to establishing necessary steps to make the Select Agent Program more effective. This approach places the emphasis on effective and thorough background checks, rather than “filling out forms, filing reports and counting units of self-replicating organisms.”<sup>133</sup> The author states that the current Select Agent Program regulatory environment that mandates an FBI background check would not have stopped the Amerithrax

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<sup>130</sup> National Research Council, 53-54.

<sup>131</sup> Ibid., 115.

<sup>132</sup> Ibid., 133.

<sup>133</sup> Victoria Sutton, "Smarter Regulations," *Science and Engineering Ethics* 15, no. 3 (July 10, 2009): 303-09, doi:10.1007/s11948-009-9141-6, 307.

mailings early in 2001. The FBI background check, which is very similar to the background check needed to purchase a firearm, would not have been enough considering the prime suspect was supposedly subject to even further scrutiny. The suspect was a civilian employee at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). USAMRIID is under the Department of Defense and military personnel and civilians are all subject to even stricter background checks that look for any potential spot for aberrant behavior all the way back to high school. The suspect was given complete clearance despite the fact that he had a well-documented history of homicidal threats. The author disparages the background check system as ineffective and postulates that if more emphasis were placed on it, potential insider threats would be stopped before any harm could be accomplished.<sup>134</sup>

### **Current Regulations Enforced or Upgraded**

Although there are written materials detailing the extent of reasoned and perceived problems with the regulations in the Select Agent Program, not everyone is in agreement. Within registered entities, one person is the designated Responsible Officer (RO) who serves as the select agent biosafety officer and lab safety manager. It is the duty of the RO to make sure that all necessary paperwork is submitted correctly and in an orderly process. They are also the entities' liaison between the registered facility and federal authorities. The RO acts as the go-to staff member for all things regarding compliance, safety, and necessary submission of standard operating procedures (SOPs) which are the documents necessary for any sort of select agent research. The following is a summary of an interview conducted with a university-level RO.

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<sup>134</sup> Ibid., 305-307.

There exists a large amount of frustration within the scientific community regarding federal regulations. For example, in order to hire a foreign graduate student to perform controlled scientific research, a lengthy background check will need to be conducted. However, a lot of the regulations are a necessary evil in today's globalized world. A University-level RO was interviewed and had the following to say in regards to federal regulations,

Regulations are often seen as roadblocks, so what [my department] does is have the Principal Investigators (PI) adhere to the minimum requirements needed... even the American Society for Microbiologists did not have a say in what was selected to be select agents; the selection took place at the federal level with federal scientists and even Congress having the ultimate say.

She goes on to describe how it's very rigorous on her department, but the rules are the rules. There were comments regarding how there used to be an old way of doing things, but since 9/11, the basic way of viewing the world changed. While they can be deleterious to efficiency, the rules are in place for the PIs' safety, the safety of the students, and the safety of the University. The problem, from her perspective, is that a lot of PIs are still used to and wanting to operate under the older system, which was even more decentralized and loose. The potential of an insider threat was just not pertinent during those times, as it is now. Once a standard operating procedure has been drawn up, research can proceed on schedule. However, that does require some foresight and necessary paperwork, which can be challenging for those who want to continue on as usual. Federal regulations, especially the Select Agent Program as administered by the CDC and USDA, is quite necessary for modern times. The overall point obtained from the interview is that regulations like the Select Agent Program are rarely seen as

conducive, but every day that something bad does not happen, is a day in which the rules worked.

The interview provides first-hand experience and expert opinion on the state and nature of the Select Agent Program. There is some definite legitimacy to the statements provided and even some evidence to suggest that overall government regulation of high-level hazardous select agent research is not regulated enough. A recent Government Accountability Office (GAO) report details that the current environment with regards to BSL-3 and BSL-4 laboratory construction is not adequate. High level laboratories are very expensive to construct and maintain ongoing operations and because there aren't any set national standards, the various labs are constructed for local requirements. While this may be beneficial for keeping costs down and the facilities design for the local requirements, it makes them very difficult to assess, inspect, and guarantee their level of safety. Local building codes are not always adequate to rely on and problems can occur. The GAO report states that construction and building maintenance standards need not be a one-size –fits-all model, but there needs to be some measure of national standardization. All that exists currently is the Biosafety in Microbiological and Biomedical Laboratories (BMBL) manual which is more of guidelines than actual rules. The GAO recommends more regulations for facilities that maintain on-site select agents.<sup>135</sup>

To further elaborate on the subject of needed regulation, and possibly more, a select agent was recently lost. On March 25, 2013, a lab at the University of Texas Medical Branch reported that a vial containing the select agent *Guanarito* virus was missing from their BSL-4 facility. *Guanarito* is a rodent-borne South American virus that can cause hemorrhagic fever in humans.

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<sup>135</sup> United States, U.S. Congress, Government Accountability Office, *High-Containment Laboratories: Assessment of the Nation's Need Is Missing*, February 25, 2013, <http://www.gao.gov/assets/660/652308.pdf>, (Accessed March 26, 2013).

When this virus has had the ability to infect humans, there has been a 23% mortality rate which is much higher than the 1918 Spanish influenza. Thankfully, the virus has never been recorded as possessing human-human transmissibility. University of Texas officials have not found the vial and believe this to be an instance of bioerror, despite the virus's potential for weaponization. The GAO and USDA have advocated that even the most secure facilities in the nation, like the BSL-4 facility in Austin, are not secure enough to prevent potential theft of dangerous microbes.<sup>136</sup>

In a different interview with a policy expert who has background on dual-use research of concern, the Select Agent Program was brought up:

**What is an instance of a problem regarding federal regulations of hazardous microbial agents?**

There was a lab that had a -80C freezer in which they stored their non-select agents as well as their Select Agents. Well, every 10-15 years, a freezer goes down and needs to be fixed. The lab in question's freezer went down and they couldn't discern which agents were the select agents and which were not; their organizational and inventory system wasn't exactly organized. Usually, when this happens with normal microbes, they get temporarily stored in someone else's freezer. A separate lab within the same facility did not have clearance to store select agents however. Even if it had, simply moving a select agent requires notification of the RO prior to and a massive amount of paperwork. When your freezer is down and the agents are thawing, there is only a finite amount of time to find another place for storage. At the time, the lab didn't have a contingency plan in place should this happen; I imagine it was simply overlooked. This crisis was figured out in time, but it does lead to the negative views of the Select Agent Program.

