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Influenza Pandemics of the Twentieth Century: An Analysis of their Chinese Origins

Author

Katherine Markle

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Univ. -Prof. Mag. Dr. Friedrich Edelmayer, MAS

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1. Introduction

The word *influenza* is a term of Italian origin first documented at the dawn of the sixteenth century to describe a malady provoked, that is, “influenced”, by the alignment of the stars.¹ While the perception of influenza has transformed drastically in the last few centuries, this designation has endured and further embodies one of the gravest threats to humanity. Influenza-like pandemics are evident throughout recorded history, though the twentieth century encountered some of the most striking episodes of this illness ever to transpire. In the years 1918, 1957 and 1968, the global populations of each period succumbed to cataclysmic events attributed to influenza. Millions perished as a newfound sense of vulnerability reverberated worldwide. The three influenza pandemics that occurred during the twentieth century all took very distinctive courses, yet were bound by one striking commonality: place of origin. Every influenza pandemic to arise during the twentieth century and the vast majority of those preceding the year 1900 are believed to have originated in a viral reservoir situated in southern China. Though contemporary research has bestowed some insight into the scientific grounds for such a phenomenon, little consideration has been granted to the external variables influential in the generation and propagation of influenza out of this area in southern China. Consequently, this intriguing, yet scantily researched topic is the contention of this thesis: arguing that the three major influenza pandemics of the last century originated in southern China, what have been the social, cultural and environmental factors in this region enabling both generation and worldwide dissemination of influenza viruses? Essentially, while the appellation may be Italian, influenza as an illness could very easily be considered a prodigy of East Asia.

Historical cases of influenza can be very difficult to identify. As an illness, the symptoms are relatively vague and may

¹ Michael B.A. Oldstone, *Viruses, Plagues and History: Past, Present and Future*. Oxford: Oxford University Press, 2010, p. 313.

be indicative of a variety of other ailments. Influenza causes first and foremost a high fever that is often accompanied by body aches, chills, cough, nasal congestion, sore throat, fatigue and loss of appetite. A smattering of these can manifest, though to varying degrees, and may actually be evidence of another type of infection, ranging anywhere from the common cold to pneumonia to the onset of certain cancers.² Thus, prior to the startling advancement of virological knowledge and technology over the course of this past century, many of the historical cases thought to be influenza are actually quite tentative. Retrospective analysis approximates the first mention of an influenza-like illness occurred during the time of Hippocrates in a handful of his records from 412 BC.³ The first major epidemic of a disease thought to be influenza spread much later during the Middle Ages, specifically the years 1173 and 1174, throughout Europe.⁴ Europe again was incapacitated by widespread bouts of influenza during the sixteenth century. In 1510, the illness disseminated from northern Africa into the southern region of Europe. Italy was especially affected by this malady that, for the first time, was designated *influenza*. Another extensive flare-up was documented in this same region in 1557, though it was an outbreak in 1580 that, according to nearly all associated scholars, constituted the first global pandemic of influenza.⁵ The pestilence began in Asia during the summer, advanced to Africa and then on to Europe, which was totally engulfed by infection after only a six-month period. From there, the illness spread to the Americas and for the first time, influenza was rampant on a global scale.⁶ While morbidity was high, mortality rates varied. Of the records available, it is known that roughly eight thousand deaths occurred in Rome alone and

² Jan C. Wilschut, Janet E. McElhaney and Abraham M. Palache, *Influenza*. Philadelphia: Mosby Elsevier Ltd., 2006, pp. 104-106.

³ Charles W. Potter, "A History of Influenza." In: *Journal of Applied Microbiology*, volume 91 (2001), p. 574; Charles W. Potter, "Chronicle of Influenza Pandemics." In: *Textbook of Influenza* edited by Karl Nicholson, Robert Webster and Alan Hay, Oxford: Blackwell Science Ltd., 1998, pp. 3-18.

⁴ Potter, "A History of Influenza", p. 574; August Hirsch, *Handbook of Geographical and Historical Pathology*. London: New Sydenham Society, 1883.

⁵ Potter, "A History of Influenza", p. 574; Gerald F. Pyle, *The Diffusion of Influenza: Patterns and Paradigms*. Totowa, New Jersey: Rowman and Littlefield, 1986, p. 23; Tom Quinn, *A Social History of Influenza*. London: New Holland Publishers Ltd., 2008, p. 16.

⁶ Pyle, *The Diffusion of Influenza*, p. 24.

some Spanish cities were nearly annihilated by the infection.⁷ For the next four hundred years, pandemics continued at an almost cyclic pace; an average of three major influenza outbreaks occurred every century, the most notable of these attacks arising in the years 1781, 1831 and 1918.⁸ Since the sixteenth century, historians of medicine assert that twelve episodes of influenza infection have materialized on a global scale. Of these twelve known pandemics, scientists can convincingly affirm that eleven have originated in China before circulating worldwide.⁹

It wasn't until the end of the nineteenth century that this pattern was first recognized, largely due to a revolution in medical science. Throughout the latter part of the 1800s, scientists began to investigate what has since become known as germ theory: "Simply put, the germ theory said that minute living organisms invaded the body, multiplied, and caused disease, and that a specific germ caused a specific disease."¹⁰ The introduction of this novel theory rivaled more conventional claims that "miasmas" (noxious gases from the earth) and filth were the roots of outbreaks.¹¹ The epidemiology of large-scale infections became an essential facet of this research and was at last made applicable when an influenza pandemic struck in 1889. What became known as the Russian flu was the first pandemic to be documented under modern-day standards.¹² It is the earliest known influenza outbreak with events substantiated by conclusive evidence and is considered the precursor, both in terms of scientific investigation and viral lineage, to the major pandemics of the twentieth

⁷ Potter, "A History of Influenza", p. 574; William I. Beveridge, "The Chronicle of Influenza Pandemics." In: *Historic and Philosophic Life Sciences*, volume 13 (1991) pp. 223-235.

⁸ Amorsolo L. Suguitan and Kanta Subbarao, "The Pandemic Threat of Avian Influenza Viruses." In: *Emerging Viruses in Human Populations* edited by Edward Tabor, Oxford: Elsevier, 2007, p. 102; Youri Ghendon, "Introduction to Pandemic Influenza through History." In: *European Journal of Epidemiology*, volume 10 (1994), p. 451.

⁹ Krysztof Kuszewski and Lidia Brydak, "The Epidemiology and History of Influenza." In: *Biomedicine and Pharmacotherapy*, volume 54 (2000), p. 188.

¹⁰ John M. Barry, *The Great Influenza: The Story of the Deadliest Pandemic in History*. New York: Penguin Books, 2004, p. 49.

¹¹ *Ibid.*, p. 50.

¹² Karl D. Patterson, *Pandemic Influenza 1700-1900: a Study in Historical Epidemiology*. Totowa, New Jersey: Rowman and Littlefield, 1986, p. 118.

century.¹³ The illness was first reported in Russia in May of 1889, thus acquiring the aforementioned label. Nevertheless, both then and even more so now, scientists concede that this pestilence in fact originated in China.¹⁴ This detail inspired one of the first scientific observations of China's bewildering penchant for influenza.

The Hong Kong-based British physician James Cantlie was the first to officially acknowledge southern China's predisposition to pandemic influenza viruses. A brief excerpt published in *The British Medical Journal* in 1891 by Cantlie reflected on the then recent pandemic of 1889 and its striking association with China:

“The Russians style the disease ‘Chinese influenza’, and just as the people in the West of Europe call their epidemic Russian influenza, so the Russians in turn call it Chinese. I claim that the Russian are right in their statement, and that in September and October, 1888, the disease certainly appeared in Hong Kong, and probably in the South of China generally, and that it very soon afterwards seems to have travelled across Siberia, and by 1889 had reached St. Petersburg. Further, from inquiries made, I am almost of the belief that influenza is endemic in China.”¹⁵

Even so, Cantlie's untimely speculation in 1891 never fully actualized given that medical science around the turn of the century lacked the necessary knowledge and means to properly pursue such a topic. Nearly a century passed before the role of southern China in influenza pandemics was revisited. In 1982, Kennedy Shortridge collaborated with Charles Stuart-Harris and published a concise, albeit innovative article entitled “An

¹³ Joan Lane, *A Social History Medicine: Health, Healing and Disease in England, 1750-1950*. London: Routledge, 2001, p. 150.

¹⁴ Quinn, *A Social History of Influenza*, p. 120.

¹⁵ James Cantlie, “The First Recorded Appearance of the Modern Influenza Epidemic.” In: *The British Medical Journal*, volume 2, number 1600 (1891), p. 491.

Influenza Epicentre?” that expanded on the premise set forth by Cantlie.¹⁶ Shortridge, who remains today chair professor of microbiology at the University of Hong Kong, has since become the definitive advocate for this meagerly explored theory.

The article explored the variables inherent to southern China that are responsible for the proliferation of new influenza viruses, those most apt for rousing an outbreak of pandemic proportions. The two professors concluded that the farming methods and consequent proximity to livestock endemic to southern China provide a breeding ground for the transmission of influenza viruses. It was further asserted that a high population density and tropical climate facilitates the propagation of this pestilence both within and out of this viral reservoir.¹⁷ Shortridge returned solo in 1997 to this topic in another article entitled “Is China an Influenza Epicentre?”, affirming yet again southern China’s undeniable role in influenza pandemics.¹⁸ Naturally, the essence of this thesis is strongly aligned with Shortridge’s research. However, in comparison to his two and five page articles, respectively, this examination is far more elaborate.

Upon investigating the history of pandemics, I found that the vast majority of sources alluded only briefly to this association between China and influenza and further portrayed it as merely a subsidiary notion to the argument at hand. Most of the literature attributed not more than one or two pages, leaving the cause of this phenomenon an intriguing mystery to a curious reader. It required multiple steps before stumbling across the work of Shortridge, who is more or less the only primary supplier of such material, as no comprehensive document exists. One of the objectives of this thesis is to provide a broader examination of southern China’s role in perpetuating influenza pandemics and to do so more directly than the currently available literature. It will by no means be all-inclusive, but will hopefully shed a glimmer of light on what may be a very pertinent issue in the management of influenza pandemics.

¹⁶ Kennedy Shortridge and Charles Stuart-Harris, “An Influenza Epicentre?” In: *The Lancet* (9 October 1982), pp. 812-813.

¹⁷ Ibid.

¹⁸ Kennedy Shortridge, “Is China an Influenza Epicentre?” In: *Chinese Medical Journal*, volume 110, number 8 (1997), pp. 637-641.

Much of this investigation has been derived from secondary sources. I realized that most of the information vital to the development of this argument has already been done; it was simply a matter of piecing it together. To study the social, cultural and environmental variables influential in China's role as a viral reservoir, I had to oscillate between literature involved with both the natural and social sciences. A great deal of the material related to the structure and behavior of influenza as a virus was obtained from scholarly journals in the fields of epidemiology and virology. This was then merged with data gathered from assorted discourses in the social disciplines, particularly sociology and history. The ultimate goal of these efforts is to illustrate the reciprocal relationship between external socio-cultural factors and biological processes, that is, to bridge the traditional gap between the "hard" and "soft" sciences as a means of acquiring a more complete understanding of the complex system behind influenza pandemics.

The thesis as a whole assumes a historical tone, since past pandemics are used to demonstrate China's propensity for influenza viruses. The three influenza pandemics that occurred during the twentieth century as per the standards of the World Health Organization most accurately reflect the argument of this examination. While the majority of pandemics documented throughout recent history are thought to have begun in China, it is those that transpired during the twentieth century that boast more conclusive origins, largely due to contemporary scientific advancements. Accordingly, a larger amount of valid literature is available regarding the pandemics of 1918, 1957 and 1968, providing enough substance to sustain the development of this thesis. Thus, I have chosen to focus only on the three influenza pandemics that occurred during the twentieth century.

The structure of this examination is straightforward. A chapter is provided initially to elucidate the terms and processes necessary for grasping the overall argument. The following three chapters chronologically evaluate each pandemic of the twentieth century individually, focusing mostly on their Asian origins. The influenza outbreak of 1918, the deadliest in history, has a more contentious beginning, one that is argued in this thesis to have occurred in China. The subsequent chapters delve into the events of 1957 and 1968, both of which irrefutably disseminated out of southern China. Following these three illustrations of China's

prominent role in the generation of pandemic influenza viruses, an analytical chapter is provided to assess the contributing social, cultural and environmental factors pivotal for establishing a reputation as an “influenza epicenter”. Similar to Shortridge’s claim, an integrated farming system, a propinquity to livestock, a tropical climate and a high population density are all identified as key variables that, when combined, have the capacity to instigate an influenza outbreak of pandemic proportions. The aim of the final chapter, the conclusion, is to clarify the importance of recognizing southern China as a likely fountain of detrimental influenza viruses. Methods of pandemic surveillance, prevention, response and containment can all be enhanced if the source of these outbreaks is better understood. Southern China is by no means the only area that should be monitored; nevertheless, its reputation has undoubtedly classified it as a serious threat when it comes to influenza pandemics, a detail that should not be disregarded.

2. Definitions: Understanding Viruses, Influenza and Pandemics

The components that set in a motion a large-scale influenza outbreak are complex. Nevertheless, to understand the nature of influenza pandemics, one must understand the intricacies that cause such an event, ranging from the basic constituents and behavior of viruses to the global network of surveillance. The next few pages will expectantly illustrate the terms and processes necessary for comprehending not simply the contention of this thesis, but the fundamental concepts inherent to the development, conduct, propagation and containment of influenza. This explanation will progress in size, beginning with a description of the building block of a pandemic, the influenza virus. Details regarding the contraction and transmission of this infection will proceed, followed by insight into how this illness manifests from an isolated event into one of global proportions. Lastly, a fleeting portrayal of the global system of response, one orchestrated by the World Health Organization, will be presented to illustrate the sheer magnitude of this submicroscopic pathogen.

Influenza is a type of virus. A virus is nothing more than a submicroscopic fragment of genetic material enclosed in a protein membrane, yet it is an entity that has subsisted for millennia. Though this illness has been recognized for centuries, its source has only recently been identified. While investigating diseased tobacco plants in 1898 at the height of germ theory research, two scientists, Russian-born Dmitri Losifovich Ivanovski and the Dutch Martinus Beijerinck, discovered an agent that passed freely through filters used to isolate bacteria. The filtrated solution would grow on the plants, but not on the media used for cultivating bacteria. This discovery provoked the highly controversial postulation that viruses, defined then for the first time as “subcellular entities that could cause distinct forms of tissue destruction”, existed.¹⁹ Even so, the work was theoretical, since viruses, 500 times smaller than bacteria, were invisible to any

¹⁹ Oldstone, *Viruses, Plagues and History*, pp. 15-16.

known instrument of the period.²⁰ It wasn't until the 1930s that viruses were finally proven to be true agents of disease. Due to the work of Richard Shope with swine infected during the 1918 pandemic, viruses by this point had been linked as the potential cause of influenza.²¹ The advent of the electron microscope in the late 1930s allowed scientists for the first time ever to both isolate and observe these submicroscopic organisms.²² However, information about viruses remained limited, until the discovery of genetic material, of DNA, in the 1950s. It was only then that scientists realized a virus is "simply a bundle of genes, in the form of DNA or RNA, wrapped in a coating of proteins and lipids."²³

Despite these profound breakthroughs, viruses remain an elusive endeavor in scientific disciplines. A variety of theories exist concerning the origin and evolution of viruses. There are scientists who claim that viruses potentially arose independently and are the manifestation of the most primal molecules with a capacity for replication. Others champion the assumption that viruses are actually rogue pieces once part of a cell that seceded and subsequently evolved separately. However, the majority believe the viruses as we know them today are actually a diminished product in comparison to the earliest forms. Viruses likely began as complex living cells and devolved over time to possess a simpler structure and function. Simplicity certainly characterizes the behavior of a virus; its single objective is to replicate itself, a task that viruses are paradoxically unable to perform on their own.²⁴

Thus, one of the greatest debates in science is whether or not viruses constitute a living organism:

"Viruses do not eat or burn oxygen for energy. They do not engage in any process that could be considered metabolic. They do not produce waste. They do not have sex. They make no side products, by accident

²⁰ Quinn, *A Social History of Influenza*, p. 22.

²¹ Oldstone, *Viruses, Plagues and History*, p. 316.

²² Quinn, *A Social History of Influenza*, pp. 161-162.

²³ Gina Kolata, *Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus that Caused It*. New York: Touchstone, 1999, p. 71.

²⁴ Barry, *The Great Influenza*, p. 99.

or design. They do not even reproduce independently. They are less than a fully living organism but more than an inert collection of chemicals.”²⁵

While viruses have the ability to survive autonomously, they require a host for reproduction. Viruses contain the same form of genetic material as every other living organism, yet cannot encode proteins independent of a host. The sole motive of a virus is reproduction, yet it lacks the necessary means to replicate unaided. Its demeanor oscillates between a living organism and parasitic inanimate entity. What is certain, however, is that viruses, in this plight for procreation, incite detrimental repercussions upon entering a host.

Viruses in general work by invading an organism’s cells and have the ability to enter any cellular form of life ranging from plants and animals to fungi, bacteria or protozoa.²⁶ They insert viral genetic material, ribonucleic acid, into these cells that ultimately binds with the host’s own genome. Coded with genetic material from these foreign invaders, the host cell then begins spawning viral proteins that eventually form new viruses. These viral copies escape, killing the host cell in the process, yet fulfilling the fundamental goal of replication. The cycle develops exponentially as these fledgling viruses infect other cells in the host, quickly churning out millions upon millions of new pathogens.²⁷ This process proves destructive to the host, as viruses capture and destroy cells required for proper systemic functioning. As cells die, one becomes ill as a result of imminent system failure, especially when virus populations become too overwhelming for the host’s immune response. Furthermore, as the host battles this infection, the immune system weakens from the crushing effort, predisposing the victim to secondary bacterial infections; with influenza, pneumonia is by far the most threatening infection to ensue.²⁸

While this illuminates the basic process of viral infection and replication, viruses have the capacity to affect the host in very

²⁵ Ibid.

²⁶ Oldstone, *Viruses, Plagues and History*, p. 10.

²⁷ Barry, *The Great Influenza*, p. 100.

