Fatal Flu: History, Science, and Politics of the 1918 Influenza Pandemic

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INTRODUCTION

As the First World War raged through Europe, in the spring of 1918, a second crisis in America killed more people in one year than the Great War did in four.¹ Almost forgotten among historians by its last appearance in 1919, the world’s most lethal influenza pandemic would contribute to more deaths in one year than the Black Death took in the mid-14th century and AIDS in twenty-four years.² With the progressive development of American public health in larger cities and with the founding of prestigious scientific institutions, in the early 1900s, it seemed that for the first time in history more soldiers would die on the battlefield than in hospital beds from disease. Epidemiologists formulated the germ theory of disease by the mid-19th century. Specialists from Robert Koch to Louis Pasteur achieved victories over cholera, smallpox, and yellow fever.³ Therefore, as word spread of an unusual influenza outbreak in Fort Riley, Kansas, in March 1918, little alarm was taken as thousands of soldiers went overseas. However, by mid-October modern medicine and its first generation of scientists would be forced to test their skills and knowledge of the scientific theory against “the deadliest epidemic in human history.”⁴

The influenza epidemic of 1918-1919 not only devastated the nation and the world, it was also a professional and political disaster. It revealed the national government’s failure to respond effectively to a public health crisis. Without the

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³ For more information on 19th century medical achievements refer to Charles Rosenberg’s The Cholera Years, the introductory chapter of John M. Barry’s The Great Influenza, and Jacalyn Duffin’s History of Medicine: A Scandalously Short Introduction.
⁴ Barry, 87.
virology and antibiotics that would be developed by scientists later in the century, public health officials lacked necessary tools to control the epidemic in 1918. Specifically, this thesis asks the question: what caused the 1918 influenza pandemic to become so fatal? There is no simple answer. Although scientific knowledge in the United States had greatly improved since the middle of the nineteenth century, neither physicians nor scientists were equipped to control this influenza. Without a complete understanding of how the influenza virus spread, public health officials found themselves disorganized and overworked as they fought a losing battle to reduce the number of people dying. The pressure to keep a steady flow of troops traveling to and from Europe exacerbated the crisis. However, the genetic makeup of this particular strain of influenza may also have caused the virus to become more deadly than expected. With an unusually high case fatality rate, the 1918 virus was probably more virulent than previous and future influenza pandemics seen in the last century.

Nearly a century later, an avian influenza epidemic threatens the world, because we lack a mechanism for controlling pandemic influenza. It is impossible to predict an emergence of a future influenza pandemic, when or where it might occur, what subtype it will be, and what degree of morbidity and mortality it will produce. Since 1977, H1N1 and H3N2 viruses have both produced seasonal global epidemics causing approximately 36,000 excessive annual deaths in the United States. None of these viral descendants, however, compares to the pathogenicity of the 1918 parent virus. Therefore, in terms of

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predicting and preparing for future pandemics, the 1918 “Spanish Flu” provides the best case study for scientists, historians, and public health officials.

**Historiography and Methodology**

To understand how the influenza outbreak of 1918 turned into one of the world’s deadliest pandemics in history, I will take a unique approach to tackling the mystery of the “Spanish Influenza” by interpreting the high fatality rate from both a social and natural scientific approach. This paper contains two distinct parts. First, the will provide an historical analysis of the events of 1918. Second, this thesis will discuss current scientific research of the 1918 influenza virus. Chapters one to four will answer the following questions: first, what caused the pandemic to become so fatal? Second, what was the social response to the disease and how did the United States cope with the crisis of the war and outbreak of influenza simultaneously? Third, what non-pharmaceutical interventions were implemented and how effective were they in thwarting the pandemic? Finally, within the last century how have virologists and medical historians remembered and portrayed the 1918 pandemic?

This thesis belongs to present day analyses of the history of medicine. Although the field of medical history is fairly new, it has transformed radically within the last century. As Charles Rosenberg points out in *Explaining Epidemics*, the early pioneers of medical history were primarily professionals trained in medical schools, of which the majority made their living practicing medicine. Medical history, therefore, served as a celebratory practice to honor

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the accomplishments achieved within the scholars’ own crafts. As a result, the academic history of medical advancement took precedence over social, cultural, and economic contexts of health and disease. An unspoken rule began to develop that only those with clinical experience possessed the tools necessary to document and understand the history of the profession. Therefore, until the latter part of the twentieth century, medical history was written primarily by physicians for physicians.

However, an interesting phenomenon developed within the last fifty years. As scientific knowledge had continued to progress at an alarming rate, pre-medical studies as well as medical school training have included a smaller amount of humanities courses within their curriculum, something the older medical historians took for granted. At the same time, a general interest in the history of medicine and medical ethics has also grown both within and beyond the professional world. As a result, the social aspects of medicine and its relationship to cultural values have created an interest among professional historians who have filled the gap of documenting medical history. However, unlike physicians, historians of medicine are less concerned about past accomplishments in the field of medical research and more concerned with how doctors’ and patients’ experiences created new ways in which the body mediated gender, racial, and class relations.

Historians interested in the social and political aspects of medical history have portrayed these interests through numerous works. For example, Charles Rosenberg’s *The Cholera Years* is a historical account of three cholera epidemics
occurring in the United States in 1832, 1849, and 1866. However, Rosenberg’s objective is not to simply describe these epidemics but to understand the social relations of America during the “cholera years.”7 For example, as Rosenberg notes, a disease that was believed to have been caused by sin and corruption in 1832 became the consequence of faults in sanitation by 1866. Rosenberg showed the potential of medical history to be something more than a celebratory field, and instead to represent the intellectual, cultural, and social texture of an age.

In the twentieth century, a generation of critics of the American medical system also laid the framework for a political interpretation of medical history. This has developed around the economic and institutional problems of American medicine. Mainly, how can we afford to pay for healthcare? Beatrix Hoffman’s *Wages of Sickness* is one book that has examined this question through an analysis of medical legislation that was debated in New York State in the twentieth century.8 The United States has remained the only Western-developed nation not to implement a national health care system. In her book, Hoffman analyzes this exceptionalism and demonstrates through close examination of New York legislation that there have been periodic moments of public debate about health insurance policies in the United States. In addition these instances reveal the economic forces and cultural beliefs that have hindered reform processes and, as Hoffman argues, placed a political stigma on “socialized medicine” that has continued to inhibit our abilities to assure access to health care.


As noted, some historians of medicine are more concerned with studies on social values while others have focused on political issues. In this thesis I will be looking at both. The first chapter focuses more on the social response to the disease and how the United States dealt with the pressures of the pandemic while trying to maintain their support and patriotism for the federal government during the time of the war. The second and third chapters focus more on the political conflicts that developed during the height of the pandemic. On one level, disputes between federal and state authorities created a disorganized system of communication between the United States Public Health Service and local state departments. In addition, the continuing pressures of World War I also created disputes between civilian and military authorities as concerns for winning the war took precedence over concerns for containing the spread of the pandemic.

Specific to the study of 1918, there are a number of secondary sources that I will be drawing from throughout this paper. First published in 1976, Alfred W. Crosby’s America’s Forgotten Pandemic: The Influenza of 1918 offers an early comprehensive account of the 1918 influenza pandemic. In his book, Crosby analyzes the pandemic and measures the impact it had on America society, while also questioning the lack of interest in the pandemic, and emphasizing its significance to future public health disasters. Building from Crosby’s work, a series of other recently published books have also contributed to further understanding of the influenza pandemic. Most notably, Gina Kolata’s Flu: The Story of the Great Influenza Pandemic and the Search for the Virus that Caused It integrates accounts of personal experiences with modern research to bring the
historical aspects of Crosby’s book up to date with the recent achievements in the field of scientific research. In addition, John M. Barry’s book, *The Great Influenza Pandemic: The Epic Story of the Deadliest Plague in History*, has provided a more recent historical analysis with statistics and personal accounts that illustrate the personal reactions of individuals of the time.

Historical analysis of the 1918 pandemic has only been able to answer part of the question as to why this particular epidemic had an unusually high case fatality rate. The second part of this paper, therefore, will be a scientific examination of the 1918 virus in a present day setting. For 75 years scientific research failed to answer the most basic questions surrounding the virulence of the virus, and as a result historical evidence provided the only answers for scholars hoping to uncover questions surrounding the epidemic. In 1995, a breakthrough came as a scientific team identified archival influenza autopsy materials collected in the autumn of 1918 and sequenced small viral RNA fragments to determine the genomic structure of the virus.\(^9\) Within a few years, the entire genomic sequence of the virus was determined, which has now made it possible to produce studies mapping the virulence of the virus. Once again I will be asking the question of what caused the virus to become so fatal. In this second section of the paper, I will interpret and answer this question with a biological explanation. The second question will be, what were the genetic origins of the 1918 pandemic? Third, specifically what effect on viral replication do the cellular protein P58 and viral protein NS1 contribute to? Some of these studies were the

focus of my scientific research at the Katze Lab in Seattle, Washington and will be discussed in the second part of this paper.

This thesis will take a unique approach to studying the 1918 “Spanish Flu” pandemic by integrating historical knowledge of the 1918 epidemic into present day scientific methods for combating disease. Typically historic and scientific disciplines have not intersected. However, in order to understand the 1918 pandemic and apply this knowledge to current preparedness plans for pandemic influenza, it is necessary to take an interdisciplinary approach. By answering key questions from both fields, I hope this thesis will provide a new insight to ways in which we can study disease through unconventional forms of translational research.

Chapter Outline

In the first chapter I will discuss the overall national threat created by the onset of the 1918 influenza pandemic in the fall of 1918. Specifically, my analysis will focus on the significance of the United States Public Health Service (USPHS) and its response to the pandemic of 1918. Sill in its infancy, the United States Public Health Service faced many initial challenges and the pandemic exposed the need for stronger government involvement and expanded federal role in safeguarding the nation’s health. I will explore how the American society reacted and responded to the threat of a pandemic, and how the USPHS both increased and reduced the fear and threat of disease on the home front.

To do this, I will be drawing from a number of sources. The American Journal of Public Health provides the best account of the bureaucratic struggles
between federal and state authorities that resulted in an unorganized plan for quarantining and delivering care to areas greatly affected by the pandemic. Throughout the year of 1918 the journal also describes the poor surveillance methods and lack of communication amongst hospitals. These practices led to inaccurate reports of morbidity and mortality statistics, which hindered the efforts of the United States Public Health Service to control the rapid spread of the epidemic. There are also two secondary sources from which I will be drawing. The first, Alfred Crosby’s *America’s Forgotten Pandemic*, provides the best overall history of the 1918 pandemic and includes a great description of the formation of the United States Public Health Service. Carol A. Byerly’s *Fever of War* specifically focuses on the impact of the epidemic on the American army during the war. As a result, her analysis includes a detailed account of the failures of the national government, health care professionals, and medical officers that led to the worst epidemic on American soil.

The second and third chapters will focus on the non-pharmaceutical interventions proposed by government and public health officials during the later stages of the pandemic. In 1918, it was still unknown that influenza was caused by a virus, and while vaccines had been created for certain viral diseases, there was little concern for protection against influenza prior to the onset of the pandemic. In the second chapter I will outline and define the use of nonpharmaceutical interventions and examine the implementation of these interventions across the United States in 1918. Howard Markel’s epidemiological research through historical archives provides a great resource for
statistical data of non-pharmaceutical interventions nation-wide as well as trends and graphs depicting the gradual spread of the epidemic. His collection of material includes data collected from seven different cities that reported relatively few (if any) cases of influenza and no more than one influenza death during the second wave of the pandemic. Using Markel as a template for my research methodology, I will be drawing from primary sources collected by the University of Michigan Medical School’s Center for the History of Medicine. I will therefore be evaluating measures that led to the success of these cities including population size, geographic location, and the time at which nonpharmaceutical interventions were implemented during the second-wave of the pandemic. I will later come back to the use of nonpharmaceutical interventions when evaluating the pandemic preparedness plans in place for dealing with current threats of global and national pandemics.

The third chapter will include detailed localized case studies of Princeton, New Jersey, New York City, New York, and Syracuse, New York, and the success and failures of these cities in controlling the spread of influenza through the use of nonpharmaceutical interventions. I have chosen these cities based on their variable size, location, and degree of success in preventing deaths from influenza during the second wave of the pandemic. Each city shared a commonality due to its proximity to either a port or military base and therefore experienced similar challenges of protecting the civilian community from soldiers potentially suffering from influenza. The collection of primary sources I will be

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10 The database of Howard Markel’s research can be found at The Center for the History of Medicine: University of Michigan Medical School, “Influenza Digital Archive,” http://www.med.umich.edu/medschool/chm/influenza/.
referring to in the case study of Princeton, NJ was also part of The University of
Michigan’s digital influenza collection, of which excerpts from *The Princeton
Packet* have provided the best reference. *The New York Times* and *The Syracuse
Herald* have been the best primary sources for my analysis of New York City and
Syracuse, NY, which were obtained through the use of Syracuse University’s
digital newspaper archives.

Following the publication of Crosby’s study in 1976, there have been a
numerous other works published on the 1918 pandemic within the last 10 years.
However, prior to this time there was virtually no mention of the pandemic in
American history books nor were there extensive studies done with the
overwhelming amount of historical data present from 1918. Among college
students, most have more familiarity with the Black Plague of the fourteenth
century than they do with the “Spanish” flu, despite the latter occurring more
recently and more relevant to the history of America. In addition there have been
two other major flu epidemics since 1918, but neither one has stayed in the
memory of Americans - particularly virologists in science, and medical historians
in the social sciences - for long. In chapter four I will attempt to give an
explanation as to how the biological nature of the virus coupled with the events of
the war, made it so easy to forget the most devastating pandemic in recent history.
I will also briefly evaluate the coming and going of the two other twentieth
century influenza epidemics and how our perceptions of 1918 have changed since
their passing.
Following my historical analysis of the 1918 epidemic, I will discuss why this crisis has reemerged in national consciousness in the present decade. I will connect this discussion to a scientific analysis of recent developments in virology. Prior to 1997, without a complete eight gene sequence of the 1918 influenza virus strain, we only had weak theories surrounding either mystery. However, following the extremely difficult task of piecing together small RNA fragments from tissues of human lungs embedded in the permafrost of Alaska, a killer virus was recreated. In chapter five I will be explaining the recent scientific progress made from the recreation of the 1918 influenza virus strain. I will draw from the primary source papers that published the genetic sequence of the virus as well as groundbreaking studies that have helped us to better understand the mechanisms of viral infection.

Since the recreation of the virus numerous labs have been able to develop studies based off of specific cellular and viral proteins that aid in the replication and virulence of the influenza virus. Specifically, the Katze Lab in Seattle, Washington has focused on the genomic and proteomic characterization of the influenza virus as well as its contributions to virulence through studies on the host-immune response following viral infection. This chapter will be a discussion of two specific proteins I have studied over the last two years. The first protein, NS1, is a highly conserved viral protein that is known to suppress the interferon response in the host cell, which delays the immune response and allows the virus to continue replicating without a counterattack from the organism’s immunes system. Secondly, the cellular protein P58 is believed to be hijacked by the
influenza virus to aid in viral replication by down-regulating the interferon-induced protein kinase, PKR, which regulates translation. This chapter will include an overview of both protein functions and the potential of each protein’s ability to aid in the replication of more virus and perhaps their contributions to increased virulence. I will be drawing from papers previously published in the Katze Lab as well unpublished data on the expression of P58, which was generated this summer. Reexamining the ways in which the national government handled the pandemic of 1918 could be valuable in formulating a modern day government preparedness plan. In addition, connecting present day scientific research with analyses of past historical events can serve as a model for future interdisciplinary collaborations.
Chapter 1

National Threat: The development of the United States Public Health Service and the national response to pandemic influenza.