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<sup>136</sup> "Easily Weaponized Virus Goes Missing from Texas Lab," RT USA, March 25, 2013, <http://rt.com/usa/virus-texas-lab-guarnarito-812/>, (Accessed March 25, 2013).

The regulations aren't necessarily bad; the PI just needs to do their job with much more advanced planning. You can't procrastinate or do things on a whim when you're working with a select agent. The PI, at the time, didn't know he wouldn't be able to play it by ear in case something unexpected came up. The crisis did force him to make changes to his inventory management and that is a critical component of this type of research.

## **Discussion**

There are two definite countervailing arguments set forth here. One side will have it be believed that the current regulatory environment of the Select Agent Program is not conducive to scientific research. On the other hand, it has been argued from professionals in the day-to-day process that the regulations are not the problem. PIs can help the process along by filing the proper paperwork on time and working with their Responsible Officers.

Disagreement about the Select Agent Program could potentially worsen in the coming years with the introduction of the Tiered system. A December 2012 informal survey found that many registered entities were not going to opt into the requirements to certify them for Tier I select agent study. The director of the Laboratory Services Division of Colorado's Department of Public Health and Environment, stated that his lab removed all Tier I agents in April 2012 in order to reduce their regulatory burden. All state-operated public labs in North Carolina have also opted away from Tier I agent storage.<sup>137</sup> While pandemic influenza is not a Tier I agent, animosity towards the Select Agent Program may incite many laboratories around the country to forgo all select agent research. However, as stated in the interview with the university RO, the current environment is different than what it has historically been. The fact remains that bioterrorism is a reality and there are many different agents which could cause a grave amount of

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<sup>137</sup> Roos, 2012.



damage. Domestic, private, and state-sponsored terrorism is the reality of the 21<sup>st</sup> century as opposed to the nuclear war threats of the 20<sup>th</sup> century. There must be stringent protections, procedures, and oversight placed on the most dangerous microbes in existence because their effects could be greater and more widespread than that of a nuclear explosion. However, a balance between security and research has to be achieved, or else the knowledge gained from research will not outweigh the regulatory security that has been put in place.

There appears to be a potential miscommunication or lack of understanding between researchers and the regulators. PIs have legitimate claims with regards to being potentially overburdened, but those entrusted to enforce government regulations have an equally justifiable reason to be frustrated. Both sides are working towards a common goal, but appear to have different methods and ideas of the path to get to that goal. There is a large body of work in existence with regards to the Select Agent Program being too much regulation and stifling to research. Despite anecdotal accounts, there are few, if any, conclusive estimates given to feelings and opinions from the regulators' points of view. A potential avenue for future research should be conducted to assess the implementers' attitudes towards the various contentious arguments made against the Select Agent Program. Also, it has to be recognized that the heightened regulatory environment associated with select agents has only been in place for a little over a decade. Many PIs have been conducting scientific research long before the Patriot and Bioterrorism Acts came into being. One potential explanation for the lack of acceptance for federal regulations could be from simple reticence towards change. Habits and attitudes usually establish themselves at a young age. Another avenue of potential future research could be assessments of attitude towards the Select Agent Program amongst PIs who were conducting research prior to 9/11 and those who began after.

A large amount select agent research is funded via the federal government. While there is an argument to be made that regulations are costly, the difference has been accounted for with the increased federal expenditures following 9/11. Regardless, consistent federal funding is no longer a given in 21<sup>st</sup> century America. Depending on the timing and amount of political fiscal negotiations and deals (or lack thereof), a study needs to be undertaken within two years to assess the impact that reduced federal dollars had on select agent research. It is my hypothesis that should federal expenditures for nonexempt nondefense spending be reduced by 9% (which is the current forecast within the scientific community), there will be a statistically significant negative correlation to the amount of select agent projects begun.<sup>138</sup>

### Dual Use Research of Concern: Few Options

#### **New Regulations**

In the wake of the H5N1 controversy, the Obama administration's Office of Science and Technology began the first in a series of government policies to target the problem of dual use research of concern. In March 2012, the "U.S. Government Policy for Oversight of Life Sciences Dual Use Research of Concern" was published. The policy is meant for federal agencies that fund potential DURC research. Prior to funding, a review process must be administered to make sure that the research, methodologies, and facilities are all adequate to warrant the federal dollars. Recently, the White House released the complementary policy titled "United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern" for public review and comment. This policy is tailored to the institutions that will conduct DURC research and makes stipulations regarding their conduct, procedures,

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<sup>138</sup> James, Wappes and Lisa Schnirring, "Re: FW: Influenza Sequester Information Request," E-mail message to author, March 26, 2013.

and reporting in order to utilize the federal funding. Both policies utilize the definition of DURC as,

Life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products or technology that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel or national security.<sup>139</sup>

While the institutional policies are important feedback mechanisms, the policy that is most important is the “U.S. Government Policy for Oversight of Life Sciences Dual Use Research of Concern.” If a proposed study doesn’t qualify in the initial review process, the federal government will deny funding for the project. There are seven key pieces of criteria which the proposal has to meet:

1. There can be no artificially engineered enhancements of the microbe’s existing harmful attributes. For example, if a virus already causes respiratory problems, insertion of genetic material that cause high-grade fever cannot be added.
2. The pathogen cannot be made to evade current immunities. Upon completion of vaccine treatment, millions become immune to diseases such as polio or measles. These pathogens cannot be altered as to allow the new viral strain to evade the immunity given through vaccination.