²⁸ Quinn, *A Social History of Influenza*, p. 23.

diverse ways. Structure and size vary among all viruses, each equipped with particular proteins and genetic material that correspond to specific cells in a host. It is this detail that allows viruses to infiltrate a host undetected and further recognize the specific cells necessary for replication. This disparity results in a variety of reactions that materialize as distinctive ailments with assorted symptoms and degrees of severity.²⁹ Though they represent only a minute percentage, measles, smallpox, polio and HIV exemplify some of the more recognizable illnesses caused by specific viruses; nevertheless, the viral malady relevant to this examination is influenza.

Influenza is nothing more than a circular membrane pouch enveloping the eight gene segments that characterize the virus's function. It is 1/10,000 of a millimeter in diameter, more than five hundred times smaller than the average bacterium. Under an electron microscope, the virus has an almost floral appearance, as the spherical encasing is coated with two types of spiky protuberances jutting out like a corona of petals. These appendages are the proteins that enable the virus to firstly bind to a receptor cell in a host and secondly incise the cell from within following replication to release the progeny viruses. The former protein is called hemagglutinin. Its thorny structure allows it to conform securely to the targeted protein sialic acid that lines the receptor cells of a host. Once locked in place, the hemagglutinin of the influenza virus continues to bind to the protein sheath of the receptor cell until the cell's membrane begins to weaken under the tension. To complete this process of adsorption, the influenza virus breaks through the deteriorated surface and inserts itself entirely into the cell, a feat that allows influenza viruses to evade the host's immune response. Within, the virus then reshapes itself, almost as if folding inside out, exposing a new set of hemagglutinin that dissolves the virus's outer membrane and empties its contents into the host cell. The viral genetic material infiltrates the nucleus of the cell, combines with the cell's genome and institutes a new set of orders to produce proteins for the virus. These proteins are then saturated with novel copies of viral genes produced with the aid of the host cell, nearly concluding the process of replication. The final step is evacuation of the cell, which is the responsibility of the latter of the two aforementioned

²⁹ Ibid.

proteins, neuraminidase. Neuraminidase is a stocky extension on the outside of an influenza virus that functions during the lysis of the host cell. It first degrades the sialic acid on the outside of the receptor cell to prevent adhesion upon exit and further cleaves the cell membrane to release the progeny viruses, destroying the cell in the process. This step completes the initial replication and the cycle continues as these new influenza viruses contaminate and reproduce with more cells in a host, rapidly initiating an infestation. The entire process, from initial attachment to a host cell to the time the cell ruptures, takes an average of ten hours and produces from a single host cell anywhere between one hundred thousand and one million new influenza viruses outfitted to carry on the ritual.³⁰ As these viruses continue their exploit, more and more cells within the host die; the repercussions of this loss manifest as the symptoms commonly associated with the flu: headache, chills, fever, cough, fatigue and loss of appetite.³¹

The two proteins that enable this process, hemagglutinin and neuraminidase, are also what identify different strains of influenza. The influenza viruses that affect humans are classified into three groups of severity: influenza A, B, and C. Influenza C is the least mild of the three and produces symptoms on par with the common cold. Influenza B is more serious and has the ability to cause epidemics, though it is A-type influenza that is by far the most devastating, with a capacity to incite pandemics.³² Every influenza virus mentioned in this thesis is an A-type influenza, and thus no further distinction will be made between these classifications. Influenza A is known to affect not only humans, but a variety of other mammals including horses, seals, and pigs and can additionally infect an array of birds.³³ Aquatic birds, especially ducks, are considered to be natural carriers for influenza viruses, providing a favorable environment in their intestinal tracts for incubation.³⁴ These viruses, however, develop poorly in humans due to tissue tropism specific to different strains of viruses. Influenza viruses correspond to an exclusive type of

³⁰ Barry, *The Great Influenza*, pp. 103-104.

³¹ Oldstone, *Viruses, Plagues and History*, p. 313.

³² Quinn, *A Social History of Influenza*, p. 36.

³³ Oldstone, *Viruses, Plagues and History*, p. 318.

³⁴ Robert Webster, Maya Yakhno, Virginia Hinshaw, William Bean, and K. Gopal Murti, "Intestinal Influenza: Replication and Characterization of Influenza Viruses in Ducks." In: *Virology*, volume 84 (1978), pp. 268-278.

receptor cell in every susceptible species, a phenomenon known as tissue tropism. The tissue tropism of human influenza, that is, the affinity of an influenza virus for a specific type of cell, targets respiratory epithelia, which conveniently have a surface sheathed in the highly coveted protein sialic acid described previously.³⁵ It is this reason why human nasal and respiratory tracts are the milieu of influenza infections, for this area of the human body accommodates the most easily accessible corresponding receptor cells.³⁶

Despite this variance in physiology, zoonotic transmissions are what perpetuate influenza viruses. Zoonosis is the process by which infectious diseases, in this case influenza, are spread between different species. With influenza, the capacity for interspecies infection is highly dependent on the animals involved. For the sake of this examination, it is essential to understand the viral relationship between birds, swine and humans, the most common triad in the zoonotic transmission of influenza.³⁷ The most pertinent example of an atypical cross-infection occurs between avian and human influenza viruses. A difference in the virus's structure and bodily location was once thought to make transmission of influenza between human and avian species impossible; however, contemporary research has shown that such an event can transpire, though it is extremely rare and requires long-term, continual exposure to the identifiable strain. It is firmly believed today that the virus responsible for the 1918 influenza pandemic was a product of a direct transfer between birds and humans.³⁸

³⁵ Adolfo Garcia-Sastre, Russell Durbin, Hongyong Zheng, Peter Palese, Rachel Gertner, David Levy, and Joan Durbin, "The Role of Interferon in Influenza Virus Tissue Tropism." In: *Journal of Virology*, volume 72, number 11 (1998), pp. 8550-8558.

³⁶ John Nicholls, Anthony Bourne, Honglin Chen, Yi Guan, and JS Malik Peiris, "Sialic Acid Receptor Detection in the Human Respiratory Tract: Evidence for Widespread Distribution of Potential Binding Sites for Human and Avian Influenza Viruses." In: *Respiratory Research*, volume 8, number 73 (2007), pp. 1-10.

³⁷ Kennedy Shortridge, "Pandemic Influenza: A Zoonosis?" In: *Seminars in Respiratory Infections*, volume 7, number 1 (1992), pp. 11-25.

³⁸ Ann Reid and Jeffery Taubenberger, "The Origin of the 1918 Pandemic Influenza Virus: A Continuing Enigma." In: *Journal of General Virology*, volume 84 (2003), p. 2286.

More often, however, zoonosis employs an intermediary host to introduce novel viruses into a species' gene pool. Pigs most commonly provide an avenue for viral transfers between the incompatible avian reservoir of influenza and humans, as swine are biologically susceptible to infections from both species.³⁹ The transfer is made possible through the marvel of antigenic shift. Antigenic shift occurs when an intermediary host, such as a pig, is contaminated with two different types of the influenza virus; within this "mixing vessel", these two varieties of the virus can reassort to produce a novel strain of influenza with characteristics from both originals. Thus, when swine are exposed simultaneously to both an avian and human strain of the flu, this tendency for genetic reassortment, that is, antigenic shift, fabricates a virus capable of transcending multiple species.⁴⁰

When these reassorted viruses infect humans, they set off pandemic outbreaks as a result of their novelty. Human populations subjected to new strains boast little, if any, immunity. Immunity to influenza is something that is acquired through exposure. When an infection is detected, the body releases antibodies that correspond to the hemagglutinin and neuraminidase on specific strains of influenza. These antibodies build up over time and can endure for decades after an infection, consequently rendering a person partially resistant to that particular strain. As such, annual epidemics of influenza are on average quite mild, since people are generally exposed to recurrent varieties of the virus.⁴¹ However, following a rare episode of antigenic shift, no prior immunity exists to the novel strain and the malady quickly becomes disastrous among a highly vulnerable population. Such was the case in both the 1957 and 1968 influenza pandemics.⁴²

In addition to this practice of genetic reassortment, influenza viruses maintain their ability to both cause and further

³⁹ Christoph Scholtissek, "The Nucleoprotein as a Possible Major Factor in Determining Host Specificity of Influenza H3N2 Viruses." In: *Virology*, volume 147 (1985), pp. 278-294.

⁴⁰ Christoph Scholtissek, "Pandemic Influenza: Antigenic Shift." In: *Perspectives in Medical Virology*, volume 2 (2002), pp. 87-100.

⁴¹ Stuart Swell, *Immunology, Immunopathology and Immunity, Sixth Edition*. Washington DC: ASM Press, 2001, p. 184.

⁴² Reid and Taubenberger, "The Origin of the 1918 Pandemic Influenza Virus", p. 2287.

sustain massive outbreaks through a process known as genetic or antigenic drift. Many viruses, including influenza, have the capacity to constantly mutate, transforming their genetic makeup over time to keep pace with the mounting immunity of exposed populations. This ability is a product of evolution, as it ensures viruses can persevere in light of the adaptable human immune system. As viruses genetically mutate, humans begin to lose their acquired resistance to specific subtypes of influenza, thus perpetuating not only annual flare-ups, but pandemic outbreaks as well.⁴³ Genetic shift continually enhances the potency of influenza viruses, subjecting humans and their immune systems to a near constant challenge of fighting off these pathogens. Antigenic shift can develop gradually over time or occur so suddenly that huge populations are left unprotected. It is this propensity for genetic mutation that causes the multiple wave pattern evident in most pandemics. All three of the influenza pandemics evaluated in this thesis experienced several peaks throughout the course of each outbreak. In 1918, 1957 and 1968, an initial and less severe phase was always followed a few months later by a highly lethal and infectious strain of the virus before gradually subsiding.⁴⁴ The second phase in each of these episodes was a result of genetic shift; the virus adapted following preliminary contact, augmented its potency and eluded any previous resistance possessed by these populations.

When influenza mutates through either antigenic shift or drift, the change appears in both the structure and function of the hemagglutinin and neuraminidase proteins that identify particular strains of the virus. Influenza A viruses have thirteen hemagglutinin and nine neuraminidase subtypes, all of which combine to form different varieties of the flu. While nearly all of these are evident among avian species, humans are predisposed to only three forms of hemagglutinin and two types of neuraminidase.⁴⁵ Each protein is represented quite simply, hemagglutinin with an *H* and neuraminidase with an *N*, to

⁴³ Quinn, *A Social History of Influenza*, pp. 35-36.

⁴⁴ Jeffrey Ryan and Jan Glarum, "Defining the Response at the Local Level." In: *Pandemic Influenza: Emergency Planning and Community Preparedness* edited by Jeffrey Ryan, Boca Raton, Florida: CRC Press, 2009, p. 151.

⁴⁵ Yoshihiro Kawaoka, Scott Krauss, and Robert Webster, "Avian-to-Human Transmission of the PB1 Gene of Influenza A Viruses in the 1957 and 1968 Pandemics." In: *Journal of Virology*, volume 63, number 11 (1989), p. 4603.

describe the characteristics of different subtypes. It is from this that viruses acquire their designation; for instance, the 1918 virus was an H1N1, 1957 was an H2N2, and the pandemic of 1968 was caused by an H3N2. Each connotes the structure and behavior unique to each viral subtype. Phylogenetic analyses have shown that the 1918 H1N1 virus contracted directly from an avian source reassorted into the 1957 H2N2 virus cultivated in swine that further mutated into the H3N2 strain of 1968.⁴⁶ Phylogenetic analyses are used to scientifically determine the lineage of an influenza virus and the series of transformations it undergoes through genetic drift or shift. This method of research has revealed the evolution of the subtypes responsible for the three pandemics of the twentieth century and how each entered and further proliferated among human populations. Techniques such as phylogenetic analysis assist in understanding the nature of influenza viruses, an advantage in the detection of novel strains.⁴⁷

Throughout this past century, the World Health Organization has been the primary orchestrator in the global network of influenza detection and surveillance. The roots of this system emanated from the devastation of the First World War, with the establishment of the League of Nations Health Organization in 1920 to address global health issues. This organization transformed into the World Health Organization (WHO) under the direction of the United Nations following its inception in 1945.⁴⁸ When the WHO's constitution was signed in 1948, one of the many tasks it enacted was a worldwide network of influenza surveillance that has expanded greatly over the course of this past century. The continuously developing system is comprised of National Influenza Centers (NICs), today representing nearly every region of the world in more than one hundred countries. These institutions collect samples from patients with flu-like symptoms and report findings to WHO Collaborating Centers (CCs). CCs then use this data to perform phylogenetic analyses on collected specimens to assess the status

⁴⁶ Jeffrey K. Taubenberger and David M. Morens, "1918 Influenza: The Mother of All Pandemics." In: *Emerging Infectious Disease*, volume 12, number 1 (January 2006), pp. 15-22.

⁴⁷ Kanta Subbarao, David Swayne, and Christopher Olsen, "Epidemiology and Control of Human and Avian Influenza." In: *Influenza Virology: Current Topics* edited by Yoshihiro Kawaoka, Norfolk, England: Caister Academic Press, 2006, p. 235.

⁴⁸ Quinn, *A Social History of Influenza*, p. 153.

of influenza on a worldwide scale. It is through this process that imminent pandemics are potentially predicted.⁴⁹

The WHO is the institution that ultimately defines what constitutes an outbreak of pandemic proportions. The differentiation between an epidemic and pandemic infection is stated quite simplistically by the organization: “A disease epidemic occurs when there are more cases of that disease than normal. A pandemic is a worldwide epidemic of a disease.”⁵⁰ The WHO has traditionally characterized influenza pandemics in phases to better evaluate the severity of the situation, an approach that is modified every few years. The current system involves six key phases to portray the global status of influenza. If classified within the first three phases, few, if any, human infections have been identified, though an animal influenza virus may be in circulation. Phase four transitions into a more serious stage in which the virus is not only evident in humans, but human-to-human transmissions have been observed on a very localized level. Phase five is the expansion of this infection to at least two countries in one of the six global regions in the WHO network. It is this stage that implies a pandemic is forthcoming. Phase six is described as the “pandemic phase”; it is at minimum representative of an influenza outbreak in at least one other country in a different region of the world.⁵¹

As shown in this system, much of what defines a pandemic is geography. It is an outbreak that transcends multiple regions of the world. Furthermore, high morbidity, that is, the prevalence of the illness within a population, is essential in characterizing a malady of global scope. High mortality, however, is not a key variable in determining a pandemic, though it is often mistaken as an indicator. While pandemics can be fatal, as demonstrated at its most extreme in 1918, a large death rate is not a necessity.

⁴⁹ “WHO Global Surveillance Network.” *World Health Organization*, 2010. Accessed 15 June 2010, <<http://www.who.int/csr/disease/influenza/surveillance/en/index.html>>.

⁵⁰ “Pandemic Preparedness.” *World Health Organization*, 2010. Accessed 15 June 2010, <<http://www.who.int/csr/disease/influenza/pandemic/en/index.html>>.

⁵¹ “Current WHO Phase of Pandemic Alert for Avian Influenza.” *World Health Organization*, 2010. Accessed 15 June 2010, <http://www.who.int/csr/disease/avian_influenza/phase/en/>; “WHO Consultation on Priority Public Health Interventions Before and During an Influenza Pandemic.” *Department of Communicable Disease and Response, of the World Health Organization*, Geneva, Switzerland, 16-18 March 2004. Accessed 15 June 2010, <http://www.who.int/csr/disease/avian_influenza/final.pdf>.

Mortality can actually contradict the objective of a pandemic, widespread infection, by killing off people too quickly before the disease can be transmitted.⁵²

Accordingly, transmissibility is of the utmost importance in the propagation of a global outbreak. Influenza is a natural candidate, as it is an exceedingly contagious illness. The flu is spread by droplet infection. When an infected person coughs or sneezes, tens of thousands of microscopic droplets are sprayed into the air. These droplets can either infect a person directly by landing on a susceptible bodily surface, such as an open mouth or wound, or indirectly by contaminating an object, such as a door handle, before spreading the virus upon contact. Thus, little effort is required to contract influenza. Closed quarters and frequent human contact can easily infect a large group of people.⁵³

Because the flu is highly contagious, a global system of influenza surveillance, such as that implemented by the WHO, proves beneficial to the prevention and containment of outbreaks. When a potential pandemic is detected, the NICs and CCs mentioned previously use their acquired data to respond to the infection. Even so, the system is not perfect.⁵⁴ Vaccines are developed based on annual research, though the process is both lengthy and speculative. Much of the vaccine production associated with influenza is merely a prediction of what strain is most likely to arise the following season.⁵⁵ If vaccines are not created until a pandemic is already underway, the response is often too late and has a reduced effect on assuaging the impact, as happened in both 1957 and 1968. It is very difficult to treat influenza. As a viral malady, antibiotics have no curative effect. The few medications that exist today to alleviate influenza are neuraminidase inhibitors, impeding the virus's process of replication. Nevertheless, these medications are limited in

⁵² Quinn, *A Social History of Influenza*, pp. 24-25.

⁵³ Alan Sipress, *The Fatal Strain*. New York: Viking, 2009, pp. 50-51.

⁵⁴ V.N. Milouchine, "The Role of WHO in International Studies on the Ecology of Influenza in Animals." In: *Comparative Immunology, Microbiology, and Infectious Diseases*, volume 3, issues 1 and 2 (1980), pp. 25-31; "World Health Organization, 50 Years of Influenza Surveillance: A Challenge for the 21st Century Meeting 17-19 February 1999, WHO, Geneva." In: *Vaccine*, volume 20 (2002), pp. 1-4.

⁵⁵ Ai Ling, Alan Hampsen, Lance Jennings, and John Tam, "Seasonality and Influenza Virus Strains in the Asia-Pacific Region." In: *International Congress Series*, volume 1263 (2004), pp. 426-429.

quantity, expensive and cannot be administered until an infection is already evident.⁵⁶ Thus, vaccines are the most favorable method of fighting influenza outbreaks on a large scale. Vaccines work by introducing a small amount of an influenza strain, the one predicted to be the most troublesome in the next season, to a host; the host then builds up the necessary antibodies to fight the infection, making them resistant once the virus appears at full force. This, of course, is only effective if the predicted strain is the one that actually materializes.⁵⁷

The intricacies of influenza pandemics only add to the enormity of these events when they occur. Not only are pandemics overwhelming on multiple fronts, their mystery can incite a fear that exacerbates the whole situation. Just over a hundred years ago, much of the aforementioned material was unknown. The twentieth century was by far the most pivotal era for influenza discovery and research. Consequently, the three pandemics that occurred in 1918, 1957 and 1968 were undoubtedly the most accurate ever to be observed. Furthermore, they were enormously influential in shaping what is known today about this illness, a field of research that is still developing regularly. Though this definitions chapter has only skimmed the surface of the complexities associated with influenza, it will hopefully provide enough of a background to appreciate the following glimpse into the origins and nature of the three major influenza pandemics of the twentieth century.

