AN ABSTRACT OF THE DISSERTATION OF

Barbara C. Canavan for the degree of Doctor of Philosophy in History of Science, presented on December 4, 2015

Title: Opening Pandora's Box at the Roof of the World: The Past and Present of Avian Influenza Science

Abstract approved:

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Anita Guerrini

By means of a case study and historical analysis, this dissertation examines the past and present of avian influenza. By integrating disconnected histories of human and animal influenza, this dissertation links historical insights with the concerns of contemporary avian flu science. It is not only a natural history of avian influenza but also a snapshot of avian flu science in progress. To understand human influenza, its path and potential, one must be aware of how avian influenza viruses came to play such a central role in human influenza ecology.

Building on a history of influenza in both its human and avian forms, a contemporary case study examines the unprecedented emergence of an avian virus among wild birds on the Qinghai-Tibet Plateau (Roof of the World) beginning in 2005. Events at Qinghai stimulated an interdisciplinary and international approach among researchers, and accelerated the use of technological tools to track avian influenza.

Evidence suggests that the escalation of global bird flu events is not merely a matter of chance mutations in flu viruses but is the result of antecedent conditions related to human activities. Events and science at Qinghai serve as real-world examples to

understand avian influenza and to envision the unintended consequences of human and natural forces over the coming decades.

This synthesis of avian influenza history and science can serve as a resource for historians of medicine, environmental historians, biologists, virologists, ecologists, and the broader public.

Opening Pandora's Box at the Roof of the World:
The Past and Present of Avian Influenza Science

by
Barbara C. Canavan

A DISSERTATION

submitted to

Oregon State University

in partial fulfillment of
the requirements for the
degree of

Doctor of Philosophy

Presented December 4, 2015
Commencement June 2016

Doctor of Philosophy dissertation of Barbara C. Canavan presented on December 4, 2015.

APPROVED:

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I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Barbara C. Canavan, Author

ACKNOWLEDGEMENTS

I thank my major professor, Anita Guerrini, for her generous encouragement and guidance. She is a superb mentor who encouraged both scholarship and creativity. I am also indebted to my committee members, Michael Osborne, Steve Rubert, David Bernell, and Jake Hamblin for sharing their expertise. I had outstanding opportunities to learn from top scholars.

My participation at the Hertog Global Strategy Initiative (The History and Future of Pandemic Threats) at Columbia University was an extraordinary experience. I also thank the staff at the Rockefeller Archive Center for their support and for the opportunity to conduct research there.

For Doug, my gratitude for your support, encouragement, and inspiration is beyond words. I give special thanks to Lillian and Patrick for always being there, cheering me on. The wisdom and encouragement from my professors, my family, and fellow students made this goal possible.

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Chapter One: Introduction

1.1 Overview: Avian Influenza in Nature and Society

From a broad perspective, much of what is familiar about the history of human civilization is the direct result of a stable interglacial period suitable for agriculture and prolonged human settlement over the past millennia. It is challenging to comprehend the scale of changes in our human-constructed and natural worlds. In particular, there is no historical analog for understanding the impact of such changes on the microbial world. This dissertation seeks to examine changes for one familiar and recurring aspect of that microbial world: the influenza virus.

The volume of avian influenza (bird flu) outbreaks in the first few years of the twenty-first century has already exceeded the total number of outbreaks recorded for the entire twentieth century.[1] In poultry, bird flu has gone from being an exceedingly rare disease to one that emerges continuously, seemingly an evolution in fast forward. The World Health Organization characterized the continued presence of the influenza virus in wild birds and poultry farms as a global health crisis and one of the most extensive animal diseases ever recorded.[2] There is fear that if an avian influenza virus were to become transmissible among humans (currently, it is not) it would herald a pandemic worse than the one of 1918. Even absent a catastrophic pandemic, some experts see bird flu as a "dress rehearsal" for future zoonotic disease, one in which the pathogen originates in the animal world.[3]

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[1] Ruth Cromie et al., "Responding to Emerging Challenges: Multilateral Environmental Agreements and Highly Pathogenic Avian Influenza H5N1," *International Wildlife Law and Policy* 14, no. 3–4 (2011): 206–42.

[2] Anthony J McMichael, Maria Neira, and David L Heymann, "World Health Assembly 2008: Climate Change and Health," *Lancet* 371, no. 9628 (June 7, 2008): 1895–96.

[3] Ian Scoones, *Avian Influenza: "Science, Policy and Politics"* (Routledge, 2012), 3. Zoonotic disease is a disease that can be passed between animals and humans. Zoonotic diseases can be caused by viruses, bacteria, parasites, and fungi.

Much of the impetus associated with influenza virus research has been a direct result of the frequent pandemics that occur within the human population. Yet, for decades, both medical and veterinary experts dismissed bird viruses as irrelevant to human health. The acknowledged presence of bird flu in humans since 1997 has reinforced the need for a more detailed understanding of the natural history and ecology of wild birds.

By means of a case study and historical analysis, this dissertation argues that to understand human influenza, its path and pandemic potential, one must be aware of how flu viruses in birds came to play such a central role in human disease ecology. Building on a history of influenza in both its human and avian forms, a contemporary case study examines the unprecedented emergence of an avian flu virus among wild birds at the Qinghai-Tibet Plateau (known as The Roof of the World) beginning in 2005. While chickens die of bird flu, some aquatic birds do not get sick. Sometimes, they fly off to other parts of the world carrying the virus.

1.2 Qinghai Case Study Context

The case study follows a shift within environmental history to a more place-centered approach. The vast Qinghai-Tibet Plateau [Qinghai] of western China is at the center of a region that stores more snow and ice than anywhere outside earth's polar regions. Qinghai Lake became an unlikely hotspot for the suspected spread of avian influenza along the migratory routes of wild birds to Europe and Africa.

The Qinghai case study examines how an interdisciplinary network of experts converged at this remote region to study the spread of influenza among wild and domestic birds. This scientific community tracked avian flu viruses not only under the microscope but also across migratory bird flyways. Surveillance of wild birds over these vast spatial and temporal scales required a collaborative effort among researchers.

The technology used for a spatiotemporal analysis of viruses on a landscape scale is both fascinating and important for continued virus research. Primary research conducted at Qinghai is well documented in the scientific literature of both basic and applied sciences. However, few studies have assessed the ecological and historical precedents of avian influenza, knowledge now greatly informed by events at Qinghai. The literature review provides a framework to relate my research to previous findings.[4] No single treatment has been of sufficient scope to encompass the social, environmental, and geopolitical contexts of avian flu viruses at Qinghai.

Although remote in location, Qinghai offers an unprecedented opportunity to study connections among microbial, environmental, and human factors. This dissertation provides a synthesis of natural events and scientific studies that can serve as a resource for historians of medicine, environmental historians, evolutionary biologists, virologists, researchers, and the broader public. The history of bird flu events at Qinghai, and the science emerging from these events, is significant not only for understanding natural events but also for informing contemporary policies.

1.3 Research Goals, Questions, and Arguments

This dissertation focuses on how viruses, particularly flu viruses, connect to other phenomena in nature, and what is known and unknown about viruses' relationship with animal and human hosts. The fact that the historical and potential future consequences of viruses are almost unrivalled among infectious diseases is one reason that avian influenza warrants more attention from historians, ecologists, bioethicists, and scientists from diverse fields. This dissertation links historical insights with the concerns of contemporary avian flu science.

[4] See chapter two for literature review.

Specific research questions and dissertation arguments include:

What are the shifting dynamics in nature and society that permit avian flu viruses to flourish with increasing frequency? Based on historical analysis, avian flu epidemics prior to 1997 were, with few exceptions, confined to single farms or geographic areas. Exponential increases in bird flu outbreaks are not merely a matter of chance mutations in flu viruses but are a result of antecedent conditions. Environmental disruption, industrial poultry farms, human and animal population density, and agricultural practices that mix wild and domestic birds are factors that act synergistically to create a perfect storm for bird flu. The Qinghai case study provides real-world examples that bring these factors into sharp focus.

What does history reveal about shifts in the production of knowledge about influenza in humans and animals? The history of avian influenza reveals a remarkable interconnected viral web among birds, swine, horses, and people. The accumulation of scientific knowledge for such a complex system has been incremental. Beginning in the 1930s, influenza was thought to be a human-only disease but by mid-century, there was a limited understanding of the kinship between animal and human flu viruses. During the 1940s, researchers came to the realization that flu viruses change so often that new vaccines had to be manufactured for each flu epidemic season. The 1950s introduced a persistent legacy in influenza research to attempt to predict the timing and severity of potential pandemics based on characteristics of the flu virus itself. During the 1976 "swine flu fiasco," predictive theories of influenza proved to be unreliable. By 1974, researchers had evidence that flu viruses in birds were the primordial source of human influenza. This introduced another paradigm shift in scientific understanding that took decades to win acceptance among the scientific community. By 1997, scientists understood that a bird virus could transmit

directly to humans, another monumental realization. During 2005, it became evident that wild birds could carry pathogen flu viruses over long distances. This dissertation claims that avian flu science today is at the forefront of a reinvigorated ecological approach to the study of microbes and disease. The mutable nature of the flu virus itself has shaped scientific assumptions and knowledge about influenza for decades and continues to do so. Knowledge about flu viruses is incomplete, always changing.

How did the bird flu crisis at Qinghai stimulate new scientific understanding about the ecology of influenza at the human-animal interface? Qinghai became a natural experiment that energized a community of virus hunters, stimulated an interdisciplinary and international approach, and accelerated the use of technological tools to track the virus along bird migration flyways. Technological expertise, outside of the virologists' traditional methods, became essential in producing new knowledge about the ecology of avian viruses. Based on the evidence presented in the case study, raising bar-headed geese near domestic poultry presented a plausible route for the evolution of the avian virus to its highly pathogenic form. This dissertation claims that Qinghai is at the center of complex evolutionary changes in viruses that coincide with human exploitation and climate-induced shifts in the environment.

What are the points of controversy about the potential role of bird migration in spreading avian flu viruses into new geographic areas? This dissertation argues that, based on scientific evidence, wild birds (not poultry trade) carry an avian flu virus (H5N1) from Qinghai westward to many countries in Europe and Africa. Domestic poultry play a significant role at the local level and are the means by which bird flu transmits to humans. This dissertation claims that wild migratory birds have become, under some circumstances, vectors of a disease that had previously been pathogenic only for domestic poultry.

1.4 Chapter Summaries

Chapter two (Theoretical Framework, Methods, and Literature Review) provides details for a hybrid theoretical framework that is unique to this dissertation. This framework engages with historical perspectives considered part of natural history: environmental history, historical ecology, history of disease, and public history. Chapter two also describes how the dissertation makes use of Actor Network Theory as a descriptive tool. Hybrid methods are used to characterize the enormous volume of bird flu research. The literature review provides a framework to relate my research to previous findings and histories.

Chapter three (Ecological Dimensions of Viruses) examines the nature of viruses and their place at the boundary of living and non-living organisms. Tracing the changes over time in scientific understanding of viruses, this chapter summarizes current knowledge about the transmission of viruses among humans and animals. The chapter also examines environmental conditions that can drive the emergence of infectious diseases. There is a history of ecological approaches to microbes and disease from the 1930s, and how contemporary avian flu science has reinvigorated this ecological tradition.

Chapter four (Avian Influenza: Biography of a Cross-Species Virus*)* provides a natural history of the influenza virus. Historical perspectives include details of avian flu outbreaks among poultry recorded since the late nineteenth century, the escalating number of bird flu outbreaks since the 1990s, and changes over time in the scientific understanding of influenza. There is a discussion of today's industrial factory farms and their potential links to the frequency and scale of avian influenza outbreaks. Chapter four details the circumstances under which the avian flu virus infected people beginning in 1997 and how bird flu infections escalated following the events at Qinghai.

Figure 1 Qinghai Case Study Logo, B. Canavan, 2015.

Chapter five (Qinghai Case Study: Opening Pandora's Box at the Roof of the World) introduces the case study actors beginning with the high altitude train across the Qinghai-Tibet Plateau. Outlining the sequence of events at Qinghai since 2005, this chapter traces the path of the H5N1 avian virus and how scientists tracked it along the flyways of migratory birds. This chapter also examines the potential role of climate change and other environmental disruptions in the emergence of avian flu. Finally, by means of systematic mapping, the chapter analyzes the characteristics of the scientific literature about events at Qinghai.

Chapter six (High Politics and Pandemic Predictions) addresses the challenges of influenza prevention through vaccines. Currently, there is no vaccine available to protect people from the most dangerous strains of avian influenza should it become transmissible among humans. Addressing shifts in the production of new knowledge of influenza, this chapter focuses on influenza research beginning in the 1930s and includes contemporary controversies surrounding avian flu research. The history of predictive theories for pandemics is informative to explain how these theories became part of the legacy of influenza science.

The dissertation conclusion considers broader meanings and connections related to influenza at the boundary of human, animal, and environmental domains.