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<sup>139</sup> Franca Jones, "Proposed Policy Targets Dual Use Research of Concern," The White House, February 21, 2013, <http://www.whitehouse.gov/blog/2013/02/21/proposed-policy-targets-dual-use-research-concern>, (Accessed April 03, 2013).

3. In the same context, a pathogen cannot be altered to allow it resistance to known treatments. As stated earlier, CRE is a type of bacteria that has acquired resistance to known antibiotics. Conferring drug resistance to currently treatable illnesses is deemed too risky.

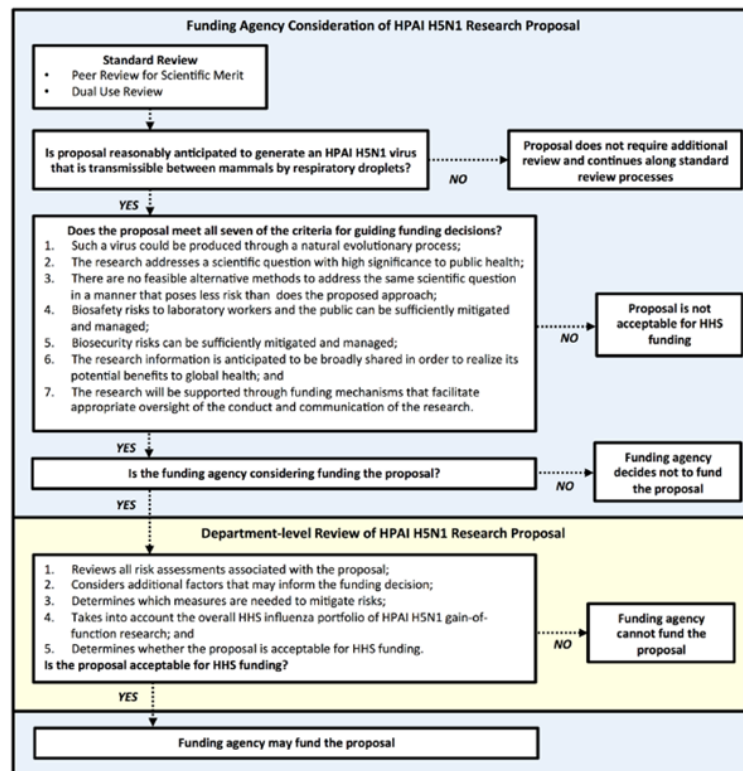
4. Increasing a pathogen's transmissibility is not allowed. Currently, HPAI H5N1 has made the jump from animal to human. Cultures of the virus acquired from infected patients and altered so that it easily spreads from person to person is subject to federal disqualification.

5. Increasing a pathogen's

ability to spread to different organisms is not allowed. Influenza subtype B is endemic almost exclusively to humans. Altering the viral genetic code so that it can easily spread to other species is deemed too risky for study, especially for domesticated livestock.

6. Increasing the susceptibility of existing hosts is unacceptable. A previous year's seasonal influenza vaccine has the potential to grant a degree of immunity to the subsequent year's

Figure 8



Reproduced from National Institutes of Health, "Funding Agency Consideration of HPAI H5N1 Research Proposal," Digital image, 2 - 21 - 20 13 A Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses That Are Transmissible among Mammals by Respiratory Droplets, February 21, 2013, <http://oba.od.nih.gov/oba/biosecurity/meetings/Dec2012/funding-hpai-h5n1.pdf>, (Accessed April 4, 2013).

influenza strain. Artificially altering a strain to the degree that more animals or humans are susceptible is subject to disqualification.

7. Re-creation of extinct or eradicated pathogens is prohibited from federal financing.

Viruses are in a constant state of evolution and some strains have caused significant problems throughout history. To recreate a deadly strain that either burned itself out, mutated into a less dangerous form, or was systematically wiped out will not receive federal funding.<sup>140</sup>

Because of the exact nature of the H5N1 controversy, the U.S. government published another policy specifically aimed at DURC research for HPAI H5N1. The 2011 research conducted by Dr. Kawaoka was funded by the National Institutes of Health and in order to make sure that the NSABB was not put in such a tough position again, “A Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets” was released on February 21, 2013 and is also up for public comment. This specific framework, for a virus that could potentially spark a deadly pandemic, goes further than the existing DURC review process listed above. The requirements to research anything regarding H5N1 are:

1. The virus that is being altered has to have the ability to naturally evolve along a similar path. A chimera virus that would never evolve naturally cannot be produced.
2. The study has to answer a needed question in relation to public health.

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<sup>140</sup> Anthony S. Fauci, M.D., "Dual Use Research of Concern: Balancing Benefits and Risks," Testimony Before the Committee on Homeland Security and Governmental Affairs United States Senate, April 26, 2012, <http://www.niaid.nih.gov/about/directors/Documents/DURCfinalClearedTestimony.PDF>, (Accessed April 02, 2013).

3. The study has to consider alternative measures to answer the question. If a safer alternate exists to answer the question, that route must be done.
4. Laboratory biosafety has to have competent and effective management. There can be no gaps or lags in biosafety.
5. Facility biosafety has to be completely up to code, fully secured, and managed effectively.
6. The results of the research, regardless of the outcome, will be openly disseminated.
7. There must exist funding mechanisms that will ensure all the above listed management and oversight as well as eventual information dissemination.

Figure 8 shows the step-by-step process as listed by the National Institutes of Health for specific funding of HPAI H5N1 Influenza. While various private institutions may conduct federal research on H5N1, the Department of Health and Human Services is one the largest sources for funding of the privately conducted research. These new policy rules are going to have a dramatic impact on the type, scope, and nature of future scientific research in both HPAI H5N1, but select agents in general.<sup>141</sup> However, these rules only apply to federal financing; there is no policy that takes into account the possibility that unfettered research could still be conducted as long as federal funding was not an issue.