⁵⁶ Quinn, *A Social History of Influenza*, p. 181.

⁵⁷ Mary Ellen Kitler, Pilar Gavino, and Daniel Lavanchy, "Influenza and the Work of the World Health Organization." In: *Vaccine*, volume 20 (2002), pp. 9-10.

3. The Influenza Pandemic of 1918

In the year 1918, humanity was engrossed in the shattering events of the First World War; however, a submicroscopic conflict was brewing that would prove far more lethal than the hostility of combat. The deadliest influenza pandemic in history swept across the globe at an alarming pace in the winter of 1918-1919, crippling the health and morale of a world already ravaged by warfare. The timing of this virulent outbreak has forever enmeshed the pandemic in the events of the First World War, so much so history has habitually diminished the enormity of this pestilence to a mere episode of the conflict. Specific facets of the outbreak, ranging from its common title to worldwide dissemination, have been distorted and ultimately defined by the tactical protocol of wartime. However, while the First World War undeniably shaped the nature and understanding of the outbreak, the influenza pandemic of 1918 was an incident unto itself.

The influenza of 1918 struck in three waves, first in early spring of that year and then with unimaginable intensity throughout the following winter. In April and May of 1918, infection was reported in the United States, Great Britain, Germany, Italy, and Spain. During the summer months, cases cropped up in North Africa, China, New Zealand and the Philippines before the illness began to momentarily lull.⁵⁸ While a high percentage of these populations were affected, the nature of the virus during this initial bout was comparably unexceptional and death rates were on par with seasonal outbreaks, thus signifying no imminent danger.⁵⁹ This composure was quickly dispelled. The infamous second wave developed into a far more alarming situation, devastating the global population between September and November of 1918. When weighed against the first phase of the 1918 outbreak, the second wave was exceedingly more contagious with a 10-fold increase in the death rate.⁶⁰ Medically, it was unlike anything the world had ever seen.

The first victims of the illness demonstrated typical flu-like symptoms: achiness, fatigue, and lack of appetite accompanied by a

⁵⁸ Potter, "A History of Influenza", p. 575.

⁵⁹ Taubenberger and Morens, "The Mother of All Pandemics", p. 17.

⁶⁰ Potter, "A History of Influenza", p. 576.

high temperature, cough and nasal congestion.⁶¹ However, by the peak of the second phase in the fall of 1918, these symptoms had not simply worsened, but had manifested into nightmarish extremes: patients were cyanic -some so severely, their extremities appeared black- literally drowning within from fluid-filled lungs; those suffering were bedridden with persistent headaches and coughs, inflamed eyes, noses and throats, soaring temperatures, and overwhelming exhaustion. Even so, the most disturbing symptom was the hemorrhaging, with blood flowing liberally from both the nose and ears during the worst stage of the illness, the point at which the upper internal body cavity had more or less liquefied; doctors at the time recorded “that the only comparable damage they had seen in lungs was caused by deadly mustard gas used in the trenches during war.”⁶² Time until death ranged from a few hours to a few days, and those aged twenty to forty, conventionally the healthiest social demographic, were the likely targets. As Gina Kolata writes in her book *Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus that Caused It*: “The death curves were W-shaped, with peaks for the babies and toddlers under age 5, the elderly who were aged 70 to 74, and people aged 20 to 40.”⁶³ During a pandemic described as being of “biblical proportions”, it was frightening for those involved to witness the most able-bodied of society fall prey, for it implied everyone was susceptible to what was a seemingly unstoppable force.

This facet of the pandemic, the age and vigor of its primary victims, was the most impacting both psychologically and socially. An excerpt in Pete Davies’s book *The Devil’s Flu: The Deadliest Influenza Epidemic and the Scientific Hunt for the Virus that Caused It* truly captures the collective turmoil of the period:

“The hospitals were so choked that it was impossible to move the dead quickly enough to make room for the dying. The streets and lanes of the cities were littered with corpses. The postal and telegraph systems were completely disorganized. The train service continued, but at all principal

⁶¹ Quinn, *A Social History of Influenza*, p. 125.

⁶² Ibid., p. 133.

⁶³ Kolata, *Flu*, p. 5.

stations the dead and dying were removed from the trains...the Medical Service, itself severely stricken with the epidemic, was incapable of dealing with more than a tiny fraction of the cases. Almost every household was lamenting a death. Terror and confusion reigned everywhere.”⁶⁴

The intense second wave of the pandemic slowed by December of 1918. A third fatal, though more isolated, wave occurred during the first months of 1919 and was followed by trailing reports of influenza cases until the illness finally subsided by the end of the year, disappearing almost as quickly as it had emerged.⁶⁵ The impression left by the raging pandemic was deep. To use but one example from the United States, the life expectancy of an American in the year 1917 was roughly fifty-one years old according to that year’s almanac; the following year, the year of the great pandemic, the life expectancy had dropped to thirty-nine years old, before jumping again to a half century in 1919.⁶⁶ Leading scholars and scientists have proposed anywhere from twenty million to more than one hundred million influenza-related deaths occurred between 1918 and 1919, far exceeding the estimated sixteen million lives lost in the First World War.⁶⁷ Moreover, the origin of this highly lethal pestilence that devastated the global population in 1918-1919 has become one of the twentieth century’s most elusive enigmas, one that even today remains highly contentious and speculative in nature.

The pandemic of 1918 became known as the “Spanish Influenza” and many, both then and now, mistakenly associate the origin of the outbreak with this European country. As Tom Quinn notes in his analysis entitled *Flu: A Social History of Influenza*, this

⁶⁴ Pete Davies, *The Devil’s Flu: The World’s Deadliest Influenza Epidemic and the Scientific Hunt for the Virus That Caused It*. New York: Henry Holt and Company, LLC., 2000, p. 47.

⁶⁵ Taubenberger and Morens, “The Mother of All Pandemics”, p. 17.

⁶⁶ Kolata, *Flu*, p. 8

⁶⁷ Peter Simkins, *The First World War: The Western Front 1914-1916*. New York: Routledge, 2002, p. 89.

misleading designation is largely a consequence of defensive wartime etiquette:

“The fact that the pandemic of 1918-1919 was called the ‘Spanish’ flu at all is a reflection of the political situation of the time and has absolutely no foundation in the real origins of the disease. With the censorship of the press of combatant nations across war-torn Europe, the only country that publicly mentioned the new disease was neutral Spain. Because this new virulent kind of flu was first mentioned in Spain it was seen -quite wrongly- as having originated there.”⁶⁸

Thus, Spain’s unrestricted publications and broadcasts concerning the pandemic in its early stages eternally linked the country to the inception of this virulent pestilence. Even so, it is now known that the mysterious disease had actually surfaced months, potentially even years before its first public recognition. Under the guise of national security, most documentation of the illness in its initial phase was largely disjointed and concealed, leaving a segregated and complex trail to the actual place and time of origin. As Gina Kolata indicates in her book *Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus that Caused It*:

“There were no requirements in those days to report cases of influenza- that became a practice in the United States only after, and as a consequence of, the second wave of the 1918 flu. And there was no reason in those days of war to keep track of what seemed like a minor illness. Reports on the flu’s reaches were sporadic, reflecting mostly the practices of organizations such as prisons, the military, and some industries, which simply recorded

⁶⁸ Quinn, *A Social History of Influenza*, p. 125.

absentees. There was no systematic attempt to track an epidemic.”⁶⁹

As such, the source of the 1918 influenza is currently among the most controversial components of the pandemic, one that has fostered arduous research and deliberation by contemporary scientists and historians alike.

Accurate assessment regarding the origins of the 1918 influenza pandemic has not simply been clouded by the First World War, but has been further complicated by the lack of medical knowledge and technology available at the dawn of the twentieth century. While medicine had advanced tremendously in the few decades directly preceding the outbreak, viruses and more specifically their connection to influenza was purely theoretical and frequently disputed. The concept of viral entities had come to the fore only twenty years before the 1918 pandemic when the two scientists Ivanovski and Beijerinck were investigating diseased tobacco plants and discovered an agent that passed freely through filters used to isolate bacteria.⁷⁰ Nearly half a century passed before the theoretical work by Ivanovski and Beijerinck on viruses was scientifically validated following the identification and isolation of both swine and human strains of the influenza virus in the 1930s.⁷¹ Even then, information about the fundamental building blocks of viral influenza remained limited until the discovery of genetic material in the 1950s.⁷² Thus, those who endured the 1918 influenza pandemic struggled with great difficulty to grasp the true cause of the illness.

The 1918 pandemic had been called the “three-day fever” in the beginning and was eventually linked to *Bacillus influenzae*, also known as “Pfeiffer’s bacillus”, a bacterium discovered by the German physician Richard Pfeiffer after an earlier bout with the flu.⁷³ However, this notion was quickly nullified, as autopsies revealed few victims were infected with this bacterium. The non-filterable pathogen again became a mystery and in the search for an answer, a fury of preposterous explanations ensued:

“It was blamed on mists rising from
Flanders fields disturbed by millions

⁶⁹ Kolata, *Flu*, p. 10.

⁷⁰ Oldstone, *Viruses, Plagues and History*, pp. 15-16.

⁷¹ Reid and Taubenberger, “The Origin of the 1918 Pandemic Influenza Virus”, p. 2290.

⁷² Kolata, *Flu*, p. 71.

⁷³ Barry, *The Great Influenza*, p. 261.

of exploding shells; in Italy silk-worms were seen as the carriers of the disease; elsewhere bedbugs were blamed, or chewing gum, or the position of the planets. Some British doctors blamed the wind; an American astrologer blamed the position of Jupiter.”⁷⁴

Such conjecture permeates the unsystematic documentation of the 1918 influenza pandemic. This facet of the outbreak portrays one of the greatest difficulties in analyzing this event in hindsight; the variety of interpretations regarding the origins of the disease makes retrospectively classifying actual cases and their routes of transmission a grueling and ambiguous task for modern-day scholars.

In consequence, a variety of hypotheses exist today concerning the origin and worldwide diffusion of the 1918 influenza pandemic. As more conclusive evidence has been unearthed through persistent research and technological advancement, the essence of the 1918 pandemic should have expectantly become clearer; conversely, these revelations have only invigorated the preexisting debate. Areas of the United States, France and even Sierra Leone have all been key contenders for the source of the 1918 outbreak, though more recently southern China has gained notoriety as the leading culprit. While each school of thought is persuasive in its own right, it is both personal opinion as well as growing consensus among scientists that the pandemic of 1918-1919 boasts Chinese origins.

During the great influenza pandemic of 1918, the disease was unjustly presumed to have originated in Spain.⁷⁵ At the time, little attention was dedicated to tracing the actual source of the illness, as treatment and containment were the immediate priorities.⁷⁶ Record keeping, even in places renowned for dependable data under normal conditions, received even less consideration, as the accelerated pace

⁷⁴ Quinn, *A Social History of Influenza*, p. 140.

⁷⁵ Howard Phillips and David Killingray, *The Spanish Influenza Pandemic of 1918-1919: New Perspectives*. London: Routledge, 2003, p. 7.

⁷⁶ Alfred Crosby, *America's Forgotten Pandemic: The Influenza of 1918*. Cambridge, England: Cambridge University Press, 1989, p. 10.

and nature of the outbreak overwhelmed medical services. As such, the first attempt to quantify the 1918 influenza pandemic occurred nearly a decade after the event in 1927. A study sponsored by the American Medical Association aimed to calculate a more comprehensive death toll of the pandemic to better assess its epidemiological qualities.⁷⁷ Because documentation had been most consistent in the United States and Europe, largely a consequence of the war, the initial evidence associated these regions with the source of the outbreak. Accordingly, subsequent research concentrated on the United States and Europe, particularly France, as the pandemic's starting place. This evidence has more or less persisted throughout the last century and has influenced those today who affirm the United States, France or both housed the origins of the 1918 pandemic.

In 1927, Edwin Jordan was one of the first to contemplate the source of the 1918 influenza pandemic. His work chronicled outbreaks in various places around the globe, including France and China, before the scholar settled on the United States as the likely point of inception. Essentially, Jordan's conclusion was derived through process of elimination; he discounted his range of potential sources as merely isolated bouts of endemic influenza leaving only the United States, with its episode of early spring outbreaks, as the frontrunner in the plight for causality.⁷⁸ Expanding on Jordan's groundbreaking work, one of the leading theories at present avowing to the 1918 pandemic's American origins has been proposed by John M. Barry in his book *The Great Influenza: the Story of the Deadliest Pandemic in History*. Barry suggests that the influenza virus acquired its virulent characteristics early in 1918 in a small cantonment located in Haskell County, Kansas. Subsequently, the author claims:

“this virus traveled east across the state to a huge army base, and from there to Europe. Later it began its sweep through North America, through Europe, through South America, through Asia and Africa,

⁷⁷ Barry, *The Great Influenza*, p. 396.

⁷⁸ Edwin Jordan, *Epidemic Influenza: A Survey*. Chicago: American Medical Association, 1927.

through isolated islands in the Pacific,
through all the wide world.”⁷⁹

According to this argument, the pandemic followed the path of American troops, first from the Midwest to the Eastern Seaboard of the United States before crossing the Atlantic to Europe with the invasion of France.

The work of other scholars, such as Charles Potter and Alfred Crosby, corroborates Barry’s general assertion, though deviates slightly when detailing the spread of the infection. Potter similarly claims the outbreak began in the United States, insisting the massive mobilization of American troops deployed to military bases in Europe, particularly those in Bordeaux, France, carried the virus across the Atlantic. By April and May of 1918, the infection had reached Great Britain, Germany, Italy, and of course, Spain. During the summer months, Potter indicates that cases cropped up in North Africa, China, New Zealand, and the Philippines, initiating the pandemic phase of the 1918 influenza virus in late spring of that year.⁸⁰ Crosby too recognizes the United States as the commencement site of the pestilence, acknowledging both San Quentin prison in California and Camp Funston in Kansas as potential sources of the widespread infection that began in March of 1918. Even so, Crosby admits that the outbreak could have easily begun elsewhere and/or earlier; records from institutions and organizations, such as prisons or those affiliated with the military, unjustly painted the only clear picture of the contagion’s alleged origins, as these places “had complete jurisdiction over their members and had to take care of them when they got sick.”⁸¹

Crosby further claims the pandemic of 1918 did not acquire its highly virulent attributes until August of that year, months after the initial flare-ups recorded in American prisons and military bases. In his book entitled *America’s Forgotten Pandemic: the Influenza of 1918*, Crosby observes in detail the “three explosions” that occurred in Africa, Europe and America almost simultaneously in late August of 1918. The historian notes that while the spring phase of the infection likely began in the United States, it was a mutated strain of this virus that had manifested throughout the summer months that triggered the most legitimately pandemic phase of the entire ordeal; this strain,

⁷⁹ Barry, *The Great Influenza*, p. 92.

⁸⁰ Potter, “A History of Influenza”, pp. 575-76.

⁸¹ Crosby, *America’s Forgotten Pandemic*, p. 19.

according to Crosby, emerged in the sea ports of Boston, Brest and Freetown.

As per Crosby, a British ship traveling to Sierra Leone was the first to fall victim to the more lethal form of the virus, quickly spreading among those on board and in port. The author claims that by passing through the relatively unexposed and thus unresistant immune systems of the Africans, the influenza virus mutated and in doing so, secured an advantage even over those with some acquired resiliency from earlier contact, hence erupting into pandemic proportions. A week after disembarkation in Freetown on August 24, physician reports already revealed a high number displaying flu-like symptoms.⁸² Africa became widely infected, as did many in East and Southeast Asia connected to this trading center. A simultaneous upsurge in Brest, France, a hub for wartime activity, quickly overwhelmed all of continental Europe. Transit across the Atlantic from Europe extended the transformed pestilence to the United States, first involving Boston, the chief point of departure for men and supplies destined for the Western Front, before disseminating throughout most of North America. In a mere two months, the pandemic became a global affair, reaching from the Alaskan wilderness to remote islands in the Pacific.

Crosby's examination seemingly implies multiple points of origin for the 1918 influenza virus, depending on both how and when one defines a pandemic's beginning. Barry and Potter's assessments concentrate on the early months of 1918 as the start of the outbreak, using evidence from flare-ups in the United States and the contagion's subsequent spread to Europe. Crosby also acknowledges these outbreaks, but focuses more so on later eruptions beginning in late summer of 1918 as the first to have qualities of a truly global and virulent pandemic. If one determines the start of a pandemic based on the appearance of atypical qualities in comparison to seasonal outbreaks, such as extreme transmissibility or morbidity, Crosby's "three explosions" hypothesis is more accurate. However, if one aligns the pandemic's origin with the first appearance of the specific influenza virus at fault, as Barry and Potter attempt to do, then all three previously mentioned scholars are incorrect, especially when weighed against work like that of John Oxford.

⁸² Ibid., p. 37.