Chapter Two: Theoretical Framework, Methods and Literature Review

A central tenet of modern humanistic scholarship is that everything exists in a context that is historically, geographically, and culturally particular.[5] Accordingly, a history of avian influenza requires an analysis that covers not only the details of tracking viruses but also integrates environmental, social, and geopolitical factors. The interplay of humans, birds, and other animals across temporal and geospatial dimensions suggests that an integrative approach is most suitable for this analysis.

2.1 Theoretical Framework

The theoretical framework consists of an interdisciplinary approach, a natural history or ecological perspective, descriptive elements from Actor Network Theory and the Theory of Black Swan Events. These elements frame the analysis of past events to examine the history, ecology, and social contexts of avian influenza. This hybrid theoretical framework is specific and unique to this research.

Interdisciplinarity

Interdisciplinarity, a key component of systems theory, remains a rather ambiguous term. The National Science Foundation (NSF) defines interdisciplinarity as:

> …a mode of research by teams or individuals that integrates information, data, techniques, tools, perspectives, concepts, and/or theories from two or more disciplines or bodies of specialized knowledge to advance fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline or area of research practice.[6]

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[5] Cronon, *Uncommon Ground*. William Cronon, ed., *Uncommon Ground: Rethinking the Human Place in Nature* (W. W. Norton & Company, 1996).
[6] National Science Foundation, Committee on Facilitating Interdisciplinary Research, Committee on Science, Engineering, and Public Policy, *Facilitating Interdisciplinary Research*, 2.

The most relevant aspect of the NSF definition for this dissertation is the concept of integrating science from two or more disciplines. For this dissertation, an integrated approach emphasizes an ecological or natural history perspective to understand avian flu as a disease that spans wildlife, veterinary, and human medical disciplines.[7] Interdisciplinarity provides the conceptual framework to investigate natural and human phenomena from a holistic perspective. Historical perspectives from natural history and ecology, both complex interdisciplinary systems, are quite relevant for this dissertation.

Historians Kohler and Olesko argued that disciplinary boundaries have separated humanistic disciplines from the natural sciences since the mid-nineteenth century and have, at times, prevented the dissemination of knowledge across broad fields of study.[8] According to virologist Paul Ewald, science and medicine in particular focus on specialization, "…pressuring researchers to focus on particular trees – often the molecules within the cells of the leaves of the trees – instead of the forest."[9] Such a disciplinary approach can lead to a loss of focus on the larger picture, one that is stripped of context and reduced to what can be measured without being deeply understood.[10]

Philosopher/historian Rheinberger advised scholars that in order to follow the development of epistemic things rather than concepts, disciplines, institutions, or researchers we must locate our inquiries in the boundaries of these systems.[11] This dissertation locates viruses at this cross-disciplinary level by tracing the path of an avian virus as an "epistemic object," one that has a changing or unfolding character. This requires abandoning specific

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[7] Christian Sandrock, "Editorial," *Comparative Immunology, Microbiology and Infectious Diseases* 32, no. 4 (July 2009): 253–54.
[8] Robert E. Kohler and Kathryn M. Olesko, "Introduction: Clio Meets Science," *Osiris* 27, no. 1 (January 1, 2012): 1–16, 6.
[9] Paul Ewald, *Plague Time: The New Germ Theory of Disease* (New York: Anchor, 2002), x.
[10] Kohler and Olesko, "Introduction," 7.
[11] Hans-Jorg Rheinberger, "Cytoplasmic Particles," in *Biographies of Scientific Objects*, ed. Lorraine Daston (Chicago: University of Chicago Press, 2000), 273.

classifications in the history of science such as history of microbiology, or biochemistry or virology. As Polanyi explained, the force of epistemic objects lies in what they might become without knowing the precise path.[12]

The bird flu events at Qinghai have sparked the interest of researchers from many fields. However, for the most part, they were unaware of each other's work. A wild bird expert in Britain was not aware of how a high altitude railway played a role in explaining the dissemination of avian flu over parts of Europe beginning in 2005. Nor did the German wildlife expert and historian know of experiments conducted with wild birds at Qinghai. Some infectious disease researchers, including those working with influenza, were not aware of how the environmental and social factors at Qinghai had an impact on the course of new and potentially dangerous strains of avian flu. It is a goal of this dissertation to bring these stories forward in a way that crosses disciplinary boundaries.

Historical Perspectives

Natural history is the systematic study of any category of natural objects or organisms.[13] Some scientists consider natural history as the search for and description of patterns in nature.[14] Historian John Lewis Gaddis argued that historians typically find common cause with those who study the natural world as it changes over time.[15] Natural history forms part of the foundation of a diverse set of disciplines including biology, ecology, and botany. Ecologist Charles Elton declared in 1927 that ecology was just a new name for

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[12] Rheinberger, "Cytoplasmic Particles," 272.
[13] Lesley Brown and William Little, eds., *The New Shorter Oxford English Dictionary on Historical Principles* (Oxford: Clarendon Press, 1993).
[14] Terry A. Wheeler, Lyman Entomological Museum, 2012
[15] John Lewis Gaddis, *The Landscape of History: How Historians Map the Past* (Oxford: Oxford Univ. Press, 2004).

natural history.[16] According to ecologist Thomas Fleischner, the scope of natural history has narrowed from its earliest incarnations when natural history examined everything.[17] Many experts concur that natural history is, most of all, interdisciplinary.[18]

For the study of viruses, natural history provides a context for examining the avian virus within its host environment. This dissertation also engages with historical perspectives closely related to or considered part of natural history: environmental history, historical ecology, history of disease, and public history.

Environmental historians examine history as an interaction between and among the human and nonhuman components of the natural world.[19] An environmental history perspective relates to several themes within the dissertation: how disrupted environments link to emerging viruses and other pathogens and how climate change is affecting the environment at the Qinghai-Tibet Plateau.

Historical ecology involves understanding the human-environment relationship in order to gain a full picture of all of its accumulated effects.[20] Historical ecology focuses on the interactions between humans and their environment over long time frames, typically over the course of centuries. It is particularly applicable to sources of data at the landscape scale. The historical ecology of the Qinghai-Tibet Plateau underscores that this is a region with abrupt changes in climate.

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[16] Charles Elton, *Animal Ecology* (Chicago: University Of Chicago Press, 1926).
[17] Thomas Lowe Fleischner, "Revitalizing Natural History," *Wild Earth*, 1999.
[18] Natural History Network, 2015.The Natural History Network is a consortium of institutional and individual advisors from the sciences, arts, and humanities to promote the value of natural history.
[19] Donald Worster, *Nature's Economy: A History of Ecological Ideas*, (Cambridge University Press, 1994); Cronon, *Uncommon Ground*; Alfred Crosby, *Ecological Imperialism : The Biological Expansion of Europe, 900-1900*, (Cambridge Univ. Press, 2004); Carolyn Merchant, *Radical Ecology: The Search for a Livable World*, (Routledge, 2005); Susan D. Jones, "Body and Place," *Environmental History* 10, no. 1 (January 2005), 47-48.
[20] W Balée, *Advances in Historical Ecology* (New York: Columbia University Press, 2002).

In 2014, an *American Historical Review* [AHR] roundtable entitled "History meets Biology" addressed how historians can engage with human biology, environmental history, and the co-evolutionary history of humans and other species.[21] Paleontologist Norman MacLeod argued that engaging biologists with historical analysis opens the door for a new range of explanations for historical events.[22] With this framework in mind, this dissertation not only includes perspectives from historians but also from virologists and ecologists among others.

Public History, history applied to real-world issues, is also a significant focus of this dissertation. MacLeod argued that history is a dialog with the past to understand the present in order to make reasoned choices about the future.[23] According to historian J.A. Thomas, historians can and perhaps should examine more closely the role of humans in contemporary history through activities such as agriculture and technology that threaten earth's "life support systems."[24] This dissertation provides not only a natural history of avian influenza but also a snapshot of avian flu science in progress.

One characteristic of contemporary history is the enormous volume of information. The relevant sources for such recent history are not the work of individual scientists but of collaborative groups.[25] Historian Lorraine Daston has argued that sciences that are dependent on abundant data (such as the studies at Qinghai) collected by many hands (such as the study of avian viruses), use methods of analysis that are just as historical as those from archives.[26] Historian Bruno Strasser agreed that collections of data (in this case, about avian viruses),

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[21] AHR Roundtable, "History Meets Biology."
[22] N. Macleod, "Historical Inquiry as a Distributed, Nomothetic, Evolutionary Discipline," *The American Historical Review* 119, no. 5 (December 1, 2014): 1608–20.
[23] Macleod, "Historical Inquiry as a Distributed, Nomothetic, Evolutionary Discipline."
[24] J. A. Thomas, "History and Biology in the Anthropocene: Problems of Scale, Problems of Value," *The American Historical Review* 119, no. 5 (December 1, 2014), 1590.
[25] Doel and Söderqvist, *The Historiography of Contemporary Science, Technology, and Medicine*.
[26] Lorraine Daston, "The Sciences of the Archive," *Osiris* 27, no. 1 (January 2012): 156–87.

when gathered in electronic databases, can be subsumed under the same category as other historical collections, such as natural history collections of plants, animals, or fossils.[27] For these reasons, this dissertation is as much an examination of science in progress as it is a history of disease. I not only rely on archival and scientific reports but also consider the avian viruses themselves as primary sources with a significant history of their own.

2.2 Qinghai Case Study Methods

The analytical tools outlined here include a case study methodology; a method to describe "actors" in the case study; a theory to analyze the unpredictable nature of events at Qinghai; and a systematic mapping method to characterize empirical evidence from Qinghai.

The Qinghai case study requires multiple lenses to bring the total picture into focus. This dissertation focuses on a mid-picture view based in the case study, one that combines large-scale views with micro studies. Historian William Cronon suggested that the best historical narratives "take flight on both wings" to consider the broader picture as well as the details.[28] For the details, medical historian/physician Guenter Risse recommended the use of local, specific case studies to expose the web of causality for disease. Risse suggested that historians include contemporary knowledge about fluctuating ecosystems and their impact on human health and disease.[29] This dissertation takes up these challenges by including an analysis of environmental disruption as part of the Qinghai case study.

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[27] Bruno J. Strasser, "Collecting Nature: Practices, Styles, and Narratives," *Osiris* 27, no. 1 (January 2012): 303–40.
[28] William Cronon, "Breaking Apart, Pulling Together," *Perspectives on History* 50, no. 5 (2012): six.
[29] Personal communication with Guenter B. Risse, May 2013. Dr. Risse is Professor Emeritus, Department of Anthropology, History and Social Medicine, at the University of California, San Francisco, and Affiliate Professor of Bioethics and Humanities at the University of Washington in Seattle.

Case Study Methodology

Social scientist Robert Yin defined a case study as an empirical inquiry that investigates a contemporary phenomenon in depth and within its real-life context. According to Yin, the case study research method is appropriate for "how" or "why" questions when the investigator has little control over events and the focus is on a contemporary phenomenon within a real-life context.[30] Relevant to this research, the Qinghai case study examines potential causal links about "how" and "why" this remote place became a hotspot for the spread of avian influenza.

However, "why" questions in evolutionary biology are inherently difficult, as researchers do not understand why viruses respond to pressures in the natural world. Real-life context is often quite different from laboratory experimental results. Indeed, the rapid evolutionary path of viruses makes them resistant to human purposeful ends. Although the case study method certainly informs the narrative, a limitation of Yin's case study method is that it cannot address why viruses do what they do.

The case study method calls for multiple sources of evidence in a triangulating fashion and the development of converging lines of inquiry. Yin claimed that the strength of a case study is in its ability to deal with a variety of evidence including documents, observations, and interviews.[31]

Actor Network Theory

Although Actor-Network Theory (ANT) carries "theory" in its name, this research employs ANT as a descriptive method to reveal connections among the actors. According to

[30] Robert Yin, *Case Study Research : Design and Methods* (Los Angeles, CA: Sage Publications, 2009), 2.
[31] Ibid., 11.

ANT, actors or actants can be humans, animals, objects and concepts; all have equal standing in the narrative. Historian Bruno Latour, a developer of ANT, urges the researcher to follow the actors in the story wherever they may go.[32]

The actors in this case study include a wild goose that migrates over the Himalayas; a high-altitude railroad to Tibet that traverses a vast permafrost landscape; technology deployed to build the railway; an avian virus that first appeared in 1997; and a context within contemporary bioscience and geopolitics. As a place, the Qinghai-Tibet Plateau is the broad constant among mutable factors on the micro scale, one of which is the avian virus. Viruses serve as actors in their role to stimulate scientific discovery at the intersection of microbe, environment, and human conditions at Qinghai.