Prior to the outbreak of influenza in the United States, it appeared that the United States Public Health Service was in control of health conditions in the army and civilian populations. Army camps and local towns implemented surveys on sanitary conditions, and it seemed the Public Health Service had an adequate staff to carry out measures for improvements within their targeted areas. However, while military physicians were confident in their ability to deal with communicable diseases, it never occurred in their minds that there would be one disease during the war that they would not be able to fix through cleanliness and sanitation. As the influenza epidemic spread through the United States during the second wave, the United States Public Health Service learned very quickly that it lacked the tools required to fight this new epidemic, which included a strong centralized presence, the ability to enforce quarantine measures within individual states, and an adequate staff with proper resources.  

This chapter will focus on the early development of the influenza epidemic in the United States and the response of the United States Public Health Service as the disease spread throughout the nation. In 1918, the United States Public Health Service was still in its infancy, and there had not been a clear designation of authority between state, federal, civilian, and military personnel. Consequently, there was little communication and designation of duty in regard to containment zones, public relations, morbidity and mortality reports, and

11 Barry, 9.
interpretation of data. This chapter will argue that the United States Public Health Service failed to assert itself as the dominant authority during the pandemic, which led to an unorganized response amongst public health officials on every level.

Nearly a year prior to the onset of the influenza epidemic, the Public Health Service was successfully taking active measures to reduce communicable diseases in the army and in civilian populations. According to the Assistant Surgeon General, John Trask, not only was the United States Public Health Service (USPHS) protecting the health of the troops by providing them with the best possible sanitary and health conditions, but it also improved facilities on the Atlantic seaboard, “to meet any emergency which may arise in connection with returning troop ships with communicable diseases.”

Understanding how disease spread and that mobilizing troops for war contributed to this potential risk, the leaders of the USPHS felt confident that they were taking the proper active measures.

Besides improving sanitary conditions, the USPHS also specifically targeted other communicable diseases it knew how to prevent. This included supervising the fly nuisance, cleaning public water to prevent malaria, issuing vaccines against smallpox and prophylactic inoculations against typhoid fever. In regards to its relationship with the local and state boards of health, the Public Health Service officials also felt confident in their ability to communicate efficiently and cooperatively with the proper officials when needed. Surgeon

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13 Ibid.
General William Gorgas, best known for his success at combating yellow fever and malaria, expressed his satisfaction with the achievements in the health of the army and was confident these improvements could be extended to the nation as a whole.\footnote{Barry, 135-136.}

However, neither sanitation nor pharmaceutical interventions would provide the Public Health Service with enough weaponry to fight the invading influenza epidemic they would face in the summer. In addition, the USPHS was focused on the damaging effects the war had on the civilian populations and their doctors. As Trask noted, “There is danger that a considerable proportion of our all too few trained doctors will leave their work to join the fighting forces without having trained others to do their work in city and state health departments.\footnote{Ibid.}”

While during the war many physicians felt obligated to fulfill their patriotic duty by serving the troops, they were also abandoning their practices at home without leaving an adequate replacement. The stretching of resources would result in a serious problem as the country was hit in full force by the epidemic.

Even with the right resources, the United States Public Health Service was not organized properly to provide the best communication and health care delivery needed during a crisis. In 1918, both influenza and tuberculosis were diseases that were not considered significantly reportable and therefore, unless a doctor deemed it appropriate, they were not forced to report cases of influenza in their communities. In Philadelphia alone, among the approximately 80 hospitals located in the city, only 23 of them provided detailed statements of
both the morbidity and mortality statistics in their hospital. However, even among these 23 hospitals no two were comparable.\textsuperscript{16} Boston faced similar problems of its own, as state commissioner Eugene Kelly and epidemiologist B.W. Carey noted in their report. According to Kelly and Carey, “The earliest and most striking feature that came to our attention in planning our campaign for combating the pandemic of influenza … was the absence of uniform methods of organization in the various health agencies upon whom we were obliged to rely.”\textsuperscript{17} In their report, Kelly and Carey believed that the proper method of fighting the pandemic influenza was to have a strong localized board to issue uniformed tasks throughout the state and local governments, which Boston was then lacking. Therefore, without adequate local boards of health in some of the major cities, it would have been unlikely to expect anything different at the state and local level.

As the nation went to war, citizens witnessed and became accustomed to the rapid expansion of the federal government. With the war occurring at the latter phase of the Progressive Era (1890-1920), American citizens not only wanted, but expected a more professional and centralized national administration. In health care, public officials and reformers assembled only partially effective government institutions through a blend of both public and private establishments to smooth out increasing problems generated by industrialization, immigration, and urbanization. Late in the nineteenth-century, medical and government

\textsuperscript{17} Eugene R. Kelly et al., “Centralized Health and Relief Agencies in an Influenza Epidemic,” \textit{The American Journal of Public Health} 8, no. 10 (1918): 744-746.
officials became more active in public health related topics and assumed greater medical responsibility for sicknesses connected with poverty and deprivation.\textsuperscript{18}

In addition, progressivism accelerated the professionalization of the medical and nursing professions and produced a range of medical institutions such as state and local government health departments, health insurance programs, and hospitals.\textsuperscript{19}

However, war mobilization and the onset of the influenza pandemic would make it clear there were still problems within the health care system. Although there was an increase in centralized government and health care support, there was no standardized system of hierarchy between state and federal health departments.

In its relationship to the local health boards, there was little the United States Public Health Service could do to improve their conditions. On August 9, 1918, before the influenza epidemic had reached the Atlantic coast, the U.S. Navy Bureau of Medicine and Surgery in Washington, D.C., issued a bulletin warning that influenza was prevalent throughout Europe, Hawaii, and elsewhere. Seven days following this report, the Surgeon General of the United States Public Health Service ordered the medical officers in charge of quarantines around various ports to be on alert for influenza on European vessels and to hold ships with flu patients on board until the local health authorities were notified.\textsuperscript{20} Other than this, there was not much more that the Public Health Service could do to prevent the spread of influenza since federal authorities did not have the legal power to quarantine areas governed by the states. Due to World War I, even if the Public Health

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\textsuperscript{18} Rosenberg, \textit{Explaining Epidemics}, 270.  \\
\textsuperscript{19} Byerly, 42.  \\
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Service had the authority to implement these quarantines within the states, it would have been highly unlikely that they would have received approval from the federal government. A strict maritime quarantine would have reduced the flow of troops and supplies to the Western front, delaying the pace of the war and leaving the Central Powers with the greater advantage.  

While it did not have the right on its own to step in and interfere with the sanitary work of the states, the United States Public Health Service could be authorized to cooperate and assist state departments. This included appropriating money to establish hospitals and sanitariums and awarding grants to aid in state health administration. These grants could act as tools for the federal government to monitor state regulations by requiring certain standards that warranted federal inspections. Furthermore, during wartime, the health powers of the United States could be extended beyond state lines to protect the health of soldiers. However, as then Johns Hopkins University president Frank J. Goodnow observed, these extended powers were usually “infrequently exercised and consequently have little permanent influence.”  

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21 The importance of quarantines and restriction of travel was understood to be at least partially effective by health officials. Unfortunately, with a newly formed national public health department, the roles and obligations between federal and state authorities were not clearly defined. Following the war, the president of Johns Hopkins University, Frank J. Goodnow, addressed the problem with the limitations of Federal health authority. In his article “Constitutional Foundations of Federal Public Health Functions,” Goodnow unravels the legal complexities of this issue explaining that the control of public health is a function of commerce. Therefore, in regards to international and interstate transportation, whether this refers to products or people, the federal government has the right to regulate and limit these operations when necessary. Of importance to public health, this includes the power to establish quarantines and to deny the right of entry into the United States or of transportation from one state to another. However, similar with commerce regulation, the federal government does not have the right to implement these actions within the jurisdiction of the states. For more, see Frank J. Goodnow, LL.D. “Constitutional Foundations of Federal Public Health Functions,” American Journal of Public Health 9, no. 8 (1919): 561-566.

22 Ibid.
in 1918, as little priority was initially given to public health concerns of containment both within and outside the army. In 1919, Goodnow had high hopes that a greater national interest would eventually improve communication among health departments, as the influenza pandemic demonstrated public health concerns must be more than a local responsibility. He called for a keener realization that “epidemics are not respecters of state or even national lines,” and proposed “a broader interpretation of existing powers [that] may well result in constitutional amendment.”23 However, it will be discussed in a later chapter that the federal government and the Centers for Disease Control and Prevention currently still stood by the original interpretation.

In addition to conflicts between state and local boards of health, medical officers in the military assumed two roles during the war, which included serving the government as well as caring for their patients. This combination of military authority and public health powers of vaccination and quarantine allowed the Medical Department to function as an integral agency within the military. Unfortunately, these two roles were not always compatible, and often difficult for civilian trained physicians to balance.

As the United States became more involved with the war, the Medical Corps began to face a dilemma to problems of untrained soldiers in the military. As more troops were needed overseas, there was an increase in the mobilization of raw untrained male civilians who were hurried into their transformation into effective soldiers. Likewise, the Medical Corps would bring into service large numbers of untrained civilian doctors who were not prepared to do all that was

23 Ibid.
required of a military surgeon. Surgeon General Gorgas not only understood this problem, but also knew that the larger number of men called for duty meant that there would be greater difficulties in maintaining their health, especially during the first year when volunteers suffered a higher rate of disease than regulars.\textsuperscript{24} For civilian doctors, not only was there an overwhelming responsibility to care for these soldiers, but they were also expected to treat as a mass entity rather than collective individuals. Therefore, the Medical Department was responsible primarily for the corporate health of the army as a whole, and secondarily the health of individual soldiers.\textsuperscript{25} For many new military medical officers, this approach was a sharp contrast with the individual focus of private practice, with which they were familiar.

The first priority of medical officials was to “preserve the strength of the Army in the field,” and therefore proper preventative health care was not always closely followed. With the final authority resting in the hands of non-medical military personnel, advice on quarantine, personal hygiene, and problems of overcrowding were not always adequately addressed during stressful wartime.\textsuperscript{26}

Toward the end of September, as the pandemic raged throughout the country, the USPHS continued to sit back on its hands, doing little to provide the public with comfort, aid, or solutions. Issuing a bulletin in early October, Surgeon General Rupert Blue finally tried to take a proactive measure by firmly recommending a quarantine policy across the whole country by dispatching

\textsuperscript{25} Byerly, 44.
\textsuperscript{26} Ibid, 40-41.
telegrams to all state health officials. The extent of these telegrams recommended each official to close all public gatherings in communities threatened by the epidemic to help control the spread of disease. The next day hundreds of communities listened up and acted on the Surgeon General’s request. Unfortunately for cities such as Philadelphia, New York, Boston, and St. Louis, this warning came a little too late.²⁷ Towards the height of the pandemic, Rupert Blue tried to fend against how little he had done to protect the nation. Through public announcements he tried to advise the public on ways to avoid influenza, but his information was often general and provided little comfort. Some of the reassuring suggestions Blue offered to the public included avoiding needless crowding, smothering sneezes, and, “when the air is pure breathe all of it you can – breathe deeply.”²⁸ For a nation suffering from death and dying at home and abroad, needless advice did not help ease their fears of the war or of the pandemic (Figure 1).

![Posters Issued by the United States Public Health Service](image)

Fig. 1: The United States Public Health Service issued several posters during the influenza pandemic of 1918. By educating the public on how influenza spread, the USPHS officials hoped to reduce the number of influenza cases. (Courtesy of http://1918.pandemicflu.gov)

²⁷ Crosby, 74.
²⁸ Barry, 311.
While there was a greater expectation for the government to support American citizens at home and abroad during the war, this responsibility was not unidirectional. An increase in government control and expansion became a “social contract” with American citizens who had increasing expectations. Since a democratic republic cannot effectively enter a war without its citizens’ consent to finance and serve in the military, the federal government had an important role on the home front to maintain support for the war with the general public. Every element of the nation at home mattered, which meant the government saw control of information as necessary to sustain public moral.29

Advertising was about to emerge as an industry, and President Woodrow Wilson would take full advantage of this to shape public opinion of the war. As the first president to address the International Congress of Salesmanship in 1916, he urged its members to “go out and sell goods that will make the world more comfortable and more happy, and convert them to the principles of America.”30 Establishing the Committee on Public Information the following year with former journalist George Creel as chairman, they set up a massive advertising campaign in the name of foreign policy. Known as the Creel Committee, its purpose was to address the problem of censorship and solicit the public’s participation and understanding of the war effort.31 To do this, Creel used tens of thousands of press releases that were routinely run unedited by newspapers that instituted a self-censorship.

29 Ibid, 205.
Originally, Creel only intended to report facts (although carefully selected), and only conduct a positive campaign absent of the use of fear tactics. Creel himself wrote, “We believe passionately in the purity of our motives…and we felt that in order to win unity, in order to gain the verdict of mankind, all we had to do was to give facts in the interest of full understanding.”

However this attitude did not last long as Creel began to demand “100% Americanism,” and increased pressure for American citizens to not only support the war effort, but to contribute financially. One example was a poster aimed at selling Liberty Bonds that warned, “I am Public Opinion. All men fear me! … [I]f you have the money to buy and do not buy, I will make this No Man’s Land for you!”

The U.S. government supported these efforts as they called upon its citizens to pay increased taxes and buy war bonds. Wilson in return promised a war to save democracy and assured Americans that the army would take good care of their soldiers by provided them with benefits and the best medical care possible.

However he gave no reservation as he also demanded during a liberty loan drive for “Force! Force to the utmost! Force without stint or limit! The righteous and triumphant Force which shall make Right the law of the world, and cast every selfish dominion down the down in the dust.”

This type of vigor would indirectly enhance the attack of influenza, as it mobilized citizens to travel around the country to spy and attack anyone criticizing the war (Figure 2).

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33 Quoted in: Barry, 127.
34 Byerly, 43.
35 Quoted in: Barry, 128.
During a time when proper quarantine measures should have been addressed, the selling and buying of Liberty Bonds put many citizens at risk. In addition, these resources could have been better spent aiding organizations like the Red Cross, which worked tirelessly to provide medical treatment to those at home and abroad. The reparations of the liberty loan drives would come full force in Philadelphia, where the campaign would raise millions of dollars, but at a severe price for its citizens. Despite reports of influenza sweeping through Philadelphia naval installations, and warnings from Boston and the Great Lakes, where the pandemic had already devastated civilian populations, Wilmer Krusen, director of the city’s Department of Public Health and Charities, declined to issue a quarantine for the city. He defended his decision because there had not been any cases in the civilian population.

As Crosby writes in his chapter on the pandemic in Philadelphia, “If forewarned had really meant forearmed in 1918, then Philadelphia would have come through the pandemic with little damage.”

Prior to the outbreak in Philadelphia, Boston had already seen the worst of the pandemic. Within just two

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36 Crosby, 70.
weeks of the first appearance of influenza, two thousand officers and men of the First Naval District had contracted influenza. To make matters worse, city officials in Boston were caught off guard when three civilians died from influenza in early September, providing the fearful evidence that the epidemic had officially moved from the confines of the military to the general public. Before the month would end, the city would see over 1,000 civilian deaths. Therefore, there was a likely probability that the appearance of influenza in the Philadelphia Naval Yard on September 11 would spread to the civilian population in Philadelphia. However, even knowing the consequences of the epidemic in Boston, director of the Department of Health and Charities Wilmer Krusen informed the public that there was little chance the epidemic would spread widely among Philadelphia’s civilians.