Conventional thought often situates the start of the 1918 influenza pandemic in the early months of that same year. However, recent research by Oxford and his colleagues has offered a radical alternative. Oxford proposes the influenza virus that caused the 1918 pandemic actually surfaced during a “herald wave” in the winter of 1916-1917 in France. While “herald wave” typically describes late seasonal outbreaks of flu used to predict trends in the following year, Oxford applies the term for the first time to the analysis of an emerging pandemic.⁸³ The sudden and seemingly simultaneous appearance around the world of the lethal influenza in late summer of 1918, as described in Crosby’s thesis, implies the virus had both spread and “seeded” itself much earlier. Oxford claims this “seeding” occurred in army bases in northern France.⁸⁴ Military encampments in this region provided ideal settings for the emergence of an infectious influenza virus, as they were extremely overcrowded, unhygienic and located in close proximity to livestock.⁸⁵ Records from a British army base outside of Etaples, France, from late December of 1916 affirmed this notion with descriptions of a new and acutely contagious respiratory infection characterized by heliotrope cyanosis and high mortality, distinctive symptoms of the 1918 influenza.⁸⁶ Additional descriptions that surfaced in French and British military bases in March of 1917 emulated the literature of the 1918 infection, so much so that a group of British doctors in 1919 reflected on the astonishing similarity:

“We emphasise our view that in essentials the influenza pneumococcal purulent bronchitis that we and others described in 1916 and 1917 is fundamentally the same condition as

⁸³ J.S. Oxford, A. Sefton, R. Jackson, W. Innes, R.S. Daniels, and N.P.A.S. Johnson, “Early Herald Wave Outbreaks of Influenza in 1916 Prior to the Pandemic of 1918.” In: *International Congress Series*, volume 1291 (2001), p. 159; W. Paul Glezen, Robert Couch, and Howard Six, “The Influenza Herald Wave.” In: *American Journal of Epidemiology*, volume 116 (1982), pp. 589–598.

⁸⁴ Oxford, et al., “Early Herald Wave Outbreaks of Influenza”, p. 156.

⁸⁵ J.S. Oxford, R. Lambkin, A. Sefton, R. Daniels, A. Elliot, R. Brown, and D. Gill, “A Hypothesis: the Conjunction of Soldiers, Gas, Pigs, Ducks, Geese, and Horses in Northern France during the Great War Provided the Conditions for the Emergence of the ‘Spanish’ Influenza Pandemic of 1918-1919.” In: *Vaccine*, volume 23 (2005), p. 942.

⁸⁶ Ibid.

the influenza pneumonia of this
present 1918 pandemic.”⁸⁷

In summation, Oxford too suggests this to be the birth of the outbreak that emerged at full force in 1918. He attributes the two year delay between the winter of 1916-1917 and 1918 to the absence of air travel and travel restrictions enforced during wartime. Ultimately, it was the demobilization of troops and their return home to various parts of the globe in the fall of 1918 that caused the pandemic to advance so abruptly.⁸⁸

However, while Oxford’s theory is credible, his work overlooks an essential feature during this interval of the First World War. In the winter of 1916-1917, the very period Oxford marks as the beginning of the great influenza pandemic, groups of Chinese laborers poured into France. During the First World War, both the French and British militaries relied on China for assistance behind the frontlines, recruiting in total a workforce of more than 140,000 known as the Chinese Labor Corps.⁸⁹ China’s engagement in the First World War stemmed from the country’s revolutionary movement toward nationalism during this period, one characterized by “a growing desire to join the world, become a modern nation-state, and a strong and powerful country.”⁹⁰ The notion for China to join the Allied forces began circulating as early as 1915 with the initiation of the “laborers as soldiers” scheme and was eventually enacted in July of 1916 with a mass recruitment by the French: “In July 1916, 5,022 coolies were shipped to France [by the French] ... for service with the French Labour Corps.”⁹¹ The British began employing Chinese laborers at the start of 1917, with the first batch arriving from southern China to their French-based military encampments in February of that year.⁹² Soon after in early spring of

⁸⁷ Eugene Opie, Francis Blake, James Small, and Thomas Rivers, “Epidemic Respiratory Disease: The Pneumonias and Other Infections of the Respiratory Tract Accompanying Influenza and Measles.” In: *Journal of the American Medical Association*, volume 76, number 23 (June 1921), pp. 1598-1599.

⁸⁸ Oxford, et al., “Early Herald Wave Outbreaks of Influenza.”

⁸⁹ Christopher Langford, “Did the 1918-1919 Influenza Pandemic Originate in China?” In: *Population and Development Review*, volume 31, number 3 (2005), p. 488.

⁹⁰ Xu Guoqi, *China and the Great War: China’s Pursuit of a New National Identity and Internationalization*. Cambridge, England: Cambridge University Press, 2005, p. 12.

⁹¹ Langford, “Did the 1918-1919 Influenza Pandemic Originate in China?”, p. 489; Guoqi, *China and the Great War*, p. 13.

⁹² Langford, “Did the 1918-1919 Influenza Pandemic Originate in China?”, p. 489.

1917, the American forces in France also began utilizing Chinese manpower. However, the American military never recruited directly from China, but instead benefited from the use of more than 10,000 Chinese workers drafted by the French.⁹³

The Chinese recruits took a variety of routes to France, all of which encircled the globe. Some ventured west from China, sailing through the Suez Canal or around the Cape of Good Hope before arriving in Marseilles; others traveled first to England and then crossed the Channel to France. Groups of Chinese laborers also voyaged east across the Pacific, stopping first in Japan before sailing to Vancouver, Canada. From Vancouver, workers would take a train to either Halifax or New York and then sail across the Atlantic to England or directly to France. While the duration of the trips fluctuated greatly, all involved multiple points of disembarkation around the world.⁹⁴

Recruitments to France by both the French and the British generally came from China's southern province of Guangdong or from Hong Kong, a fact substantiated by the prominent Cantonese dialect of the Chinese laborers.⁹⁵ Various records indicate a large group of these workers from southern China assembled around camps in Montreuil, France, in the winter of 1916-1917.⁹⁶ Notably, Montreuil is located roughly ten kilometers from Etaples, France, the same vicinity of the military base where Oxford identified the first major outbreak of a 1918-like influenza.⁹⁷ The notion that the influenza virus had been "seeded" prior to the 1918 pandemic is further corroborated by the extensive course taken by Chinese recruits to France and their personal association with French, British and American troops, potentially spreading the influenza virus both directly and indirectly over multiple continents in the process and establishing a basis for the simultaneous eruptions of the infection that occurred in the winter of 1918 in America, Europe and Africa.⁹⁸ The timing, proximity and origin of the enlisted Chinese workers cannot simply be coincidence; it seems only appropriate to connect

⁹³ Guoqi, *China and the Great War*, p. 136.

⁹⁴ Langford, "Did the 1918-1919 Influenza Pandemic Originate in China?", p. 490.

⁹⁵ Ibid., p. 18; Kennedy Shortridge, "The 1918 'Spanish' Flu: Pearls from Swine?" In: *Nature Medicine*, volume 5, number 4 (April 1999), p. 385.

⁹⁶ L. MacDonald, *Somme*. London: Macmillan Publishers Ltd., 1984, pp. 189-193.

⁹⁷ Oxford, et al., "The Conjunction of Soldiers, Gas, Pigs, Ducks, Geese and Horses", p. 942.

⁹⁸ Crosby, *America's Forgotten Pandemic*, p. 37.

the presence of the Chinese Labor Corps in and around British and French military bases in northern France in the winter of 1916-1917 to the onset of the great influenza pandemic of 1918.

Nevertheless, evidence supporting a Chinese origin of the influenza virus that caused the 1918 pandemic extends far beyond the incidental arrival of the Chinese Labor Corps in France in 1916. The relatively mundane impact of the 1918 influenza both in China and among the Chinese workers sent abroad implies an acquired immunity within these populations from early exposure to the virus.⁹⁹ Influenza was indeed widespread in China as elsewhere during the 1918-1919 pandemic. While records from China are relatively sparse and were mostly contrived by medical missionaries in the country during the time of the pandemic, trade reports have provided the most solid evidence reflecting the geographic scope of the infection in the country.¹⁰⁰ Of the 45 trading centers in China in 1918, 26 reported bouts of influenza among their workers. These trade junctions reached from the far northeast of China down the length of its eastern coastline to Guangdong and extended as far inland as Sichuan province. It is known today that the virus disseminated throughout China from the southern ports of Guangzhou and Shanghai.¹⁰¹ The vast region illustrated by these reports indicates the 1918 influenza was rampant in China as well during the pandemic.

However, while the virus manifested extensively throughout China, its severity was both extremely mild and far less fatal in comparison to other countries around the world in 1918-1919.¹⁰² Mortality, especially in the southern province of Guangdong, was relatively low when weighed against figures from both Europe and the United States.¹⁰³ Ironically, this detail was what encouraged Edwin Jordan to wrongfully dismiss China as the point of origin for the pandemic, maintaining low mortality indicated the outbreak was merely an endemic influenza when in fact it illustrated long-term

⁹⁹ Shortridge, "Pearl from Swine?", p. 385.

¹⁰⁰ K.F. Cheng and P.C. Leung, "What Happened in China during the 1918 Influenza Pandemic?" In: *International Journal of Infectious Diseases*, volume 11 (2007), p. 361.

¹⁰¹ Ibid., p. 362.

¹⁰² Langford, "Did the 1918-1919 Influenza Pandemic Originate in China?", pp. 490-491.

¹⁰³ Cheng and Leung, "What Happened in China during the 1918 Influenza Pandemic?", p. 361.

exposure.¹⁰⁴ A similar counter-theory proposed that the less lethal influenza virus in China in 1918 may have been different to the one affecting Europe and the United States during this time.¹⁰⁵ However, not only did the virus appear simultaneously in these regions, it also exhibited corresponding symptoms. As a medical missionary in Shanghai wrote in 1919:

“At the end of May influenza started and lasted until June. In October to November the influenza reoccurred with more serious symptoms. Earlier, most of the patients had headache, extreme fatigue, sore throat and fever; these symptoms lasted 4 to 5 days. Erythema was found on the necks and the patients were usually misdiagnosed as scarlet fever. But from September onwards the pattern of the illness was changed suddenly; the number of influenza patients was sharply increased, often with serious symptoms. Some patients were complicated with bronchitis, pneumonia, and even hemolysis. However the death toll still remained low.”¹⁰⁶

The account mirrors those found in countries around the world, with a single exception: mortality remained low. Moreover, this phenomenon was not unique to native Chinese populations, but included foreigners in China as well. This implies the Chinese were not genetically resistant to the 1918 influenza and that immunity was instead obtained by those in China, both native and foreign, through early exposure to the virus’s native environment.¹⁰⁷

According to Kennedy Shortridge, those residing in southern China may have been infected by the 1918 viral precursor as early as

¹⁰⁴ Edwin Jordan, *Epidemic Influenza: A Survey*.

¹⁰⁵ Langford, “Did the 1918-1919 Influenza Pandemic Originate in China?”, p. 491.

¹⁰⁶ Cheng and Leung, “What Happened in China during the 1918 Influenza Pandemic?”, p. 361.

¹⁰⁷ Langford, “Did the 1918-1919 Influenza Pandemic Originate in China?”, p. 491.

1915.¹⁰⁸ His assertion is based on the work of Ann Reid, Jeffery Taubenberger and a host of their colleagues who assisted in isolating the virus responsible for the 1918 influenza pandemic. For more than a decade, Reid, Taubenberger and a team of other scientists searched for the viral origins of the 1918 pandemic using preserved tissue samples from a handful of victims.¹⁰⁹ In 2005, nearly ninety years after the pandemic, Taubenberger published the definitive paper on their collective discovery of the H1N1 virus that ravaged the world in 1918.¹¹⁰ Phylogenetic analyses of the 1918 H1N1 virus showed both the hemagglutinin and neuraminidase of this particular subtype likely emerged from an avian-like reservoir just before the peak of the pandemic.¹¹¹ All eight genes of the 1918 H1N1 virus exhibit a strong correlation with avian influenza, implying an avian virus directly infected humans and adapted to them over time to increase person-to-person transmissibility.¹¹² Thus, while Shortridge claims the influenza responsible for the 1918 outbreak was first introduced to humans in 1915, he further acknowledges the probability the virus transformed gradually over a fifty-year period prior to that from a purely avian strain to one capable of infecting humans.¹¹³ This process, according to Shortridge, transpired in southern China.

Southern China is renowned as being an influenza epicenter, with the first recorded modern influenza epidemic originating there in 1889. Shortridge avows this preliminary outbreak in 1889 of an H2-like virus was actually an adaptation of a preexisting H1-like virus in circulation in this region. An H1-like virus propagated again between 1907 and 1917 in southern China and intermingled with both H2 and H3-like viruses, expediting transformation into the lethal H1N1 version to blame for the 1918 pandemic.¹¹⁴ Thus, when

¹⁰⁸ Shortridge, "Pearls before Swine?", p. 384.

¹⁰⁹ Kolata, *Flu*, p. 192.

¹¹⁰ Jeffrey Taubenberger, Ann Reid, Raina Lourens, Ruixue Wang, Guozhong Jin, and Thomas Fanning, "Characterization of the 1918 Influenza Virus Polymerase Genes." In: *Nature*, volume 437 (6 October 2005), pp. 889-893.

¹¹¹ Jeffery Taubenberger, "The Origin and Virulence of the 1918 'Spanish' Influenza Virus." In: *Proceedings of the American Philosophical Society*, volume 150, number 1 (2005), p. 95.

¹¹² Robert Belshe, "The Origins of Pandemic Influenza: Lessons from the 1918 Virus." In: *New England Journal of Medicine*, volume 353, number 21 (2005), p. 2209.

¹¹³ Kolata, *Flu*, p. 296.

¹¹⁴ Shortridge, "Pearls before Swine?", p. 385.

the virus finally manifested into the deadly pestilence characteristic of the 1918 outbreak, those in southern China had presumably been in direct contact with H1-like strains for nearly half a century. Perpetual exposure to the virus fortified the immune systems of those living in southern China during the 1918 pandemic, as evidenced in the unusually low mortality rate in this country relative to those affected around the world.

Thus, both the scientific and historical information known today about the 1918 influenza pandemic firmly imply the virus originated in southern China years before its worldwide dispersal. The virus was likely transported by Chinese laborers during the First World War, embedding the infection in various locales around the globe en route to Europe. When introduced into populations with little or no prior exposure to the H1N1 strain, the influenza thrived on the vulnerability of their defenseless immune systems, mutating into the fatal killer that so epitomized the 1918 outbreak. As Oxford correctly identifies, this mutated form first appeared in the winter of 1916-1917 in British and French military encampments near Etaples, France. The influenza progressed further in early spring of 1918, as both Barry and Potter reinforce, with serious bouts of influenza materializing in military camps and prisons throughout the United States. By the winter of 1918, the virus that had incubated for years in southern China assumed a newfound virulence, emerging simultaneously in Europe, Africa and America, as noted by Crosby, before subjecting the rest of the world to this pandemic.

Despite such compelling data, the origins of the 1918 influenza remain controversial, as not everyone is fully convinced by the aforementioned explanation.¹¹⁵ The majority of knowledge we have today about the 1918 pandemic has only been unearthed within the last two decades and a great deal of this is circumstantial. However, in agreement with the growing consensus, it seems most probable based on the available evidence that the influenza virus responsible for the 1918 pandemic indeed originated in southern China before expanding globally. While the peak of this outbreak occurred in the winter of 1918-1919, the impact of the pandemic endured for years to come. Jeffery Taubenberger has deemed the 1918 outbreak “the mother of all pandemics” and it certainly is so for multiple reasons.¹¹⁶ The social implications were undeniably

¹¹⁵ Kolata, *Flu*, p. 296.

¹¹⁶ Taubenberger and Morens, “The Mother of All Pandemics.”

devastating. The pandemic was by far the deadliest in history, killing millions more than the total number of casualties during the First World War. The fatal illness left the world both in mourning as well as in a newfound state of fear and vulnerability. More significantly, however, the 1918 influenza virus became the precursor for all other major influenza pandemics that have since occurred throughout the twentieth century. Through viral reassortment, the H1N1 strain that caused the outbreak of 1918 gave rise to the viruses responsible for both the 1957 and 1968 influenza pandemics, truly making this influenza virus from southern China “the mother of all pandemics”.

4. The Influenza Pandemic of 1957

Humanity succumbed to yet another worldwide influenza outbreak nearly forty years after the great pandemic of 1918. Though relatively minor in contrast to the episode in 1918, the influenza pandemic of 1957 was of startling magnitude considering the advancements that had occurred in the preceding decades. Research inspired by the 1918 pandemic had uncovered the viral components of influenza in the early 1930s, generating revolutionary approaches to vaccines and antiviral medications. Furthermore, an international network promoting scientific and medical cooperation among different nations had been instituted first in the form of the League of Nations Health Organization in 1920 and later as the World Health Organization in 1947. A mere two years following its inception, the World Health Organization established a system with the specific purpose of combating influenza viruses, one that today spans more than 45 countries and includes nearly 100 laboratories.¹¹⁷ Nevertheless, a new strain of influenza surfaced in 1957 that prompted yet another global pandemic of this virulent malady.

Every major outbreak of influenza that has materialized over the course of this past century has been reviewed in comparison to the events of 1918. Such an approach is certainly justified; the pandemic of 1918 was devastating in every conceivable aspect as it unfolded and further spawned the viruses responsible for the major outbreaks of influenza that occurred during the twentieth century. The pandemic of 1957 was the first serious threat of influenza to arise following the so-called Spanish flu and while unknown at the time, was a direct product of the deadly 1918 pestilence. The viral origins of the H2N2 strain of influenza that arose in 1957 have been scientifically traced to the H1N1 virus that instigated the 1918 pandemic.

During the affliction of 1918, humans were not the only mammals infected with influenza. In the fall and winter of 1918 throughout the fatal second wave of the pandemic, millions of pigs in the United States, Europe and China fell ill with a severe respiratory infection that manifested similarly to human

¹¹⁷ Quinn, *A Social History of Influenza*, p. 163.

influenza.¹¹⁸ Teams of pigs experienced symptoms that included nasal discharge, elevated temperatures, and epiphora just like their human counterparts. Additionally, mortality rates were alarmingly high among hog farms, with thousands of pigs dying in a matter of days.¹¹⁹ An American inspector in the animal industry during the time of the pandemic named J.S. Koen was the first to recognize the clinical and pathological parallels between the two species, deeming the newly observed illness in pigs “swine influenza.”¹²⁰ Subsequent research revealed the animal virus was indeed influenza and was likely transmitted to pigs from humans during the second and highly lethal phase of the pandemic in late 1918, circulating thereafter epizootically in both humans and swine until 1920.¹²¹ While the virus then diminished among humans, it continued to appear annually in swine populations in America, Europe and Asia, ultimately provoking the revolutionary research of Richard Shope and his isolation of the swine influenza virus in the early 1930s.¹²²

Thus, the H1N1 virus of 1918 survived for decades following the so-called Spanish flu pandemic in swine populations around the globe. Exposure to the virus had relegated most of the human population immune to this particular strain, though pigs continued to become infected with both the H1N1 virus of 1918 as well as new varieties of influenza that surfaced annually. This habitual infection among swine populations stemming from the 1918 virus directly led to the pandemic influenza of 1957. While the 1918 virus was rather exceptionally derived in its entirety from an avian-like virus that had adapted to humans, the 1957 influenza

¹¹⁸ Edwin Kilbourne, “Influenza Pandemics of the 20th Century.” In: *Emerging Infectious Diseases*, volume 12, number 1 (2006), p. 9; J. Chun, “Influenza Including its Infection among Pigs.” In: *National Medical Journal of China*, volume 5 (1919), pp. 34–44.