Theory of Black Swan Events [black swan]

Economist and author Nassim Nicholas Taleb introduced the metaphor of the black swan, a bird once thought not to exist, to explain financial events. He extended the black swan concept beyond finance to explain difficult-to-predict and rare events in history and the present.[33] Taleb defines a black swan event as one this is outside the realm of expectation and carries extreme impact. Taleb argued that human nature makes us concoct explanations for the occurrence of a black swan event after the fact, making it explainable and predictable.[34]

Gaddis encouraged the use of metaphors (such as the black swan) to help historians find larger patterns in history.[35] Applying the theory of black swan events to the Qinghai

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[32] Bruno Latour, *Science in Action : How to Follow Scientists and Engineers through Society* (Cambridge, Mass.: Harvard University Press, 1987).
[33] Nassim Nicholas Taleb, *The Black Swan* (New York: Random House Trade Paperbacks, 2010), xviii.
[34] Ibid., xxi–xxii.
[35] Gaddis, *The Landscape of History*, 2.

case study highlights that an unpredictable, high-impact event has major social, environmental, economic and political implications.[36]

Systematic Mapping of Qinghai Case Study Sources

Systematic mapping is a repeatable and transparent scientific method used to identify, categorize and map literature relevant to a topic.[37] The purpose of a systematic or topic map for this dissertation is to identify and describe the nature, volume, and characteristics of avian flu research, a topic with over seven thousand articles published since 1997. This dissertation uses systematic mapping as a form of historiography, a way of gathering and interpreting the source material with new findings and insights.

The process and rigor of the systematic mapping exercise is similar to a statistical meta-analysis, except there is no quantitative synthesis. The latter would require a statistical analysis that is beyond the scope of this dissertation. Systematic maps also differ from meta-analyses in that the topic area can be much broader, the scope can be tailored to fit the research questions at hand (as long as the method is transparent), and the types of sources included may be descriptive and derive from a broad range of published and unpublished literature and books.[38]

The study inclusion criteria for this dissertation include only those articles or documents that are relevant avian flu research (subtype H5N1) from 1997 to 2015 as well as relevant to the Qinghai case study from 2005 through 2015. To map scientific reports from

[36] See chapter five for a detailed discussion of black swan events.
[37] Systematic Mapping Methods (Collaboration for Environmental Evidence, 2014).
[38] The search terms for the Qinghai case study systematic map include the key actors defined by the case: Qinghai, H5N1, wild birds, virus, railway, influenza, ecohealth, climate change, ecology, and environment. Search strings (combination of terms using Boolean characters) are methods used to pool different searches run separately.

empirical science, I use Web of Science (WoS), Google Scholar, and Medline to aggregate the source data by research category. Journals are the focus of WoS and Medline, selected for inclusion by humans based on scholarly criteria by literature review committees. The WoS is interdisciplinary and covers all scientific areas, but only includes what it considers the most authoritative journals. Articles in Medline and WoS also have tags with important information about their structure. Review articles are particularly valuable for this broad systematic mapping.

I supplement searches with Google Scholar results to capture conference proceedings, books, and reports that are not included in WoS or Medline. Because Google Scholar searches the full text of articles, one can find information that is not necessarily in the citation or abstract of an article. However, in contrast to WoS and Medline, Google Scholar is not a human-curated database but a search engine of the whole internet that narrows the internet results based on machine-automated criteria. Both Google Scholar and WoS track the number of citations by other articles, books, or sources.[39]

It is clear that no one database can provide a comprehensive picture of the Qinghai case research. WoS is the primary search database for this dissertation because it provides tools to group results by author, publication year, institution, subject category, document type, source title, language, or country.

[39] In a preliminary search of "Qinghai" and "H5N1", Medline produced 67 articles but missed 14 articles from WoS because the latter were articles from environmental or ecological sources. Since this research focuses on an ecohealth approach, this would leave a gap in the analysis. In a search of "Qinghai" and "H5N1" and "Railway" WoS yielded no results. However, Google Scholar yielded about 40 relevant articles, some relevant for this dissertation, from university scholar archives, professional organizations, international health organizations, digital commons, books, on-line resources, avian workshop outcomes, and other sources. Thus, Google Scholar is a critical resource despite its limitations as a blunt tool that produces too much unrelated material.

Using provisional data, **Figure 2** shows a visual map with results from several searches organized by number of articles retrieved, number of research category, and whether the studies involved collaboration across multiple disciplines.

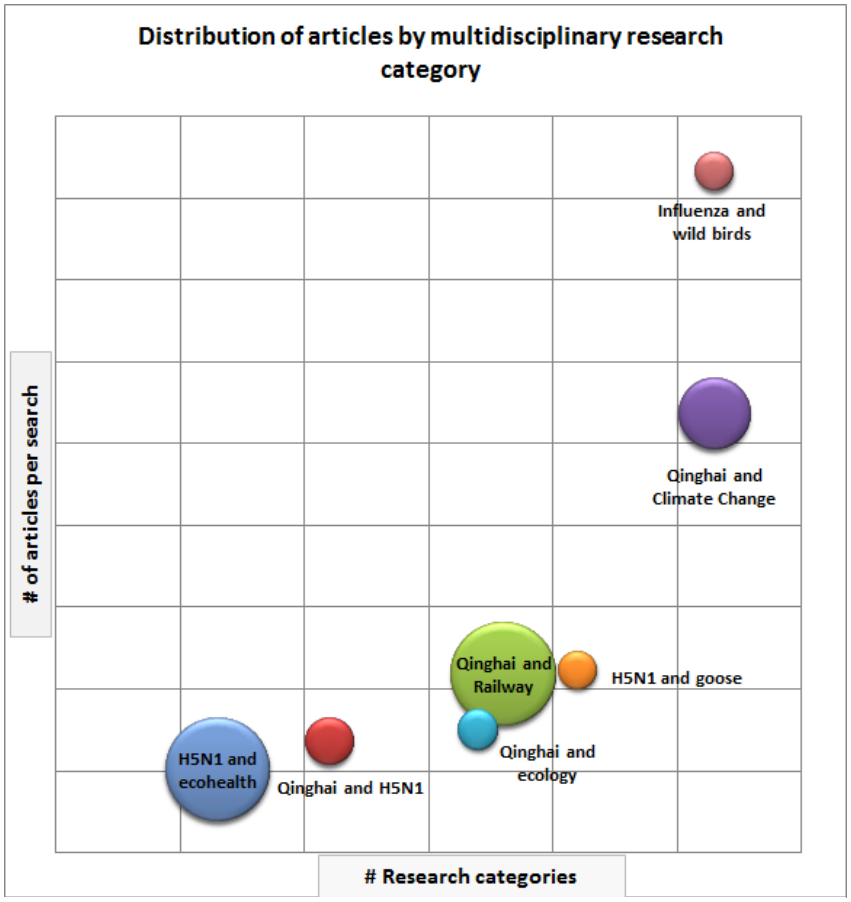

Figure 2 Systematic Mapping sample. B Canavan, 2015.

Figure 2 illustrates results from several sample literature searches. The size of the circles represents the percent of articles for that search that are marked "multidisciplinary" by the WoS. For example, the result for "H5N1" and "ecohealth" reveals a small number of articles and research categories but a high percentage of these are interdisciplinary. This makes sense – by definition, ecohealth is an integrated approach. Alternatively, the search for "influenza" and "wild birds" reveals a high number of articles and research areas.

However, these studies stay within disciplinary boundaries of virology or avian disease and only about 10% of articles marked as "multidisciplinary."

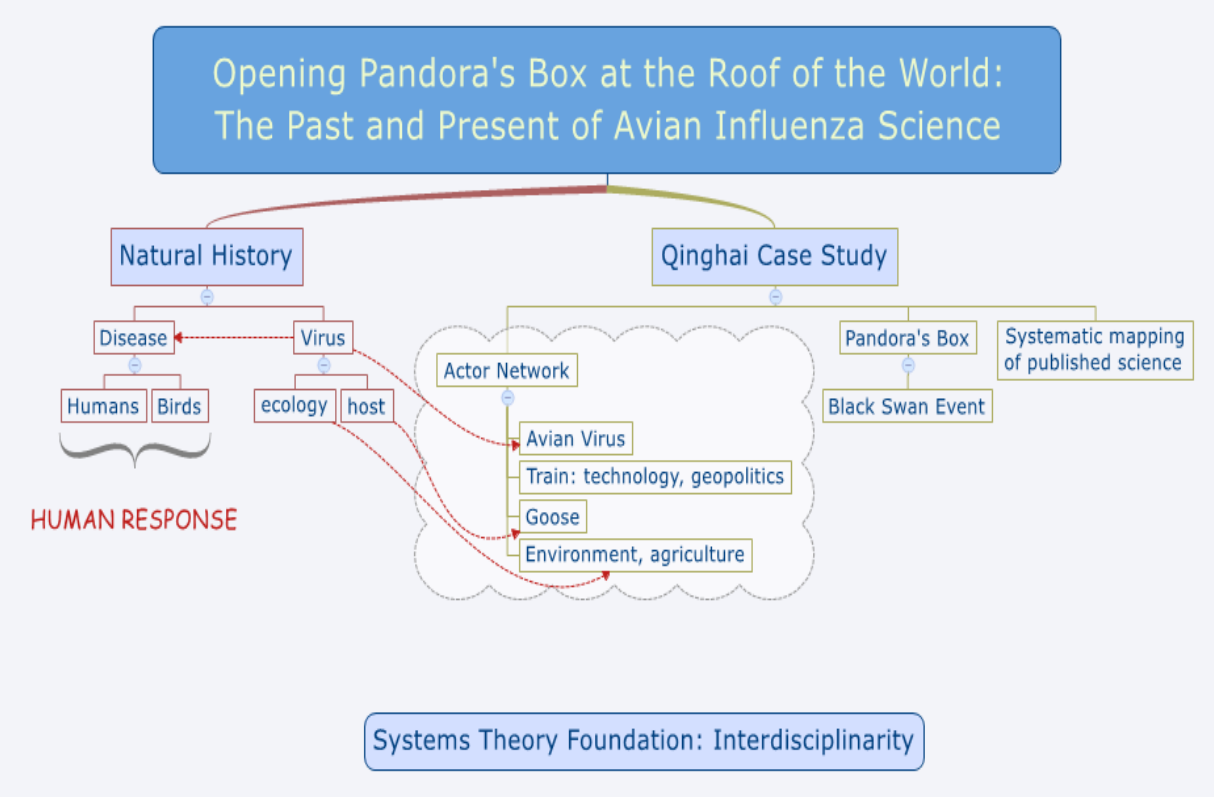

Figure 3 Theoretical Framework, Canavan 2015.

Figure 3 visualizes key elements from the theoretical foundation outlined in this chapter. The theoretical framework consists of two major elements with a foundation an interdisciplinary perspective, a method from systems theory. First is the natural history of the virus and its ecology. The influenza virus produces disease in humans and other animals, particularly birds. Secondly, the Qinghai Case Study displays the actors in the case - virus, train, goose, and environment. The train serves as a method to capture the environmental, technological, and geopolitical aspects of the Qinghai region. The theory of black swan events and the systematic mapping are part of the case study framework.

2.3 Literature Review and Primary Sources

Highlighting the most relevant sources, I organize this literature review by major themes within the dissertation. These themes encompass the scientific understanding of the virus as an infectious agent; the history of influenza in humans; the history of influenza in horses, pigs, and birds; the intersecting paths of human and animal influenza; and the Qinghai case study.

Historical Perspectives: The Virus and Virology

Until the beginning of the nineteenth century, observers believed that diseases were from one of two poisons: virus or miasma. A "virus" was a visible poison such as saliva from a rabid dog or snake venom. Miasma was an invisible gas from swamps, decaying vegetation and carcasses thought to cause infectious disease and plagues.[40] After confirmation of the Germ Theory of Disease, the word "virus" became a convenient term for referring to infectious agents not yet identified. It was not until the late 1890s that the word "virus" was applied to submicroscopic agents. Despite their long history as infectious agents, it was only during the past century that the concept of the virus as a separate entity emerged.

Focusing on the Golden Age of Bacteriology in the 1880s and 1890s, historian Sally Smith Hughes examined the initial understanding of viruses as agents that pass through a bacteria filter and remain virulent.[41] In addition to the discovery of filterable agents, historians of science have emphasized theories concerning the origins of viruses, the

[40] Dorothy Crawford, *The Invisible Enemy: A Natural History of Viruses* (Oxford University Press, USA, 2003).
[41] Sally Smith Hughes, *The Virus : A History of the Concept* (London; New York: Science History Publications, 1977).

experimental developments in the field, and the placement of virology as an independent science by the mid-twentieth century.[42]

By the early twentieth century, the term "virus" became entangled with questions concerning both the nature of life as well as the etiology of disease.[43] Waterson and Wilkinson, who mapped the progress of fowl plague beginning in Italy in 1901, not only saw virology as the development of a new discipline but also as the progressive unveiling of the nature of the virus particle itself.[44] Physician/historian Scott Podolosky described three ways to conceptualize the virus: as a metaphor for life itself, as an operational model for understanding how life emerged, and as a historical entity or living fossil. This dissertation uses the latter concept of a virus - an entity with a history of its own.