This lack of acknowledgement, coupled with the pressure to continue on with patriotic duties in support of the war, would lead to one of the greatest blunders of the pandemic. As the cases of influenza rose past 600 at Philadelphia’s naval yard, the Bureau of Health become a little more concerned and finally made influenza a reportable disease. However, on the same day, Dr. Paul Lewis isolated what they believed was the cause of influenza, *Pfeiffer’s bacillus*. Believing this was the cure all for the pandemic, officials saw no reason to cancel the fourth Liberty Loan drive to raise more money in support of the war. On September 28, over 200,000 gathered to watch the parade span 23 blocks through the city (Figure 3). Similar parades across the nation continued in the

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38 Crosby, 71.
midst of the epidemic, including Chicago and New York. However, in the days following the parade in Philadelphia, the pandemic exploded full force within the city. Three days after the parade, 635 new civilian cases were reported in a single day and over 10,000 deaths would be reported in the month of October alone.

As the cases of influenza rose in Philadelphia, city officials faced a problem synonymous with every major city nationwide. Caught up in the idea of patriotism and opportunities for career advancement, an overwhelming amount of the country’s doctors had already joined the war. Rupert Blue noted that “the practices of emergency surgery are being tried out on a scale so vast as to baffle the imagination,” as he admired the amount of physicians curious about participating in the war. With so many doctors and nurses doing their duty to support of the war overseas, there were not enough resources on the home front to handle the mass casualties of the pandemic. Twenty-six percent of Philadelphia’s

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39 Ibid, 72.
40 Ibid, 60.
41 Quoted in: Byerly, 26.
3,500 physicians were serving in the military, leaving the remaining doctors and nurses overworked and short staffed. The city health authorities appealed for the assistance of additional physicians and nurses, but because every other city was facing the same problem, there was no one that could be sent.\footnote{Pennsylvania Closes all Meeting Places: Philadelphia Appeals for Physicians to Check Rapid Spread of Influenza There,” \textit{The New York Times}, October 4, 1918, pp. 24.}

In addition, although it was known that there were deaths widespread throughout the city, there was no communicating the morbidity and mortality statistics of the disease outbreak amongst the various hospitals. As Dr. Scott Miller of Philadelphia’s Bureau of Public Health noted, “While the vital statistics showed the disease to be widespread in character, it became a question of local interest whether one particular part of the city was affected more than another … No one was able to answer these queries. As a result, preventive and educational work could not be concentrated and data of general character was distributed to all classes in all sections of the city.”\footnote{Miller, “Hospital Statistics as an Aid to Public Health Administration – The Philadelphia Plan.”} Within the Bureau of Public Health there was no organization for effective communication at the local level. Similarly this pattern of organization continued up to the federal government, allowing for the pandemic to go unchecked throughout many areas of the country.

Rupert Blue and the United States Public Health Service did a lot wrong and a little right during the influenza crisis. However, one success of Blue’s stint as the Surgeon General included organizing the “Home Defense Nurses” to take care of the general public. These nurses were fully professional, but unable to serve in the military due to age, disability, or marriage. In addition, through the help of Frank Persons and the Red Cross, they were able to organize relief and
divide the labor amongst the organizations. While most of these measures ended up being too little and too late, it did save Rupert Blue’s career as the Surgeon General from being a complete disaster.

However, with the lack of a true centralized presence and a plan to organize a uniform method of delivering aid, the responsibility of organizing relief efforts and quarantines was left to the local and state boards. Of those doctors left to take care of the civilian population, there was very little they could have done to relieve the spread of disease. Many did what they could to work around the clock to produce a saving vaccine to end the Spanish influenza. Dr. C.Y. White of Philadelphia was one of the physicians who believed he had produced the “miracle” vaccine, which was distributed free to hundreds of doctors who immediately inoculated thousands of Philadelphians. However, in 1918, it was not known that influenza was even caused by a virus and Dr. Paul Lewis had originally misdiagnosed it as a bacteria. These vaccines ended up being only a mix of filtered blood and mucus of flu patients that at best did nothing and at worst helped aid in the spread of the pandemic. While valuable time and resources were spent trying to find a cure for the disease, the virus was continuing to spread across the country. However, not every city suffered as badly as others, and those that managed to reduce the mortality rate did so through the use of prevention and quarantine. These next two chapters will look at the non-

\[44\] Barry, 313.
\[45\] Crosby, 84.
pharmaceutical interventions used by these cities and to what extent these practices were effective in preventing the spread of disease.
Chapter 2

Implementation of non-pharmaceutical interventions

Despite achievements in medical research and practice, in 1918 the influenza virus still mystified medical researchers in their attempts to produce an effective vaccine. It would be another twelve years before the first virus would be viewed underneath an electron microscope and at this time influenza was still considered to be caused by a bacterial agent. Therefore, with limited medical resources, the primary defense outlined by the United States Public Health Service focused on non-pharmaceutical interventions rather than clinical treatment. Here, non-pharmaceutical interventions are defined as measures used for prevention and control that do not require pharmaceuticals such as vaccines or antiviral medications. These methods can be classified into further categories that involve limiting the international spread of the virus, reducing the spread in local and national populations, reducing the individual person’s risk for infection, and communicating the risks and educating the public. For the purposes of this paper, I will limit my definition to interventions used to prevent the spread the influenza in the United States at the local and national levels. Classifying these interventions into three categories I will specifically focus on school closings, cancellation of public gatherings, and isolation and quarantine measures.


48 For more information on specific non-pharmaceutical interventions refer to Howard Markel’s report to the Defense Threat Reduction Agency on Non-pharmaceutical interventions.
Non-pharmaceutical interventions (NPIs) are intended to reduce infectious contacts between persons during outbreaks of disease. Although it is improbable to expect these interventions to prevent a pandemic, theoretical modeling research has suggested that non-pharmaceutical interventions might play a role in delaying the effect of the outbreak by reducing the overall peak and attack rate and reducing the number of cumulative deaths. 49 These measures could provide valuable time for an effective vaccine to be widely distributed, decreasing the burden placed on health care services. The 1918 influenza pandemic represents one of the largest recorded events with the use of NPIs to alleviate the spread of a highly virulent influenza virus strain. It provides a useful tool, therefore, for understanding the effectiveness of NPIs nationwide, allowing experts to evaluate the effectiveness of these interventions for future pandemic preparedness.50

Nationally, the use of non-pharmaceutical interventions was limited as the federal government did not have the authority to control the spread of the epidemic within the individual states where it would have been the most effective. Similar to problems faced by the army when the war broke out, the USPHS health officials were not ready for the job which they were expected to do. The first major problem of controlling the pandemic was similar to what Philadelphia had faced on a local scale. The USPHS had no way of accessing information on the latest progress of the pandemic and therefore could not distribute forces efficiently to the places that needed them the most. In addition, at the beginning

of the second wave, although the number of influenza deaths began to rise, there was still censorship and inaccurate reporting of influenza in the newspapers. This created more confusion and fear among health officials and laypeople. Instead of using reporting to its advantage in limiting the amount of contacts among infectious people, posters and pamphlets that were generated provided little comfort and no effective advice.\textsuperscript{51}

Within the army, Surgeon General Rupert Blue made strict recommendations to limit the clustering of “crowds” within the military encampments. The incident at Camp Devens on September 26 raised concern for both military and local health officials, when the disease officially spread to civilian populations. Accordingly Blue issued a report that camp commanders were not authorized to transfer “contacts” of any communicable disease. Unfortunately this notice came too late as there were 18 camps across the country that were heavily infected by the end of September, 1918. In addition, to mitigate the outbreaks of influenza already present in the 16 camps, Blue suggested that the degree of crowding among the infected individuals should be reduced by giving each man a minimum of 50 square feet of floor space in barracks or tents (Figure 4).\textsuperscript{52}

\textsuperscript{51} Crosby, 49.
\textsuperscript{52} “Recommendations to the War Department for the Control of the Influenza Epidemic,” War Department Annual Report to the Secretary of War Fiscal Year Ending June 30, (1919): 1036-1037.
The warnings issued by Blue did not come soon enough. Whether the use of NPIs occurred in the military or civilian populations, the success at which they were effective would depend largely on the combination of the NPIs used and the timing of implementation. In civilian populations, officials who issued quarantine measures prior to reaching the peak of the pandemic within their city were more effective at reducing the number of deaths. Therefore, if being held to the same standards of analyses, the military’s use of NPIs was not effective enough to reduce the level of casualties in the camps. By the time Rupert Blue issued any use of non-pharmaceutical interventions, there were 16 military camps suffering severely from disease. Although Blue claimed these camps followed orders, there were not enough military officials to monitor these camps and ensure that Blue’s orders were carried out effectively. Influenza is not easy to diagnose, and with thousands of soldiers transferred from one camp to another there would have been a relatively high probability that some were carrying the disease with them.  

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53 Crosby, 74.
With influenza prevalent in so many military camps, the next concern among military officials was to prevent the disease from spreading to civilian populations. Although Camp Devens in Boston had been struck by surprise, the others had prior warnings of this highly virulent form of influenza. Military officials were aware that if it were to spread to civilian populations outside their camps, they would be facing an uncontrollable catastrophe. Due to the strict guidelines of military and civilian authority, once the virus spread outside the confines of the military, the authority for containment would be left in the hands of the local governments. Knowing this Rupert Blue did issue a pamphlet “Spanish Influenza,” “Three-Day Fever,” “The Flu,” which provided advice on general NPIs civilians could practice to guard themselves against influenza (Figure 5). Perhaps the only useful advice provided was to limit overcrowding whenever possible. Of less help, he advised, “In short make every possible effort to breathe as much pure air as possible,” ending with the rhyme “Cover up each cough and sneeze, if you don’t you’ll spread disease.”

Unfortunately, these recommendations had little effect on the prevention of disease and did not provide individuals with the comfort they were looking for.

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In early October, Blue’s telegram recommending quarantines of infected areas was sent to thousands of communities. However, some authorities took advantage of this message and followed his recommendations while others did not. The editorial writer of the *Philadelphia Inquirer* saw little use of Blue’s advice, writing, “It is difficult to understand what is to be gained by shutting up well ventilated churches and theaters. The authorities seem to be going daft. What are they trying to do, scare everybody to death?”\(^\text{55}\)

Similarly, Crosby argues such closings recommended by Blue in reality “did little to limit the spread of flu in Philadelphia, Washington, St. Louis, or any of the other large cities where it was tried.”\(^\text{56}\) However, this was not the case in every major city. For example, Howard Markel argues that New York City successfully limited the number of influenza deaths with the use of NPIs, primarily through enforcement

\(^{55}\) Quoted In Crosby, 74.  
\(^{56}\) Ibid, 74.
of isolation and quarantine procedures.\textsuperscript{57} However, they were not completely free from mistakes as these measures were lifted prior to the end of the influenza epidemic, which led an increase in the number of unavoidable deaths.\textsuperscript{58} In addition, although some city officials did not officially implement quarantine measures, some citizens chose to voluntarily participate. For example, in Chicago the highest percentage of absentees occurred on approximately October 21, four days later than the date of the greatest incidence of disease in the city. A survey conducted by the division of child hygiene showed that only a partial percent of these absences were from illness and much more were due to either the illness or death of a family member or because the parent voluntarily chose to keep their child from school to prevent them from contracting the disease.\textsuperscript{59} Perhaps if specific advice on avoiding schools and public places was more widely distributed from the surgeon general to laymen in these larger cities, they would have been able to make their own decisions similar to those made by the parents of Chicago children. Besides these larger cities there were also those of medium size that fared better than others in reducing the number of influenza cases partially due to their use of non-pharmaceutical interventions.

In some cities, in particular San Francisco, citizens took it upon themselves to reduce the spread of influenza. Going above the requirements recommended by Blue, public health director William Hassler shut down the

\textsuperscript{57} Markel, “Nonpharmaceutical Interventions Implemented by US Cities.”
\textsuperscript{58} A more in depth criticism of the non-pharmaceutical interventions in New York City will be provided in the case study in chapter three.
\textsuperscript{59} “Report of an Epidemic of Influenza in Chicago Occurring During the Fall of 1918,” accessed through Models of Infectious Disease Agent Study, \url{https://www.epimodels.org/midas/catdoc.do?methodToCall=view&catalogDocId=594&mode=view}
entire city for the second wave of the epidemic, by issuing quarantines on all naval institutions prior to any reported cases within them or the city. Unlike the Philadelphia reporter who believed quarantine measures would instigate fear, Hassler recruited hundreds of volunteers to help keep medical supplies stocked and distribute masks to thousands of citizens. Since they had something productive to do, the people of San Francisco were informed and in control of the influenza epidemic. They understood the danger and were assigned specific tasks. Building off the ideology of patriotism for the war, Hassler was able to create an active community that was not paralyzed by the fear of a potential pandemic.60 To Hassler’s advantage, he also had the benefit of receiving a clear warning that the pandemic was on its way. This allowed congress to vote on a one-million dollar appropriation to fight the flu before the first deaths reached the city.61

In 2005, the Center for the History of Medicine at the University of Michigan Medical School conducted a study on American communities that had experienced very low rates of influenza during the 1918 pandemic. San Francisco was among these communities. Others included Gunnison, Colorado, Princeton, New Jersey, Western Pennsylvania Institute for the Blind, Trudeau Tuberculosis Sanatorium, Bryn Marr College, and Fletcher, Vermont. A team of historians visited these communities to locate and collect available primary source material,

60 Barry, 375.
61 Crosby, 91.
and created an extensive influenza digital archive.\textsuperscript{62} A report published by Howard Markel and colleges provided an in depth analysis of these seven communities, which were not only chosen because of their low death rates (zero to one) during the second wave of the influenza pandemic, but also because of, to some degree, their use of non-pharmaceutical interventions.\textsuperscript{63}

Conclusions from this study showed that the use of NPIs could have played a role in reducing the fatalities during the pandemic, but other factors may also have contributed the success of these communities. These factors included population density, the patterns of infected individuals within the community, and geographic location. Communities isolated from military bases and frequent travelers fared a better chance of avoiding the spread of the disease. In addition the seven communities studied by Markel and colleagues were all relatively small in size making it easier for public health officials to maintain order and issue quarantine measures. In addition, the study concluded that political and legal authority needed to be transparent with harmonious corporation between state and federal health officials. Markel and colleges stated, “Internecine rivalries or disagreements between local, state, and federal agencies have a strong potential to detract from pandemic influenza prevention and containment.”\textsuperscript{64} Drastic differences between the outcomes of Philadelphia and San Francisco provides one of the best examples of how important communication is from the different

\textsuperscript{63} Markel, “A Historical Assessment of Non-pharmaceutical Disease Containment Strategies Employed by Selected U.S. Communities During the Second Wave of the 1918-1920 Influenza Pandemic.”
\textsuperscript{64} Ibid.
branches of public health. Consequently, it is difficult to provide a precise blueprint for pandemic influenza planning on historical evidence alone, due to the varying factors that contributed to differences among communities during the pandemic.