¹¹⁹ Kolata, *Flu*, p. 67.

¹²⁰ Wenjun Ma, Robert Kahn, and Juergen Richt, “The Pig as a Mixing Vessel for Influenza Viruses: Human and Veterinary Implications. In: *Journal of Molecular and Genetic Medicine*, volume 3, number 1 (2009), p. 160; J.S. Koen, “A Practical Method for Field Diagnoses of Swine Diseases.” In: *American Journal of Veterinary Medicine*, volume 14 (1919), pp. 468–470.

¹²¹ Richard Shope, “The Incidence of Neutralizing Antibodies for Swine Influenza Virus in the Sera of Human Beings of Different Ages.” In: *Journal of Experimental Medicine*, volume 63 (1936), pp. 69–84.

¹²² Richard Shope and Paul Lewis, “Swine Influenza.” In: *Journal of Experimental Medicine*, volume 54 (1931), pp. 373–385.

virus was a more customary product of antigenic shift.¹²³ Pigs contain receptor cells that are susceptible to both human and avian forms of influenza, making them ideal facilitators for interspecies transmissions.¹²⁴ Following the 1918 pandemic, swine populations were contaminated year after year with multiple strains of influenza from both birds and people, providing a model environment for viral genetic recombination.¹²⁵ The H1N1 strain of influenza introduced into swine by humans in 1918 mixed over time in pigs with an avian H2 strain, gradually evolving through the process of reassortment into the novel H2N2 virus at fault for the 1957 outbreak.¹²⁶ Evidence of this reassortment was discovered in the genetic material of the 1957 influenza; four genes of the new virus were derived from the 1918 H1N1 strain.¹²⁷ The H2N2 virus was composed in total of eight gene segments, five of which were human and three of which possessed avian origins.¹²⁸ When this freshly evolved virus was transferred from swine back to humans, the H2N2 influenza preyed on people's highly vulnerable immune systems, triggering the pandemic that swept the globe in 1957.

In contrast to the disputable origins of the 1918 outbreak, the influenza pandemic that consumed the world in 1957 was verifiably rooted in southern China. However, as with the pandemic of 1918, the 1957 influenza outbreak was mistakenly presumed, though only temporarily, to have begun elsewhere. Singapore was the first country in early spring of 1957 to issue reports on an international scale about a deadly new strain of the flu.¹²⁹ Hong Kong too was strongly linked to the threat of a pandemic following a news article published in the *New York Times* in April of 1957 that chronicled an influenza epidemic involving

¹²³ Ann Reid, Jeffrey Taubenberger, and Thomas Fanning, "Evidence of an Absence: the Genetic Origins of the 1918 Pandemic Influenza Virus." In: *Nature Review Microbiology*, volume 2 (2004), p. 909.

¹²⁴ Ian Brown, "The Epidemiology and Evolution of Influenza Viruses in Pigs." In: *Veterinary Microbiology*, volume 74 (2000), p. 30.

¹²⁵ Davies, *The Devil's Flu*, p. 28.

¹²⁶ W. Paul Glezen, "Emerging Infections: Pandemic Influenza." In: *Epidemiologic Reviews*, volume 18, number 1 (1996), p. 68.

¹²⁷ C. Scholtissek, W. Rhode, V. von Hoyningen, and R. Rott, "On the Origin of the Human Influenza Virus Subtypes H2N2 and H3N2." In: *Virology*, volume 87 (1978), p. 13.

¹²⁸ Davies, *The Devil's Flu*, p. 28.

¹²⁹ Sipress, *The Fatal Strain*, p. 140.

more than 250,000 people in this region.¹³⁰ Following these initial reports, scientists were gradually able to trace cases of this virulent influenza back to the actual source. The pursuit ended in the southern Chinese province of Yunnan, where serious outbreaks had originally surfaced in February of 1957.¹³¹ This elementary association with various locations in Asia fittingly labeled this new strain the Asian influenza.

The pandemic of Asian influenza was the first with conclusively known origins, primarily due to the influence of the newly instituted World Health Organization. The WHO became involved following the flare-up recorded in Singapore and quickly discovered the source of the infection in southern China.¹³² A meeting was held in May of 1957 to assess the nature and threat of the H2N2 virus and in hindsight, did so with great accuracy. It was predicted the virus would spread first to the southern hemisphere infecting that region during its winter before causing severe flare-ups in the northern hemisphere starting in October.¹³³ As expected, the earliest accounts of the influenza of 1957 were from the southern hemisphere with critical bouts recorded in India, Australia and Indonesia in May. By June and July, nearly every major continent had documented cases of Asian influenza, though the gravity of the illness remained low similarly to the spring phase of the 1918 pandemic.¹³⁴ The virus had been transmitted via land and sea routes, since public air travel was still a scarcely used form of transport in the 1950s. The infection had traveled from Southeast Asia through Russia to Scandinavia and Eastern Europe, spreading thereafter throughout the rest of the European continent.¹³⁵ The influenza had disseminated quickly throughout the Americas following the homecoming of roughly

¹³⁰ Kilbourne, "Influenza Pandemics of the 20th Century", p. 10; "Hong Kong Battling Influenza Epidemic." In: *New York Times*, volume 17, number 3 (April 1957).

¹³¹ Lachlan Strahan, "An Oriental Scourge: Australia and the Asian Flu Epidemic of 1957." In: *Australian Historical Studies*, volume 26, issue 103 (1994), pp. 182-201.

¹³² C.M. Chu, C. Shao, and C.C. Hou, "Studies of Strains of Influenza Virus Isolated during the Epidemic in 1957 in Changchun." In: *Voprosy Virusologii*, volume 2 (1957) pp. 278-281.

¹³³ A.M. Payne, "Symposium on the Asian Influenza Epidemic, 1957." In: *Proceedings of the Royal Society of Medicine*, volume 51 (1958), pp. 1009-1015.

¹³⁴ Potter, "A History of Influenza", p. 577.

¹³⁵ Alexander Langmuir, "Epidemiology of Asian Influenza." In: *American Reviews of Respiratory Diseases*, volume 83 (1961), pp. 2-18.

eighteen hundred representatives from a convention held in Grinnel, Iowa. Participants had connections with more than forty U.S. states and a handful of foreign countries. The two hundred cases of influenza that had been reported at the conference quickly turned into thousands as these infected individuals returned home.¹³⁶

Over a six month period, the virus seeded itself in populations around the world. Throughout the summer months of 1957, the Asian influenza evolved into the more virulent pandemic strain that ultimately erupted worldwide in late October.¹³⁷ As with the 1918 outbreak, the peak phase of the Asian influenza pandemic transpired during the winter months of 1957-1958 and occurred in two waves characterized by excess mortality, first in October and November of 1957 and secondly, in January of 1958.¹³⁸ Victims of this pandemic strain of influenza experienced a range of symptoms. The illness began abruptly with the onset of a fever and an overwhelming sense of fatigue. This was followed by recurring episodes of chills, body aches, nasal congestion and an irritating rawness of the throat and upper respiratory tract.¹³⁹ At its worst, patients suffered from volatile fits of dry coughing, profuse perspiration, and fevers upwards of 102°F (39°C). Elevated temperatures often persisted for days before subsiding, exacerbating all aforementioned symptoms.¹⁴⁰ While the manifestations of the 1957 Asian influenza were not atypical in form, they became exceptionally acute and instigated an alarming number of cases in comparison to seasonal epidemics.

Unlike the pandemic of 1918 that devastated an entire generation of young adults, the most prone demographics in 1957 were young, school-age children and the elderly, though deaths

¹³⁶ Potter, "A History of Influenza", p. 577.

¹³⁷ Glezen, "Emerging Infections", p. 67.

¹³⁸ N.J. Cox and K. Subbarao, "Global Epidemiology of Influenza: Past and Present." In: *Annual Review of Medicine*, volume 51 (2000), p. 413.

¹³⁹ John Fry, "Influenza A (Asian) 1957: Clinical and Epidemiological Features in a General Practice." In: *British Medical Journal*, volume 2, number 226 (February 1958), pp. 259-261.

¹⁴⁰ Herbert Blumenfeld, Edwin Kilbourne, Donald Loria, and David Rogers, "Studies on Influenza in the Pandemic of 1957-1958. I. An Epidemiologic, Clinical and Serologic Investigation of an Intrahospital Epidemic, with a Note on Vaccination Efficacy." In: *Journal of Clinical Investigation*, volume 38 (1959), pp. 203-204.

occurred principally in the latter.¹⁴¹ Among the elderly victims, those most affected had preexisting conditions or specific underlying issues that made them especially susceptible to influenza; in general, deaths during the 1957 pandemic resulted not from influenza per se, but rather an untreatable form of viral pneumonia induced by the existing infection.¹⁴² In contrast to the outbreak of 1918, the Asian influenza pandemic had a relatively low mortality rate, with an estimated two million casualties occurring worldwide as a result of the flu.¹⁴³ The death toll in 1957 was significantly alleviated by the first ever implementation of a flu vaccine during a pandemic. Unlike the 1918 virus that was only isolated within the last decade, the H2N2 virus had been identified in May of 1957 before the peak phase of the pandemic even occurred.¹⁴⁴ The WHO quickly set in motion a team of scientists to create a preventative vaccine; however, the speed at which vaccines were able to be produced and their actual effectiveness when administered were deficient in 1957, especially during the overwhelming circumstances of a pandemic. Though research had begun in the spring, the vaccine was ready for distribution only at the end of 1957 following the start of the peak phase of the pandemic.¹⁴⁵ Unfortunately, for vaccines to be thoroughly valuable, they must be administered a reasonable amount of time prior to an outbreak.¹⁴⁶ In addition to the delayed administration of vaccines in 1957, supplies and worldwide distribution were insufficient. As such, the death rate continued to rise in the autumn and winter, though it would have undoubtedly been higher had no vaccine been provided during the pandemic of 1957.¹⁴⁷

¹⁴¹ A. Langmuir, M. Pizzi, W.Y. Trotter and F.L. Dunn, "Asian Influenza Surveillance." In: *Public Health Report*, volume 73 (1958), pp. 114-120.

¹⁴² Neville Oswald, R.A. Shooter and M.P. Curwen, "Pneumonia Complicating Asian Influenza." In: *British Medical Journal* (November 1958), pp. 1305-1311; Donald Louria, Herbert Blumenfeld, John Ellis, Edwin Kilbourne, and David Rogers, "Studies on Influenza in the Pandemic of 1957-1958. II. Pulmonary Complications of Influenza." In: *Journal of Clinical Investigation*, volume 38 (1959), p. 262.

¹⁴³ F.L. Dunn, "Pandemic Influenza in 1957: Review of International Spread of New Asian Strain." In: *Journal of the American Medical Association*, volume 166, number 10 (1958), pp. 1140-1148; Quinn, *A Social History of Influenza*, p. 167.

¹⁴⁴ Cox and Subbarao, "Global Epidemiology of Influenza", p. 413.

¹⁴⁵ Quinn, *A Social History of Influenza*, p. 167.

¹⁴⁶ Fry, "Influenza A (Asian) 1957", p. 261.

¹⁴⁷ Quinn, *A Social History of Influenza*, p. 167.

Though the vaccine administered at the end of 1957 belatedly decreased the overall mortality rate of the pandemic, its preventative potential was only realized throughout the following years. A meeting held in 1960 retrospectively assessed the utilization of flu vaccines to assuage the impact of pandemics, focusing specifically on the situation in 1957. It was realized that vaccinations should be done in greater quantities to hasten the antibody response necessary for avoiding infection.¹⁴⁸ Even so, despite the inadequacies of the vaccination program employed in 1957, it proved beneficial. The vaccine not only halted the pandemic's development, but increased immunity to imminent seasonal flu epidemics. Additionally, the population at large developed an enhanced response to inoculations, boosting their efficiency.¹⁴⁹ Thus, following the Asian influenza pandemic of 1957, seasonal outbreaks of flu dwindled. However, this fortuity lasted only a decade. In 1968, the last major influenza pandemic to occur during the twentieth century erupted, its origins firmly rooted in southern China.

¹⁴⁸ Kilbourne, "Influenza Pandemics of the 20th Century", p. 10.

¹⁴⁹ Ibid.

5. The Influenza Pandemic of 1968

Echoes of the 1957 Asian influenza outbreak reverberated a mere eleven years later when the world was yet again overwhelmed by a viral infection of pandemic proportions. The H2N2 strain that circulated perniciously in 1957 was replaced via genetic shift by an H3N2 subtype in 1968, condemning the world population to another state of immunological vulnerability. The contagion that materialized in the late 1960s strikingly paralleled the events of 1957-1958. As with Asian influenza, the pandemic of 1968 had a relatively low rate of mortality, but a high degree of morbidity. The events of 1968 similarly transpired over two phases of critical infection, as is characteristic of most influenza pandemics, with the second wave assuming the more lethal form. Most notably, however, propagation of the 1968 malady mirrored that of 1957, expanding outward along corresponding routes from the viral reservoir situated in southern China.

An article issued on 12 July 1968 by *The Times* in London was the first to report a prevalent manifestation of a severe, flu-like respiratory infection in the southeastern region of China.¹⁵⁰ The illness appeared first in the southern Chinese province of Guizhou before spreading to Hong Kong where the virus notoriously contaminated a large percentage of the population; nearly 500,000 people in Hong Kong became infected over the course of two weeks.¹⁵¹ Accounts of the virulent influenza only came to the fore once cases had reached Hong Kong, a British colony at the time. China was still an isolated country governed by a totalitarian regime in 1968, a factor that concealed early evidence of the imminent pandemic; in China, “all talk of problems and epidemics, famine or poor harvests was condemned as ‘bourgeois’ and ‘counter-revolutionary’.”¹⁵² Thus, any information regarding the illness on a global scale was first filtered

¹⁵⁰ Graeme Laver, “Influenza Virus Surface Glycoproteins, Hemagglutinin and Neuraminidase: A Personal Account.” In: *Influenza* edited by C.W. Potter, Amsterdam: Elsevier Sciences B.V., 2002, p. 43.

¹⁵¹ Quinn, *A Social History of Influenza*, p. 168; Chloe Sellwood, “Brief History and Epidemiological Features of Pandemic Influenza.” In: *Introduction to Pandemic Influenza* edited by Jonathan Van-Tam and Chloe Sellwood, Cambridge, Massachusetts: CAB International, 2010, p. 49.

¹⁵² Quinn, *A Social History of Influenza*, p. 168.

through Hong Kong. Only five days after the publication in *The Times*, the influenza virus at fault was isolated by scientists at the Influenza Center based in the British colony. Cultures of this novel strain were forwarded to the World Influenza Center and various laboratories throughout the global network to initiate the production of a vaccine.¹⁵³ The affair naturally inspired a great deal of media attention, all of which linked Hong Kong to this new variety of influenza. As with both of the previously examined pandemics, the name of the 1968 outbreak was derived from the location where it was first widely publicized, not from the actual source in southern China. Thus, the affliction of 1968 was popularly deemed the Hong Kong flu.

Resembling the course of the 1957 outbreak, a critical number of cases emerged initially in Hong Kong and Singapore at the start of August in 1968. The pandemic advanced further into the southern hemisphere, with incidents of flu arising in the Philippines, Taiwan, Vietnam and Malaysia by late August. By September, the illness surfaced in various locales stretching from Thailand to Australia and progressed westward with bouts recorded in India and parts of the Middle East, particularly Iran.¹⁵⁴ In late September, the virus appeared in both Europe and North America and subsequently progressed into Africa and South America, respectively.¹⁵⁵ While the Hong Kong flu virus proliferated via land and sea routes as with previous pandemics, it notably was the first to spread through an increased use of air transport. Over 160 million people traveled internationally on commercial flights during the pandemic in 1968-1969, transmitting the virus both faster and farther than ever before.¹⁵⁶

The winter of 1968 is considered to be the first phase of the Hong Kong flu pandemic. While morbidity was both high and evident worldwide, clinical manifestations of the illness were

¹⁵³ W. Charles Cockburn, P.J. Delon, and W. Ferreira, "Origin and Progress of the 1968-69 Hong Kong Influenza Epidemic." In: *Bulletin of the World Health Organization*, volume 41, number 3 (1969), pp. 345-346.

¹⁵⁴ Ibid; A.C. Saenz, F.A. Assaad, and W.C. Cockburn, "Outbreak of A2/Hong Kong/68 Influenza at an International Medical Conference." In: *The Lancet*, volume 293, issue 7585 (1969), pp. 91-93.

¹⁵⁵ Sellwood, "Brief History and Epidemiological Features of Pandemic Influenza", p. 50.

¹⁵⁶ Rebecca Grais, J. Hugh Ellis, and Gregory Glass, "Assessing the Impact of Airline Travel on the Geographic Spread of Pandemic Influenza." In: *European Journal of Epidemiology*, volume 18 (2003), p. 1065.

unremarkable in comparison to standard epidemics. Most affected regions during this first phase of the outbreak exhibited a “smoldering” pattern of infection; the impact of the contagion, particularly in Europe and Asia, was mild, with negligible mortality rates and an imperceptible burden on medical services.¹⁵⁷ However, the United States exceptionally endured a far more acute response to the novel influenza virus during the winter of 1968. The disease had allegedly spread to the United States in September when American troops returned to California from the war in Vietnam. By December, the flu was widespread in North America and did not subside until the spring of 1969.¹⁵⁸ The percentage of flu-related deaths in both the United States and Canada was nearly double that of contaminated regions around the world, particularly among those older than sixty-five years of age.¹⁵⁹ The extreme reaction experienced in North America would not emerge worldwide until the following winter of 1969 amidst the second and more lethal phase of the pandemic.