### **Dual Use Research: A Catch-22**

A university-level policy expert in the areas of bioterrorism and dual-use issues was interviewed and she was able to offer particular insight into the realm of dual use research and

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<sup>141</sup> National Institutes of Health, "A Framework for Guiding U.S. Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses That Are Transmissible among Mammals by Respiratory Droplets," 2012.

the implications of the new policies proposed and enacted by the federal government. She states that overall, the federal government is doing a much better job at engaging the scientific community for expert opinions in the realm of dual use research policy formulation. For example, the American Society for Microbiology has been consulted and asked to submit opinions on the new rules. Overall, she states that the newer regulations are not nearly as restrictive as they could have been and that the government is finding decent amounts of middle ground. The main areas that it is failing on is relaying to researchers two pieces of information: who exactly is going to be making the final call on certain research projects and IF the results of a research project come back with potentially dangerous information, will the results be published no matter what? These matters are not addressed specifically and they are still important. As she states,

The new rules don't really answer how and who will determine whether research should be done in the first place. In the rules, I don't see a clear and unambiguous determination of who will make the final judgment call. If we want people to continue to do important work in the dual use arena, they need to know the exact rules of the game. Even writing a grant is a highly labor intensive and scientists deserve to know who is going to deny or approve of their project proposal. On the government's end, they also don't state exactly how they are going to determine whether or not certain dual use research will ever see publishing. Can it be in full or redacted? The events that unfolded at Madison and in the Netherlands provided an example of a situation that researchers do not want to be in.

The new rules are a step in the right direction, but they do not answer all the needed questions. Written previously in this paper were the arguments made both for greater academic freedom in researching select agents as well as the counter argument for greater security. The following is

two questions from the interview which tough on the argument, as well as the overall danger posed by a possible influenza mutation.

**The back and forth PNAS pieces between Palese and Wang and Osterholm and Kelley make for an interesting dynamic. Palese argues that caution should be thrown to the wind and science should continue unabated whereas Osterholm pushes for a more conservative and thoughtful approach to researching H5N1. Do their arguments hold legitimacy?**

As far as who is right on the percent mortality thing is irrelevant. One of the larger arguments between them is whether it's 60% or 10-20% mortality. In all honesty, it doesn't matter if H5N1 has a 60% mortality rate or a 6%; either way, the effects that that disease would have on the world population and economy would be catastrophic. One of the estimated mortalities of the 1918 Pandemic was only 2%. Even if we could conservatively agree that H5N1 is equivalent to 1918, that's still disastrous for society in the 21<sup>st</sup> century. Peter is highly informed and very prominent in his field and he was one of the first to work with the recreated strain of the 1918 flu, but mortality rates are irrelevant.

**What about Palese's statements regarding the likelihood of human-human transmissibility of the H5 strains? The only strains that have that ability have been H1, H2, and H3 from a historical point of view. Since influenza has been out in nature and interacting with humans for so long, and it's never made that leap, Palese argues that there's no need to assume that it will do so in the near future.**

Just recently there have been cases of H7 infecting human beings. This has never happened before and had you asked researchers last year the likelihood of human infections of H7, most would have dismissed it as highly impossible. When you're working with economies of scale to the extent that that is present in the 21<sup>st</sup> century, the statistical likelihood is significantly



increased. Our population has never been higher and we have industrialized agriculture with more domesticated farm animals than ever before. When billions of viruses are interacting with one another in this environment and reassorting themselves, the magnitude is mind-boggling. The likelihood for some sort of mutation to occur is greater now. [See Appendix for remainder of interview]

In a recent workshop that went over many of the problems, pitfalls, and Catch-22s associated with dual use research of concern, there was still disagreement within the community. Many panelists stated that the risks to gathering new and needed information cannot be hindered by regulations whereas others stated that the risks needed to be addressed and (if need be) avoided. Many of the comments on both sides of the argument reinforced answers from the transcript above. A large problem with dual use results is the fact that there is no secure method to disseminate the information in a selective format, especially in the 21<sup>st</sup> century. Even if that were possible, the fact is that regulations of dual use topics are an attempt to decide what is inherently right or wrong to research; even the most respected scientists in the field of virology can't decide what is right or wrong!<sup>142</sup>

Workshop participants also stated that the topic of dual use research is very emotional as it basically boils down to potential limitations on academic and scientific freedom. However, given the large amount of influence within the scientific community and the fact that any sort of total infringement of research is counter to Western academic beliefs, there probably won't be total revocation of rights to research. Speaking to regulatory authority and responsibility, Anthony Fauci, Director of the National Institute of Allergy and Infectious Disease at NIH,

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<sup>142</sup> National Research Council, *Perspectives on Research with H5N1 Avian Influenza: Scientific Inquiry, Communication, Controversy: Summary of a Workshop*, Washington, DC: National Academies Press, 2013, [http://www.nap.edu/catalog.php?record\\_id=18255](http://www.nap.edu/catalog.php?record_id=18255), (Accessed April 18, 2013).

stated that the research institutions were of greatest importance. The decision of whether or not a study should be conducted should take place at the research institution itself before publication is even a question.<sup>143</sup>

## **Discussion**

The deep divide within the scientific community does not bode well for any measure of resolution and/or progress to be made with deciding a direction with dual use research of concern and its role in researching potentially dangerous strains of influenza. There are two sides of the argument and both have very valid points; redacting scientific results or halting them altogether will drive away research or force it overseas. However, allowing all research to move forward without thinking about long term results could yield potentially dangerous information that could do more harm than good. Highly prestigious researchers in the field of microbiology are divided on the notion of dual use. Without a reasonably united voice on the issue, the federal government cannot make strong and solid policy.