The first viruses researched were those in clinically or agriculturally important hosts: yellow fever in humans, mosaic disease in tobacco, foot-and-mouth disease in livestock.[45] Yet, the nature of the virus remained an open question through the early 1930s, even as the fowl plague virus, bacteriophage, and tobacco mosaic virus provided some of the competing models for its resolution. Historian Angela Creager produced a comprehensive history of the tobacco mosaic virus that served as a model system for virology and molecular biology from the 1930s through the 1960s.[46] There was no serious attempt to integrate the findings among disparate virus fields until Salvador Luria's textbook appeared in 1953.[47] Luria focused on

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[42] Hughes, *The Virus*; Alfred Grafe, *A History of Experimental Virology* (New York: Springer-Verlag, 1991); Susie Fisher, "Are RNA Viruses Vestiges of an RNA World?" in *Darwinism, Philosophy, and Experimental Biology*, ed. Ute Deichman and Anthony S. Travis (Dordrecht: Springer Netherlands, 2010), 67–87.
[43] Scott Podolsky, "The Role of the Virus in Origin-of-Life Theorizing," *Journal of the History of Biology* 29, no. 1 (1996): 79–126.
[44] A. P Waterson and Lise Wilkinson, *An Introduction to the History of Virology* (Cambridge; New York: Cambridge University Press, 1978).
[45] Angela N. H. Creager, *The Life of a Virus: Tobacco Mosaic Virus as an Experimental Model, 1930-1965*, (University Of Chicago Press, 2001).
[46] Ibid.
[47] S. E. Luria, *General Virology*, (Hoboken, NJ: J. Wiley and Sons, 1953).

the similarities of viruses to encourage a uniform view among animal, plant, and bacterial viruses.

Thus, throughout the first half of the twentieth century, the study of viruses encompassed different branches of science, each involving a different group of hosts: plants, vertebrates, insects, and bacteria.[48] This early history suggests that the study of viruses did not readily lend itself to an interdisciplinary approach. This legacy and culture may be an enduring feature of viral research. However, the science conducted as Qinghai may be an exception because of its cross-disciplinary engagement. Alternatively, avian science at Qinghai it could be the leading edge of new ways to produce scientific knowledge.

By mid-century, important theoretical and social changes took place in virus research. Scientific interest grew and virology soon emerged as a unified field with its own conferences, journals and textbooks.[49] Van Helvoort described how at least six journals dedicated to virology started during the 1950s that were critical to continuing virus research.[50] Institutions devoted to virological research emerged at the University of California, Berkeley and at the Max Planck Institute at Tübingen, Germany.[51] Historian Grafe detailed the path of discovery to catalog 200 insect viruses, 300 plant viruses, and 200 animal viruses by the late 1950s.[52]

By the 1970s, the reassortment theory of viruses, in which genetic mixing occurs between human and animal strains, came to the fore.[53] Reassortment occurs when two different influenza viruses infect the same host; the segments from the two viruses can swap

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[48] Erling Norrby, "Nobel Prizes and the Emerging Virus Concept," *Archives of Virology* 153, no. 6 (2008): 1109–23.
[49] Hughes, *The Virus*, 104–105.
[50] van Helvoort, "When Did Virology Start?"
[51] Hughes, *The Virus*.
[52] Alfred Grafe, *A History of Experimental Virology* (Berlin; New York: Springer-Verlag, 1991).
[53] Nathan Wolfe, *The Viral Storm: The Dawn of a New Pandemic Age* (NY: St. Martin's Griffin, 2012).

in many different ways. This had important implications for influenza science, as reassortment explained potentially unlimited viral mutations.

Since the 1970s, the focus for viral research shifted to one of anticipation or even control over viruses. For the study of virology since the 1970s, epidemiologist Erwin Rijswoud divides the field into five stages, based on the alternation of times of crisis and of control.[54] The late 1970s was the age of perceived "control" over infectious diseases. The period of 1982-1993 was the first crisis in modern virology with the HIV-AIDS crisis. From 1993-1997 was a time of relative stability, of controlling the crisis. By 1997-2003, however, the second crisis in modern virology occurred with the first human avian flu death and the SARS crisis. Rijswoud characterized the period after 2003 as one of anticipating future crises with emphasis on viral composition and genetic history. My research engages with Rijswoud's second crisis in modern virology characterized by the avian flu dilemma.

The next sections explore the history of influenza as a persistent viral disease, one that infects not only humans but also a range of species.

Historical Perspectives: Influenza in Humans

For this review, I focus on those sources that provide (or at least, consolidate) accounts of human influenza epidemics and pandemics, as well as interpretations from historians of medicine and virologists. The purpose of this section is to provide a condensed history of human influenza as background and comparison for the history of influenza in other animals, especially birds.

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[54] Erwin Rijswoud, "Virology Experts in the Boundary Zone Between Science, Policy and the Public: A Biographical Analysis," *Minerva* 48, no. 2 (May 28, 2010): 145–67.

Historical reports authored jointly by virologist/historian David Morens and virologist Jeffrey Taubenberger, scientists at the U.S. National Institutes of Health, provide a framework for my own examination of influenza disease history. Collaborating with the National Library of Medicine, Morens and Taubenberger produced a rich historical resource not only about the clinical history of influenza but also about the flu viruses themselves.[55] This provides a significant resource to achieve my dissertation goal of tracing how the divergent histories of human and animal influenza interconnect.

Morens and Taubenberger developed criteria for classifying influenza pandemics prior to the year 1889, and they use specific historical timeframes - 1194 BCE to 875 CE; 876 to 1491; 1492 to 1728; and 1729 to 1888. Pandemic (from the Greek, "of all the people") refers to the widespread occurrence of a disease over one or more regions of the world. Pandemic criteria include documentation of symptoms with fever and respiratory symptoms; high attack rates across a broad age range; relatively low mortality; and rapid spread in at least two geographical regions. These criteria presented their own challenges.

According to Morens and Taubenberger, until the 1500s, there was little appreciation of influenza as a distinct disease; until the mid-1700s, scientists did not view influenza as a distinct pathological entity; until the 1830s, there were few measurements of flu incidence; and until the late 1800s, flu mortality rates were not calculated.[56] There has long been

[55] David M. Morens and Jeffery K. Taubenberger, "Pandemic Influenza: Certain Uncertainties," *Reviews in Medical Virology*, June 27, 2011; J.K. Taubenberger and D.M. Morens, "Pandemic Influenza – Including a Risk Assessment of H5N1," *Revue scientifique et technique (International Office of Epizootics)* 28, no. 1 (April 2009): 187–202; J. K. Taubenberger and D. M. Morens, "Influenza: The Once and Future Pandemic," *Public Health Reports* 125, no. Suppl 3 (2010): 16; David M Morens, Michael North, and Jeffery K Taubenberger, "Eyewitness Accounts of the 1510 Influenza Pandemic in Europe," *The Lancet* 376, no. 9756 (December 2010): 1894–95; David M. Morens et al., "Pandemic Influenza's 500th Anniversary," *Clinical Infectious Diseases* 51, no. 12 (December 2010): 1442–44.

[56] Morens and Taubenberger, "Pandemic Influenza."

disagreement about which historical outbreaks were from actual influenza pandemics and which were not.

Accepting historical reports of flu back to the 1500s requires a willingness to accept unproven evidence that epidemics behave as they have in the modern era. Such evidence includes uncatalogued publications, monastery chronicles, newspapers, and diaries. In the absence of definitive proofs, retrospective diagnoses may be mere speculation. Some historians advocate complete avoidance of retrospective diagnoses to identify a modern disease.[57] In addition, there may be bias in the historical record in the form of missing evidence about significant flu epidemics. Virologic data with laboratory confirmation only reaches back to the 1930s.[58]

However, detailed investigations of ancient DNA of infectious diseases have demonstrated that the study of disease evolution at a genetic level can be successful.[59] This is particularly relevant for avian flu science as phylogenetic information can provide a clear history of particular viral strain including its ancestry.[60]

While the Morens and Taubenberger criteria for pandemics are more robust compared to others, I do depart from their framework to consider other historical accounts. I weave their histories together with accounts from other experts who have examined the evidence of disease from many centuries past. At times, of course, these accounts do not agree. Disagreement increases among experts the further back one goes in the history of influenza.

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[57] Piers D. Mitchell, "Retrospective Diagnosis and the Use of Historical Texts for Investigating Disease in the Past," *International Journal of Paleopathology* 1, no. 2 (October 2011), 82.
[58] C. W Potter, "A History of Influenza," *Journal of Applied Microbiology* 91, (October 1, 2001): 72–79.
[59] Taubenberger et al., "Reconstruction of the 1918 Influenza Virus"; Taubenberger et al., "Characterization of the 1918 Influenza Virus Polymerase Genes."
[60] See chapter 5 for more details about phylogenetic analysis.

For the first designated historical period (1194 BCE to 875 CE) for influenza pandemics, Morens and Taubenberger claimed that information is insufficient.[61] No reports of epidemics met their criteria for a pandemic due to imprecise clinical and epidemiological descriptions. However, there are numerous reports of disease from historians and scientists that might constitute local flu epidemics. Based on examination of primary source documents, nineteenth-century medical historian August Hirsch concluded that disease outbreaks might have been influenza in the following years: 412 BCE, 591-2, 817, 876, 889, and 927.[62] Hirsch claimed that flu epidemics have occurred since at least the Middle Ages, if not since ancient times. Microbiologist C.W. Potter also argued for a possible influenza epidemic based on early Greek writing of 412 BCE.[63]

For their second designated historical period (876 to 1491), there were many historical reports of febrile coughing disease attributed to local or pan-European influenza epidemics; however, none of these met the Morens and Taubenberger criteria for a pandemic.[64] From a different perspective, nineteenth century medical geographer Frank Clemow argued for pandemics spanning multiple geographical regions in 927, 1173-74, and 1386-87.[65] Hirsch, medical historians Mirko Grmek and K. David Patterson, and virologist Beveridge were in accord that the first influenza epidemic with recognizable symptoms was in 1173–74.[66] Hopkirk reported that there was sufficient evidence to establish influenza

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[61] Morens and Taubenberger, "Pandemic Influenza."
[62] August Hirsch, *Handbook of Geographical and Historical Pathology, Volume 1*. (London: New Sydenham Society, 1883).
[63] Potter, "A History of Influenza."
[64] Morens and Taubenberger, "Pandemic Influenza."
[65] F. Clemow, "Epidemic Influenza," *Proceedings of the Society of Medical Officers of Public Health. Public Health* 2 (1890): 358–67.
[66] Hirsch, *Handbook of Geographical and Historical Pathology*; Grmek, *Les maladies an l'aube de la civilisation occidentale*; W. I. B Beveridge, *Influenza: The Last Great Plague, An Unfinished Story of Discovery* (Prodist, 1978); K. David Patterson, *Pandemic Influenza 1700-1900* (Rowman & Littlefield Publishers, 1986).

epidemics in the years 1323 (all the inhabitants of Florence afflicted), 1386-87, 1403, and 1410 (in Paris 100,000 persons attacked in each year).[67]

For the third designated historical period (1492 to 1728), influenza reports became more consistent during this age of European exploration. Morens and Taubenberger emphasized that the 1510 pandemic was the first recognizable pandemic that met their pandemic criteria.[68] In fact, they argued for three major pandemics in the sixteenth century: 1510, 1557, and 1580.[69] These pandemics arrived in Mediterranean Europe from the trade routes and spread northwesterly. Beveridge also pointed to evidence for a 1510 pandemic, believed to come from Africa, that raged all over Europe.[70]

Theophilus Thompson, a notable physician in Victorian London, reviewed primary accounts from sixty-five physicians during twenty local epidemics in England from 1510 to 1897. His history featured meteorological conditions and other coincident phenomena. For example, following the epidemic of 1510, Thompson described "great swarms of locusts in Seville," and "in the next year, a comet." An epidemic in 1557 was preceded by "ill-smelling fogs," "a comet," and an eruption of Mount Etna.[71] Entomological theories of flu included those in which the victims swallowed injurious insects.[72] Hopkirk also compiled a unique digest of ancient epidemics, one that combines clinical symptoms of influenza with meteorological conditions such as atmospheric conditions in general and volcanic eruptions

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[67] Arthur F. Hopkirk, *Influenza: Its History, Nature, Cause, and Treatment* (The Walter Scott Publishing Co., 1914), 64-65.
[68] Taubenberger and Morens, "Pandemic Influenza – Including a Risk Assessment of H5N1"; D. Finkler, *Influenza in Twentieth Century Practice, Ed. Stedman* (London: Sampson Law & Marston, 1899).
[69] Morens and Taubenberger, "Pandemic Influenza: Certain Uncertainties," 3.
[70] Beveridge, *Influenza*.
[71] Theophilus Thompson, *Annals of Influenza or Epidemic Catarrhal Fever in Great Britain from 1510 to 1837.* (London: The Sydenham Society, 1852).
[72] G B Risse, "Epidemics and Medicine: The Influence of Disease on Medical Thought and Practice," *Bulletin of the History of Medicine* 53, no. 4 (1979): 505–519; Hopkirk, *Influenza*, 76.