When the second wave of Hong Kong flu peaked in the winter of 1969, as many as four million people were infected worldwide. Symptoms were typical though exacerbated, prompting an influx in hospital admissions and an escalated mortality rate.¹⁶⁰ While the majority of deaths during the first wave occurred in North America, fatalities in the winter of 1969 exhausted populations primarily throughout Europe and Asia.¹⁶¹ The delayed impact of the Hong Kong flu throughout the Eurasian continent has since been attributed to a preexisting immunity to the neuraminidase of the H3N2 virus responsible for the 1968 pandemic.

As in 1957, the 1968 virus was a product of antigenic shift. The H2N2 strain that had circulated during and after the Asian flu pandemic was replaced in 1968 by the H3N2 subtype following

¹⁵⁷ Cecile Viboud, Rebecca Grais, Bernard Lafont, Mark Miller, and Lone Simonsen, “Multinational Impact of the 1968 Hong Kong Influenza Pandemic: Evidence for a Smoldering Pandemic.” In: *Journal of Infectious Disease*, volume 192, number 2 (2005), p. 236; Sellwood, “Brief History and Epidemiological Features of Pandemic Influenza”, p. 50.

¹⁵⁸ Ibid., p. 49; Quinn, *A Social History of Influenza*, p. 168.

¹⁵⁹ Viboud, et al., “Multinational Impact of the 1968 Hong Kong Influenza Pandemic”, p 233, 235.

¹⁶⁰ Quinn, *A Social History of Influenza*, p. 168.

¹⁶¹ Sellwood, “Brief History and Epidemiological Features of Pandemic Influenza”, p. 50.

genetic reassortment. Phylogenetic analyses have shown the H3N2 virus had components of both avian and human influenza viruses.¹⁶² Swine again posed as the necessary mixing vessels for the reassortment process that generated the H3N2 virus. Significantly, the strain responsible for the 1968 pandemic was isolated in Hong Kong from pigs that had come from southern China, the origin of the outbreak.¹⁶³ In this region, H2N2 viruses had circulated widely following the 1957 pandemic, causing seasonal epidemics throughout both Asia and parts of Europe. The total mortality rate induced by H2N2 subtypes in Eurasian populations far exceeded those recorded elsewhere around the world and from this, scientists have deduced a greater overall exposure in this region to H2N2 strains directly preceding the 1968 shift to the H3N2 virus.¹⁶⁴ Because both varieties share a nearly identical neuraminidase, those in Asia and Europe had acquired over years of contact a partial immunity to the Hong Kong flu of 1968, resulting in an extremely mild reaction in these regions during the first wave of the pandemic in comparison to that in North America.¹⁶⁵

It was not until the 1968 H3N2 virus underwent the process of antigenic drift that it became a true threat to Eurasian populations. Following its peak in North America between December of 1968 and early spring of 1969, the pandemic lulled as the virus lost its potency and more people gained the necessary antibodies to defeat the infection. By winter of 1969, however, the virus had mutated into a more lethal form, victimizing even those who had acquired partial immunity. In its entirety, the Hong Kong flu pandemic that occurred in the winters of 1968 and 1969 killed roughly one million people worldwide.¹⁶⁶ Though small in comparison to the casualties of 1918 and 1957, the death toll in 1968 was staggering considering the medical and scientific knowledge of the era. From the isolate obtained in July of 1968 in Hong Kong, scientists associated with the

¹⁶² Kawaoka, et al., "Avian-to-Human Transmission of the PB1 Gene", pp. 4603-4608; Scholtissek, et al., "On the Origin of the Human Influenza Virus Subtypes H2N2 and H3N2", pp. 13-20.

¹⁶³ Hiroshi Kida, Kennedy Shortridge, and Robert Webster, "Origin of the Hemagglutinin Gene of H3N2 Influenza Viruses from Pigs in China." In: *Virology*, volume 162 (1998), pp. 160-168.

¹⁶⁴ Viboud, et al., "Multinational Impact of the 1968 Hong Kong Influenza Pandemic", p. 241.

¹⁶⁵ *Ibid.*, pp. 241-242.

¹⁶⁶ Quinn, *A Social History of Influenza*, p. 168.

WHO were able to produce and distribute a vaccine that attenuated the overall impact of the pandemic, though as with 1957, were criticized for responding too slowly. It was recognized even then that the demand of the pandemic surpassed the scope of available resources. Nevertheless, notable improvement had been made since 1957 and far more has transpired following lessons learned in 1968.¹⁶⁷

Unlike the viruses that caused the 1918 and 1957 pandemics, the virus to blame for the Hong Kong flu outbreak of 1968 has not yet been replaced through genetic reassortment. The H3N2 virus continues to circulate today, sporadically evolving to regain capacity, and until very recently remained the leading and most troublesome subtype for humans.¹⁶⁸ However, people are not alone in their susceptibility to this strain; the virus has been perpetuated in swine herds around the world, causing some of the most severe epidemics among pig populations in the last forty years. The H3N2 virus of 1968 has since reassorted in these swine populations, generating novel H3N2 lineages that contain components of porcine, avian and human influenza.¹⁶⁹ The viral mutations that have occurred over the last half century with this particular influenza subtype have all developed in pigs from southern China, raising serious concern that another pandemic may emerge from this influenza reservoir.¹⁷⁰ The unusual status of southern China as an influenza epicenter is certainly not new. While this reputation has considerably influenced methods of influenza surveillance over the last century following the emergence of three major outbreaks from this region, little attention has been devoted to the root cause of this predilection to pandemic viruses in southern China.

¹⁶⁷ Cockburn, et al., "Origin and Progress of the 1968-69 Hong Kong Influenza Epidemic", p. 348.

¹⁶⁸ Kilbourne, "Influenza Pandemics of the 20th Century", p. 12.

¹⁶⁹ Hai Yu, Rong-Hong Hua, Qiang Zhang, Tian-Qiang Liu, Hai-Li Liu, Guo-Xin Li, and Guang Zhi-Tong, "Genetic Evolution of Swine Influenza A (H3N2) Viruses in China from 1970 to 2006." In: *Journal of Clinical Microbiology*, volume 46, number 3 (2008), p. 1067; N.N. Zhou, D. A. Senne, J. S. Landgraf, S. L. Swenson, G. Erickson, K. Rossow, L. Liu, K. J. Yoon, S. Krauss, and R. G. Webster, "Genetic Reassortment of Avian, Swine, and Human Influenza A Viruses in American Pigs." In: *Journal of Virology*, volume 73 (1999), pp. 8851-8856.

¹⁷⁰ Yu, et al., "Genetic Evolution of Swine Influenza A (H3N2)", p. 1074.

6. Chinese Origins

While the three influenza pandemics that occurred during the twentieth century each exhibited distinct characteristics, they are all unified by a common denominator: place of origin. Southern China has been regarded contemporarily as an “influenza epicenter”, habitually generating the multitude of influenza viruses responsible for both seasonal outbreaks and worldwide catastrophes. Although this pattern is retrospectively evident throughout the history of influenza pandemics, it is with the modern outbreaks of 1918, 1957 and 1968 that scientists have been able to more conclusively deem southern China a repository for influenza viruses. Epidemiological mapping and phylogenetic analyses have methodically linked this region of Asia to the source of former outbreaks; while much has been invested in the virology of these various strains of influenza, little consideration has been devoted to the sociological, cultural and environmental factors that cultivate this viral hotbed situated in southern China.

Influenza viruses thrive under specific circumstances. High population density and close proximity to livestock, specifically pigs and waterfowl, have been scientifically determined to enhance the viability of influenza viruses.¹⁷¹ Additionally, climate plays an essential role in the behavior of flu viruses; temperate conditions foster seasonal outbreaks and greater transmissibility, whereas tropical regions experience year-round circulation and increased exposure to influenza.¹⁷² A number of areas around the world exhibit a range of these conditions, though it is a unique combination of these factors in southern China that sustains the region’s prevalence for pandemic influenza.

The area of southern China most prone to influenza viruses primarily involves the province of Guangdong, though

¹⁷¹ L. Scott Chavers and Sten Vermund, “An Introduction to Emerging and Reemerging Infectious Diseases.” In: *Emerging Infectious Diseases* edited by Felissa Lashley and Jerry Durham, New York: Springer Publishing Company LLC., 2007, p. 9; Rene Snacken, Alan Kendal, Lars Haaheim, and John Woods, “The Next Influenza Pandemic: Lessons from Hong Kong, 1997.” In: *Emerging Infectious Diseases*, volume 5, number 2 (1999), pp. 195-203.

¹⁷² Cecile Viboud, Wladimir Alonso, and Lone Simonsen, “Influenza in Tropical Regions.” In: *PLoS Medicine*, volume 3, number 4 (2006), pp. 468-471.

extends outward as well to include the vicinity of present-day Hong Kong and Macau. The territory is nestled along the Pearl River estuary and has traditionally been a center for both agri- and aquaculture.¹⁷³ Historically, the tropical region was a hub for international trade and religious activity, facilitating global transmission of far more than just capital and culture.¹⁷⁴ The overall environment of southern China has for centuries maintained features conducive to the generation and transmission of influenza, though it was not until the late nineteenth century that such a connection was scientifically acknowledged.

Southern China's notable predisposition to pandemic influenza viruses was first, albeit fleetingly recorded more than a century ago by the Hong Kong-based British physician James Cantlie.¹⁷⁵ It was in this same locale in the early 1980s that microbiologist Kennedy Shortridge revisited this concept more thoroughly, expanding Cantlie's original premise by examining the particular social, cultural and environmental contributory factors intrinsic to this region. Shortridge's initial two-page article entitled "An Influenza Epicentre?" concentrated specifically on the influence of the unique farming methods employed in southern China on developing radically new strains of influenza capable of instigating a pandemic.¹⁷⁶ Roughly fifteen years later in 1997, Shortridge published yet another definitive paper on the topic titled "Is China an Influenza Epicentre?" in which the microbiologist elaborated on the historical institution of particular farming techniques, most specifically the domestication of waterfowl, in southern China and the resulting long-term effect on viral production.¹⁷⁷ His hypothesis has initiated further insight into the role of southern China in influenza pandemics, though much of the relevant literature features merely a brief reference or at most a superficial overview of the subject.

With the goal of developing a more comprehensive examination of southern China's reputation as a viral reservoir,

¹⁷³ Lau Yee-cheung, "History." In: *Guangdong: Survey of a Province Undergoing Rapid Change* edited by Y.M. Yeung and David K.Y. Chu, Hong Kong: Chinese University Press, 1998, p. 472.

¹⁷⁴ Ibid. p. 475.

¹⁷⁵ Cantlie, "The First Recorded Appearance of the Modern Influenza Epidemic."

¹⁷⁶ Shortridge, "An Influenza Epicentre?"

¹⁷⁷ Shortridge, "Is China an Influenza Epicentre?"

this chapter will elaborate on Shortridge's analysis, investigating further the causal factors inherent to this region. Southern China has historically possessed all of the aforementioned conditions that provide a favorable environment for influenza viruses: high population density, proximity to livestock and waterfowl, and year-round viral circulation. These factors are further exaggerated by the social and cultural values of southern China. With regard to the three influenza pandemics of the twentieth century, this chapter will analyze firstly the effect of farming in southern China on the generation of influenza viruses. This will be augmented by a glimpse at the regional cultural tendencies that contribute to southern China's status as an influenza epicenter. Furthermore, both the high population density and tropical climate in this region will be explored as additional causal elements. In total, the assessment of these four vital characteristics will bestow a deeper understanding of the social, cultural, and environmental factors responsible for southern China's inclination to pandemic influenza viruses.

Proximity to livestock and waterfowl plays an essential role in both the evolution and transmission of influenza viruses, as it provides a favorable environment for antigenic shift and zoonosis. Every known subtype of influenza has been traced back to wild avian species, specifically waterfowl such as ducks, given that these birds are the natural carrier hosts of the virus.¹⁷⁸ Influenza viruses incubate in the intestinal tracts of ducks and contain a larger variety of hemagglutinin sequences, whereas humans boast a different variety of receptor cells located in the upper respiratory tract.¹⁷⁹ Because avian influenza viruses do not replicate efficiently in humans, interspecies transmission between humans and birds is incredibly rare, though not unheard of, and more commonly,

¹⁷⁸ V.S. Hinshaw and R.G. Webster, "The Natural History of Influenza A Viruses." In: *Basic and Applied Influenza Research* edited by A.S. Beare, Boca Raton, Florida: CRC Press, 1982, pp. 79-104.

¹⁷⁹ Webster, et al., "Intestinal Influenza."

influenza spreads zoonotically through an intermediate host.¹⁸⁰ Pigs have been identified as the most probable intermediary for viral genetic reassortment, as they are physiologically susceptible to both avian and human strains of influenza.¹⁸¹ While the 1918 virus was an exceptional case of a direct avian to human transfer, both the 1957 and 1968 outbreaks resulted from a reassortment that transpired within a swine “mixing vessel”.¹⁸² The creation of such a virus that spans multiple species and is further introduced into an immunologically vulnerable group results in an influenza infection of pandemic proportions. For this process of zoonosis to occur, geographical propinquity among these three species must exist. Such is the case in southern China, where specific farming methods have facilitated for centuries a close relationship between humans, pigs and ducks.

China was the first place to domesticate ducks, with evidence dating as far back as four thousand to ten thousand years ago during the New Stone Age.¹⁸³ Pottery and pictorial depictions of ducks have been excavated in the Yan-shi-menkou Mountains of the southern Chinese province of Fujian, indicating probable domestication during this era.¹⁸⁴ Though little is available on early domestication, it is known that farmers were responsible for selection and propagation, largely to satisfy the comestible tastes

¹⁸⁰ Eric Claas, “Pandemic Influenza is a Zoonosis, as it Requires Introduction of Avian-like Gene Segments in the Human Population.” In: *Veterinary Medicine*, volume 74 (2000), p. 136.

¹⁸¹ Hiroshi Kida, Toshihiro Ito, Jiro Yasuda, Yukio Shimizu, Chitoshi Itakura, Kennedy Shortridge, Yoshihiro Kawaoka, and Robert Webster, “Potential for Transmission of Avian Influenza Viruses to Pigs.” In: *Journal of General Virology*, volume 75 (1994), pp. 2183-2188.

¹⁸² O.T. Gorman, W.J. Bean, Y. Kawaoka, I. Donatelli, Y. Guo, and R.G. Webster, “Evolution of Influenza A Virus Nucleoprotein Genes: Implications for the Origins of H1N1 Human and Classical Swine Viruses. In: *Journal of Virology*, volume 65 (1991), pp. 3704-3714.

¹⁸³ Kenneth Kiple, *A Movable Feast: Ten Millennia of Food Globalization*. Cambridge: Cambridge University Press, 2007, p. 24; Peter Cherry and Trevor Morris, *Domestic Duck Production: Science and Practice*. Cambridge, Massachusetts: CAB International, 2008, p. 3.

¹⁸⁴ Bo Wucheng, “The Research on the Origin of the House-duck in China.” In: *Proceedings of the International Symposium on Waterfowl Production at the Satellite Conference for the 18th World's Poultry Congress in Beijing, China*, Oxford: Pergamon Press, 1988, pp.125-129.

of high officials.¹⁸⁵ Up until the Ming Dynasty, ducks were primarily domesticated for consumption, though in the fifteenth century, reports of the time indicate the utilization of ducks for farming purposes. These accounts claim ducks were used in rice paddies to control infestations of crab and a variety of other pests native to the Zhujiang [Pearl] River region.¹⁸⁶ These methods, though slightly modified, still persist today.

Rice remains the most prevalent crop in southern China. One of the most densely populated areas in the world both historically and today, the Pearl River delta must produce enough cereal to satisfy the high demand of the region. To do so, farmers have upheld traditional methods that prove both productive and cost-effective. Thus, what began during the Ming Dynasty has carried through to today; farmers in the south have employed the domestic duck in rice paddies as a natural form of pesticide, weeding and fertilizer for centuries.¹⁸⁷ It is an ecologically balanced system in which ducks naturally maintain the rice paddies and in turn, find sustenance in the fallen grain that goes unused by people.¹⁸⁸ This revolution in rice farming in Guangdong resulted in a dramatic influx in the duck population of southern China; records from this last century indicate that nearly seventy percent of the more than thirty known duck breeds in China live downstream of the Yangtze and Pearl rivers.¹⁸⁹

In addition to increasing the duck population in southern China, these farming methods encouraged more consistent interaction between humans and domesticated waterfowl. Guangdong experiences as many as five rice harvests every year; as such, with this particular farming technique, ducks have become a continual presence in this densely populated region of southern China.¹⁹⁰ For centuries, the regular mobility of ducks among human settlements in this area has facilitated direct interaction with a vast range of influenza viruses. The greatest threat,

¹⁸⁵ Y. Jung and Y.P. Zhou, "The Pekin Duck in China." In: *World Animal Review*, volume 84 (1980), pp. 11-14.

¹⁸⁶ Cherry and Morris, *Domestic Duck Production*, p. 3.

¹⁸⁷ Shortridge, "An Influenza Epicentre?", p. 812.

¹⁸⁸ Davies, *The Devil's Flu*, p. 53.

¹⁸⁹ Da-Qian He, Qing Zhu, Shi-Yi Chen, Hui-Ying Wang, Yi-Ping Liu, and Yong-Gang Yao, "A Homogenous Nature of Native Chinese Duck Matrilineal Pool." In: *BMC Evolutionary Biology*, volume 8 (2008), pp. 298-309.

¹⁹⁰ Sipress, *The Fatal Strain*, p. 140.

however, has been the incidental influence of pigs in this arrangement.

The traditional integrated system of farming in southern China primarily involves both pigs and ducks. Both species comprise the fundamental assets of a small Chinese farm and are vital to the coordination of running such an ecologically balanced structure:

“The small farm raises pigs and/or ducks, in addition to crops rotated in accordance with the seasonal climactic cycle. The animals, particularly ducks and pigs, are sources of animal protein...Pigs are fed with aquatic plants combined with kitchen leftovers, and animal manure serves as fertilizer for the crops, vegetables and fish ponds. This is a system where practically nothing is wasted.”¹⁹¹

While this approach is ecologically beneficial, it provides plentiful opportunity for interspecies transmission of viruses. Pigs are openly exposed to duck excretions that contain residual viruses from their intestinal tracts. Furthermore, swine are susceptible to human viral infections as well, affording a high probability for dual contamination. What has incessantly sustained the generation of pandemic influenza viruses in this region is the repeated contact of domesticated ducks with a large variety of feral waterfowl in rice paddies; this interaction has continually introduced new strains of influenza viruses into domesticated birds that further circulate influenza among pigs and humans via the Chinese system of integrated farming, establishing an efficient foundation for a virulent outbreak.