With regards to policy, the federal government is doing a fairly decent job given the difficult nature of the task at hand. The government only has validity to regulate research it funds, but that encompasses a large portion. Determining a set of criteria in which HHS will determine whether a study, especially H5N1, receives funding is a good method by which researchers can determine whether their avenue of research has the potential to be responsible in regards to DURC. However, the interview did point out two large components that need to be addressed in federal guidelines: who will decide whether research should be done and will the results be published regardless of the outcome? Researchers need to know who will decide

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<sup>143</sup> Ibid., 30, 37.

whether their studies happen or do not because that may be the difference in whether they choose to go a certain direction. The newest agency rules, both enacted and those up for public comment, should clearly designate the office, chairperson, or committee who will decide what project receives funding and which do not. These are qualitative decisions and highly suspect to personal and potentially fallible judgment. A clearly defined designation of responsibility should be inserted into the documents.

The newest Health and Human Services rules regarding the study of biological dual use and especially pandemic influenza are still very new and their impact has yet to be fully felt. The process of government oversight and regulation is not a perfect system, hence the ability to amend the rules to be a better fit. The impact of federal oversight of dual use research of concern should be studied in the future. Within about two years, enough time will have passed that a clearer picture can be established. Taking into account fiscal problems, this study should view the number of rejected or amended grant proposals based on their potential danger. Also, a comprehensive survey of research institutions needs to be conducted to assess whether PIs changed their research areas or directions on account of their perceived inability to pass federal overview. The number of grants rejected based on the grounds of potential dual use danger may not compare to the number of aborted studies never enacted to begin with.

## CHAPTER 5

## SUMMARY

This paper has provided a comprehensive overview of the nature and danger posed by the pandemic influenza. The threat that something may happen in the coming years is not decreasing, but actually becoming much more likely for a variety of factors. Viruses evolve at a rate that is uncontrollable and influenza in particular poses a danger because of its segmented form and HA and NA proteins constantly changing. The human population on this planet has never been higher and modern technology combined with globalism has allowed microbes to spread at an unprecedented rate. While the most devastating pandemic in modern history occurred slightly less than 100 years ago, the potential still exists. 2009 saw the emergence of the novel H1N1 influenza virus that, while not extremely lethal, found an ability to spread quickly throughout the world. H5N1 is still present and while it has not achieved human-human transmissibility, it is still killing people (the most recent being a 26 year old Egyptian male).

Currently, H7N9 is beginning to cause concern. As of April 18, 2013, confirmed clusters of humans were being identified in China. While the China CDC cannot confirm whether the virus is acquiring the ability to spread via human-human, roughly 40% of the 87 confirmed cases thus far have had no direct contact with poultry (H7N9's reservoir animal group). Of those 87 confirmed cases, Chinese authorities have stated that 17 have been fatal. While the current mortality rate for H7N9 is 20% and likely to drop further, this is still too high. As mentioned before, the H7 influenza strain has never infected people to this magnitude within documented science. The potential for pandemic influenza is a growing concern.

There are many aspects and avenues that the government takes with regards to the study of pandemic influenza and this paper focuses on two key areas; the Select Agent Program and

dual use research of concern. Given the ricin letters that were sent to Capitol Hill and the White House, bioterrorism is still a very pertinent concern more than a decade post 9/11. The Select Agent Program is tasked with trying to make sure that only the proper individuals with the right clearance and procedures are allowed access to dangerous microbial agents. However, whenever a highly academic area is regulated, friction will occur. Principle Investigators and Responsible Officers require a higher exchange of dialog and mutual understanding more akin to a partnership rather than mutual roadblocks. Regardless of what researchers desire, the fact is that the 21<sup>st</sup> century is not the same as the 20<sup>th</sup>. Bioterror and bioerror are not theoretical; they are very real problems.

Dual use research of concern is problematic in that while the Select Agent Program is challenging, it is more of a frustration rather than an actual hindrance. There is a stark and deep divide within the scientific community regarding dual use research with some stating that there should be free and total non-censorship of scientific pursuit while others stress caution and forward thinking. Influential individuals in the community have written for and against potential government regulation and the provided interview transcript showcases a torn and conflicting judgment call. Unfortunately, dual use research of concern does not have a solid solution at the time; the best that can be hoped for is that if rules and regulations are enacted, they can be quickly amended if shown to be highly problematic. Jerry Jaax, Associate Vice President for Research Compliance and University Veterinarian at Kansas State University sums up the nature of the Select Agent Program and Dual-Use Research of Concern: “Most of the stuff that is coming out as far as security and scientific regulation is making it harder, but you have to be

convinced that you are making it [the research environment] better too. A regulatory environment is the cost of doing business.”<sup>144</sup>

Many areas of pandemic preparedness, mitigation and study require high amounts of financial resources. A county-level emergency management coordinator provides a valuable insight into this problem,

[Pandemic policy] is a very valid area that needs to be studied. ...it is one of the many areas that all of us wish we could put more money towards, but I see things getting much worse when it comes to funding our capabilities to be able to respond to something like this. It may happen, but right now decision makers are often faced with immediate needs like potholes in roads that needs to be taken care of now, so next year we'll budget for something that may happen. When the next year's budget comes around, then it becomes year after that in which we'll budget for something that may happen and I don't see things getting any better.

Pandemic influenza is one of the largest threats to the United States and global community in the 21<sup>st</sup> century. Whereas war and even a potential nuclear detonation affects only certain areas and is generally containable, a lethal pandemic could conceivably cause total market and possible government collapse worldwide. History has shown us that a devastating influenza outbreak is well within the realm of possibility, making the problem less “if” and more “when.” We can take measures to safeguard our nation, but only with proper support and cooperation between the federal government and scientific community.

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<sup>144</sup> NIH video

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## APPENDIX A

## UNIVERSITY LEVEL R.O. INTERVIEW

**Can you comment on the researcher's frustrations in regards to administrative regulations? For example, to simply hire a graduate student to do research, months of background checks are needed and by the time it's done, the student may be almost finished with their education.**

I can say that it's not an Environment Health and Safety (EH&S) policy, or a university policy, or even a state policy; it's a federal law. I can understand the frustration. Regulations are often seen as roadblocks, so what EH&S does is have the Principal Investigators (PI) adhere to the minimum requirements needed. Even if one person, in one lab, goes somewhere else... we have a large amount of paperwork that has to be done. EH&S did not pick the agents or develop the regulations and have no say in the subject. Even the American Society for Microbiologists did not have a say in what was selected to be select agents; the selection took place at the federal level with federal scientists and even Congress having the ultimate say. We have animal, human and plant pathogens. There is one plant pathogen that doesn't even exist in the United States, but is still on the list. I can agree that there are frustrating aspects of it, but we still have to follow the rules and laws. There used to be an old way of doing business with biological organisms and with the newer rules may seem as roadblocks. It's a pain for them, but it's sometimes a pain for us as well.