in particular.[73] Historian Margaret DeLacy emphasized that these reports were consistent with traditional beliefs that invisible emanations might be the root cause of widespread epidemics.[74]

By the seventeenth century, the term “influenza” was common in Europe, although regional variations persisted. For centuries, natural philosophers believed the position of the stars "influenced" outbreaks of a disease of what could have been influenza. Many observers referred to a sixteenth century Edinburgh epidemic as “a newe acquayntance.”[75] Other terms in Europe included "the gentle correction", "the new delight," "the Dunkirk rant," and "the knock-me-down fever."[76] During the eighteenth century, the French began calling the disease “la grippe.”[77] In parts of Germany, influenza was “the chirp.”[78]

Thus, descriptions of influenza by the eighteenth century were euphemistic expressions, more like waltz names than terrible earthy emanations. Clearly, there had been a shift in understanding of disease. Influenza was one of many infections and diseases and perhaps not the worst of them. However, there were exceptions. Writing after a devastating early eighteenth century European-wide epidemic of an influenza-like illness, English country doctor John Huxham characterized it as the “morbus omnium maxime epidemicus” or the “greatest of all sicknesses.”[79]

For the fourth historical period (1729 to 1889), Morens and Taubenberger claimed that pandemics originated in Asia in 1719, 1733, 1781, 1833, and 1889 and spread westward

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[73] Hopkirk, *Influenza*, 12.
[74] See also John Huxham’s history of influenza certainly reflects this “neo-hippocratic” tradition. DeLacy, “Influenza Research and the Medical Profession in Eighteenth-Century Britain,” 42–43, 50–51,64.
[75] Crawford, *The Invisible Enemy*, 2003, 91.
[76] Hopkirk, *Influenza*, 9.
[77] Beveridge, *Influenza*, 25.
[78] Morens and Taubenberger, “Historical Thoughts on Influenza Viral Ecosystems.
[79] *John Huxham, Observations on the Air and Epidemic Diseases from the Year MDCCXXVIII to MDCCXXXVII Inclusive (*London: J. Hinton and H. Whitfield, 1759*).* Hopkirk, *Influenza*, 57.

through Russia and northern Europe. Between 1789 and 1889, the Western Hemisphere exhibited influenza patterns disconnected from Europe and the rest of the world.[80]

Comprehensive accounts of influenza-like illness in Europe for the eighteenth and nineteenth centuries appeared in the historical reports from Edmund Thompson and Hirsch.[81] Patterson examined influenza outbreaks using primary source documents; he counted ten pandemics from 1700 through 1900, or three to five per century.[82] Medical geographer Pyle argued that some epidemics corresponded with the establishment of the Hanseatic League and the rapid expansion of cities along the Baltic coast.[83]

Prior to the twentieth century, patient treatments for influenza varied greatly. After the pandemic of 1782, English physicians apparently accepted that influenza was a distinct and contagious disease.[84] By the early nineteenth century, physicians increasingly acknowledged that bloodletting and purgatives were harmful to the patient during influenza epidemics. Small doses of opium, however, were considered beneficial.[85] By the end of the nineteenth century, the perception was that influenza was a nuisance but not necessarily a disaster. This perception would change soon enough.

According to Patterson, the "Russian" flu of 1889-90 was the first influenza pandemic documented to be truly global in scale and range.[86] The "Russian" flu pandemic took only four months to circumnavigate the world, peaking in the United States 70 days

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[80] D. Finkler, *Influenza in Twentieth Century Practice* (London: Sampson Law & Marston, 1899).
[81] Hirsch, *Handbook of Geographical and Historical Pathology*; Edmund Thompson, *Influenza, Or Epidemic Catarrhal Fever: An Historical Survey Of Past Epidemics In Great Britain From 1510-1890* (Nabu Press, 2010); Charles Creighton, *A History of Epidemics in Britain.* (Cambridge, UK: Cambridge Univ Pr, 1891); Finkler, *Influenza in Twentieth Century Practice.*
[82] Patterson, *Pandemic Influenza 1700-1900*, 83.
[83] Gerald F. Pyle, *The Diffusion of Influenza: Patterns and Paradigms* (Rowman & Littlefield, 1986).
[84] Hopkirk, *Influenza*, 96.
[85] Thompson, *Annals of Influenza or Epidemic Catarrhal Fever in Great Britain from 1510 to 1837*, 246.
[86] Patterson, *Pandemic Influenza 1700-1900*, 49.

after its initial peak in St. Petersburg.[87] The rapid progression of the 1889 pandemic demonstrated that even relatively slow surface travel by rail and steamship sufficed to spread the pandemic across all of Europe and the United States in several months. Since 1889, all pandemics, by definition, have been global.

By all accounts, the 1918 influenza pandemic was one of the most dramatic events in medical history and possibly the most devastating disease outbreak since the plague swept Europe and Asia in the fourteenth century. The 1918 influenza virus infected a third of all people on earth and killed more people than were killed in combat during World War I.[88] Microbiologists have argued that no other human viruses known thus far have shown the pathogenicity of the 1918 virus.[89] Influenza had become not only an inescapable part of modern life but also a disease that endangers the health and economic welfare of the state itself.[90]

Morens, Taubenberger and Fauci produced numerous historical and virological articles about the 1918 pandemic, one they referred to as "the mother of all pandemics."[91] Historians including Alfred Crosby, John Barry, and Patterson provided in-depth chronicles

[87] Alain-Jacques Valleron et al., "Transmissibility and Geographic Spread of the 1889 Influenza Pandemic," *Proceedings of the National Academy of Sciences* 107, no. 19 (May 11, 2010): 8778–81,
[88] Carl Zimmer, "In 1918 Flu Pandemic, Timing Was a Killer," *The New York Times*, April 30, 2014.
[89] Terrence M. Tumpey et al., "Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus," *Science* 310, no. 5745, New Series (October 7, 2005): 77–80.
[90] Andrew T. Price-Smith, *Contagion and Chaos: Disease, Ecology, and National Security in the Era of Globalization* (The MIT Press, 2008); M. Bresalier, "Uses of a Pandemic: Forging the Identities of Influenza and Virus Research in Interwar Britain," *Social History of Medicine* 25, no. 2 (December 15, 2011): 15.
[91] Taubenberger and Morens, "1918 Influenza: The Mother of All Pandemics"; Morens and Fauci, "The 1918 Influenza Pandemic"; Morens, Taubenberger, and Fauci, "The Persistent Legacy of the 1918 Influenza Virus"; Morens and Taubenberger, "1918 Influenza, a Puzzle with Missing Pieces."

of the social history of the 1918 pandemic and its human toll.[92] From the virological perspective, Beveridge and Burnet produced comprehensive accounts.[93]

The Asian Flu (1957-58) pandemic spread globally tracing shipping routes and, to a lesser extent, airline routes.[94] This was the first pandemic to appear in the modern era of virology. Today, researchers speculate that in 1957, somewhere in southern China, a bird flu virus may have infected either a pig or a person already suffering from the regular H1N1 seasonal human flu, and an "unholy viral matrimony" took place.[95] Historian of science George Dehner provided an account of the mid-century attempts to produce a timely influenza vaccine in the United States.[96] Although the public health response to the 1968 Hong Kong Flu pandemic was quicker than 1957, the pandemic peaked before release of vaccine. Investigators attempted to outrun the influenza virus to predict the next big pandemic.[97] This would become a common theme in influenza research.

In 1976, an outbreak of swine flu struck Fort Dix Army base, killing a young soldier and infecting hundreds of others. Experts quickly determined that this was a novel virus very similar to the deadly 1918 influenza virus. Confident in their ability to forecast the next pandemic, the U.S. Public Health Advisory Committee warned that a major antigen change – creating a novel flu virus - signaled that a global pandemic was looming.[98] Vaccine

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[92] Crosby, *Epidemic and Peace, 1918*; Barry, *The Great Influenza*; Barry, "1918 Revisited: Lessons and Suggestions for Further Inquiry"; Patterson and Pyle, "The Diffusion of Influenza in Sub-Saharan Africa during the 1918–1919 Pandemic"; Beveridge, *Influenza*, 1978; Burnet, *Natural History of Infectious Disease*.
[93] Beveridge, *Influenza*; Burnet, *Natural History of Infectious Disease*.
[94] Theodore C. Eickhoff, *The Epidemiology of Asian Influenza, 1957-1960, A Descriptive Brochure* (Atlanta: CDC, 1960); Pyle, *The Diffusion of Influenza*.
[95] William Graeme Laver, Norbert Bischofberger, and Robert G. Webster, "The Origin and Control of Pandemic Influenza," *Perspectives in Biology and Medicine* 43, no. 2 (2000): 173–192.
[96] George Dehner, *Influenza: A Century of Science and Public Health Response*, (Pittsburgh: University of Pittsburgh Press, 2012).
[97] See chapter six for discussion of pandemic predictions.
[98] CDC Liability Proposal, "Recommendation of the Public Health Service Advisory Committee on Immunization Practices/Influenza Vaccine Preliminary Statement." RG 442, Box 8, NARA-SE Region.

production was rushed and the U.S. vaccinated forty million people in ten weeks.[99] Alas, the pandemic never materialized, vast sums of money were spent without a real threat to human health, and there were serious adverse reactions to the vaccine. In a lesson about the capricious nature of viruses, experts soon realized that a novel influenza virus does not necessarily lead to a pandemic. Although the 1976 Swine Flu did not turn into a pandemic, it became a pivot point that changed U.S. public health response to flu from one of attempting to predict the next pandemic to one of preparing for the inevitable.[100]

In 2009, the Swine Flu pandemic spread quickly and globally, a reassortment of avian, human and swine viruses.[101] This flu strain took global public health officials by surprise. They were keenly aware of the avian influenza spreading throughout Asia, a catastrophe for chickens, with occasion human cases and deaths. Thus, avian influenza appeared to be the most likely source of the next human pandemic. However, the 2009 pandemic was a swine viral subtype, not avian. Despite harried but successful multinational vaccination campaigns, the 2009 pandemic strain was relatively mild. The World Health Organization faced widespread criticism for labeling swine flu a pandemic in 2009, a label that did not communicate the mildness of the virus.[102]

In summary, despite accounts that were imprecise and fragmentary, gathering details from many sources provides a picture of human influenza disease for at least 500, and possibly 1000 or more, years.[103] Allowing for the shortcomings of retrospective diagnosis, this history reveals that characteristic symptoms of flu remain reasonably consistent. The

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[99] Richard E. Neustadt and Harvey V. Fineberg, "Policy-Making and the Swine Flu Scare," in *the Case Study Anthology*, ed. Robert K. Yin, (Thousand Oaks, CA: SAGE Publications, 2004).
[100] See chapter six for a full discussion of the 1976 Swine Flu.
[101] Morens and Taubenberger, "Pandemic Influenza."
[102] Wolfe, *The Viral Storm*.
[103] Morens, North, and Taubenberger, "Eyewitness Accounts of the 1510 Influenza Pandemic in Europe."

distinguishing feature of influenza is that many people get sick but relatively few die.[104] There are exceptions, with the 1918 pandemic being the most prominent. Yet, historical evidence of pandemic occurrence provides no obvious cyclic patterns over the centuries.[105]

From their perspective, Morens and Taubenberger argued that influenza pandemics represent brief moments in which fit viruses temporarily get a step or two ahead of human immunity.[106] Human immunity is a layered defense that includes each individual's exposure to prior influenza viruses or vaccines. The dilemma is the potential emergence of a flu virus that is so novel, so different from any in current circulation, that the human immune system has no memory of it. Researchers are beginning to get a glimpse of what factors may be in play and from what sources the next pandemic will emerge.[107]

For example, through genomics, researchers have come to understand that all twentieth century pandemic influenza viruses - 1918, 1957, 1968, and 2009 - acquired some or all of their gene segments from the avian influenza gene pool.[108] This raises the question of how scientists came to understand influenza as not only a disease for humans but also for birds and other animals. Influenza is a phenomenon with an array of animal hosts larger than anyone had thought possible and may be more evolutionarily flexible than previously realized. In the next section, I explore historical accounts of influenza at the boundary of human and animal life.

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[104] Patterson, *Pandemic Influenza 1700-1900*, 86; Hopkirk, *Influenza*.
[105] Morens and Fauci, "The 1918 Influenza Pandemic."
[106] Morens and Taubenberger, "Pandemic Influenza."
[107] See chapters three, four, and five.
[108] Morens, Taubenberger, and Fauci, "The Persistent Legacy of the 1918 Influenza Virus."

Influenza at the Human-Animal Boundary

Accounts of disease at the human-animal boundary by both historians and scientists provide historical context for examining a cross-species virus such as influenza.[109] The study of disease at the human-animal interface reveals a common narrative thread: microbes appear, disappear, but ultimately evade total human control.

In addition to humans, influenza infects warm-blooded animals including horses, pigs, and especially birds. The focus here is to highlight historical accounts of circumstances under which a flu virus may have jumped from its animal host to humans.[110] Most researchers acknowledge, based on current understanding, that wild aquatic birds are the natural reservoir for human influenza (subtype A) viruses.[111] In fact, aquatic birds carry all the known influenza viruses, and these viruses usually cause the birds no harm.