While there are likely a number of areas worldwide that maintain a similar system of farming, the situation in southern China is unique due to its longevity and continuity. Ducks were tamed in southern China more than fifteen hundred years before

¹⁹¹ Medina Delmendo, “A Review of Integrated Livestock-Fowl-Fish Farming Systems.” In: *Integrated Agriculture-Aquaculture Farming Systems* edited by Roger S.V. Pullin and Ziad H. Shehadeh, Manila, Philippines: International Center for Living Aquatic Resources Management, 1980, p. 59.

the next known domestication in Europe and their use in Chinese integrated farming was not only the earliest, but has been maintained consistently in this region for centuries.¹⁹² The cycle of zoonotic transmission via this system of integrated farming has a long-standing evolution, one that has produced a proficient network for the creation of a virulent influenza capable of spanning multiple species.

While the system of farming in southern China has perpetually facilitated the spread of influenza, cultural habits related to food have further expedited the process. Inhabitants of southern China have a marked preference for fresh food, both historically and today.¹⁹³ This tendency is strongly encouraged by the concept of *ch'i*. Infused within traditional Chinese philosophy, religion and medicine is the notion that the human body possesses a “vital energy” known as *ch'i*.¹⁹⁴ This “strength” is derived directly from food, both in the manner of preparation and consumption.

The strong correlation between *ch'i* and food is evident on even the most fundamental level, that is, the etymology of the Chinese character for the word. The character is comprised of two distinct segments; a pictogram signifying “rising vapor” is positioned over the pictogram for “rice”. In this case, rice is synonymous for “food”. As such, the character for *ch'i* can be literally interpreted as “vapors rising from food”.¹⁹⁵ It is from the digestion of food that one acquires “nutritive essence, blood, body juices and life energy”, all of which are the embodiment of *ch'i*.¹⁹⁶

¹⁹² Cherry and Morris, *Domestic Duck Production*, p. 3.

¹⁹³ Kennedy Shortridge, “Severe Acute Respiratory Syndrome and Influenza: Virus Incursions from Southern China.” In: *American Journal of Respiratory and Critical Care Medicine*, volume 168 (2003), p. 1417.

¹⁹⁴ Frederick J. Simoons, *Food in China: A Cultural and Historical Inquiry*. Boca Raton, Florida: CRC Press Inc., 1991, p. 18.

¹⁹⁵ Paul U. Unschuld, *Medicine in China: A History of Ideas*. Berkeley and Los Angeles: University of California Press Ltd., 1985, p. 72.

¹⁹⁶ Claus Schnorrenberger, *Chen-Chiu- the Original Acupuncture: a New Healing Paradigm*. Somerville, Massachusetts: Wisdom Publications, 2003, p. 60.

Consequently, immense significance is placed on food in Chinese culture, as it is believed to provide the essence of one's spirit. It is within this paradigm that great emphasis is put on both frugality and freshness when it comes to food. People in China are renowned for embracing uncommon forms of sustenance and wasting very little of their edibles, a trait reflected throughout all class levels of society. Excessive or conspicuous consumption of food was traditionally considered taboo in China, a detail especially accentuated during the Communist era of the twentieth century.¹⁹⁷ Despite such frugality, quality in Chinese cuisine is never sacrificed. Freshness of ingredients is of the utmost importance, especially in southern China:

“Southern or Cantonese cuisine stresses attention to freshness of ingredients, lightness, crispness in cooking, texture, taste of each ingredient, and eating foods in season. Its chefs use virtually everything that grows or moves...Southern meals include a wide variety of foods, with roasted meats a regional specialty.”¹⁹⁸

This necessity for fresh foodstuffs, particularly meat, is best illustrated in the way such edibles are purchased.

Live-animal markets, also known as “wet markets”, are the most popular arenas for buying fresh food in China, particularly the province of Guangdong. Such markets have existed for centuries throughout Asia and specialize in selling small mammals, poultry, fish and reptiles, all live.¹⁹⁹ Southern China is renowned for its live animal markets, as it is generally believed in this region that eating freshly killed wild animals promotes both vitality and good health. As such, a wide variety of animals are available for purchase, ranging from cats, dogs, snakes, or bats to the more

¹⁹⁷ Simoons, *Food in China*, p. 18.

¹⁹⁸ Jacqueline Newman, *Food Culture in China*. Westport, Connecticut: Greenwood Press, 2004, p. 94.

¹⁹⁹ Robert Breiman, Meirion Evans, Wolfgang Preiser, James Maguire, Alan Schnur, Ailan Li, Henk Bekedam, and John MacKenzie, “Role of China in the Quest to Define and Control SARS.” In: *Learning from SARS: Preparing for the Next Disease Outbreak*, Washington D.C.: National Academy of Sciences, 2004, p. 58.

traditional sources of meat, such as pigs or poultry.²⁰⁰ These animals are often caged in confined quarters and in close proximity not only to each other, but to humans grazing the market for a potential meal.

The unsanitary conditions of these markets make them a prime target for epidemiological research. Inspired by the Hong Kong flu pandemic of 1968, studies in the early 1970s linked live animal markets in the vicinity of southern China to the production and spread of avian influenza viruses.²⁰¹ These “wet markets” bring together a variety of hosts in a high-density venue, affording an ideal environment for genetic reassortment and zoonotic transfers.²⁰² Furthermore, animals in these establishments may stay for a matter of days or even weeks, with new additions introduced on a regular basis; such a dynamic encourages both amplification and perpetration of infectious diseases like influenza, as novel viruses circulate among these animals constantly.²⁰³ As one of the primary locations for food purchases, these markets are teeming with people as well. Animals are often sold live or slaughtered in front of customers, emitting hazardous fluids and excretions seeping with potential infection.²⁰⁴ These establishments endemic in southern China amplify exposure to novel strains of influenza capable of instigating a global pandemic and pose enough of a threat to stir a controversial debate over the closure of traditional live animal markets in Asia.²⁰⁵ The plight for frugality and freshness inherent to Chinese gastronomic culture has historically been and is at present a key contributor to the proliferation of pandemic influenza viruses.

²⁰⁰ Jeffrey R. Ryan and Jan F. Glarum, *Biosecurity and Bioterrorism: Containing and Preventing Biological Threats*. Oxford: Elsevier Inc., 2008, p. 113.

²⁰¹ Shortridge, “Pandemic Influenza: a Zoonosis?”

²⁰² Ming Liu, Shiqin He, David Walker, NanNan Zhou, Daniel Perez, Bing Mo, Fan Li, Xiaotian Huang, Robert Webster, and Richard Webby, “The Influenza Virus Gene Pool in a Poultry market in South Central China.” In: *Virology*, volume 305 (2003), p. 267.

²⁰³ Robert Webster, “Wet Markets: A Continuing Source of Severe Acute Respiratory Syndrome and Influenza?” In: *The Lancet*, volume 363 (2004), p. 234.

²⁰⁴ P.J. Li, A. Rahman, P.D.B. Brooke, and L.M. Collins, “Asia.” In: *Long Distance Transport and Welfare of Farm Animals* edited by M.C. Appleby, V. Cussen, L. Garces, L.A. Lambert and J. Turner, Cambridge, Massachusetts: CAB International, 2008, p. 292.

²⁰⁵ Webster, “Wet Markets”, p. 236.

Population growth and increasing population density greatly facilitate the spread of an infectious illness such as influenza. A large and compact populace creates a suitable environment for chronic endogenous transmission of pathogens, including influenza viruses, and further stimulates the mutation and adaptation of these agents via frequent contact with a range of hosts.²⁰⁶ China, especially southern China, has a remarkably sizeable concentration of people, both historically and at present, that contributes significantly to this region's predilection for pandemic outbreaks.

For centuries, East Asia has boasted roughly a third of the world population, with the majority of this percentage derived from China. In AD 600, China's population ranged from sixty to seventy million inhabitants; this number doubled by the year 1500.²⁰⁷ Only four hundred years later, the population of China more than tripled, growing exponentially to amass roughly four hundred million citizens by the year 1900.²⁰⁸ At present, China is home to more than one billion residents, by far the most populated country in the world. This staggering growth has been evident throughout the country, though southern China has traditionally exhibited the most drastic rise in population. Historically, northern China was inflicted regularly with popular uprisings, warlike invasions and natural disasters that interrupted its demographic development. Southern China was affected less so and further enticed settlers with the fertile agricultural valley of the Pearl River delta, allowing for more rapid growth in the south over time.²⁰⁹ This disposition of southern China established a foundation for an abounding population that has contemporarily manifested into one of the most densely inhabited regions of the world.

²⁰⁶ Andrew T. Price-Smith, *Contagion and Chaos: Disease, Ecology and National Security in the Era of Globalization*. Massachusetts Institute of Technology, 2009, p. 26.

²⁰⁷ Victor I. Koslov, "Environment and Population." In: *History of Humanity* edited by Mohammed Adnan Bakhit, New York: Routledge, 2000, p. 19.

²⁰⁸ Angus Maddison, *The World Economy in the 20th Century*. Paris: OCDE/OECD, 1989, p. 129.

²⁰⁹ Koslov, "Environment and Population", p. 19; Xiaojian Zhao, *The New Chinese America: Class, Economy and Social Hierarchy*. New Jersey: Rutgers University Press, 2010, p. 44.

During the window of the three influenza pandemics of the twentieth century, China experienced a staggering influx in population. The country's populace expanded from roughly five hundred million residents in the first few decades of the century to nearly nine hundred million citizens by 1970 following the demise of the last influenza pandemic in the twentieth century.²¹⁰ Furthermore, these excess inhabitants were redistributed around the country in a non-traditional manner, with masses shifting variably between both the countryside and metropolis. In addition to international involvement in the First World War, China was domestically overwhelmed by revolutionary warlords around the time of the 1918 pandemic. After the overthrow of the Qing dynasty in 1911, the country fell into a state of political and social turmoil ruled by militaristic warlords. These militarists mobilized much of the population and by 1918, had an army upwards of one million. Warlords primarily found militia among impoverished rural peasants, introducing many for the first time to urban settings across the country.²¹¹ Mass mobilization within China among both rural and urban centers continued throughout the first half of the twentieth century, as exhibited in the Long March in the mid-1930s, the Sino-Japanese War and the Second World War. At the start of the Great Leap Forward in 1958, the height of the Asian flu pandemic, urbanization in China skyrocketed as agrarian communities migrated to the cities to assist with industrial development. However, during the mid-1960s after the end of this economic and social plan when agricultural production fell dramatically, many of those who relocated during the Great Leap Forward returned home to their rural villages, just prior to the pandemic of 1968.²¹² To say that such sizeable migrations are the cause of influenza pandemics is far too simplistic. What they do illustrate, however, is a capacity for large groups of people oscillating between urban and rural settings to potentially increase the viability and transmission of novel viruses.

²¹⁰ Ouyang Kang and Steven Haverkamp, "China's Environmental Puzzle: Theory and Practice. In: *Modernizing China* edited by Dharendra Vajpeyi, Leiden, The Netherlands: E.J. Brill, 1994, p. 31.

²¹¹ Hsi-Sheng Chi, *Warlord Politics in China, 1916-1928*. Stanford, California: Stanford University Press, 1976, pp. 79-80.

²¹² Paul Bairoch, *The Economic Development of the Third World since 1900*. Berkeley and Los Angeles: University of California Press, 1977, pp. 156-157.

In addition to a fluid and dense domestic population, China has historically been prone to international inhabitants, the vast majority most consistently concentrated in the south. The southern province of Guangdong borders both Macau and Hong Kong, each occupied continually by foreign inhabitants for centuries. A historical entrepot for both trade and religion, this southern region of China has experienced a dynamic amalgamation of international communities. This trend was reciprocated as China, specifically around the start of the twentieth century, began sending masses of Chinese citizens abroad for an assortment of motives.²¹³ This incessant, variable and global mixture of people has additionally facilitated, though to an unknown extent, the contraction and diffusion of viruses in and out of this influenza epicenter.

At present, the southern region of China is among the most densely populated areas in the world, a status that has progressively mounted over the last few centuries. Significantly, this highly crowded region has been comprised of both native Chinese from various areas of the country, as well as foreigners from around the globe. Though certainly not the sole contributing factor to China's penchant for influenza pandemics, this trait has undoubtedly provided a plethora of hosts for cultivating viruses. Influenza viruses have a greater chance of survival among compact populations like that in the region of southern China, with considerably enhanced opportunity for both exposure and transmission.

In addition to the aforementioned variables instrumental in southern China's role as a viral reservoir, the tropical climate of the region sustains an environment conducive to year-round circulation of influenza. In temperate regions, influenza surfaces seasonally, most often during the colder winter months. Dissimilarly, tropical regions experience perennial exposure to viruses.²¹⁴ Research has yet to conclusively explain this disparity; even so, tropical climates, as in southern China, are evidently in more frequent contact with novel

²¹³ Jonathan Spence, *The Search for Modern China*. New York: W.W. Norton & Company Inc., 1990.

²¹⁴ Viboud, et al., "Influenza in Tropical Regions", p. 468.

viruses, thus increasing the likelihood a pandemic influenza may evolve.

Temperate regions succumb to seasonal flare-ups of influenza, specifically during the winter months. In northern latitudes, influenza is prevalent from November to March, while the southern hemisphere is more susceptible between May and September.²¹⁵ Although concrete evidence is lacking in regards to the seasonal tendency of influenza in these regions, various theories have been proposed, all of which induce impairment of immunological capacity. Immune competence may be compromised by lower levels of melatonin or vitamin D during the winter.²¹⁶ Behavioral changes with the season, such as school attendance or a general increase in indoor crowding due to the wintry weather, may affect the viability and effectiveness of influenza viruses. A variety of potential environmental factors have been identified as well with an influx in influenza cases during the winter, such as a decrease in temperature and relative humidity and a change in the direction of air flow in the upper atmosphere.²¹⁷ Though speculative, research suggests that it is likely a combination of these variables that contributes to higher rates of infection during the winter in temperate regions. What is certain, however, is that influenza is cyclic in these areas with a transmission rate of roughly sixty percent during the winter, nearly double the rate observed during the summer.²¹⁸

²¹⁵ Anice Lowen, Samira Mubareka, John Steel, and Peter Palese, "Influenza Virus Transmission is Dependent on Relative Humidity and Temperature." In: *PLoS Pathogens*, volume 3, number 10 (2007), pp. 1470-1476.

²¹⁶ S.F. Dowell, "Seasonal Variation in Host Susceptibility and Cycles of Certain Infectious Diseases." In: *Emerging Infectious Diseases*, volume 7, number 3 (2001), pp. 369-374; J.J. Cannell, R. Vieth, J.C. Umhau, M.F. Holick, W.B. Grant, S. Madronich, C.F. Garland, and E. Giovannucci, "Epidemic Influenza and Vitamin D." In: *Epidemiology and Infection*, volume 134, number 6 (2006), pp. 1129-1140.

²¹⁷ R. Eccles, "An Explanation for the Seasonality of Acute Upper Respiratory Tract Viral Infections." In: *Acta Oto-laryngologica*, volume 122, number 2 (2002), pp. 183-191; G.W. Hammond, R.L. Raddatz, and D.E. Gelskey, "Impact of Atmospheric Dispersion and Transport of Viral Aerosols on the Epidemiology of Influenza." In: *Reviews of Infectious Diseases*, volume 11, number 3 (1989), pp. 494-497.

²¹⁸ Jerome Schulman and Edwin Kilbourne, "Transmission of Influenza Virus Infection in Mice. II. Some Factors Affecting the Incidence of Transmitted Infection." In: *Journal of Experimental Medicine*, volume 118, number 2 (1963), pp. 267-275.

This highly predictable trend in temperate regions deviates from the behavior of influenza in tropical zones, such as southern China. Influenza perpetuates steadily throughout the year in tropical regions, with only a slight escalation during the rainy season.²¹⁹ Even so, the illness manifests mildly in comparison to the recurrent flare-ups in temperate zones. These particular characteristics of influenza have been attributed, albeit conjecturally, to a disparity in both humidity and temperature in each climate. Research has shown that cold and dry weather conditions are more optimal for transmission of viruses, partially explaining the seasonality of influenza in temperate regions. Three general mechanisms occur under such conditions that elucidate this inclination for influenza to spread in low humidity and temperature. Firstly, inhalation of dry, cold air desiccates mucosa located in the nasal and upper respiratory tract, rendering people more susceptible to viral infection.²²⁰ Secondly, studies have shown that influenza viruses are most stable, most viable, in environments with a lower relative humidity. Lastly, evaporation of water from contaminated bioaerosols occurs more rapidly at lower humidity, ultimately resulting in small droplet nuclei awash with infectious material. A higher humidity causes these respiratory droplets to conversely assume water, expand and settle more rapidly out of the air.²²¹ Droplet nuclei that are produced in lower humidity are significantly smaller in size and remain airborne for a longer period of time, thus enhancing the probability of viral transmission in colder and drier climates.²²² As such, temperate regions exhibit favorable conditions for the spread of influenza.

While influenza may diffuse more easily in colder and drier climates, tropical zones are essential in perpetuating novel viruses. Contemporary research indicates that new strains of influenza, those most likely responsible for pandemic outbreaks, arise in tropical

²¹⁹ Viboud, et al., "Influenza in Tropical Regions", p 468; Lynette Pei-Chi Shek and Bee-wah Lee, "Epidemiology and Seasonality of Respiratory Tract Virus Infections in the Tropics." In: *Paediatric Respiratory Reviews*, volume 4, issue 2 (2003), pp. 105-111.

²²⁰ Lowen, et al., "Influenza Virus Transmission is Dependent on Relative Humidity and Temperature", p. 1473.

²²¹ Raymond Tellier, "Review of Aerosol Transmission of Influenza A Virus. In: *Emerging Infectious Diseases*, volume 12, number 11 (2006), pp. 1657-1662.