One particular flaw of Markel’s data is that the communities he observed were all relatively small in size and therefore it is difficult to deduce the effect NPIs would have on a city of a larger size. In the following chapter I will use Howard Markel’s research design methods outlined in this study and apply them to three different case studies of communities that varied in size and location. The first of these cities is Princeton, NJ, which was among the communities Markel and colleagues selected as being successful at protecting its citizens against influenza. I will also be focusing on New York City, which as a large port city was at a higher risk of being hit by the influenza pandemic. Third, I will focus my research on the local response in Syracuse, NY. As a medium sized city in 1918, Syracuse did not have the same advantages of isolation as Princeton, NJ, but also was not a port city like New York City and therefore received some protection. Each of these cities also had a military base nearby and were chosen because of similar risks faced from mobilized troops spreading diseases from one camp to another.
The awkward communication among the state, local, military, and civilian health departments greatly hindered the prevention of the spread of the pandemic. Not surprisingly, due to the lack of communication between various rankings of public health authorities, there was not a consistent response or outcome of the pandemic in each city across the United States. In addition, varying sizes and geographic locations also played a role in helping or hindering communication between public health officials and the general public. The effectiveness of non-pharmaceutical interventions implemented by the local authorities was dependent on a number of these factors along with the degree of military involvement and mobilization surrounding these communities. This chapter, therefore, provides a case study of Princeton, NJ, New York City, NY, and Syracuse, NY, three different communities that varied in size, geographic location, and outcome of influenza cases during the second wave of the 1918 pandemic. Building from the study done by Howard Markel, this case study does not only look at those cities that were successful, but also ones that faced problems in maintaining their isolation during the pandemic.

The Success at Princeton

At the height of the pandemic, Princeton University remained secluded with the protection of a small suburban town in Central New Jersey. With a university of 1,142 men, the small community of Princeton, New Jersey was not significantly larger, with an approximate total population of 5,700. At the time of
the pandemic this community would not only benefit from the little dependence it
had on commerce and manufacturing, but through its strong connections to the
university. Similar to other universities throughout the country, in 1918,
Princeton University was being temporarily used as a training camp for U.S.
military troops being sent overseas. With hundreds of men being shipped in and
out of the university, the training camp became a potential threat for many.
However, Princeton utilized the military structure to its advantage, and was able
to implement strict non-pharmaceutical interventions and policies in the
community and at the university that would have been difficult without the strong
military presence.65

In 1918, an overwhelming (roughly 92 percent) number of students at
Princeton University entered into the various branches of the military including
the Army, Navy, Aeronautical, and Paymaster’s school. Of these students, 706
were included in the Student Army Training Corps (SATC), and 341 in the
Student Navy Training Corps (STNC). Only the students enrolled in the graduate
program, under the age of 18, or physically disqualified did not belong to the
program.66 Therefore, upon the start of a new semester, Princeton was able to
adopt a new army plan where “the members of the corps would lead a strict
military life.”67 With most of the students participating in military activities,
every aspect of their life was regulated, from physical exams to the food they ate
in the mess halls.

65 Markel, “A Historical Assessment of Non-Pharmaceutical Disease Containment Strategies.”
66 Ibid.
Also beneficial to the town of Princeton, the Student Army Training Corps and the Student Navy Training Corps were essentially divided in their daily activities and in the classroom. As a result, they were theoretically geographically isolated from each other and therefore, in the event of an influenza outbreak, they already had a system in place to prevent a rapid spread throughout the university. This theory of isolation would be tested with the first cases of influenza appearing on September 5, 1918 in the Navy Paymaster’s School. Immediately isolating anyone showing symptoms of an upper respiratory problem, the university proved its isolation measures were successful with only five cases appearing during the month of September. Their abilities to continue this success would be tested further in the beginning of October with the arrival of 200 new soldiers from Naval Training Camp at Pelham Bay Park in New York, a camp that experienced high influenza and mortality rates during the pandemic. To prevent the spread of influenza among these men, each person was examined for symptoms of influenza and they all were given a nasopharyngeal spray consisting of chlorazene solution and menthol.68

In addition to the strict inspections of the men arriving from New York, greater regulations on daily activities were enforced throughout the entire university. An article in the Princeton Packet announced on September 27 that the university would be placed under local government control, abiding by the same rules as West Point and Annapolis. Among the changes to the university, newly enrolled students were expected to submit themselves to a physical exam. Travel off university campus would be limited, wardrobes would be provided to

68 Markel, “A Historical Assessment of Non-Pharmaceutical Disease Containment Strategies.”
the students by the university, and room decorations would be restricted and monitored. In essence, while they were under the control of the United States Navy and War Departments, “every phase of the college life will be under military discipline.”

Shortly after the governmental take over of the university, these non-pharmaceutical interventions were also extended to the Princeton community. With the first death occurring in Princeton from the “Spanish Influenza” on October 3, the reality of the epidemic hit the town immediately. The following day, panic instilled as the town published a series of precautionary measures in the *Princeton Packet*, issuing a closure of public gatherings and schools. Churches, motion picture houses, bowling alleys, billiards and poolrooms as well as several other places were now deemed a danger to the public health of the city. Considering these measures advisable primarily as a formality, the Board of Health was specifically clear that these precautions were not due to any unusual sickness present at the time being. However, their urgency in maintaining these quarantines was clear as “the new board has been given unlimited authority to enforce all federal and state sanitary codes, and to regulation of conditions through the town. Should any public places violate the rules, they will be dealt with in the most severe manner.” While hoping to implement these new quarantine regulations without an increase in public alarm, the Board of Health was also aware of the seriousness involved with the first death from influenza.

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70 “Two Spanish Influenza Victims Here,” *The Princeton Packet*, October 4, 1918.
As the influenza epidemic escalated through the university and in the town, further measures had to be enacted by the Board of Public Health to ensure that isolation and quarantine regulations were abided by. Succeeding where Philadelphia did not, the Board of Health was able to postpone its fourth liberty loan drive for fear of contributing to a larger influenza outbreak. Nevertheless, Princeton would not allow the influenza epidemic to handicap its bond buying efforts as it found other means to promote wartime patriotism. Mainly through the use of local boy scouts, bonds were sold door to door instead of during the parade. While still allowing for the potential spread of influenza, door to door interactions between the boy scouts and homeowners still provided a safer method of selling and collecting bonds than allowing for thousands to crowd the streets during the parade. Implementing a similar style, the Red Cross also chose to extend door to door efforts in hopes of collecting more linen for the troops stationed in France. With the closure of churches, schools, and movie theaters, it became increasingly difficult to gain news and raise efforts to support the men overseas. Therefore, creative measures were used to keep up wartime morale on the home front.

As the outbreak spread, maintaining and forcing quarantine measures became increasingly difficult at the university with an anxious student body. As a part of preserving order and discipline, guards were placed on campus. To ensure that no student left the university unaccounted for, lines of sentries surrounded the

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72 Almost nonexistent prior to the fourth liberty loan, the influenza epidemic escalated a few days after the parade. For more information on the liberty loan drive refer to John Barry’s *The Great Influenza.*


dormitories preventing anyone from coming or going without the proper pass. As an article in the Princeton Packet describes, “the campus had changed from a free and easy place, within which the night owl might roam, into a well policed camp.” However, the extent to which these new sentinels were able to enforce quarantine mandates is debatable. Consisting largely of freshman, and only distinguishable from other students with a patch on their arm, these sentinels were faced with the difficult task of maintaining authority amongst upper class students entwined in school tradition and customs. During one such occurrence, a freshman tried to prevent an upperclassman from entering certain quarters upperclassmen had been traditionally given for years. Not allowing himself to be subjected to the authority of someone he deemed inferior, the upperclassman refused to abide by the rules of the freshmen sentinel and continued on his way. Without any way of forcing the comings and goings of students other than their mere presence, other young sentries faced similar experiences with similar outcomes. In essence the purpose of these guards served more as an image of security rather than as a means of actually providing the students with feelings of heightened safety.

Despite the misgivings of the security and the potential spread of influenza that the door to door bond selling may have caused, Princeton was able to dodge a bullet unlike many other towns and cities in the nation. After nearly a full month of quarantine the Board of Health officially lifted its hold in Princeton on November 3. Due in part to the measures they implemented, there were only 68

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75 “Guards on Campus,” The Princeton Packet, October 18, 1918, pp.12.
76 Ibid.
cases of influenza and no deaths among the SATC cadets during the second wave of the pandemic. On the university, only one death was recorded of a faculty member who died of pneumonia. Throughout the town, there were a total of 32 deaths, showing quite favorably that measures taken by the Board of Health in Princeton may have contributed to their success in avoiding a crisis.\textsuperscript{77}

In addition to the use of proper non-pharmaceutical interventions, the size and location of Princeton may have also contributed to their successes. Had Princeton been a larger university, keeping track of and controlling the daily movements of the students and cadets would have been more difficult. For instance, the University of Michigan, home of the largest SATC organization in the United States at the time, suffered from 1,207 cases of influenza in their 2,270-member SATC.\textsuperscript{78} Larger cities such as Boston, New York, and Philadelphia also suffered more deaths due to the epidemic. In some cases these deaths may have been unavoidable with the constant trading and traveling amongst these larger cities. However, in some cases the use of non-pharmaceutical interventions was almost nonexistent in the heavily populated cities. Therefore, while the success of Princeton may have been hard to duplicate, the disaster that occurred in New York City may have also been avoidable had health officials modified Princeton’s methods to accommodate for the size and location of New York.

\textit{Outbreak of Influenza in New York City}

\textsuperscript{77} Markel, “A Historical Assessment of Non-Pharmaceutical Disease Containment Strategies.”

\textsuperscript{78} Ibid.
Facing thirty-three thousand deaths, New York City was hit extremely hard in the early stages of the second wave of the pandemic. With little warning and limited advice on successful defenses for this new epidemic, city officials were caught off guard. Despite the reputation as the best municipal public health department in the world, the New York City Department of Public Health failed to acknowledge the influenza warnings from abroad as a potential threat to the safety of the city. Faced with political conflicts both internally and externally, proper quarantine measures such as those in Princeton, NJ were not enacted in New York City until the influenza epidemic had already escalated beyond the control of the board of public health.\textsuperscript{79,80}

Prior to the epidemic in 1918, the New York City Department of Public Health had demonstrated its ability to successfully implement quarantine measures within the city. Initially a priority in 1866, with the onset of the third cholera epidemic of the nineteenth century, the Board of Health demonstrated its ability to activate quarantines and initiate measures to ensure a cleaner city.\textsuperscript{81} A decade prior to the influenza epidemic, the Board repeated these measures to protect against two polio epidemics.\textsuperscript{82} In 1918, however, the success of evading diseases through prevention was forgotten as wartime politics interfered with science. Through ties of loyalty rather than qualifications, Royal Copeland, who was not an M.D., was appointed as the commissioner of health in 1918. Failing to notice the influenza as the primary bronchial disease contributing to the epidemic

\textsuperscript{79} Barry, 269.
\textsuperscript{80} For more information on successful examples of other cities refer to Markel’s report on the Assessment of Non-Pharmaceutical Disease Containment Strategies.
\textsuperscript{81} Rosenberg, *The Cholera Years*, 146-147.
\textsuperscript{82} Barry, 270.
in 1918, Copeland proved his ignorance by refusing to do anything to prevent the spread. \(^{83}\)

Copeland’s first mistake as health commissioner came when he neglected to recognize the arrival of the Norwegian freighter, *Bergensfjord*, as a potential threat to the health of the city of New York. Carrying a crew of over 200 people sick with disease, ambulances transported many members to nearby hospitals for treatment. \(^{84}\) In a report to the *New York Times* eight days later, Copeland concealed the potential threat of influenza with claims that outbreaks were caused by a bronchial form of pneumonia, and what cases did appear to be caused by the Spanish influenza were mild and therefore no alarm was needed. \(^{85}\) Failing to notice a freighter filled with influenza victims became Copeland’s first mistake in dooming the city to an epidemic. His second was the refusal to take active measures once it became apparent that his first judgment and actions went horribly wrong.

It was only a matter of time until the influenza virus spread from the ship’s crew to the people of New York City. Shortly after Copeland’s announcement reassuring the people that the influenza epidemic was a “mild form,” over 100 new cases of influenza were reported within the city. In an attempt to mask the real problem, Copeland remained optimistic with the success of the Board of Health to document and report all new cases. Copeland chose to direct his focus toward isolating the “bacillus” for vaccine purposes, rather than working with officials to prevent the current epidemic from raging through the city. With his

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\(^{83}\) Ibid, 268-270.

\(^{84}\) Ibid, 181.

main priority aimed at keeping public morale, he refused to close the schools during this crucial period of needed quarantine.\textsuperscript{86} Eleven days following Copeland’s decision, the \textit{New York Times} published another report on the conflicting interests of Copeland and former health commissioner and director of Mt. Sinai Hospital, Dr. S. S. Goldwater. Goldwater, seeing the effects of the epidemic first hand within the walls of Mt. Sinai, issued a public statement warning that the conditions of the epidemic were far worse than what was being reported by the board of health. Pleading for government intervention, Goldwater anticipated that the shortage of doctors, nurses, and hospital beds would be detrimental to the city of New York. Despite this, Copeland again denied the existence of a problem, refusing to admit the need for outside help. However, with the incidence of cases of influenza reaching beyond two thousand people within the five Burroughs, it was becoming more and more difficult for Copeland to continue to hide the influenza problem.\textsuperscript{87} On October 7, another article published in the \textit{New York Times} summed up the fears among New Yorkers affected by the epidemic. The author expressed concerns about keeping the schools open. He also feared the effects of the nursing shortage, as he wrote, “The closing of schools is a debatable question. Dr. Copeland’s reasons for keeping them open are not altogether convincing. There is one thing health officials everywhere should do. As doctors are few and nurses are scarce, families should be educated by clear and simple bulletins to look after their

sick.”\textsuperscript{88} However, Copeland neglected the warnings of the Public Health Board and the general public until the epidemic reached a point where even the strictest quarantines would prove ineffective.

As the panic increased, Copeland finally initiated quarantines, but the damage had already been done. With death rates higher than anywhere else in the country, statisticians were no longer able to keep track of people. With the failure to gain government support from the city and Federal Boards, it was evident that there was an increasing fear among patients that they would not receive the care they would need. Panicking, these patients resorted to desperate measures, going so far as to kidnap nurses to ensure treatment and care.\textsuperscript{89} I argue that a rapid non-pharmaceutical response would have been more effective because the occurrence of influenza deaths within New York City showed that the size of the city, and to some extent the officials running the Board of Public Health, were ill prepared to face a pandemic of this proportion. Laboratories in New York claimed to have isolated \textit{Bacillus influenzae} and were in the midst of producing liters and liters of the bacteria in hopes of creating a vaccine.\textsuperscript{90} However, for the people in the city of New York, their discoveries would be irrelevant, as a proper vaccine would do nothing to save the 33,000 victims already.

Unlike Princeton, NJ, New York City did not have the luxury of a small town with minimal contact from larger surrounding areas. While Princeton was able to successfully combat the influenza epidemic, its size and isolated location had a lot to do with its success. Therefore, maintaining similarly strict

\textsuperscript{89} Barry, 277.
\textsuperscript{90} Ibid, 278-280.
quarantines in a city with the population size of New York would have been extremely hard to maintain, if not impossible. However, although Howard Markel argues that New York City did implement quarantine measures eleven days prior to the arrival of the first influenza cases, the evidence shows that they did not maintain these measures in practice. The schools were never closed, and although Dr. Copeland tried to initiate a quarantine regulation, he was not able to maintain these regulations throughout the course of the epidemic. Whereas we saw with Princeton, NJ, the quarantine was not lifted until the Board of Health was sure the epidemic within Princeton and the surrounding cities was under control. Therefore, size, location, and response played a combining part in the toll influenza had on both Princeton and New York City.