Physicians and veterinarians from the eighteenth and nineteenth centuries provided accounts of the prevalence of influenza-like illness in animals before, during, and after visitations of human influenza. There were reports of coincident and overlapping occurrences of influenza-like illnesses in both humans and animals beginning in the late fifteenth century. Many were anecdotal accounts from farmers, physicians, eyewitness accounts, newspapers, and diaries. Morens and Taubenberger claim that animal disease records remained incomplete and fragmented until the late nineteenth century.[112]

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[109] Robert G. Wallace, "Breeding Influenza: The Political Virology of Offshore Farming," *Antipode* 41, no. 5 (November 2009): 916–51; Richard P. Tucker, *Insatiable Appetite: The United States and the Ecological Degradation of the Tropical World, Concise*, (Rowman & Littlefield Publishers, 2007); Susan D. Jones, *Death in a Small Package: A Short History of Anthrax*, Johns Hopkins Biographies of Disease (Baltimore: Johns Hopkins University Press, 2010); Andrew Lakoff and Stephen J Collier, eds., *Biosecurity Interventions: Global Health & Security in Question* (New York: Columbia University Press, 2008); William C. Summers, *The Great Manchurian Plague of 1910-1911: The Geopolitics of an Epidemic Disease* (New Haven: Yale University Press, 2012).

[110] See chapters four and five in this dissertation.

[111] Webster et al., "Evolution and Ecology of Influenza A Viruses."

[112] Morens and Taubenberger, "Historical Thoughts on Influenza Viral Ecosystems," 3.

Influenza in Horses

There is no doubt that horses can and do get their own horse-adapted influenza, but is there evidence that horses and humans have shared the same circulating influenza virus? Because of people's close association with horses, these were among the first reports of influenza-like illness in animals. For example, Fleming referenced reports of influenza among French soldiers and their cavalry of horses during the Thirty Years' War (1646-47).[113] Reporting on a human influenza epidemic in 1760, naturalist John Rutty noted there was scarcely a horse in Dublin that did not have influenza.[114] In 1829, veterinarian Thomas Forster indicated "…an epidemic catarrh followed all over Europe, beginning among horses and ending with men as is frequently the case."[115]

Historian Hirsch observed that it was extraordinary how many reports there were about horses affected with the same influenza as people during epidemics.[116] According to Beveridge's historical review, during the eighteenth and nineteenth centuries outbreaks of influenza-like illness in horses were associated with human influenza epidemics in twelve epidemic periods. He cautioned, at the time of his writing in 1927, that these reports must be regarded with "fanciful speculation" and skepticism.[117]

Morens and Taubenberger conducted historical analyses of horse influenza to determine if there were any facts to support the purported pattern between human and equine influenza.[118] Their findings showed, from 1658 until the early 20th century, there was a close

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[113] George Fleming, *Animal Plagues: Their History, Nature, and Prevention.* (London: Chapman and Hall, 1871); J. Law, "Influenza in Horses," in *Commission of Agriculture (ed.): Report of the Commissioner of agriculture for the Year 1872* (Washington, DC: Government Printing Office, 1874), 203–48.
[114] John Rutty, *A Chronological History of the Weather and Seasons, and of the Prevailing Diseases in Dublin:* (Robinson and Roberts, 1770), 158-159.
[115] Thomas Forster, *Illustrations of the Atmospherical Origin of Epidemic Disorders of Health* (London: T. & G. Underwood, 1829), 162.
[116] Hirsch, "Handbook of Geographical and Historical Pathology."
[117] Beveridge, *Influenza*, 55.
[118] Morens and Taubenberger, "Historical Thoughts on Influenza Viral Ecosystems", 5.

temporal-geographic association between horse and human influenza. This was particularly true in 1872, when there was a severe and well-documented epidemic of influenza illness among horses in communities near Toronto.[119] The equine epizootic quickly devastated horse populations all over North America and shut down commerce in the U.S. for weeks, preventing travel, transport, mail, and delivery of goods.[120] Morens and Taubenberger emphasized evidence for the explosive 1872-73 Western Hemispheric pandemic that they associated with an equine epizootic (a disease that is temporarily widespread in an animal population).[121] During that time, there were some outbreaks of human influenza, known at the time as "the zooty" as they were so closely associated with the equine flu.[122]

Morens and Taubenberger found that outbreaks consistent with equine influenza were associated with human epidemics and pandemics more often than not. In fact, they claimed that from the seventeenth through the nineteen centuries "…influenza was almost as much of an equine disease as it was a global human disease."[123]

It is difficult to dismiss historical reports of influenza in horses in light of new scientific findings. Researchers now suggest that, based on genomic analysis of the evolutionary relationships of influenza virus across different host species over time, many viruses circulating globally since the early 1870s are related to those that infect horses.[124]

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[119] Hopkirk, *Influenza*, 50; Law, "Influenza in Horses"; Judson, "A Report on the Origin and Progress of the Epizootic among Horses in 1872."
[120] David M. Morens and Jeffery K. Taubenberger, "An Avian Outbreak Associated with Panzootic Equine Influenza in 1872: An Early Example of Highly Pathogenic Avian Influenza?" *Influenza and Other Respiratory Viruses* 4, no. 6 (November 1, 2010): 373–77.
[121] Morens and Taubenberger, "Historical Thoughts on Influenza Viral Ecosystems."
[122] "Zooty" was a plot device in the novel *Rambling Rose* by C. Willingham (New York: Delacourt Press, 1972); Law, "Influenza in Horses"; Judson, "A Report on the Origin and Progress of the Epizootic among Horses in 1872."
[123] Morens and Taubenberger, "Pandemic Influenza," 5; Morens and Taubenberger, "Historical Thoughts on Influenza Viral Ecosystems."
[124] Michael Worobey, Guan-Zhu Han, and Andrew Rambaut, "A Synchronized Global Sweep of the Internal Genes of Modern Avian Influenza Virus," *Nature* 508, no. 7495 (February 16, 2014): 254–57.

Evolutionary results do not allow for a determination of whether the virus jumped from birds to horses to humans or any specific transmission pattern. The genomic clock methods used for this analysis are quite new and the peer-review process is in its early stages.

Influenza in Swine

While it was common knowledge that horses harbored influenza viruses, it was surprising that pigs might also be susceptible to influenza infections. In 1919, veterinarian Koen, an inspector for the U.S. Bureau of Animal Husbandry, was convinced that what he called "swine flu" was the very same "Spanish flu" that infected humans during the 1918 pandemic.[125] Of course, local pig farmers rejected this claim. However, with a study of a swine influenza epidemic in 1928-29 in Iowa, the start of a new story about influenza began to emerge.

Rockefeller virologist Richard Shope, familiar with hog farming, took a keen interest in swine illnesses. In the early 1930s, using a bacteriological filter, Shope isolated an influenza virus from sick pigs and used the fluid to infect healthy pigs. [126] Shope initially proposed that swine influenza was the surviving prototype of the 1918 pandemic virus based on his experimental results.[127] He was adamant that hogs caught the flu from humans in the 1918 pandemic.[128] Virologist Peyton Rous remarked "…in 1918 from the pig's point of view – and Shope's too I might add – human beings served as intermediate hosts to a virus that

[125] JS Koen, *A Practical Method for Field Diagnosis of Swine Diseases*, vol. 14 (Veterinary Publishing Company, 1919).
[126] Richard E. Shope, "Swine Influenza," *The Journal of Experimental Medicine* 54, no. 3 (July 31, 1931): 349–359.
[127] Richard E. Shope, "The Incidence of Neutralizing Antibodies for Swine Influenza Virus in the Sera of Human Beings of Different Ages," *The Journal of Experimental Medicine* 63, no. 5 (April 30, 1936): 669–684; Jeffery K. Taubenberger and David M. Morens, "Influenza Revisited," *Emerging Infectious Diseases* 12, no. 1 (January 2006): 1–2.
[128] Francis to Sippy, May 29, 1936, Folder 6, Box 50, Series 4, RG 5, IHD Records, FA115, RF, RAC; Richard E. Shope, "Swine Influenza".

some unlucky swine received."[129] Beveridge claimed that the 1918 virus became so well adapted that it has persisted in pigs since that time.[130] In fact, since 1918 the swine flu virus has circulated in pig populations, becoming one of the most common causes of respiratory disease on North American pig farms. Yet, it remains unclear whether humans gave the virus to swine or swine gave it to humans in 1918.[131]

Researchers now understand that pigs are susceptible to infection with both avian and human influenza strains (in addition to their own swine flu strains), and are thus a "mixing vessel" for flu viruses with pandemic potential for humans.[132] Virologist Robert Webster carried out crucial experiments in the early 1970s to demonstrate how this mixing takes place. He housed pigs infected with 1968 Hong Kong virus (human strain) with pigs who had swine influenza (swine strain). Within a week, a hybrid influenza virus appeared. Different flu viruses that co-infect the same cell can swap gene segments with each other.[133] Webster referred to this genetic mixing process as "viral sex."[134] Viral diversity generated through this genetic reassortment process is vast and plays an important role in the evolution of influenza viruses.[135]

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[129] Peyton Rous, 1957, "Presentation of the Kober Medal to Richard Shope," p. 32, Folder 2, Biographical General 1935-1965, Box 1, FA199, Richard E. Shope Papers, RU, RAC
[130] Beveridge, *Influenza*, 86.
[131] Barry, *The Great Influenza*, 446.
[132] Webster et al., "Evolution and Ecology of Influenza A Viruses." Webster is the Chair in Virology at St. Jude Children's Research Hospital and Director of the World Health Organization Collaborating Center on othe Ecology of Influenza Viruses in Lower Animals and Birds, a laboratory designed to study influenza at the animal-human interface. As a leading bird flu expert, Dr. Webster is regarded as the "pope" of influenza researchers. Experts credit him as the one who first discovered the part avian influenza plays in triggering all known human pandemics at some point in distant past.
[133] R.G. Webster, C.H. Campbell, and A. Granoff, "The 'in Vivo' Production of 'new' Influenza a Viruses," *Virology* 44, no. 2 (May 1971): 317–328.
[134] Michael Rosenwald, "The Flu Hunter | Science & Nature," *Smithsonian Magazine*, January 2006.
[135] John Steel and Anice C. Lowen, "Influenza A Virus Reassortment," in *Influenza Pathogenesis and Control - Volume I*, ed. Richard W. Compans and Michael B. A. Oldstone, vol. 385 (Cham: Springer International Publishing, 2014), 377–401.

The swine flu virus continues to circulate during contemporary flu pandemics, as seen during the 2009 pandemic. As a "mixing vessel," pigs can serve as a critical link in passing novel flu strains to humans, although not in all cases. Pigs are as numerous now as horses were in the earlier centuries. Morens and Taubenberger argued that since the early twentieth century, "…pigs have replaced the horse as a secondary extra-human mammalian influenza reservoir" of influenza viruses.[136]

Influenza in Birds

Most relevant to this research are the historical perspectives about avian influenza. This section highlights those sources that provide historical or public policy perspectives.[137]

Historical viewpoints of avian influenza include Wilkinson and Waterson's discussion about the first recorded fowl plague in Italy in 1878.[138] Virologist Christoph Scholtissek provided a history of research for avian viruses during the twentieth century in which he highlighted ecological studies that revealed the huge reservoir of avian influenza viruses in waterfowl, from which an avian virus can pass from birds to mammals.[139]

Veterinarians Lupiani and Reddy traced the history of avian flu outbreaks among birds and humans through 2009. During the early days of virology in the 1950s, the avian flu virus served as a model agent, particularly because of the relative ease of using chickens as experimental animals. By 1955, virologists had demonstrated the close kinship of the fowl plague virus with human influenza viruses.[140] Shortly thereafter, the WHO promoted studies

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[136] Morens and Taubenberger, "Historical Thoughts on Influenza Viral Ecosystems" 7.
[137] See chapter four for a detailed history of avian influenza.
[138] Waterson and Wilkinson, *An Introduction to the History of Virology*.
[139] Christoph Scholtissek, "History of Research on Avian Influenza," in *Monographs in Virology*, ed. H.-D. Klenk, M.N. Matrosovich, and J. Stech, vol. 27 (Basel: Karger, 2008), 101–17.
[140] W. Schaefer, "Comparative Sero-Immunological Studies of the Viruses of Influenza and Classical Fowl Plague," *Z. Naturforsch* 10 (1955): 81–91.

of the ecology of viruses in wild animals. By the 1960s, serologic surveys of wild birds demonstrated the presence of avian influenza virus [AIV] infection in wild birds in the U.S., Australia, and Russia.