²²² Lowen, et al., "Influenza Virus Transmission is Dependent on Relative Humidity and Temperature", pp. 1473-1474.

climates before spreading outwards to temperate zones. Though transmission is more adept in temperate regions, the tropics endure persistent circulation of novel influenza viruses. In addition to continual exposure to these viruses, infectious epidemics can and often do occur in the tropics during the intermediate months that fall between the influenza season typical of temperate regions.²²³ Antigenic drift has been noted as more efficient in tropical regions as a result of this high background infection rate. Viral mutations that arise in temperate zones are most often observed to be a secondary effect to those that have occurred in a tropical source. It is this detail that explains how influenza viruses, specifically hemagglutinin components, continue to thrive and adapt worldwide across seasons when there is little evidence of antigenic drift on the scale of localized epidemics in temperate regions.²²⁴ Accordingly, it is most probable that influenza viruses develop and diffuse outwards from a tropical reservoir, with southern China as the likely culprit.

Southern China embodies all of these basic variables that contribute to the generation and spread of influenza viruses. Proximity to livestock, social and cultural gastronomic habits, a high and diverse population density, and a tropical climate together fashion a suitable foundation for the creation of an influenza virus of pandemic capacity. It is the combination of these fundamental factors endemic to southern China that maintain this regions reputation as an influenza reservoir. Novel influenza viruses are generated in the plethora of waterfowl native to this region. Specific farming methods and social and cultural customs related to food assist in the zoonotic transmission of new strains of influenza. Furthermore, a high population density and tropical climate facilitate the propagation of these viruses that subsequently disseminate worldwide.

²²³ Viboud, et al., "Influenza in Tropical Regions", p. 468.

²²⁴ Andrea Rambaut, Oliver Pybus, Martha Nelson, Cecile Viboud, Jeffrey Taubenberger, and Edward Holmes, "The Genomic and Epidemiological Dynamics of Human Influenza A Virus." In: *Nature*, volume 453 (2008), p. 616.

Elements of these variables undoubtedly exist in various locales around the world, though not in the same concoction. It is the unique and long-existing amalgamation of each factor that verifies southern China's status as an influenza hotbed. Even so, these features by no means exemplify every contributing cause, but rather paint a portrait of the most essential constituents in the proliferation of influenza viruses. Every influenza pandemic that occurred during the twentieth century, and many of those pre-dating 1900, stemmed from this particular region in southern China. Understanding this phenomenon is not simply informative, but may prove practical in the surveillance, containment and/or prevention of future influenza pandemics.

7. Conclusion

Influenza remains today one of the most serious threats to human health. Annually, the malady impairs countless around the globe and causes anywhere between 250,000 and 500,000 deaths worldwide.²²⁵ Moreover, these numbers are derived from typical yearly flare-ups, paling in comparison to those encountered during an influenza pandemic. A detail such as this rouses justifiable concern for imminent outbreaks and provokes preemptive action not only as a means of reinforcement, but to potentially avert a catastrophic infection altogether. To achieve a state of pandemic preparedness, it is essential to evaluate and learn from previous events of comparable magnitude. Accordingly, the significance of understanding the prominent role of southern China in the generation and propagation of influenza viruses is to better prepare for the inevitable onset of future pandemics.

Another massive outbreak of influenza is bound to happen. Pandemics have maintained a cyclical pattern over the course of the last few centuries and the twenty-first century should be no different.²²⁶ One of the primary issues with influenza is that it is ineradicable. Nevertheless, influenza is treatable via antiviral medications and vaccines, though these are most effective only after the illness emerges. As such, the current measures for pandemic preparedness are mostly concerned with containment as opposed to absolute avoidance of an outbreak. At present, a general inventory of strategic criteria has been proposed by the WHO to better suppress global afflictions:

²²⁵ Anthony Fauci, "Emerging and Reemerging Infectious Diseases: the Perpetual Challenge." In: *Academic Medicine*, volume 80, number 12 (2005), p. 1082.

²²⁶ W.R. Dowdle, "Influenza A Virus Recycling Revisited." In: *Bulletin of the World Health Organization*, volume 77, number 10 (1999), p. 820.

- Support Member States for the implementation of national capacities for epidemic preparedness and response in the context of the IHR(2005), including laboratory capacities and early warning alert and response systems;
- Support national and international training programs for epidemic preparedness and response;
- Coordinate and support Member States for pandemic and seasonal influenza preparedness and response;
- Develop standardized approaches for readiness and response to major epidemic-prone diseases (e.g. meningitis, yellow fever, plague);
- Strengthen biosafety, biosecurity and readiness for outbreaks of dangerous and emerging pathogens (e.g. SARS, viral haemorrhagic fevers);
- Maintain and further develop a global operational platform to support outbreak response and support regional offices in implementation at regional level.²²⁷

A host of scientists have adapted these conditions more specifically to pandemic outbreaks of influenza, focusing predominantly on regions of Asia. In summation, six key actions have been identified as vital to the containment and elimination of a worldwide influenza infection:

“(1) rapid identification of the original case cluster, (2) rapid, sensitive case detection and delivery of treatment to targeted groups, preferably within 48h of a case arising, (3) effective delivery of treatment to a high proportion of the targeted population, preferably 90%, (4) sufficient stockpiles of drug, preferably 3 million or more courses of oseltamivir, (5) population cooperation with the containment strategy and, in particular, any social distance measures introduced, (6)

²²⁷ “Global Alert and Response.” *World Health Organization*, 2010. Accessed 15 June 2010, <<http://www.who.int/csr/en/>>.

international cooperation in policy
development, epidemic surveillance
and control strategy
implementation.”²²⁸

If such a plan of action is successfully actualized, it becomes highly possible to not only prevent millions of deaths, but avoid countless cases of infection as well.

Rapid detection and accurate surveillance are of the utmost importance in enacting the aforementioned scheme. Past pandemics have proven that a swift response is of the essence during threatening bouts of influenza. Across the vast expanse of the Earth’s surface, knowing where to identify a likely source can save time, money and ultimately, lives. From both actual experience and laboratory simulations, scientists have ascertained that impeding the spread of pandemic influenza is considerably more effective if detected within the first couple of weeks of the eruption.²²⁹ Upon detection, antiviral medications, such as oseltamivir or zanamivir, provide the most prompt means of inhibiting the spread of the virus. Even so, these must be administered within one to two days following the manifestation of flu-related symptoms to obtain the desired effect, further necessitating efficient surveillance.²³⁰ It is speculated that such prophylactic measures are possible if the WHO stockpiles a minimum of 120,000 courses of treatment for all outbreak foci and these are dispensed comprehensively in an expeditious fashion.²³¹ The allocation of antiviral medication is further augmented by regulated social distancing. In the early stages of a pandemic, the combined intervention of antiviral treatment and quarantine affords the most favorable method for short-term, immediate containment,

²²⁸ Neil Ferguson, Derek Cummings, Simon Cauchemez, Christophe Fraser, Steven Riley, Aronrag Meeyai, Sapon Iamsirithaworn, and Donald Burke, “Strategies for Containing an Emerging Influenza Pandemic in Southeast Asia.” In: *Nature*, volume 437, number 7056 (2005), p. 213.

²²⁹ Ira Longini, Azhar Nizam, Shufu Xu, Kumnuan Ungchusak, Wanna Hansaoworakul, Derek Cummings, and M. Elizabeth Halloran, “Containing Pandemic Influenza at the Source.” In: *Science*, volume 309 (2005), p. 1087.

²³⁰ Ira Longini, M. Elizabeth Halloran, Azhar Nizam, and Yang Yang, “Containing Pandemic Influenza with Antiviral Agents.” In: *American Journal of Epidemiology*, volume 159, number 7 (2004), p. 629.

²³¹ Longini, et al., “Containing Pandemic Influenza at the Source”, p. 1087.

imparting a window of opportunity to adequately develop a vaccine.²³² The WHO surveillance network assists in monitoring an extensive stretch of the globe, but due to the exigency of a timely response, understanding on which regions to concentrate is both pivotal and may prove to be highly advantageous.

As the relationship between southern China and influenza pandemics has received greater consideration, the WHO has responded accordingly by increasing collaboration with affiliated laboratories in this region of the world, improving the surveillance network steadily over the last two decades. This progress has been marked by an increase in the number of viral isolates acquired in China that have been vital to recent influenza research.²³³ The results of these analyses have strikingly substantiated the supposition put forth in this thesis and related works; more than half of the viral strains used for vaccine production in the past twenty years have been derived from samples isolated in China.²³⁴

The most prevalent strains of influenza detected in this region remain among the native duck population. Over a four year study, forty-three of the forty-six viral combinations of hemagglutinin and neuraminidase unearthed in southern China originated in ducks.²³⁵ This naturally has facilitated a high degree of exposure to variant strains with the potential for acquiring lethal characteristics among humans. In 1997, a very unlikely transmission between an avian source and humans occurred, igniting dire concern another influenza pandemic was underway. The first cases of what would become known as the H5N1 Avian influenza were documented in Hong Kong, though research has confirmed the strain actually

²³² Juxin Chin, Geoffrey Koh, and Dong-yup Lee, "How Necessary is a Fast Testkit for Mitigation of Pandemic Flu?" In: *Journal of the Royal Society Interface*, volume 7, number 48 (2010), p. 1033.

²³³ Alan Hampson, "Surveillance for Pandemic Influenza." In: *Journal of Infectious Disease*, volume 176 (1997), p. 12.

²³⁴ Hitoshi Oshitani, "Further Development of Influenza Surveillance in China and Global Impact on Influenza Control." In: *International Congress Series*, volume 1219 (2001), p. 120.

²³⁵ Kennedy Shortridge, "Avian Influenza A Viruses of Southern China and Hong Kong: Ecological Aspects and Implications for Man." In: *Bulletin of the World Health Organization*, volume 60, number 1 (1982), p. 129.

originated in mainland China, likely the province of Guangdong.²³⁶ At its onset, the virus possessed an alarming rate of fatality. Even so, transmissibility remained low and while this strain of influenza still lingers as a serious threat, it has yet to infect on a pandemic scale.²³⁷

The next major influenza pandemic did not arise until the twenty-first century. In 2009, the WHO declared a global outbreak of an H1N1 virus derived from swine, hence its designation as “swine flu”. The infection was portrayed as having begun in Mexico before following tourist routes back to the United States, Europe and parts of Asia.²³⁸ However, the virus responsible for this worldwide infection had actually surfaced years before in southern China. In 2006, scientists detected a human-like H1N1 swine virus among pig populations in Guangdong province.²³⁹ In hindsight, it was likely the movement of these pigs between Asia and North America that cultivated the pandemic virus of 2009.²⁴⁰ The gene segments of the strain that erupted in Mexico in 2009 are known to have circulated undetected for an extended period prior to its appearance. Phylogenetic analyses have shown that the Asian strain likely reassorted with a comparable North American virus to produce the unique combination of influenza discovered in Mexico in 2009.²⁴¹ Though more indirectly than previous outbreaks, the pandemic of 2009 was in fact a product of an influenza virus that had originated in southern China.

²³⁶ K.S. Li, et al., “Genesis of a Highly Pathogenic and Potentially Pandemic H5N1 Influenza Virus in Eastern Asia.” In: *Nature*, volume 430 (2004), pp. 209-213.

²³⁷ John Tam, “Influenza A (H5N1) in Hong Kong: an Overview.” In: *Vaccine*, volume 20 (2002), pp. 77-81.

²³⁸ Guillermo Domínguez-Cherit, et al., “Critically Ill Patients with 2009 Influenza A (H1N1) in Mexico.” In: *Journal of the American Medical Association*, volume 302, issue 17 (2009), pp. 1880-1887.

²³⁹ Hai Yu, Yan-Jun Zhou, Guo-Xin Li, Gui-Hong Zhang, Hui-Li Liu, Li-Ping Yan, Ming Liao, and Guang-Zhi Tong, “Further Evidence for the Infection of Pigs with Human-like H1N1 Influenza Viruses in China.” In: *Virus Research*, volume 140 (2009), pp. 85-90.

²⁴⁰ Gavin J. D. Smith, et al., “Origins and Evolutionary Genomics of the 2009 Swine-Origin H1N1 Influenza A Epidemic.” In: *Nature*, volume 459 (2009), p. 1125.

²⁴¹ Rebecca J. Garten, et al., “Antigenic and Genetic Characteristics of Swine Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans.” In: *Science*, volume 325, issue 197 (2009), pp. 197-201.

Thus, the trend has continued as expected in the twenty-first century and will likely persist for the vast majority of future influenza pandemics. As such, it is all the more important to understand this association between southern China and influenza pandemics as a means of preparation. Even so, while southern China should undoubtedly remain a key component of influenza research, it should not overshadow other potential hotspots for viral production. As highlighted in this thesis, it is the unique combination of farming techniques, proximity to livestock, gastronomical and cultural habits, population density, and climate that make southern China a breeding ground for influenza viruses with pandemic tendencies. These factors prove by far the most influential, though by no means embody all of the idiosyncrasies inherent to this region that sustain southern China's penchant for pandemic influenza viruses. As more light is shed on this topic and more advancements are made in the field of virology, hopefully one day this undeniable link between southern China and influenza pandemics will be valuably understood.

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Abstract

Influenza pandemics have been regular occurrences throughout much of history, yet have only recently been accurately explored due to the development of modern technology and scientific insight. The three influenza pandemics of the twentieth century were among the first to be evaluated in such a fashion, imparting more knowledge than ever before about this particular affliction. In the years 1918, 1957 and 1968, the world was overwhelmed by the viral infection influenza and for the first time, had an ever-advancing foundation for understanding the malady at fault. Among the most contentious facets of this research became the origin of these global outbreaks. Investigations over the course of the last century have revealed that viruses responsible for influenza pandemics hold a striking association with the region of southern China. This thesis maintains that the devastating events of the 1918, 1957 and 1968 illnesses all began in this area of the world, as did the vast majority of influenza pandemics recorded throughout history. By reflecting on the origins of the three major infections of the twentieth century, this examination contemplates the social, cultural and environmental factors inherent to southern China that contribute to its undeniable proclivity for generating pandemic influenza viruses. Farming techniques, living arrangements, cultural and gastronomical habits, population density and tropical climate are identified as the key variables fostering conditions conducive to the mutation and spread of influenza. The importance of analyzing a highly potential

source for influenza pandemics such as southern China is to enhance methods of prevention, preparation, containment and response for the inevitable emergence of future infections.

Kurzfassung

Obwohl Grippepandemien im Laufe der Geschichte immer wieder auftraten, wurden sie erst in letzter Zeit genauer untersucht. Möglich war dies aufgrund der Entwicklung moderner Technologien und erweiterten wissenschaftlichen Verständnisses. Die drei Grippepandemien des 20. Jahrhunderts waren unter den ersten, die auf diese Weise untersucht wurden, ermöglichten sie doch auch mehr Erkenntnisse als je zuvor über diese spezielle Krankheit. In den Jahren 1918, 1957 und 1968 wurde die Welt von durch Viren ausgelöste Grippeinfektionen überrollt. Zum ersten Mal war es dabei möglich, die Seuche zunehmend zu verstehen. Als eine der umstrittensten Facetten dieser Untersuchung stellte sich der Ursprung dieser globalen Ausbrüche heraus. Forschungen während des letzten Jahrhunderts haben gezeigt, dass die Viren, die für die Influenzapandemien verantwortlich sind, eine sehr enge Verbindung mit der Region des südlichen China aufweisen. Die vorliegende Arbeit geht davon aus, dass die zerstörerischen Vorkommnisse der Krankheit von 1918, 1957 und 1968 alle in dieser Gegend der Welt begannen, ebenso wie eine große Mehrheit der anderen Grippepandemien, von denen wir im Laufe der Geschichte wissen. Bei der Reflexion der Ursprünge der drei großen Infektionswellen des 20. Jahrhunderts beachtet die Studie die sozialen, kulturellen und umweltbedingten Faktoren, die dem südlichen China inhärent sind und die einen unbezweifelbaren Nährboden für die Entstehung pandemischer Influenzaviren schaffen. Landwirtschaftstechniken, Lebensformen, kulturelle und gastronomische Gewohnheiten, Bevölkerungsdichte und tropisches Klima werden als die

Schlüsselvariablen identifiziert, die die wesentlichen Voraussetzungen für die Mutation und Verbreitung der Grippe schaffen. Die Bedeutung der Identifizierung einer hoch potenten Quelle für Grippepandemien wie das südliche China liegt darin, dass Methoden der Vorsorge, Vorbereitung, Eindämmung und Reaktionen beim unvermeidbaren Ausbruch künftiger Infektionen verbessert werden können.

Curriculum Vitae

Education

Bachelor of Arts, Global Studies (Emphasis in Culture and Ideology)

Academic Minor: Spanish

University of California, Santa Barbara, CA, USA.

Date of Graduation: June 2007, Summa cum Laude (Highest Honors).

International Academic and Professional Experience

Teaching Assistant,

United International College

Zhuhai, Guangdong, China (08/07-07/08)

Instructed first and second year Linguistic, TESL and Academic Writing tutorials. Graded weekly journals, exams, and short essays. Coordinated on-campus organizations, including the Science Club and the Dance Club. Assisted in organizing activities for Student Affairs. Volunteered as a UIC staff English instructor at local, underdeveloped primary schools.

University of California EAP Exchange Student,

University of Stirling

Stirling, Scotland (09/06-06/07)

Studied International Politics throughout a year-long program, supplemented with courses in Scottish history and culture. Increased international awareness through academic studies, campus involvement and travel experiences.

University of California EAP Exchange Student,

Lunds Universitet

Lund, Sweden (06/06-08/06)

Explored International Business and Politics with Swedish university students in a 10-week academic program. Completed an introductory course in Swedish language, culture, and history.

Silk Road to the Future Program, Legends of China Foundation

Beijing, Xian, and Shanghai, China (07/05)

Participated in a cultural exchange with Chinese university students. Acted as an Ambassador of Peace representing the United States.

University of California EAP Exchange Student,

Universidad Michoacana de San Nicolas de Hidalgo

Morelia, Mexico (06/04-08/04)

Completed a 10-week Spanish language and culture immersion program through the University of California Education Abroad Program.