**Local Response: Syracuse, NY**

With a population in between that of New York City and Princeton, Syracuse, NY did not have the advantages of cutting itself off from the rest of the nation like Princeton but also did not have to deal with the arrival of hundreds of sick soldiers from overseas like New York. Located in Central New York, like many other areas in the country, Syracuse served as a training base for soldiers during the war and therefore placed itself at risk for communicable diseases from mobilizing troops. With its own Student Army Training Corps, similar to Princeton, Syracuse University also had to find a middle ground for protecting its soldiers while also working closely with the community to ensure the safety of the public through the use of non-pharmaceutical interventions.

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91Markel, “Nonpharmaceutical Interventions Implemented by US Cities During the 1918-1918 Influenza Pandemic.”
By the end of September, the city of Syracuse was already facing a serious problem due to the influenza epidemic. The resources in the city were stretched thin and many of the hospitals were filled to their maximum occupancy. As one doctor noted, “The public does not realize its danger. But the physicians of the city are giving serious thought to the situation.” Among the local hospitals there were 600 soldiers from the military camp crowding the hallways, with 150 taking place in the Hospital of the Good Shepherd and 200 in Crouse-Irving Hospital. With only 175 beds available for soldiers in the Hospital of the Good Shepherd to begin with, the doctors not only had to worry about where they were going to place the additional sick, but also how to protect the civilian patients in the hospital with other ailments.

To make more room for the influenza patients, physicians had to improvise by finding other locations and methods of taking care of the overwhelming number of sick. Giving up their own private offices, doctors and surgeons brought in soldiers and made room for them by placing cots in the reception rooms. The surrounding hospitals did the same aligning the corridors with cots, spreading them throughout the entire hospital including wards designated for women and children. In addition, Syracuse University provided room for soldiers in the students’ infirmary at the hospital, at their chapel, and in the nursing classrooms. As the epidemic worsened, Syracuse University as well as numerous fraternities located on College Place and Walnut Avenue continued

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92 “Dr. Van Duyn Urges the Preparation of Temporary Hospitals to Fight Plague,” *The Syracuse Herald*, September 26, 1918, pp. 6.
93 Ibid.
to open their doors to the soldiers in need. Houses such as Alpha Chi Rho, Phi Kappa, Psi Upsilon, Delta Kappa Epsilon, Phi Kappa Alpha, and Phi Delta Theta welcomed these soldiers by turning their houses into barracks, as well as other dormitories owned by the university such as Winchell Hall, Wilbor, Annable, and Babcock and Clark Cottages. However, not all of the Greek organizations on campus were as welcoming. The Alpha Phi, Kappa Kappa Gamma, and Chi Omega sorority houses defined themselves as “off-campus,” and therefore under the regulation of the quarantine authorities, could not be visited by the soldiers. For some of the lonely soldiers, however, the Gamma Phi Beta and Alpha Chi Omega sororities were still considered to be on campus and accessible for visits.\(^{95}\)

While Syracuse University and the community of Syracuse can take pride in their patriotism for caring for the soldiers in need, by doing so they also put themselves at a greater risk of becoming victims of the epidemic. As the hospitals crowded the hallways with soldiers infected with influenza, they were exposing other patients in the hospital to the disease as well. Similarly on campus, both the fraternities and the dormitories were now in complete contact with these soldiers who could be potentially infected. Unlike Princeton University, where 92 percent of the students were enrolled in some military organization (and predominantly male), Syracuse University was more diverse and therefore unable to adopt the strict military quarantine. In addition, while Princeton University was able to keep the college and the community separate, Syracuse University and the

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\(^{95}\) “Gods of War in Clash Now With the Little God,” *The Syracuse Herald*, October 20, 1918, p. 42.
Student Army Training Corps looked to the local hospitals for help and therefore came into closer contact with the local citizens.96

Unlike New York City, however, Syracuse did take more active measures in preventing further spread of the epidemic in the community. In an article published in The Syracuse Herald, State Health Commissioner Herman Briggs announced that he saw little use for a strict quarantine, but he did advise the public to avoid crowded places whenever possible. Unfortunately for the commissioner, his reasoning for not implementing a quarantine was flawed as he explained, “strict quarantine measures such as one would take against other infectious diseases while theoretically desirable, are not practical in view of the highly contagious character and the widespread extent of the disease and the general susceptibility to it.”97

Fortunately for the Syracuse community, the mayor of Syracuse had his own agenda placing a strict ban on all public gatherings ten days after the publication of the state commissioner’s advice on influenza. Some of the places the mayor banned from public gatherings included schools, churches, movie theaters, dance halls, and roller skating rinks, as well as lodge meetings, Liberty Loan meetings, public funerals, and unorganized gatherings on playgrounds.98 In the same article published that day, Syracuse University also made the decision to finally strictly isolate itself from the rest of the community. In a conference call between Mayor Stone, Dr. Totman, and Chancellor James R. Roy, they made the

97 “Biggs States Epidemic is Not Spanish: State Health Officer Says Influenza is Pfeiffer Bacillus,” The Syracuse Herald, September 27, 1918, p.38.
98 “Mayor’s Ban on All Public Gatherings Enforced; Syracuse University Isolated,” The Syracuse Herald, October 7, 1918, p.11.
decision together that isolating the University would be in the best interest of the safety of the local citizens and the students. In addition the quarantine, they made it clear that “students who live in Syracuse homes will not be permitted to attend classes on the hill and students from out of town will not be permitted to come to the city for any purpose.”99 In addition the university military camps were also isolated from the rest of the university.

By the end of the pandemic, Syracuse did not escape the effects as skillfully as Princeton, but did not suffer to the extent of New York City. Peaking in the middle of October, before the influenza epidemic would leave Syracuse that month, it would contribute to 678 deaths and over 20,000 cases.100,101 While Syracuse recognized the threat of the pandemic and initiated quarantine measures to reduce the spread, by the time the quarantines were in place the hospitals were already filled with influenza victims. The Syracuse community, therefore, represents a prime example of how important it was to initiate quarantine measures quickly and efficiently in order to reduce the occurrence of influenza.

99 Ibid.
101 “Out of 20,000 People Sick With Spanish Influenza Only 5 Percent Were Insured Against Loss of Wages and Doctors’ Bills,” The Syracuse Herald, October 31, 1918, pp. 25.
Chapter 4

America's forgotten pandemic? A glance back at 1918 from a present day perspective.

Perhaps the most daunting fact about the 1918 pandemic is that it killed millions of people in less than one year. An estimated one third of the world’s population was infected with an exceptional severity of disease with case fatality rates greater than 2.5%, as compared to less than 0.1% in other influenza pandemics. An estimated 50 million people worldwide and 675,000 in the United States died as a result of the pandemic, and in some communities in the U.S., 10% of the population died within a two-week period. John M. Barry has labeled the 1918 influenza pandemic as “the deadliest plague in history,” killing more people than any other outbreak the world has known. No infection, war, or famine has ever killed more people in as short a period. Even more shocking than these numbers, however, is that it has never inspired awe among citizens of any particular country including citizens of the United States. Beyond the mysteries of the virus itself, therefore, one of the greatest questions surrounding the 1918 pandemic is, “why has America tended to forget the flu’s existence?” Alfred Crosby’s book, America’s Forgotten Pandemic, published in 1976, was one of the first historical books written on the 1918 influenza pandemic and continues to be one of the best references on the event. However, since 1999, a search of www.amazon.com has listed over ten books recently published on the

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104 Barry, 4.
105 Crosby, 311.
Spanish influenza pandemic. So why is it that the world forgot this pandemic in the first place, and why in recent years has there suddenly been a greater interest in reexamining the 1918 virus both historically and scientifically?

In the years directly following the 1918 pandemic there was no indication that the government or the people were enthusiastic to relive the memory of the pandemic. In the 1920s public and private expenditures on medical research were barely one fiftieth what they would become after WWII. Of that funding, Congress made no special appropriation for influenza research and more had been done since 1918 for threats of polio, heart disease, and cancer.\textsuperscript{106} Among United States citizens Crosby noted, “The average college graduate born since 1918 literally knows more about the Black Death of the fourteenth century than the World War I pandemic, although it is undoubtedly true that several of his or her older friends or relatives lived through it and, if asked, could describe the experiences in some detail.”\textsuperscript{107} Although the 1918 pandemic is further removed from our memories since the 1970s, the fear and knowledge of the pandemic still seems to be lacking.

\textsuperscript{106} Ibid, 311. 
\textsuperscript{107} Ibid.
One reason Crosby gives for the memory loss directly following the pandemic in 1919 is that it was masked over with all the other horrors of the war. Unique to the pandemic of 1918, there was a large amount of deaths in the age group of 15-35 years, something that has not been witnessed with influenza pandemics prior to and following the one in 1918 (figure 6). While there have been many debates, with no definitive answer as to why this occurred, the fact remains that this age group of young adults was the same age as those who were lost in combat. The names of young men listed in the obituaries, therefore, were blended between those who died in the war and those who died from disease at home. Of the soldiers that died during the war, there was also an overlap between those who died of diseases and those who died of battle wounds. The obituaries never specified the actual cause of death for these soldiers. The pandemic became concealed within the war. In addition, the influenza pandemic

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108 Taubenberger, “The Mother of All Pandemics.”
was not as impressive for the time period as it would be seen today. Epidemics of cholera, yellow fever, and typhoid were common place for most of those affected by the 1918 influenza pandemic. The Spanish flu, therefore, was different in its degree of size and transmissibility, but the world was used to epidemics of some scale.\footnote{Crosby, 319.}

Beyond the horrors of the war, the physiology of victims that succumbed to the influenza virus infection allowed the disease to escape collective memory. Unlike smallpox or polio (other diseases of the early twentieth century), influenza is normally not physically disfiguring. The very nature of the virus is forgettable as it infects its victims and then disappears without a trace. The flu does not normally linger and cause chronic infections and it does not leave behind a whole population of crippled citizens to remind those decades after the disease has already passed of the severe pandemic. Also unlike polio victims, such as Franklin Delano Roosevelt, there was no spokesperson for influenza. The pandemic did not kill a world leader or leave anyone behind to fight for greater awareness of the disease, as most made a fully recovery and were just as quick to forget about it.\footnote{Ibid, 320.}

In addition, despite the number of people estimated to have died from the flu, the epidemiological characteristics of the virus prevented it from becoming feared among most Americans. Even in 1918, the highest case fatality rate estimates were around two percent. Unfortunately, since influenza is highly transmissible, approximately one third of the world’s population was infected,
resulting in a large number of fatalities. Nevertheless, even with a strain of highly pathogenic influenza like that of 1918, the majority of the people infected still survived. Therefore, although there has never been another disease that has killed more people in as short a time as the 1918 influenza pandemic, most have not come to fear it. Other diseases such as AIDS, rabies, and ebola are much more feared than influenza and although they do have a higher case fatality rate, they have not claimed as many victims.

Coming on the heels of the nineteenth-century Bacteriological Revolution, the 1918 influenza pandemic made a mockery of the United States’ new found optimism of disease prevention. It would take twelve more years until the causative agent was identified, and although the germ theory disease had been developed, it offered no protection against influenza. Prior to 1918, Americans felt relieved that infectious diseases were not as life-threatening anymore and each discovery of a new pathogen drove home the message that science was winning the war on germs. Then came the flu epidemic, and it was more comforting to push it out of America’s memory than to face the realization that there were still some diseases that science could not understand. It was much easier to “see no evil, hear no evil.” As years passed, the horrors of the pandemic quickly faded from America’s memory. However, about twenty years ago a new interest in the 1918 influenza pandemic emerged and slowly it is regaining consciousness within America’s memory.

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111 Taubenberger, “The Mother of All Pandemics.”
112 Crosby, 321.
113 Kolata, 54.
Nearly a century later, science and history scholars have regained an interest in the pandemic of 1918. One possible explanation for this occurrence is that science had finally caught up to historical analyses. Following seventy-five years of research after the pandemic, researchers still could not answer the most basic question, which was, “what caused this particular virus to become so fatal?” Although techniques for isolating influenza viruses had become much more advanced, there had been no success at obtaining viral RNA fragments from lung samples of victims in 1918 and isolating the particular strain that caused the pandemic. The first human influenza viruses were isolated in the early 1930s and, therefore, characterization of the 1918 strain had to rely on indirect evidence.\textsuperscript{114}

In 1995, a team of scientists identified archival influenza autopsy materials collected in the autumn of 1918 and began the process of sequencing small viral RNA fragments to determine the genomic structure of the causative influenza virus. An extremely difficult task, Jeffrey Taubenberger and Ann Reid worked tediously using new the polymerase chain reaction (PCR) technique to make multiple copies of RNA from paraffin-embedded tissue. Essentially, not knowing if they would even find it, they were looking for possibly a single molecule of flu virus hiding within the tissues.\textsuperscript{115} Working with extremely small pieces of RNA, Taubenberger and Reid would have to design nine degenerate consensus RT-PCR primers to amplify the small influenza protein fragments under 200 nucleotides (RNA templates larger than 200 nucleotides were not amplifiable). Using this technique they were able to successfully amplify and


\textsuperscript{115} Kolata, 203.
sequence all nine fragments of RNA. The only drawback to Taubenberger’s samples was that they were encased in chucks of paraffin and extremely small. As a result there was doubt that he would be able to find the complete genetic sequence as his 1997 paper only characterized five fragmented genes of the eight total of the influenza virus.

However, following the fame of Taubenberger’s paper, he would receive the solution to this problem from a seventy-two year old retired pathologist. In 1951 John Hultin had made a trip to Alaska to uncover tissue samples from still frozen bodies of flu victims that had been buried in a mass grave. Although Hultin failed in 1951 to isolate viral RNA from tissue samples of these victims, he believed that Taubenberger’s new methods provided the difference between failure and success. Not wanting to face government restrictions and potential liability if he found live virus among the tissue samples, Hultin planned his second trip back to Alaska on his own, funding the entire trip privately. With unbelievable luck, Hultin came across one victim that had not decayed as much as the others in the grave because she was obese and with the permafrost her lungs had remained intact. Naming her “Lucy,” Hultin carefully took the lungs out of the victim, and mailed them to Taubenberger in four separate packages. With these new preserved samples, Taubenberger and Reid’s work went along with tremendous success as they found viral RNA fragments in the lungs of Lucy as Hultin had predicted. From these tissues, Taubenberger was able to characterize the entire hemagglutinin gene and seven years later would publish the final paper in which he was able to complete the coding sequence of all eight RNA fragments.

Taubenberger, “Initial Genetic Characterization of the 1918 ‘Spanish’ Influenza Virus.”
fragments. With ethical criticisms aside, from these published eight coding sequences it was now possible to synthesize a live virus from the fall wave of the 1918 influenza pandemic. This research was done by Terry Tumpey at the Centers for Disease Control and Prevention, who confirmed the uniquely high-virulence phenotype observed with the pandemic virus (figure 7).

Finally, science had begun to catch up to historical analyses. By 2005, the entire sequence of the 1918 virus was known, and confirmed to be more virulent than normal endemic cases of influenza. One question that historians were unable to answer, therefore, scientists could now convey. The large numbers of fatalities in 1918 were not just an inefficient response by the United States Public Health Service nor were they only a factor of troops being mobilized for the war. The viral mechanism of the 1918 virus strain was unusually virulent. In contrast to other human H1N1 influenza viruses, the 1918 virus was able to replicate in the

absence of trypsin, a protease that aids in the cleavage of hemagglutinin molecules, and thought to be a prerequisite for multicycle replication. It is believed that the ability of an influenza virus to replicate in the absence of trypsin is an important determinant of its pathogenicity. In addition, to evaluate the pathogenicity of the 1918 strain in mammalian species, BALB/c mice were inoculated with 10^6 PFU (plaque-forming units) and succumbed to infection as early as three days post-infection, which was in contrast to a low pathogenic (Tx/91) strain in which the virus did not kill the mice. Not surprisingly, the lung pathology of the mice infected with the 1918 strain was more pronounced and showed acute pulmonary adema and/or hemorrhage with acute bronchiolitis, alveolitis, and bronchopneumonia.