**Are the current rules and regulations conducive to research that we perform at the university or are they inhibitive?**

I don't think that they are a stop, but they are another hoop that has to be jumped through. This is just something that we have to do and people need to get used to it.

**Is there anything in the current rules that is unnecessary?**

That's a hard question as I've been doing this for a long enough time and I've gotten used to it. Coming from the research side, I try my best to make sure that PIs, graduate students, or anyone, don't go through more hoops than they have to. I understand that doing all the paperwork is not a priority of the researchers, because they want to do research. The paperwork is not worthless though; it has to be done. This may be a difference in opinion from the PIs, but EH&S role here is not to be a block, but to assist them. We have rules in place for a reason; it's for their safety.

**So using that example as it relates to a potential bioerror, you would say that the rules in place are necessary for safety?**

I think we could operate without the rules. They weren't always here and a lot of really good research still went on without the rules. The difference is that now, the threat of terrorism is greater. 9/11 really made the government go from one extreme to another and didn't give people an intermittent time to get used to it. In our world now, it's the possibility of an insider threat. In the case of an accidental release, I think there needs to be more education. More training and earlier training starting even as young as high school... to teach kids how to work properly with

agents is the best thing. If we can teach people the right techniques early on and make it a habit, they will work with these dangerous agents in a safer way. The rule is just making SURE you've had proper training. Now, someone could go through all the rigor of education and training and know what they're supposed to do. The rules in place qualify them, but an accident can still happen. A rule will not keep you safe in the lab; the choices of the people in the lab determine it.

**Has costs increased with the new regulations like the ones after 9/11 and EO 13546?**

We have two full time personnel that work with select agents, so yes, costs have increased. For BSL-2 labs that work with plant pathogens, there were many things that needed to be put in. Keycard access, security levels, the freezers need to be locked up. Before, the plant pathogens weren't as tight with security but they are now and those upgrades were expensive. From my point of view, a lot of the federal spending coming in is more with plant pathogens than animal/human. By the time I began my position here, the majority of security assets were already in place.

**There have been statements from researchers that the new regulations detract resources from their ability to conduct research. Can you comment?**

I don't know why that would be the case. Once the security is in place, it's there. Now, it could be that the new regulations are forcing the researchers to do their paperwork and write up/file detailed SOPs. Now, this does take longer because it has to be reviewed and edited to make sure it's safe- there are SOPs that are submitted which are not at all safe and we cannot approve them to conduct research. I think it's the time that they have to devote to paperwork that is the major complaint. Even without the law, they would still need to do follow these rules. EH&S cannot approve someone to work with something as dangerous like the plague or foot & mouth disease without them having all their ducks in a row first. The thing is, they've known about the requirements for a long time. The Tiers system was announced in 2010 and they've known that the some of their agents they work with could be a Tier I agent. They've had three years to put together an SOP. They should have started the needed paperwork a long time ago.

**From your point of view, since a lot is contingent on federal funds, will the financial hardships that are being experienced at the federal level have a major impact on select agent research?**

It will be a challenge for PIs to get money, but all manners of research are going to be impacted. Salmonella, E. coli, and others which aren't select agents will find it difficult to find funding. All things will be affected by it in some way. The rules aren't going to change because of a drop in federal funds though. There shouldn't be a correlation between the amount of federal grant money available and the regulations. EH&S is funded by the university, not the grant money that the PIs receive to do research. The department's operating costs are not contingent on research funding. If the researcher's salaries are paid for with grant money, then there could be a problem. Otherwise, the only "barrier" is that the PIs have to take their own time to write the SOPs needed for their research. Once the SOPs are written, then they are good to go. The physical assets are already there and do not require any more heavy investment. The regulations are mainly concerned in regards to paperwork and for our institution, EH&S are the paper-pushers and we're funded through the university. We require the same rigor and detail-oriented

approach for both select agents and non-select agents. The main problem is the difference between what researchers want to do from an academic approach and what they have to do to do it. You can't fill out paperwork for one thing and then decide to switch to a different area and use the same paperwork; it doesn't work that way, researchers assume this will work. Those changes and the problems that come when some researchers don't fill out the correct information is what slows things down. They don't take the time to fill out the exact paper work for what they want to do; one size doesn't fit all.

**What problems with less federal spending do you see?**

Federal Select Agents Inspections may happen less often. Right now, they're once a year, but they may come once every two years or something to that extent. Now, a facility has to be signed off by the federal government before research can be conducted. The inspectors are very busy people and have a very full schedule and there is no wiggle room. Our inspector said that he has to visit 500 facilities; I can't expect him to be able to come at our convenience. When the inspectors come, the SOPs have to be ready. Last summer, when we got the inspectors here, the facility was ready to be inspected and the SOPs were not up to date. This was not on short-notice; there was plenty of time to get everything in order. We need someone to blame and some researchers blame the regulations.

**With the federal government undergoing a financial crunch, I'm worried that many of the Select Agent regulations will become total unfunded mandates... and certain labs will opt out of researching select agents to save money.**

As I mentioned before, once the security aspects are in place and the paperwork is in place, researchers would have to devote time to updating and revising SOPs and training. However, this should be standard practice for any research program.