Virologists Alexander and Brown updated an earlier history of highly pathogenic AIV. They emphasized that the period 1995 to 2008 is significant in the history of avian influenza because of the vast numbers of birds that died or were culled. The current epizootic caused by the H5N1 avian flu virus has spread throughout Asia and into Europe and Africa, causing the loss of hundreds of millions of birds as well as hundreds of human lives.[141]

Ecologist Ian Scoones, editor of *Avian Influenza: Science, Policy and Politics*, argued that there are few socio-ecological investigations of the dynamics of change leading avian flu outbreaks.[142] By means of the case study, this dissertation seeks to expand knowledge of avian influenza by integrating environmental, social, and geopolitical factors.

Archival and other Primary Sources

The primary sources for this research include historical archives, scientific reports, and interviews with scientists. Archival documents serve to illuminate changes over time in the scientific understanding of influenza in general and of avian viruses in particular. Scientific reports focus on avian influenza experiments conducted at Qinghai. Interviews provide details not found in documents and expand interpretations with insights into diverse points of view.

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[141] D. J Alexander and I. H Brown, "History of Highly Pathogenic Avian Influenza.," *Revue scientifique et technique - Office international des epizooties* 28, no. 1 (2009): 19–38,
[142] Ian Scoones, *Avian Influenza: Science, Policy and Politics* (Routledge, 2012), 10, 40.

Primary research conducted at Qinghai is well documented in the scientific literature from diverse fields – virology, microbiology, veterinary and avian science, bioscience and biosecurity, public health, climate science, geography, infectious disease, wildlife biology, remote sensing technology, cold regions science, and computational science. This dissertation contributes to this literature by assessing the historical, ecological, technological, and social contexts of avian flu viruses.

Rockefeller Archive Center [RAC], Sleepy Hollow, New York

Archives from the RAC provide rich details about how scientists attained knowledge about influenza viruses and why this understanding changed so radically in the 1930s and 1940s. In the run-up to World War II, there was close collaboration among American and British scientists. They needed an influenza vaccine that would protect the military and, ultimately, the general population. Within these records are insights about the early tests of vaccines on human subjects. In addition, one can discern the roots of pandemic prediction theories that would come to play a major role in future vaccination campaigns. The RAC archives also highlighted the transition of influenza research to the World Health Organization. RAC collections referenced include those from the International Health Board/Health Division, the Richard E. Shope Papers, and the René Dubos Papers.

Ford Presidential Library, Ann Arbor, Michigan

The Ford Presidential Library provided invaluable documentation of how White House officials and CDC scientists made decisions during the 1976 swine flu outbreak, the U.S. mass vaccination campaign, and adverse events from the vaccine itself. The "swine flu affair" is notorious in the history of influenza for lessons learned about not only influenza

viruses but also about the role of politics in decision-making. The 1976 Swine Flu events provide insights into contemporary controversies about how science addresses the risks of avian influenza viruses as well as the risks and benefits of vaccines.

U.S. National Archives and Records Administration Center [NARA]

Records from two NARA centers, College Park, MD and the Southeast Region in Atlanta, GA., provided valuable supplementary material for the examination of 1976 swine flu. Included are reports and correspondence relevant to vaccine-associated disability from 1975 and 1976.

Scientific Reports

Events at Qinghai have sparked much empirical science about avian influenza. However, the results from these studies are fragmented across many disciplines and relatively few publications have high readership. To consolidate this literature, I use the systematic mapping method.[143]

Interviews

Interviewees are key informants for the history of avian influenza as well as for the case study. They include historians of medicine, wildlife experts, virologists, a medical ecologist, an epidemiologist, and environmental scientists.[144] Several interviews are from

[143] Described in the chapter two under Theoretical Framework.
[144] The Oregon State University Institutional Review Board determined that this research does not meet the definition of research involving human subjects. Some communications are informal conversations and emails. Others are recorded interviews.

recorded interviews cited in chapter seven. Other communications are informal through email and personal communications cited throughout the dissertation.

In summary, the source material described in this chapter encompasses a wide range of disciplines including history, virology, microbiology, veterinary and avian science, bioscience and biosecurity, public health, climate science, geography, infectious disease, wildlife biology, remote sensing technology, cold regions science, and computational science. The volume of publications about bird flu (subtype H5N1) is over seven thousand articles dating from 1997-2015. For this reason, this dissertation uses a framework suitable for integrating and analyzing material across disciplines. The results of this analysis reveal that bird flu as a disease with a short history in humans, substantial economic impact for the poultry sector, as well as new field-based research methods for avian flu that go beyond laboratory science.[145] Avian flu science is in a nascent stage and there are many unknowns. Yet, investigations at Qinghai provide insights into why bird flu has become such a prominent and potentially dangerous aspect of contemporary life.

The next chapter discusses the ecological dimensions of viruses, theories about their origins, and change over time in an ecological approach to the study of microbes and disease.

[145] These methods are described in detail in chapter five, Qinghai case study.

Chapter Three: Ecological Dimensions of Viruses

This chapter provides a context for understanding viruses, one that provides sufficient depth to convey the upstream or root causes of avian influenza. Viruses have an ambiguous place at the boundary of living and non-living things. However, history and philosophy provide insights into the nature of viruses, a particular nature that straddles human, animal, and microbial worlds.

From the general to the specific, I explore these transboundary aspects of the virus, and its relationship with the host organism and the host's environment. My perspective is that the virus is in a dialectical relationship with its world. It lives both in response to its host and environment and alters that environment through disease.[146] From being abstract, disease-causing agents, there has been a slow understanding of viruses from an ecological context, one that considers the host's milieu. This chapter opens up the analysis to consider how environmental disruptions (e.g., dams, climate change) link to the emergence of infectious diseases such as avian influenza.[147]

3.1 The Nature of the Virus

Viruses infect all types of organisms, including animals and plants, as well as bacteria and archaea. This section examines the physical attributes of the virus as well as theories about the origins and evolution of viruses.

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[146] Rutger de Wit and Thierry Bouvier, "'Everything Is Everywhere, But, the Environment Selects'; What Did Baas Becking and Beijerinck Really Say?" *Environmental Microbiology* 8, no. 4 (April 2006): 755–758; L.G.M Baas Becking, *Gaia of leven en aarde* (Gravenhage: Martinus Nijhoff, 1931).
[147] Tony McMichael, *Human Frontiers, Environments and Disease: Past Patterns, Uncertain Futures* (Cambridge ; New York: Cambridge University Press, 2001).

Unique Characteristics of the Virus

During the first century C.E., the Latin word "virus" had a connotation of disease, poison, venom, or slime.[148] By the end of the nineteenth century, the germ theory of disease served to refocus the uncertain meaning of the word virus. Thus, scientists have known viruses as distinct biological entities for little more than a century. In the early years of discovery, researchers defined viruses in the negative: not captured by a porcelain filter, not quite alive, not cultivable in chemical nutrients.[149] Viruses lack all the metabolic processes needed to generate energy. They do not produce waste or have sex, nor do they use oxygen.[150] Viruses have no means of locomotion, yet they travel around the world.[151] Viruses are unaffected by antibiotics and other pharmaceuticals that often work to combat bacterial infections.

Viruses are all around us, comprising an enormous part of our environment, and infect nearly every organism. Existing in unfathomable numbers, viruses are the most abundant biological entity on earth, typically occurring at 10^6 to 10^8 per gram of seawater or soil.[152] Historian and philosopher Ed Cohen describes the virus as existing "…almost like genetic background radiation, not interesting until you begin to focus on it."[153]

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[148] Hughes, *The Virus*, Appendix A.
[149] Thomas M. Rivers, "The Nature of Viruses," *Physiological Reviews* 12, no. 3 (July 1, 1932): 423–52; David Quammen, *Spillover: Animal Infections and the next Human Pandemic* (New York: W.W. Norton & Co., 2012).
[150] Barry, *The Great Influenza*, 98; Barry, *The Great Influenza*, 98. David Quammen, *Spillover: Animal Infections and the next Human Pandemic* (New York: W.W. Norton & Co., 2012), 269..
[151] Morse, *Emerging Viruses*. Stephen Morse, Professor of Epidemiology at Columbia University Medical Center, is an expert on epidemiology and risk assessment of emerging infectious diseases (including influenza), and improving disease early warning systems.
[152] Mya Breitbart and Forest Rohwer, "Here a Virus, There a Virus, Everywhere the Same Virus?," *Trends in Microbiology* 13, no. 6 (June 2005): 278–84.
[153]E. Cohen, "The Paradoxical Politics of Viral Containment; Or, How Scale Undoes Us One and All," *Social Text* 29, no. 1 106 (April 27, 2011), 18.

Yet, researchers know very little about the biogeography of viruses and their distribution. In contrast to those of bacteria, the origins and functions of viruses are not well understood.[154] Bacteria are single-celled organisms, whereas a virus has no internal cellular structure, no cell wall or cell membrane. Bacteria carry all the "machinery" needed for their growth and reproduction. Bacteria are intercellular organisms that live in-between cells. Viruses are intracellular entities that infiltrate the host cell and live inside the cell. For the purposes of this research, the definition of virus is one used by many virologists - *an infectious obligate intracellular parasite*. Viruses are parasites because they cannot reproduce without a living cell, as we shall see.

From a structural perspective, viruses consist of a protein shell that holds a coiled string of nucleic acid (RNA or DNA).[155] This shell, or capsid, performs essential functions of the virus: to self-assemble, to protect the genome, and to introduce the genome into a host cell.[156] Most viruses (e.g. influenza and many animal viruses) have viral envelopes covering their protective protein capsids. The genome contains all the information required to replicate itself. After replication, multiple copies exit the host and reenter the environment. Since viruses are inert, they drift on air currents or float in liquids until they encounter and take root in a new host. They are like free-flowing packets of information seeking a place to

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[154] Torrey and Yolken, *Beasts of the Earth*.

[155] DNA, or deoxyribonucleic acid, is a double stranded molecule. RNA, or ribonucleic acid, is a single stranded molecule. DNA is responsible for storing and transferring genetic information while RNA acts as a messenger between DNA and ribosomes to make proteins. DNA replication takes place in the nucleus while RNA replication takes place in the cytoplasm. DNA viruses are relatively stable, whereas RNA viruses have a higher mutation rate compared to DNA viruses. Influenza viruses are RNA viruses. See Racaniello, *Influenza virus RNA genome*, May 1, 2009.

[156] Dennehy, "What Ecologists Can Tell Virologists." John J. Dennehy, "What Ecologists Can Tell Virologists," *Annual Review of Microbiology* 68, no. 1 (2014): 117–35.

dock. Virus movement is largely a product of collisions with surrounding molecules – a random diffusion by Brownian motion.[157]

Researchers measure viruses in millionths of a millimeter. As sub-microscopic particles, viruses are 10 to 100 times smaller than bacteria. For a virus, less is more. Virologist Beveridge asserted that a clump of viruses the size of an ordinary pinhead would contain about a "million million viruses."[158] Small size means that most viruses have very little genetic material. Some viral genomes including measles, yellow fever, polio, Lassa, Ebola, Hantavirus, and HIV, have fewer than ten genes. By contrast, poxviruses are quite large with 200 to 400 genes.[159] The human genome carries over 22,000 genes.[160] A single infectious viral particle can produce 100,000 viral copies in 10 hours, and the total number of viral particles in a given organism might reach 10^{12} in concentration.[161] In an aerosolized human sneeze, there are enough viruses to infect thousands. For a virus, natural selection acts to maximize transmission to the next host. Small size is very much a part of maximizing spread to gain access to another host, another cell.