With the characterization of the final polymerase genes of the 1918 influenza virus in 2005, it became possible to deduce the origins of the pandemic strain. Of the three polymerase genes that form the polymerase complex (PA, PB1, PB2), it was shown that each gene differed from the avian consensus sequence by less than ten genes. This is consistent with the hypothesis that this particular strain derived from an avian source shortly before the pandemic. Ironically, only months after Taubenberger’s first characterization of the pandemic strain in 1997, Nancy Cox of the CDC received word of a case of an avian influenza virus of type H5N1 in Hong Kong. Not only was this a strain of virus that should never have infected a human being, but the person it infected was a three-year-old boy and he had died. At the time, fear spread amongst

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119 Ibid.
120 Ibid.
121 Taubenberger, “Characterization of the 1918 influenza virus polymerase genes.”
influenza virologists that this could be the potential start of another fatal pandemic like that of 1918. Unfortunately the viral mechanisms of the 1918 virus had yet to be uncovered and therefore there was no template for understanding highly pathogenic influenza. A few months following the first case in Hong Kong things began to snowball as more cases of avian influenza were reported with eighteen people hospitalized from November to December, with eight placed on respirators and six died. Although it was found that these cases of avian influenza were not yet transmissible from human to human, it became a wake up call for those who had forgotten how devastating a case of influenza can be.

Currently without the ability to produce effective egg based avian influenza vaccines, the realization that pandemic planning efforts for influenza would have to be reorganized hit home to many academics and policy makers. With over 200 hundred deaths due to avian influenza since 2003 and an overall case fatality rate of 61 percent, scientist and historians agree that it is only a matter of time before we are faced with another influenza pandemic.\textsuperscript{122} To date, the best template we have for understanding the effects that this pandemic may have on modern day populations is the 1918 influenza pandemic. As a result, it is no longer possible to wipe away the memories of 1918. In the last twenty years, scientific research has reached a level in which it has been possible to understand the viral mechanisms that has lead to an unusually high pathogenicity of the virus. However, there is still a lot unknown about the 1918 influenza virus that science has yet to discover. Specifically, how is it that the influenza virus communicates

\textsuperscript{122} Cumulative Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO (8 April 2009).
with the host cell, and what possible advantages does the 1918 virus have over other low pathogenic viruses? This particular question would become the focus of my research in the Katze Lab at the University of Washington, through the studies of both viral and mammalian proteins that aided in the replication of influenza viruses.
Chapter 5

Translational Control and the Host-Immune Response: Determining the Virulence of Influenza

Introduction

Influenza viruses are among the most common causes of human respiratory infections and among the most significant because they cause high morbidity and mortality. With the potential to cause major outbreaks, to immunologically naïve human populations, influenza viruses are also a major threat to public health. One of the best known characteristics of influenza virus is its ability to generate particularly virulent strains that can cause global pandemics. Three of these pandemics have occurred over the last century, the worst, in 1918, resulted in over 500,000 deaths in the United States and an estimated 40 million worldwide. Since then, all influenza A pandemics and almost all cases of influenza A worldwide have been caused by a descendant of the 1918 virus, which is composed of “drifted” H1N1 viruses and reasserted H2N2 and H3N2 viruses. Current concerns of an avian influenza pandemic similar to the “Spanish Flu” of 1918 have increased the importance of understanding the virulence of the virus and the viral mechanisms of translational control.

The influenza virus belongs to the family Orthomyxoviridae, which is defined by viruses that have a negative-sense, single-stranded, and segmented RNA genome. Five different genera belong to the family including influenza

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124 Taubenberger, “The mother of all pandemics.”
viruses A, B, and C, *Thogtovirus*, and *Isavirus*. All A- and B-type influenza viruses possess eight RNA segments, while influenza C viruses only have seven. Influenza viruses contain and envelope harboring the hemagglutinin (HA), neuraminidase (NA), and the M2 proteins that protrude from the surface of the protein (figure 8).

Different influenza virus strains are named according to their genus, the species from which the virus was isolated, the location of the isolate, the number of the isolate, the year of isolation, and in the case of influenza A, the HA and NA subtypes. Therefore, influenza viruses are classified by the differences in their nucleocapsid and matrix proteins, which are structures that mutate rapidly and facilitate attachment to the host cells. The reservoir for influenza A viruses subtypes are wild aquatic birds, with only the H1-3 and N1-2 subtypes commonly

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known to infect humans.\textsuperscript{126} All three pandemics occurring in the twentieth century (1918, 1957, and 1968) occurred from three different antigenic subtypes of influenza A virus: H1N1, H2N2, and H3N2, respectively. Therefore evidence has suggested that true pandemics with changes in hemagglutinin subtypes arise from genetic reassortment with animal influenza A viruses.\textsuperscript{127}

Influenza viral replication begins through the binding of neuraminic acids (sialic acids) on the surface of cells to initiate infection. This interaction is constrained to the hemagglutinin protein, which binds to specific sialic acid receptors based on different species and their specificity toward sialic acids with different linkages. Human viruses preferentially bind to N-acetylneuraminic acid attached to the penultimate galactose sugar by an $\alpha2,6$ linkage whereas avian viruses bind to sialic acid with an $\alpha2,3$ linkage most of the time.\textsuperscript{128} One of the greater protections, therefore, against an avian strain mutating into transmissible human to human influenza is the inability of certain HA proteins to bind to some species of sialic acid receptors and not others. Although it is possible for influenza viruses to cross species, this variation makes the jump more difficult. Unfortunately, swine influenza shares the same sialic acid receptors of both human and avian influenza viruses. This makes it possible for swine to become co-infected with human and avian influenza viruses causing a possible reassortment that may lead to the emergence of new pandemic strains of

\textsuperscript{128} Knipe, Fields Virology, 1653
influenza.\textsuperscript{129} It is hypothesized that the 1918 influenza virus has its origin in avian species and that a single amino acid change allowed the HA to recognize the $\alpha$2,6-sialic acid linkage.\textsuperscript{130} The degree at which the HA protein attaches to the cell to initiate replication is, therefore, one of the determinants of pathogenicity.

Following binding to the cell, the virus is internalized through endocytosis. The low pH of the endosome activates fusion of the viral and endosomal membranes, releasing the viral nucleic proteins (vRNPs) into the cytoplasm where they are then imported to the nucleus. Inside the nucleus they serve as the template for transcription and new proteins are synthesized from viral mRNA. Newly synthesized viral RNPs are exported from the nucleus to the assembly site at the plasma membrane where new particles bud and are released.\textsuperscript{131} After the viral envelope has separated from the cell membrane, the influenza particles need to be actively released from the cell. Since the HA anchors the virus by binding to sialic acid-containing receptors, the surface glycoprotein, NA must remove the sialic acid allowing the virus to release from its host cell.\textsuperscript{132} Inhibition of the NA enzymatic activity causes viral particles to clump together at the cell surface, which results in infectivity and will severely inhibit viral replication. As a result, NA protein inhibitors are currently one of the most common approaches to the development of antiviral influenza drugs. Relenza\textsuperscript{®} and Tamiflu\textsuperscript{®} are two NA inhibitors that are currently on the market.\textsuperscript{133}

\textsuperscript{130} Knipe, \textit{Fields Virology}, 1654
\textsuperscript{131} Ibid.
\textsuperscript{132} Ibid, 1669.
\textsuperscript{133} Richard J Sugrue et al., “Antiviral Drugs for the Control of Pandemic Influenza Virus,” \textit{Annals Academy of Medicine} 37, no. 6 (2008): 518-524.
Since both HA and NA recognize the same molecule, but with opposing effects, a delicate balance exists between these two proteins and greatly contributes to the pathogenicity of individual influenza viruses. As major surface proteins that play an important role in viral entry and release, these proteins are often the targets for vaccines and antiviral medications. However, as they are on the surface of the viral envelope they are also rapidly mutating and vaccines must be continually altered to compensate for these changes.

One other ambiguous protein not as well studied in its contribution to virulence is the non-structural-1 (NS1) protein. Unlike the HA and NA genes, the NS1 protein is found within the viral envelope and highly conserved across various viral strains. The NS1 functions as an interferon (IFN) antagonist that allows efficient viral replication in IFN competent hosts. It is known to target both INF-β production and the activation of IFN-induced antiviral genes. In virus infected cells, the NS1 protein binds to double-stranded RNA and triggers the activation of transcription factors such as AFT-2/cJun, NFkB, and IFN regulatory factors (IRFs) that stimulate IFN-β production (figure 9). Once IFN-β is activated it is secreted out of the cell where it can be taken up by the same or different cells through type I IFN receptors. Signaling through the JAK (Janus Kinases) –STAT (Signal Transducers and Activators of Transcription) pathway activates key transcription factors that bind to the IFN-stimulated response elements (ISRE) in promoters to activate transcription. Among the activated genes are those encoding antiviral proteins. This induces an “antiviral state,” providing a first line of defense against viral infection. Therefore, it is believed

134 Knipe, Fields Virology, 1716.
that the main role of the NS1 protein is to inhibit IFN-β to prevent this from happening and allowing virally infected cells to “warn” neighboring cells they may develop an antiviral defense.\textsuperscript{135} It is believed that the NS1 proteins may differ among viruses in their abilities to counteract the cellular IFN system.

PKR, a double stranded RNA-activated cellular protein kinase, has been extensively studied in its role of antiviral activity. The principle substrate through which PKR mediates its antiviral effect is the translation initiation factor eIF-2\textalpha. When activated PKR phosphorylates the alpha subunit of eIF2, causing a generalized shut-off of translation initiation. Thus, activation of PKR during viral infection can lead to a block in protein synthesis. Since high levels of protein synthesis are a requirement for viral replication, viruses have evolved numerous

mechanisms to prevent activation of PKR.\textsuperscript{136} One way in which the influenza virus suppresses the PKR response is through the amino (N)-terminal dsRNA binding domain of the NS1 portion of the NS gene segment. This works in conjunction with its capabilities as a potent alpha/beta-IFN antagonist.

Interestingly, also involved with translational control and inhibition of PKR in influenza virus infected cells is the cellular protein P58\textsuperscript{IPK}. This protein was discovered over twenty years ago by Michael Katze, during influenza super infection in cells previously infected with an adenovirus mutant.\textsuperscript{137} Current research has found that P58 not only regulates influenza virus mRNA translation through inhibition of PKR, but that it may also play an important role in the inhibition of PERK and eIF-2\textsuperscript{α} kinase localized in the endoplasmic reticulum (ER) and localized during ER stress. This ability of P58 to interact and inhibit multiple eIF-2\textsuperscript{α} kinases suggests that it is both a critical regulator of cellular and viral mRNA translation.\textsuperscript{138} Currently the Katze Lab has developed in vitro and in vivo experimentation to begin to further uncover the role of P58 during viral infection.

The focus of my projects in the Katze Lab involved both the NS1 protein of high and low pathogenic influenza virus strains including the 1918 influenza virus and the cellular protein P58. The main purpose of these experiments was to further uncover the translational control mechanisms and host-pathogen


\textsuperscript{137} Michael Katze et al., “Translational Control by Influenza Virus: Suppression of the Kinase that Phosphorylates the Alpha Subunit of Initiation Factor eIF-2 and Selective Translation of Influenza Viral mRNAs,” \textit{Molecular and Cellular Biology} 6, no. 5 (1986): 1741-1450.

interactions of influenza virus infected cells. The next two sections of this chapter will specifically focus on these two proteins and my research methods and results.

**Part I: The Contribution of the NS1 Protein to the Virulence of Influenza Viruses**

The NS gene segment of Influenza A viruses encodes for both the NS1 and NEP proteins. The first 230 amino acids of the gene segment encode for the NS1 protein and the last 121 encode for the NEP protein (figure 10). Current literature suggests that the NS1 protein may contribute to the virulence of the virus via three different mechanisms. The first hypothesis is that NS1 inhibits RIG-I (retinoic-acid-inducible protein I), an RNA helicase that triggers a type I IFN mediated response, and production of IFN-β mRNA through N-terminal binding to dsRNA. The second hypothesis is that NS1 inhibits the 2’-5’oligo (A) synthetase/RNase L pathway (interferon induced proteins with anti-viral activity), through N-terminal binding to dsRNA. The third mechanism suggests NS1 inhibits CPSF (cleavage and polyadenylation specific factor I) and PAB II (poly(A) binding protein II) through C-terminal protein-protein interactions.

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It is probable that NS1 proteins from different virus isolates or subtypes function differently. In addition, the N-terminal and C-terminal contributions of NS1 to virulence are still not completely known. Although three mechanisms have been used to describe NS1, it is likely that the NS1 protein is doing more. In addition, different NS1s may preferentially utilize one strategy over another or combine the mechanisms that have been described. We have hypothesized that through a possible combination of these mechanisms that the 1918 NS1 gene is more efficient at expression of IFN-regulated genes than is the A/Texas/36/91 NS1 from a low pathogenic human influenza virus. This is on the basis of a previous paper published by Gary Geiss, who suggested that the 1918 NS1 is a better suppressor of IFN than the A/WSN/33 NS1, a low pathogenic mouse adapted virus.\(^{141}\)

A BLAST comparison of A/Brevig Mission 1/18 (1918, high pathogenic virus) and A/Texas/36/91 (Texas, low pathogenic virus) indicates that the differences in amino acid sequence between the two NS1 proteins are scattered fairly evenly throughout the N- and C-termini. The N-terminal boxed sequence that is known to be absolutely necessary for dsRNA binding is totally conserved between the two proteins. In contrast, regions in the C-terminal end that are known to bind to various cellular proteins (i.e. CPSF and PBAII) do contain differences between the two virus types. Therefore, while it does not provide proof of a mechanism it does suggest that differences in NS1 function for the Texas and 1918 viruses may be due more to differences in their ability to bind various cellular proteins than in their difference to bind dsRNA (figure 11).

Methods

The viral parent strain of influenza used for the microarray and taqman experiments was the low pathogenic human influenza virus A/Texas/36/91 [H1N1]. Using reverse genetics, Terry Tumpy at the Center for Disease Control
and Prevention created a mutant strain of the A/Texas/36/91 influenza virus with seven genes from the original strain and the eighth NS gene segment from the highly pathogenic A/Brevig Mission 1/18 [H1N1] strain of the 1918 influenza pandemic. Since influenza is a negatively stranded RNA virus, introduction of its genome RNA into cells does not result in the formation of an infectious virus. Therefore, cDNA from each of the eight genome segments was cloned and then transfected into mammalian cells along with four expression plasmids for polymerase proteins and NP.