**What would you change about the current structure of the Select Agent Program?**

When the inspector comes, I want the report within two weeks. I want to know within two weeks what deficiencies were noticed so I can fix them. Right now, all I have to go on are the notes I take during the exit interview of what needs to be corrected. I haven't received a report from either inspection in 2011 or 2012, which is frustrating for me. There aren't any dangerous deficiencies; we're approved. Its small things that we can do to make our operations better or more in line with what they want, but I can't do a lot of the needed work until I get the reports. I allow research to continue because I don't rely on the report for my needed changes, but that's because I utilize the hearsay in the exit interview. If there is a dangerous deficiency, we do not do research until it's fixed. For example, if the HVAC system wasn't operating up to code, I wouldn't allow research to go on until it's corrected.

**Anything else?**

Right now, I'm working on a Tier I suitability program. At the moment, everyone working on a Tier I agent has to undergo an FBI background check. However, the FBI check can miss things that are potential problems. If someone gets into trouble, but spends 364 days in prison, they will get a pass from the FBI because it doesn't show on your record. However, if the same

person spends 366 days in prison, they will be disqualified because that appears on your record. To work on Tier I agents, the researcher must pass an FBI background check as well as a state background check, which will hopefully catch red flags that didn't show on the person's record. We are taking a more in-depth, qualitative approach, to decide whether someone could potentially be an insider threat. Did they just undergo a really bad a divorce? Did they have a child die? Would this situation make them want to snap and become a threat? Basically, the federal government is passing down the buck to the institution.

**Since this is a local background check, could standardization problems occur? One state may differ substantially from another.**

There could definitely be some problems with this, but I'm not sure yet. I won't be making the criteria though; human resources and university legal have to decide. I'm not a lawyer or a psychologist and I don't want to make calls on people. Basically, I ask whether someone passes or whether they do not and then give them access or not depending on that decision. I don't see these people on a daily basis and it's not my place to decide. This program isn't supposed to be up and running until April so I'm not sure what it will look like yet or what long term effects will be. This suitability program is attempting to halt insider threat before it happens, so we don't have another anthrax scare



## APPENDIX B

## POLICY RESEARCHER INTERVIEW

**Can you describe your current position and responsibilities?**

I work for both a university and I contract through a civilian bioterrorism monitoring program, operated through Department of Homeland Security. Support of the monitoring program is my primary responsibility, but I also assist the university with influenza projects, which includes co-authoring various papers. However, I'm a biologist by training, which required a lot of mentorship which helped bring me up to speed with regards to policy.

**Your dissertation was with antibiotic-resistant bacteria. Can you comment on the high level of concern of carbapenem-resistant *Enterobacteriaceae* (CRE) by agencies such as the CDC?**

The level of antibiotic resistance in the community and medical setting is very problematic. I don't think the general public really considers the drastic significance of this problem. People don't remember a time prior to antibiotics because it's getting to the point where it's almost past living memory. In those days, you could get a small cut, go septic and die. This sort of thing doesn't happen anymore and I don't know whether or not the public could accept it if we were forced to revert. There are many infections that can be prevented through personal risk management, but some of them are unavoidable. What is now just an annoyance could be a life or death experience down the road.

**What is an instance of a problem regarding federal regulations of hazardous microbial agents?**

There was a lab that had a -80C freezer in which they stored their non-select agents as well as their Select Agents. Well, every 10-15 years, a freezer goes down and needs to be fixed. The lab in question's freezer went down and they couldn't discern which agents were the select agents and which were not; their organizational and inventory system wasn't exactly organized. Usually, when this happens with normal microbes, they get temporarily stored in someone else's freezer. A separate lab within the same facility did not have clearance to store select agents however. Even if it had, simply moving a select agent requires notification of the RO prior to and a massive amount of paperwork. When your freezer is down and the agents are thawing, there is only a finite amount of time to find another place for storage. At the time, the lab didn't have a contingency plan in place should this happen; I imagine it was simply overlooked. This crisis was figured out in time, but it does lead to the negative views of the Select Agent Program. The regulations aren't necessarily bad; the PI just needs to do their job with much more advanced planning. You can't procrastinate or do things on a whim when you're working with a select agent. The PI, at the time, didn't know he wouldn't be able to play it by ear in case something unexpected came up. The crisis did force him to make changes to his inventory management and that is a critical component of this type of research.

**Are the newer policies that have been coming out in the past year examples of the government attempting to engage the scientific community?**

For all the newer policies, there is outreach to the various stakeholders for review and public comment. Sometimes when new policy is made, it isn't highly publicized. Recently however, they've done a good job at trying to promote and encourage active discussion. I know they've gotten the American Society for Microbiology to submit comments for all the new rules and policies. They've gotten ABSA [American Biological Safety Association] to be aware of the new rules so that they can tell their members. There are two important issues that aren't addressed. Basically, if you're a researcher, the two most important things to you are: funding and publishing your research. The new rules don't really answer how and who will determine whether research should be done in the first place. In the rules, I don't see a clear and unambiguous determination of who will make the final judgment call. If we want people to continue to do important work in the dual use arena, they need to know the exact rules of the game. Even writing a grant is a highly labor intensive and scientists deserve to know who is going to deny or approve of their project proposal. On the government's end, they also don't state exactly how they are going to determine whether or not certain dual use research will ever see publishing. Can it be in full or redacted? The events that unfolded at Madison and in the Netherlands provided an example of a situation that researchers do not want to be in. Overall, [government and the scientific community] is much better equipped to deal with the biosafety questions; that's something you can apply metrics to. How do we make something safe is relatively easy to figure out as compared to bioethical questions.

**The way science operates is very mechanically; standard operating procedures, cause, effect, etc. Science tries to explain how, not necessarily why. Policy is formulated from a qualitative perspective which explains the why first and then goes on to figure out the how. Could this be an explanation for the lack of societal obligations within parts of the scientific community?**

That's a very reasonable hypothesis. The essence of basic science is to add knowledge to the greater body of already existing knowledge. One good thing about the new dual-use policy is that scientists now have to explain how a particular new study will expand knowledge and answer a question for which there currently is no answer to. After they answer that, they must also answer how exactly answering that question is going to be beneficial. That's really difficult for some scientists. Granted, it still gets back to the basic philosophical differences that exist with regards to new information. There are those who think all new knowledge is inherently good and that it's not their job to police how people use it. Then on the opposite side are those who want to avoid and mitigate risk and while new information may be used for good purposes, the potential goods do not outweigh the potential bad.

**Trying to determine whether all new information is inherently "good" is often tricky. Assuming it's possible, is a line of research that would combine the *Ebola virus* with the common cold a "good" thing? From a biosecurity point of view, this would be extremely worrisome.**

This is a very good example and not far from the actual truth. It sounds like something that would be fairly cut and dried as a definite bad idea. However, some of the most controversial work being conducted in dual use is in vaccine development. The *adenovirus*, which is the cause of the common cold, actually makes a really good vaccine vector. It can replicate in human cells

and it's very amendable to sticking a lot of random DNA into it. It will package the new DNA up in a way that will allow for translation in the host cells very efficiently. This is a major possibility for vaccine development and it's one of the avenues being pursued for influenza vaccines. This attenuated *adenovirus* will be able to carry influenza genes to stimulate an immune-response throughout the host organism while taking away the potential to cause normal cold symptoms. Because *adenovirus* has the ability to replicate in human lungs, the vaccine could be inhalable and thus easily administered and distributed in the lungs which would ideally give you better protection. However, if all this is published openly, who's to say that the same research couldn't be applied to anthrax? What if anthrax toxin genes were inserted into a non-attenuated *adenovirus*, so that it would easily infect person-to-person? Well, that creates a very serious bioweapon; one that makes you really sick like anthrax but is easily disseminated like the cold. Because this is such an important thing to research, it has been deemed important enough to continue.

**When using federal funds, the case can be made that what the researchers want is irrelevant; it's government money and you have to play by government rules. If research is conducted without federal funding, does the government have jurisdiction to dictate what should or should not be researched and how?**

Almost everything researched outside the United States is not funded by the United States. Therefore, all research outside of the country would not be applicable to our federal regulations. This is an argument that is often made. If you restrict research being done here in the States, that doesn't necessarily stop the research; it can be done in other parts. It goes further in that it doesn't really matter if the virus got released because the time it'd take to circumnavigate the globe is fairly short. Once the virus is out, it's out.

Now, the non-federal funding of research in the United States is a real loophole in the current rules. The rules state that if the research is being conducted outside of federal jurisdiction, they are still strongly encouraged to follow federal rules, but they're not required. I would think that the only way in which to enforce the regulations would be to issue them through OSHA, which would be very difficult. OSHA is the only agency in which you could regulate all employers, barring the crazy guy who sets up a lab in his garage scenario.

**The back and forth PNAS pieces between Palese and Wang and Osterholm and Kelley make for an interesting dynamic. Palese argues that caution should be thrown to the wind and science should continue unabated whereas Osterholm pushes for a more conservative and thoughtful approach to researching H5N1. Do their arguments hold legitimacy?**

As far as who is right on the percent mortality thing is irrelevant. One of the larger arguments between them is whether it's 60% or 10-20% mortality. In all honesty, it doesn't matter if H5N1 has a 60% mortality rate or a 6%; either way, the effects that that disease would have on the world population and economy would be catastrophic. One of the estimated mortalities of the 1918 Pandemic was only 2%. Even if we could conservatively agree that H5N1 is equivalent to 1918, that's still disastrous for society in the 21<sup>st</sup> century. Peter is highly informed and very prominent in his field and he was one of the first to work with the recreated strain of the 1918 flu, but mortality rates are irrelevant.

**What about Palese's statements regarding the likelihood of human-human transmissibility of the H5 strains? The only strains that have that ability have been H1, H2, and H3 from a historical point of view. Since influenza has been out in nature and interacting with humans for so long, and it's never made that leap, Palese argues that there's no need to assume that it will do so in the near future.**

Just recently there have been cases of H7 infecting human beings. This has never happened before and had you asked researchers last year the likelihood of human infections of H7, most would have dismissed it as highly impossible. When you're working with economies of scale to the extent that that is present in the 21<sup>st</sup> century, the statistical likelihood is significantly increased. Our population has never been higher and we have industrialized agriculture with more domesticated farm animals than ever before. When billions of viruses are interacting with one another in this environment and reassorting themselves, the magnitude is mind-boggling. The likelihood for some sort of mutation to occur is greater now.

**To our benefit, the world has already shown that it can contain weapons of mass destruction. Nuclear weapons were only used 2x and despite some close calls, they haven't been used since 1945. The power of nuclear energy has, from a utilitarian approach, done more good than harm. Can the same be applied towards biological dual use?**

Yes, because despite the dual use problem, the good results of the work can lead to large benefits, like vaccines. Science is such a distributive community and spread out all over the place. Information dissemination is the only way that researchers can learn about a topic and that requires publishing. Science has for the most part done a very good job at self-regulation. Besides, in the 21<sup>st</sup> century, the notion of censorship is not very logical; nothing really stays a secret. The WHO doesn't have any regulatory authority to enforce rules worldwide.

**Follow up question: H7N9 appears to be gaining some measure of steam in China. Is the media overly panicking with regards to its current epidemiology or is this a serious concern? Is there any natural human immunity to this virus, as there was with the 2009 H1N1?**

The media is not over-hyping the H7N9 human infections. Humans are almost never infected with H7 influenza and in the past the presentation has often been different (including pink eye—not respiratory symptoms). We have a number of cases with a significant percent of mortalities. These people are for the most part not connected to each other and they are dispersed across a relatively large geographical area. Their exposure is unknown but assumed to be birds. Now, the real question is whether or not this virus will evolve and mutate to allow for sustained human-to-human transmission. If that doesn't happen this outbreak might die out and we'll see sporadic human cases like we do currently for H5N1. Otherwise, with sustained human-to-human transmission we could have a pandemic emerge because there is very low level immunity to this virus in the human population.