Using the immortal human A549 lung epithelial cell line, the wild type and 1918 NS1 protein in the Texas backbone were infected in triplicate with an MOI (multiplicity of infection) of two. RNA was harvested at two hours, six hours, and twenty four hours post infection. A plaque assay was taken at two hours and twenty four hours post infection, which indicated that both viruses replicate to similar titers in A549 cells (figure 12).
For the microarray experiments the biological replicates were pooled so that there is 510ng total RNA (170ng from each replicate) in 17 μL of water. RNA spike-ins (A and B) used to calibrate measurements in the microarray experiment by hybridizing with a specific control probe on the target array were diluted serially as follows: 1:20, 1:800, and 1:3200. A total of 2μL of the 1:3200 mix was added to the probe labeling reagent. Depending on the spike-in, 3.2μL of master mix A (Cy3) or B (Cy5) was added to each tube of pooled RNA at a concentration of 30ng/μL. The mixture was denatured for 10 minutes at 65°C. A total of 8.5 μL of cDNA master mix was added to each sample, which was then incubated at 40°C for two hours. Transcription master mixes for Cy3 and Cy5 were prepared and a total of 60 μL of master mix was added to each appropriate tube (Cy3 or Cy5). The probes were incubated at 40°C for two hours in the dark. These pooled replicates were then compared to mock infected cells using Agilent 4x44K microarrays (figure 13).
The cDNA for the taqman experiments were prepared using the same RNA samples of the two viral strains that were provided by Dr. Tumpey. The RNA samples were diluted in RNase free water to a concentration of 13.2 ng/µL. These samples were treated with DNase using a concentration of 10x DNase 1 buffer and rDNase, followed by the addition of DNase inactivation reagent with an addition of .1 volume to each sample. Using 250ng of RNA in a 50µL reaction volume, the reverse transcription (RT) reaction was performed. The cDNA product was then diluted to 500µL using water. For the Taqman experiments, equal volumes of cDNA and 2x Master Mix are added. Each probe being tested was added in quadruplicate to the cDNA and the Master Mix solution. Using the 96-well plate, 20 µL of quadruplicate is added to each well.

**Results**

*Microarray Experiments*

While many signature genes are present in the total gene map (figure 14), the experiments clustered according to their time points and not on their viral strain. These results indicate that total gene expression is quite similar for both viruses. In addition, the total number of signature genes increases over time. The heat map suggests that the changes between the two viruses are subtle, and therefore changes in the expression between the two viruses will require a more in depth analysis.
The first direction we took was to look at the microarray data for the interferon-beta pathway. Since IFN-β is such an important upstream player in the antiviral pathway and because IFN-β transcription reflects RIG-I activation, we wanted to look at this gene specifically. The pattern of gene expression is interesting in that the differences between the two viruses are obvious at 2 and 24 hours post-infection. Fitting with our hypothesis, the 1918 NS1 seems to suppress IFN-β at the earlier time points and the suppression is not seen at 24 hours. In contrast, IFN-β is strongly up-regulated early on for the Texas NS1 protein (figure 15). Unfortunately this leaves more questions than answers. For example, does this mean that RIG-I is being suppressed by the 1918 NS1 gene? Also, how will early suppression of IFN-β affect later patterns of gene expression? And will
the overall patterns of type I IFN gene expression correlate with IFN-β expression?

To answer these questions we selectively clustered the type I IFNs and the immediate downstream targets of IFN-β (ISRE driven genes). In general, there are not major differences in gene expression patterns between the two viruses, despite the promising evidence we saw from the contrasting IFN-β activation. This suggests the type I IFN response is not a simple as the current dogma would imply (figure 9). Our data suggests that the expression patterns of many type I IFN response genes are the same whether or not IFN-β is being expressed. Therefore, IFN-β may not control IFN stimulated genes (ISGs) as tightly as first believed. It is evident over time that slightly different gene patterns do arise. A similar population of genes at the six hour time point is up-regulated in the Texas wild type but not in the 1918 NS1 mutant (figure 16). However, it does not appear that the 1918 NS1 is behaving any differently than Texas in terms of overall type I IFN response, but it might be targeting cellular genes more effectively.
We looked selectively at these cellular genes more closely in relation to inflammation, immune response, and stress. Unlike the previous two heat maps, this time we did see significant differences in gene patterns for the two viral types. These differences are most striking at six hours post-infection. From this data it appears that the NS1 is better at suppressing a specific subset of genes found more downstream of IFN-β. This suggests that the ability to specifically target genes on this list contributed to the virulence of the 1918 influenza virus (figure 17).

To validate the microarray experiments, and to specifically look at certain interferon stimulated genes, we ran a series of Taqman experiments. We were specifically interested in the Mx1 and PKR proteins, which are both key components of the IFN pathway. The expression of the Mx proteins in cell lines inhibits the growth of several RNA viruses including influenza, and it has been shown that mice lacking a functional Mx gene are sensitive to influenza virus
PKR has been previously described as an important protein in the regulation of protein synthesis. We did not observe similar patterns between these two genes as Mx1, was significantly suppressed by the 1918 NS1 and PKR was suppressed more by the Texas wild type (not shown). Similarly, other selected genes also followed these patterns, with some preferentially suppressed by the 1918 NS1 and others by the Texas NS1. Therefore, it was not possible to deduce a dominant pattern for either of the NS1 proteins. However, the most differences between the two NS1 proteins occurred early on (at either 2 or 6 hours post-infection).

Discussion

Although no dominant pattern emerged from the Taqman data, these studies did match the microarray data for specific ISGs. In addition, most of the differences between the NS1 proteins occurred early, suggesting the importance of suppressing the IFN pathway at the beginning of viral infection. The

142 Basler, “Viruses and the Type I Interferon Antiviral System: Induction and Evasion.”
microarray data showed that IFN-β transcription is turned on early in the presence of the Texas NS1 but is delayed in the presence of the 1918 NS1. However, overall patterns of type I IFN gene expression did not correlate with IFN-β expression, and they are similar in both NS1 species as opposed to differences seen with IFN-β. In addition genes related to inflammation, immune response, and stress do show different patterns of expression for the two NS1 species, especially at the six hour time point. These results suggest that the NS1 protein may be specifically targeting antiviral pathways by its ability to delay IFN-β transcription and preferentially interact with unknown cellular proteins at its C-terminus. The differences seen between the two viral species also suggest that there may be an underlying factor that allows the NS1 to contribute to the virulence of the virus.

*Part II: Protein-Protein Interactions of P58\(^{IPK}\) and Characterization of the P58\(^{IPK}\) Pathway*

For 27 years, P58\(^{IPK}\) has been extensively studied by Michael Katze and currently the Katze Lab. Past studies on P58\(^{IPK}\) have shown that it is a known inhibitor of PKR and PERK, which results in decreased eIF2-α phosphorylation. In the absence of infection P58\(^{IPK}\) is a critical regulator of ER stress homeostasis through its interaction with PERK. Since ER dysregulation is a cause of diabetes, it was not a surprise that recently generated transgenic mice lacking P58 possess a diabetic phenotype by four months of age. Since P58\(^{IPK}\) is anti-apoptotic is was also not surprising that these mice displayed increased levels of β-cell apoptosis.
as shown by both immunohistochemistry and global gene expression.\textsuperscript{143} It was hypothesized that during viral infection P58 will maintain host homeostasis of the anti-viral and inflammatory response thorough its interaction with PKR. Interestingly, through a set of experiments it was shown that there is an increased mortality in P58 -/- mice across a wide range of infectious doses. Increased PKR activation and induction of its downstream targets may have been the cause of increased pathology in the P58-/- mice.\textsuperscript{144} Therefore, it is believed that P58 acts as a virulence factor by prolonging host survival and aiding in viral replication.

Under normal physiological conditions P58 is present in an inactive complex with one or more regulatory proteins. In response to influenza virus infection P58 dissociates from its regulatory factors and is free to interact with and regulate the activity of eIF2-\(\alpha\) phosphorylation through a PKR mediated mechanism. ER stress results in the transcriptional activation of P58 and an increase in protein level through a PERK mediated mechanism; however, it is not known if ER stress similarly results in a dissociation of P58 from its regulators. In addition, P58 may also interact with other unidentified proteins to regulate additional cellular functions including apoptotic or other pathways (figure 18).\textsuperscript{145}

Based on this assumption, the goal of my research was to use proteomic approaches to examine the role of P58 in the presence and absence of virus infection through the identification of P58 interactive partners. These experiments will be done at the protein level through the use of transient

\textsuperscript{143} Alan Goodman, \textit{Unpublished Data}
\textsuperscript{144} Ibid.
\textsuperscript{145} Michael Katze, Principle Investigator, “Translational Control in Influenza Virus Infected Cells” R01 Grant revised October, 2003.
transfection in mammalian cells, protein purification, and determination of P58 interactive partners through mass spectrometry.

Recently theorized works of P58 and ER stress have been particularly useful for this experimental design. These theories have placed P58 at different locations within the cell in relation to the ER lumen. The first paper to be published by the David Ron lab suggested that P58 mediates co-translational ER protein degradation on the cytosolic face of the ER lumen, suggesting P58 is located within the cellular cytoplasm.\textsuperscript{146} However, shortly after this publication, the Randal Kaufman lab proposed the theory that P58 is an endogenous ER luminal protein serving as a BiP co-chaperone, which suggests that P58 exists as a possible membrane bound protein.\textsuperscript{147} Last year, the Ron lab conceded to this idea in another publication suggesting that P58 posses an N-terminal signal peptide that mediates translocation into the ER lumen, agreeing with the theory that some


parts of P58 may be bound to the ER lumen.\textsuperscript{148} The Katze lab has not been predominantly concerned with the position of P58, but more so with the role of P58 during viral infection. However, my experiments on the over expression of P58 supports the theory that P58 is indeed bound to the ER lumen, and our data were generated with this assumption.

\textit{Methods}

\textit{Over expression of P58}

Human P58 was first cloned into the pTriEx-3 Neo expression vector. This vector was chosen because it included both mammalian and bacterial promoters as well as a histidine-tag that can be used for purification experiments. Transient transfection in mammalian 293T cells were then performed following the invitrogen lipofectamine\textsuperscript{TM} 2000 protocol. One day prior to transfection, 25x10\textsuperscript{5} cells were plated per well in 500 µL of growth media without antibiotics and added to 6 cm plates (conditions can be scaled up or down accordingly). For each transfection sample, DNA was diluted in 50 µL of Opti-MEM\textsuperscript{®} I Reduced Serum Meduim. Lipofectamine was also diluted into 50 µL of Opti-MEM\textsuperscript{®} and incubated at room temperature for five minutes. Following incubation, the diluted DNA was combined with the lipofectamine reagent and incubated for 20 minutes. The mixed complex was then added to each well containing cells and medium. Optimal conditions resulted from a concentration of 0.4 µg/µL of lipofectamine reagent and 1.6 µg of DNA. Cells were harvested at 24 and 48 hours post-transfection and lysed with Triton X-100. Cells were instantly flash frozen and

saved for anti-P58 western blotting. Negative controls of empty vector and mock transfected samples were also prepared by the same procedure for comparison.

**Western Blots**

Optimal conditions for western blotting resulted when samples were first spun down prior to quantification of protein through the BCA protein assay kit by Thermo Scientific. The protein and pellet were separated and SDS loading buffer was then added to the samples in equal proportion to the concentration of protein. A 10% SDS-PAGE gel was used for the western blot experiments and the samples were run at 110V. The gel was then transferred at 0.3 amps for 3 hours to the membrane. The membrane was then blocked with 5% non-fat dry milk (NFDM) in TBS with 0.05% tween for two hours. The membrane was then incubated overnight with the primary mouse antibody diluted 1:1000 with 1% NFDM at 4 degrees. This antibody was washed with 0.05% tween three times for 5 minutes. The secondary P58 9F10 monoclonal antibody was then diluted 1:10000 in 1% NFDM and added to the membrane for one hour at room temperature. The anti-body was washed off following the same procedure as the primary antibody and chemiluminscent solution was added to the membrane for one minute. The membrane was placed in a film cassette and then exposed to developing film for a varied time of 30 seconds to five minutes.

**Immuno Precipitation**

Data from western blot experiments suggested that the P58 protein is bound to the ER lumen. Therefore, we attempted to purify this protein through immunoprecipitation. Using the pellet from the cell lysates we incubated the
samples with four different antibodies that included two monoclonal: 9F10 and 2F8, and two polyclonal antibodies: 1029 and 1589. The samples were incubated for two hours at 4 degrees. Protein A was then added to the samples and then incubated overnight at 4 degrees. These samples were then spun down and the supernatant "flo" was collected for analysis. The pellet was washed four times with NETN and re-suspended in SDS loading buffer to form the immunoprecipitate (IP) sample for analysis. The flo and IP samples were then analyzed through a western blot following the same procedure as the P58 protein samples.

**Mass Spectrometry**

Due to the possible weight of the P58 protein and its possible association with the ER lumen, we were unable to isolate the protein through immunoprecipitation. Therefore, we had to reformat our experimental design to prepare our protein samples for mass spectrometry. Triton X-100 was the original low-salt detergent used to lyse the 293T cells, and was chosen because P58 and other luminal proteins can be extracted from microsomes by even low concentrations of non-denaturing detergents. Unfortunately the negative charge on the triton X-100 obscures the mass spectrometry results, and by using higher salt treatments we would run the risk of stripping the microsomal membranes. Therefore, we followed the instructions of the mass spectrometry experts at the Fred Hutch Cancer Research Center and purified our samples through SDS-PAGE. We then extracted our purified protein from the gel and sent our samples
to Fred Hutch for analysis with the LQ-Orbitrap mass spectrometer and the human CPAS and X tandem libraries.

**Results**

Original experiments of isolated supernatant of the human and mouse P58 proteins did not show over expression of P58. The P58 is 58 kda in size and no band was observed at this location for either mammalian protein across two time points and three different concentrations of DNA. However, initial experiments in which the pellet was isolated and prepared did show significant over expression of P58 (figure 19). In these experiments we did not begin to spin down the pellet until directly before adding the samples to the SDS-PAGE. Therefore, when preparing the mass spectrometry samples we altered our experimental design slightly and began isolating the pellet and supernatant immediately following the harvesting of the cells. Surprisingly these experiments showed over expression of P58 in both the pellet and supernatant of the hP58 protein. This indicated that not only was it likely that the P58 protein is bound to the ER lumen, but that the addition of SDS to the samples may aid in the lysing of the cell membrane in addition to the Triton X-100, resulting in the observation of P58 within the supernatant. The empty
pTriEx vector and mock transfected cells did not show an overexpression of P58. However, a slight band in these samples suggests that P58 was being expressed under normal conditions in these cells (figure 20).

Furthermore, immunoprecipitation of the P58 protein was unsuccessful at isolating P58 protein in the IP samples. However, with the 9F10 monoclonal antibody it appears that there may be some P58 present in the flo. This would suggest that P58 may be bound to the ER lumen and therefore was too heavy to be pulled down by the protein A, and therefore was not found in the pellet portion of the precipitate (not shown).

The mass spectrometry samples were sent to Fred Hutch and analyzed in the IPI human database. Using results with over 95% confidence rate, we uploaded the identifications in the Ingenuity database. Mock-transfected and empty vector-transfected samples show enrichment of non-specific protein functions, as they are the same in both sample sets (not shown). However, the top two categories from the human P58IPK-transfected sample set are “protein synthesis” and “RNA post-transcriptional modifications” (figure 21). The “non-
specific” functions follow these. Network analysis of the “protein synthesis” and “RNA post-transcriptional modifications” categories are shown in figure 22 and 23. Translation factors and ribosomal proteins are shown to be enriched when P58\textsuperscript{IPK} is over expressed.
Discussion

The original supernatant from the 293T cell lysates did not show over expression of P58, which has led us to hypothesize that P58 is an ER luminal protein. In addition our mass spectrometry data shows that the P58\textsuperscript{IPK}-transfected samples have increase interactions with protein synthesis and RNA-post transcriptional modifications. Under normal conditions, it is believed that P58\textsuperscript{IPK} is involved protein synthesis and therefore the data is consistent with our predications.

Future directions will involve confirming that the enriched proteins do bind and interact with P58\textsuperscript{IPK} by a series of western blot experiments. In addition, we have recently begun collaboration with experts on the yeast-two hybrid system as a way of testing for further interactions that will ideally overlap with data from the mass spectrometry. We would also like to repeat these experiments under different cell conditions and selectively identify interaction partners involved in P58\textsuperscript{IPK} activation during influenza virus infection, ER dress, and during both ER stress and influenza virus infection.

The first challenge of these experiments was to ensure the specificity of the protein interactions for these experiments. There are many difficulties involved with transient transfection-based assays given the structural diversity among proteins. However, through my experiments I was able to find a stable cell line that expressed HIS-tagged P58\textsuperscript{IPK}, which will be useful for further mass spectrometry experiments. Although in our initial experiments we did not attempt to purify the P58\textsuperscript{IPK} protein by binding the his tag to a column, it is a possibility.
This would allow for further protein interaction experiments using the “pull-down” method by binding P58\textsuperscript{IPK} to a column and introduce a cellular protein mixture of potential binding partners endogenous to the P58\textsuperscript{IPK} environment.
Epilogue

Modern Day Pandemic Preparedness Plans: What Can We Learn From the 1918 Pandemic?

Most scientists and historians agree that it is only a matter of time until the next influenza pandemic occurs. While its projected severity remains a mystery, it is likely that if it would be avian in nature, it would have the potential to drastically impact global health. However, the tools needed to combat this disease both scientifically and socially continue to be debated. With the experiences of dealing with a highly pathogenic strain of influenza existing in the distant past, both historians and researchers are racing against the clock in hopes of being prepared for when the next pandemic strikes.

While scientists have been warning about the threat of an avian influenza pandemic for years, the reality of this possibility hit close to home for one small village in Indonesia in April of 2006. While other areas of the world have suffered from recent effects of avian influenza, the greatest cause for alarm in Indonesia was that its outbreak offered some of the first evidence of an H5N1 avian influenza being transmittable from one human being to another.\textsuperscript{149} While occurring in an isolated community, the threat of the spread of avian influenza from human to human was clear.

Perhaps acting as a warm-up in 2003, the SARS epidemic showed the twenty-first century how vulnerable we really are as a global community. People stopped traveling to affected areas, airports, hotels, and the travel industry felt the

\textsuperscript{149} Thomas Abraham, \textit{Twenty-First Century Plague: The Story of SARS} (Baltimore: The Johns Hopkins University Press, 2004), VII.
effects. In some areas factories and offices shut down because employees were reluctant to risk going to work. Although a relatively short epidemic, it was enough to give the world a taste of what an infectious respiratory disease epidemic caused by a new virus could be like. In many ways it became a dress rehearsal for a potential influenza pandemic. However, the lessons from the 1918 H1N1 pandemic, which killed over 50 million people worldwide, remain the best model for pandemic influenza preparing.

The continental United States in 1918 contained many features of the modern world we currently live in, including rapid transportation, automobiles, rapid means of communication, and large heterogeneous populations concentrated in urban areas. Although some were still being developed, there were also public health agencies at various levels of government. However, there were also very important differences that contributed to a difference in the effectiveness of thwarting an influenza pandemic, such as the understanding of private and civil constitutional rights as related to public health and governmentally directed measures. In addition, the general perceptions and trust of the medical field especially in relation to vaccines and treatment have significantly changed. Meanwhile, the magnitude of media exchange and travel has drastically increased with the internet and air transportation. At the same time it has become much easier to avoid human contact in the twenty-first century with the ability to conduct most of daily living through the internet. However, although much has
changed, the same idea that sparse populations and infrequent human contact are among the best defenses against influenza still stands.150

Reexamining the ways in which the national government handled the pandemic of 1918 could be valuable in formulating a modern day government preparedness plan. It would be particularly useful to understand the impact of newly emerging global diseases in the twenty-first century. Due to the rapid mutation rate of the influenza virus, although presently vaccinations for influenza are available, it takes months for scientists to develop annual vaccines to protect against particular strains present within the world population from year to year.151 Therefore, a critical responsibility of influenza planning is to develop non-pharmaceutical interventions that may play a role in delaying the effects of a pandemic and reducing the number of cumulative deaths. Influenza is still incurable, and the antigenic shift of the virus means that each year the potential threat of a pandemic strain of influenza increases as the virus continues to mutate. Therefore, understanding the limitations of vaccine development and the effectiveness of non-pharmaceutical interventions is indispensable.

In January of 2009, the Committee on Homeland Security published an updated influenza pandemic preparedness plan for the United States. This report outlined many weaknesses in the current approach to getting ready for pandemic influenza. The most immediate of these problems included the lack of a uniform system of early warning and detection, a limited authority of federal priority on

150 Markel, “A historical assessment of Nonpharmaceutical Disease Containment Strategies Employed by Selected U.S. Communities During the Second Wave of the 1918-1920 Influenza Pandemic.”
151 “Information About Influenza Pandemics,” Department of Health and Human Services, Center for Disease Control and Prevention, October 17, 2005.
pandemic preparedness, poor examples set by Executive Branch Departments and agencies working together, limited use of pharmaceutical interventions, and the lack of recommendations for non-pharmaceutical interventions. Interestingly, these were the same issues that were problematic in 1918 as well. Key recommendations, however, have been made to circumvent these problems. This has included a restoration in White House leadership of national efforts to get ready for pandemic influenza, reports on a consistent basis, a reorientation to health care delivery of very limited resources, and to fill in the gaps of federal planning.

With current technology, the likelihood that an individual would be able to survive an infection of a highly virulent influenza virus has dramatically increased since 1918. However, it is important to recognize that the level of care and resources it takes to treat a particular individual would not be available during a true pandemic. While it is extremely important for scientists to understand the mechanisms of highly pathogenic influenza strains in order to develop effective pharmaceutical treatments, it must be accepted that their availability in mass quantity will not be ready immediately. For example, even if cell-based vaccine production technology were available now, it would still take at least three months for experts to isolate the virus and produce an effective vaccine. Using current egg-based technology the window of time is six months. However, many

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non-pharmaceutical interventions that could prevent the spread of disease can be implemented at any time.\textsuperscript{153}

Many lives and dollars could be saved by a public that is prepared and informed about the dangers of pandemic influenza. Unfortunately, the only recommendations the Committee on Homeland Security gave were to practice proper hygiene and limit unnecessary individual contact.\textsuperscript{154} The World Health Organization (WHO) has provided a more detailed plan for the use of non-pharmaceutical interventions within their pandemic influenza guidelines. Last updated in 2005, they recommended improvements on communication and distribution of public health information tailored and targeted to the general population, which can be distributed at any time. In the case of infection, the WHO suggests confinement appropriate to the local population, face masks for infected persons and those seeking care, voluntary home quarantine of infected individuals, and consideration of school closures and public places when it is believed that these places are contributing to disease transmission.\textsuperscript{155}

Beyond recommendations of increased surveillance and improvements between local and government communication, these were also suggestions that were given and to some degree implemented in various cities across the United States in 1918. Therefore, it is extremely important for us to unmask the mysteries of the 1918 pandemic to the best of our abilities. In order to understand the effectiveness of these interventions in the past, it is necessary to not only

\textsuperscript{153} Ibid.
\textsuperscript{154} Ibid.
evaluate the preventative measures taken across various locations but to also understand the genetic makeup of the 1918 viral strain. Based upon my historical research, some of the non-pharmaceutical interventions that were implemented were successful in reducing fatalities. These included closing of public gatherings and schools, as well as implementation of quarantine measures. When these measures were not introduced in larger cities that had prior warning of the pandemic, they were faced with disastrous effects similar to the outbreak in Philadelphia. However, the increased fatalities in these cities cannot be blamed only on the failure of public health authorities. In addition, even in the larger cities that did institute non-pharmaceutical interventions, they did not completely avoid fatalities from influenza. Optimally, however, appropriate non-pharmaceutical intervention implementation would decrease the burden on healthcare services and critical infrastructure.

The genetic makeup of the 1918 influenza virus has allowed it to evade the body’s immunological defense system better than subsequent viruses. Although in recent years, scientists have been able to capture the 1918 virus and isolate its genetic sequence, we have yet to indentify the protein or proteins that acted as the murder weapon. However, modern day medicine has armed doctors with antiviral medications and vaccines that were not available in 1918. In addition, antibiotics will reduce the number of fatalities from pneumonia-causing bacteria that often produced secondary infections in patients infected with influenza.\footnote{Kolata, 305.}
The increased fatality of the 1918 pandemic was a combination of factors. Improvements in communication and clear distribution of power among local, national, civilian, and military authorities may have reduced the number of fatalities in varying cities. In addition, those who implemented quarantine measures and kept them throughout the duration of the second wave of the pandemic also fared better than those cities that did not. Also, it was shown that the fully reconstructed 1918 influenza virus is highly lethal, and it is believed that small genetic changes can greatly affect pathogenesis. In addition social, political, and economic factors interact with ecological factors to drive influenza viruses to respond through biological and genetic factors, thus evading human defense mechanisms. The challenge to the prevention and control of influenza as a natural threat, therefore, elucidates the ultimate challenge of addressing the convergence of factors that led to its emergence in the first place. In a modern day global community, the need for an interdisciplinary approach cannot be overstressed.

It is currently impossible to predict the emergence of a future pandemic other than to strongly suspect that one will eventually occur. It is also impossible to predict when and where this pandemic will occur, what subtype it will be, and what degree of morbidity and mortality it will produce. Although there is a high concern of an H5N1 pandemic due to its high case fatality rate, experts also anticipate other possibilities for pandemic emergence. To improve the ability to

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157 Tumpey, “Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus.”
predict influenza pandemics it is necessary to increase the knowledge of basic biology and ecology underlying host-switching events. Also, it is necessary to track current identifiable risks and enhance national and international surveillance strategies while expanding on vaccine design.\textsuperscript{159} In the meantime it is also imperative that we reexamine pandemic prevention preparedness plans and develop strategies to guard against influenza in a non-agent specific manner. In addition, influenza information and education needs to be expanded and tailored to the general public. This will lead to benefits in the control of seasonal influenza and help preemptively plan for the next pandemic.

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Summary

The purpose of my Capstone project is to explore both the historical and scientific significance of the 1918 influenza pandemic. The goal of my project is to create a better understanding of the contributions leading to one of the deadliest pandemics in our nation’s history by investigating the social and historical response, while also scientifically studying the how specific proteins of the virus affect the virulence of the virus and the host immune response.

My projected is aimed at answering the question: *what caused the 1918 influenza pandemic to become so fatal?* Using historical archives I focused my historical analysis on the response of the United States Public Health Service and how its public health officials communicated with the different levels of public health authorities. Specifically, my research was focused on the use of non-pharmaceutical interventions, which are defined as measures used for prevention and control that do not require pharmaceuticals such as vaccines or antiviral medications. These methods can be classified into further categories that involve limiting the international spread of the virus, reducing the spread in local and national populations, reducing the individual person’s risk for infection, and communicating the risks and educating the public. For the purposes of this paper, I limited my definition to interventions used to prevent the spread the influenza in the United States at the local and national levels. I classified these interventions into three categories that included school closings, cancellation of public gatherings, and isolation and quarantine measures.
An interesting discovery made by Alfred Crosby in 1976, in his book *America’s Forgotten Pandemic*, was that on average among college graduates in the United States, most students knew more about the Bubonic Plague of the fourteenth century than they did about the 1918 pandemic. Crosby went on to analyze possible explanations as to why America has tended to forget about the 1918 pandemic, and in the fourth chapter I expand on Crosby’s analysis. There were a number of factors, which included that the pandemic was masked by the horrors of the war and that the physiology of influenza infection allowed many people get over the horrors of the disease. Unlike smallpox or polio, influenza does not leave permanent scars nor is it physically disfiguring. Therefore, once the influenza pandemic passed, there was no evidence that it had occurred.

In addition to Crosby’s analysis I also ask the question: why have we suddenly gained more interest in the 1918 pandemic? Within the last ten years there has been a dramatic increase in the amount of publications (both historic and scientific) on the 1918 influenza pandemic. Part of this reason is that scientific research has finally caught up to historical analysis, with the reconstruction of the full 1918 influenza virus in 2005. In addition, the outbreak of highly pathogenic avian influenza in 1997 forced the world to remember the horrors of the 1918 pandemic. Experts agree that it is only a matter of time before we are faced with another influenza pandemic. Currently, the 1918 pandemic remains the best model we have for studying the effects that this pandemic may have on a modern global community. Therefore, it is no longer feasible to forget about the 1918 influenza pandemic.
The second part of my paper is a scientific analysis of the virulence of the 1918 influenza virus and a study of the host immune response in the presence of influenza virus infection. Specifically, this focuses on how the host cells respond to viral infection and the mechanisms that are related to an increase in the replication of the virus within the host itself. We created a mutated virus that consisted of seven genes from a low pathogenic virus and the eighth gene from a highly pathogenic 1918 virus, and compared this to a non-mutated low pathogenic virus. The NS1 protein was selected because it is very similar in sequence across different virus strains. In addition it is known to suppress interferon-beta, a cell-signaling protein that is produced by the immune system and warns surrounding cells of the presence of viral infection. Since the NS1 protein is highly conserved and because it plays an important role in limiting the response of the immune system within the host, it is hypothesized that this protein may contribute to the virulence of the virus. If this is found to be true, it would provide an additional target for vaccine development. The results of my experiment showed that the NS1 protein of the 1918 influenza virus was a greater suppressor of interferon-beta early on in viral infection; however, there was not a dominant difference in overall gene expression patterns between the two viruses.

The second part of my scientific research was a study of the cellular protein P58\textsuperscript{IPK}. This protein has been found to interact and inhibit multiple eIF-2\textalpha kinases and therefore it is suggested that it is both a critical regulator of cellular and viral mRNA translation. This means that we believe P58\textsuperscript{IPK} is an important protein that plays a part in protein synthesis under normal cellular conditions, and
in the presence of influenza virus it is hijacked by the virus to help in its replication. The goal of my project was to find a way to over express P58\textsuperscript{IPK} in mammalian cells so that it would be possible to purify this protein and identify addition protein-protein interactions of this protein besides the two pathways that we were already familiar with. I succeeded with this task, and through the use of mass spectrometry we were able to identify additional protein partners that were enriched in the presence of over expressed P58\textsuperscript{IPK}.

This project is significant because it provides a unique approach to studying the 1918 influenza pandemic that incorporates both scientific and historical analyses. Social, political, and economic factors interact with ecological factors to drive influenza viruses to respond through biological and genetic factors, thus evading human defense mechanisms. The challenge to the prevention and control of influenza as a natural threat, therefore, elucidates the ultimate challenge of addressing the convergence of factors that led to its emergence in the first place. In a modern day global community, the need for an interdisciplinary approach cannot be overstressed. Therefore, connecting present day scientific research with analyses of past historical events can serve as a model for future interdisciplinary collaborations.

While scientific research and vaccine design will be crucial to preventing future pandemics, scientific experts have yet to come up with a way to develop a universal influenza vaccine. Therefore, although scientific research cannot be ignored, it is just as crucial to develop proper preparedness plans that could delay the onset of influenza pandemics while vaccines are being produced. Therefore,
in a modern day global community it is imperative that social scientists and natural scientists work together to develop an effect plan for preventing future pandemics.