Regardless of size, all viruses depend on the machinery of a host cell contained within the bacterium, plant, person, or animal infected.[162] Viruses need to be able to evade the host's defenses, hijacking the life of the cell they invade and commandeering host cells as factories for virus production. Decoding and manipulating the cell's immune responses as part of its life cycle, the virus becomes part of cell machinery, surviving on borrowed life

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[157] Ibid., 121. Brownian motion is the erratic random movement of microscopic particles in a fluid, as a result of continuous bombardment from molecules of the surrounding medium.
[158] Beveridge, *Influenza*, 68.
[159] Michael B. A. Oldstone, *Viruses, Plagues, and History* (New York: Oxford University Press, 1998), 9.
[160] Thomas, "History and Biology in the Anthropocene," 1594.
[161] Andrés Moya, Edward C. Holmes, and Fernando González-Candelas, "The Population Genetics and Evolutionary Epidemiology of RNA Viruses," *Nature Reviews Microbiology* 2, (April 2004): 279–288.
[162] Philip Lintilhac, "Toward a Theory of cellularity—Speculations on the Nature of the Living Cell," *BioScience* 49, no. 1 (January 1, 1999): 59–68.

from cells.[163] For this reason, medical ecologist Dickson Despommier referred to viruses as the ultimate "safecrackers."[164]

How does a virus infect a cell? As described, viral infection is the result of a chance collision between the virus particle and the cell.[165] A virus is an entity with two phases, a non-living virus particle, or virion; and an infected cell, which is alive.[166] The virus particle itself (a virion) is but a packet of inert chemicals and does not have much to call its own outside the infected cell. This virion is more like a spore or a seed without the properties of life. In the infected cell, the virus is very much alive. Viruses replicate by assembly of pre-formed components in virions. In their latent or eclipse period, viruses assemble these parts and then proceed into a burst of infectivity. This is fundamentally different from the binary fission of bacteria and other living cells.[167] The mechanism by which viruses reproduce is unique in biology.[168]

Virologist Shortridge provided an anthropomorphic metaphor: "Like tiny terrorists, viruses travel light, switch identity easily and pursue their goals with deadly determination."[169] Yet, viruses themselves are passive agents with no "intent" to cause disease in their host organism, even as a viral infection weakens or destroys the host cells. Most viruses are persistent and innocuous, not pathogenic.[170] Disease in the host animal, when it happens, is merely an unintended consequence in the life cycle of the virus. In turn,

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[163] C. J. Peters and Mark Olshaker, *Virus Hunter: Thirty Years of Battling Hot Viruses Around the World*, (New York: Anchor, 1998), 72. [163] M. H. V. Van Regenmortel, "Nature of Viruses," in *Encyclopedia of Virology*, ed. Brian W. J. Mahy, Marc H. V. Van Regenmortel (Oxford: Academic Press, 2008), 398–402.
[164] Personal communication with Dickson Despommier, June 2014. Despommier, Professor Emeritus in Public Health in Environmental Sciences at Columbia University, is a microbiologist and medical ecologist with special interests in the philosophies of Rene Dubos.
[165] S. Jane Flint et al., *Principles of Virology* (Washington, DC: ASM Press, 2009), 32.
[166] Racaniello, "Can a Virus Be Revived?"
[167] Racaniello, *What Is a Virus?*
[168] Clyde Goodheart, *An Introduction to Virology* (Saunders, 1969), 1.
[169] Shortridge, "Pandemic Influenza."
[170] Cohen, "The Paradoxical Politics of Viral Containment," 18.

there is strong selection on hosts to prevent viral infection through immune activation or fevers.[171]

One of the most striking physical attributes of the virus is its structure. Virologist Wendell Stanley referred to viral structure as an intricate precision of architecture.[172] Many viruses display full icosahedral symmetry, perhaps the most esthetically pleasing symmetry in nature.[173] An icosahedron is composed of 20 facets, each an equilateral triangle, and 12 vertices as shown in **Figure 4**. This is no accident of nature, as icosahedral symmetry allows for the lowest-energy configuration of particles interacting on the surface of a sphere. This explains how the virus, despite its small size and tiny genome, can accomplish so much with so little.[174] The majority of viruses have either helical symmetry or icosahedral symmetry.

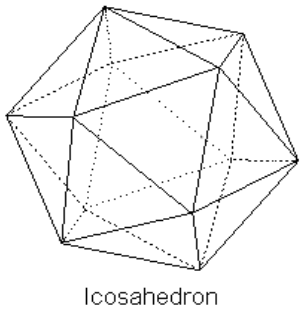

Figure 4 Icosahedron

Salvador Luria's credo about viruses, presented in his classic 1953 virology textbook, captures some of the sense of wonder about his object of study:

> There is an intrinsic simplicity of nature and the ultimate contribution of science resides in the discovery of unifying and simplifying generalizations, rather than in the description of isolated situations – in the visualization of simple, overall patterns rather than in the analysis of patchworks.[175]

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[171] Dennehy, "What Ecologists Can Tell Virologists."
[172] E. G. Stanley and W. M. Valens, *Viruses and the Nature of Life* (New York: E. P. Dutton & Company, 1965), 65.
[173] Flint et al., *Principles of Virology*, 125.
[174] Racaniello, *What Is a Virus?*
[175] S. E. Luria, *General Virology* (Hoboken, NJ: J. Wiley and Sons, 1953), 3.

Philosophy of Biology

The philosophy of biology encompasses molecular biology, ecology, evolutionary biology, and other life sciences including virology.[176] This is relevant for avian influenza because scientists continue to disagree about the nature and origin of viruses. This includes influenza viruses, so ubiquitous in nature and society.

Thousands of years before researchers could visualize the structures of a virus, ancient philosophers showed great insight into the mathematical structure of a potential life form that they could neither see nor imagine. Geometers studied the mathematical beauty and symmetry of the Platonic solids for thousands of years. Plato wrote about the Platonic solids in the dialogue *Timaeus c*.360 B.C.E. in which he associated each of the four classical elements (earth, air, water, and fire) with a regular solid.[177] Water, the icosahedron, flows out of one's hand when picked up. The symmetrical structure of the virus (and other pleasing forms) appears rooted in human imagination and our ability to observe patterns in nature. The ancients appreciated that form and shape were not only aesthetically pleasing but were also essential to life itself.

Despite the increased interest in viruses, scientists continued to disagree about the virus as an entity that is neither alive nor dead and especially about the origin of viruses.[178] The argument centers on whether viruses represent parts of a cell or whether they emerged from virus-specific components. Throughout the twentieth century, viruses have provided foci for discussing the properties and origins of life.

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[176] Maureen O'Malley, *Philosophy of Microbiology* (Cambridge, United Kingdom: Cambridge University Press, 2014), 41, 77.
[177] Donald Zeyl, "Plato's Timaeus," Stanford Encyclopedia of Philosophy.
[178] T. Rivers, "Filterable Viruses a Critical Review," *J. Bacteriology* 14, no. 4 (1927): 217–258.

Complicating the debate about the origin of viruses is the fact that they fall somewhere between the chemical and the biological.[179] Viruses have the unique capacity to lose their structural integrity but not their genomic basis. In 1957, André Lwoff was one of the first to propose a definition of virus. He declared, "viruses are viruses" to stress that viruses are a distinct evolutionary lineage, not linked to any kingdom of life.[180] He argued that viruses were a natural group of biological entities, despite their largely negative definition compared to cellular organisms: absence of growth, division, ribosomes, and only one type of nucleic acid.[181]

Scientific accounts of the evolution of viruses changed radically over the twentieth century and new ideas about the origin of viruses were particularly prevalent during the 1970s. Some researchers speculated that fragments of RNA and DNA simply "fell off" from other living things at some point along the way. For example, virologists Burnet and White argued that viruses were the descendants of cell components that gained the ability to move between cells through the process of evolution.[182] Shortly thereafter, astronomers Hoyle and Wickramasinghe arrived at a different theory: new viruses form in outer space and arrive on Earth in meteoritic dust.[183] Virologist Robert Webster described a popular hypothesis from the 1990s in which the first biosphere on earth consisted of primitive replicating RNA molecules, suggesting that viruses may be precursors to life, as we know it.[184] A twenty first-century theory, advocated by virologist Eugene Koonin, argues that viruses have always

[179] O'Malley, *Philosophy of Microbiology*, 77.
[180] A. Lwoff, "The Concept of Virus," *Journal of General Microbiology* 17, no. 2 (1957): 239–53.
[181] O'Malley, *Philosophy of Microbiology*, 79.
[182] F. M Burnet and David O White, *Natural History of Infectious Disease,* (Cambridge UK: University Press, 1972).
[183] F. Hoyle and N. C. Wickramasinghe, "Origin and Nature of Carbonaceous Material in the Galaxy," *Nature* 270, no. 5639 (December 22, 1977): 701–3.
[184] Webster et al., "Influenza--a Model of an Emerging Virus Disease."

existed as self-replicating units and coevolved with their current cellular hosts.[185] This latter theory has support among many contemporary virologists.

Other theories proposed that viruses do not evolve from or alongside cellular life at all. Virologist Nathan Wolfe examined the possibility that a life form, originating independently of our own DNA based life, might persist completely undetected on Earth.[186] This "shadow life," Wolfe argued, would most certainly consist of viruses. In a related theory, Dennehy proposed that viruses might be the dark matter of the biosphere, a hidden world that affects every living organism.[187] Biologist Lewis Thomas suggested that viruses might be a mechanism for newly evolved genetic material to remain in the widest possible circulation among living cells.[188] As argued by historian Gordin, science is ignorant of how the future will judge these contemporary theories. Some theories are cast aside as others are validated.[189]

While it is possible that viruses evolved alongside living things, the classic tree-of-life chart does not have a place for them. There is no presumed common ancestor for viruses. The definition of species, an interbreeding population of individuals, has little meaning for viruses.[190] While some debates are not resolved, philosophers and scientists agree that certain aspects of viral evolution are unique. In particular, viruses are masters of shuttling genes, manipulating hosts, and are engines of evolutionary change.[191]

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[185] Eugene V. Koonin and William Martin, "On the Origin of Genomes and Cells within Inorganic Compartments," *Trends in Genetics: TIG* 21, no. 12 (December 2005): 647–54.
[186] Wolfe, *The Viral Storm*.
[187] Dennehy, "What Ecologists Can Tell Virologists," 118.
[188] Lewis Thomas, *Lives of a Cell: Notes of a Biology Watcher* (New York: Penguin Books, 1978).
[189] Gordin, "Evidence and the Instability of Biology."
[190] Vincent Racaniello, "The Quasispecies Concept," *Virology Blog*, May 11, 2009; Vincent Racaniello, "Viral Quasispecies and Bottlenecks," *Virology Blog*, May 12, 2009.
[191] O'Malley, *Philosophy of Microbiology*, 9.

In addition to origins and evolution, viruses also challenge the human sense of temporal scale. A virus that emerged in the early twenty first century (such as avian influenza H5N1) may appear, in human time, to be so contemporary that it defies historical analysis. However, from the perspective of the life of a virus, a few years are akin to our ancient history. Humans take about twenty years to create a new generation, bacteria about 20-30 minutes, and viruses even less time – in human terms, a millennium of development in a fortnight.[192] This short generation time provides an inherent evolutionary advantage for viruses to stay ahead of their hosts in the "…race between offenses and defenses and counter defenses."[193]

Historical Perspectives: Scientific Understanding of Viruses

The past ten thousand years of human history was a time of sweeping change for both humans and viruses.[194] Until the end of the nineteenth century, the history of viruses was the unseen, unknown part of the human history of infectious disease.[195] It is likely that pathogenic viruses established themselves in human populations from domesticated animals. Yet, efforts to understand and control viruses as agents of disease are phenomena firmly situated in the twentieth century.[196]

The first understandings of viruses as filterable agents were from separate investigations of tobacco mosaic virus during the 1890s by researchers Ivanowski and

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[192] Madeline Drexler, *Emerging Epidemics: The Menace of New Infections*, Revised edition (N.Y: Penguin Books, 2009), 8.
[193] Ewald, *Plague Time*, 62.
[194] A. J. McMichael, "Environmental and Social Influences on Emerging Infectious Diseases: Past, Present and Future," *Philosophical Transactions of the Royal Society B: Biological Sciences* 359, no. 1447 (July 2004): 1049–58.
[195] Lwoff, "The Concept of Virus."
[196] Ibid., 5.

Beijerinck.[197] Because viruses are smaller that bacteria, they pass through porcelain filters allowing the filtrate to infect laboratory animals or plants. In 1902, yellow fever was the first human virus shown to be filterable through the work of Walter Reed.[198] According to Waterson and Wilkinson, during the early twentieth century there was a growing appreciation that viruses could not survive outside a living cell. Yet, there was no evidence.[199] When *Microbe Hunters* appeared in 1926, it created excitement about how scientists engaged with the microscopic world.[200] By 1927, virologists had published a compendium of all the filterable viruses discovered to date.[201] Yet, no one had actually seen a virus. The visual discovery of viruses would have to wait for the electron microscope of the 1930s.

The electron microscope provided a powerful approach for rapid viral diagnosis that revolutionized the study of viruses. It permitted a visualization and measurement, for the first time, of viral size. Soon, there was detailed information about the morphology and function of viruses.

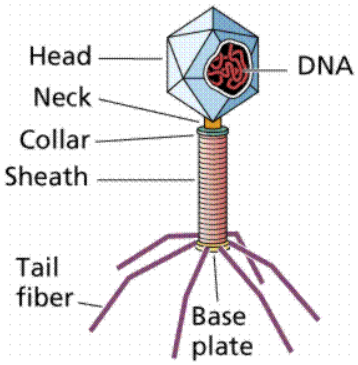

Figure 4 Phage

From the late 1930s to the early 1940s, bacteriophages ("phages," **Figure 4**) viruses that attach to bacteria, received much attention from scientists. Felix d'Herelle, co-discover of the phage, argued that only one type of phage attached to bacteria.[202] Virologist Burnet disproved this by demonstrating there that were many

[197] Mayer et al., *Concerning the Mosaic Disease of Tobacco*; Beijerinck, "Concerning a Contagium Vivum Fluidum as Cause of the Spot Disease of Tobacco Leaves."
[198] Walter Reed and James Carroll, *The Propagation of Yellow Fever Observation Based on Recent Researches* (New York: William Wood & Company, 1901).
[199] Waterson and Wilkinson, *An Introduction to the History of Virology*, 42.
[200] Paul de Kruif, *Microbe Hunters* [1926] (San Diego: Harcourt Brace, 1996).
[201] Rivers, "Filterable Viruses a Critical Review."
[202] William C. Summers, *Félix d'Herelle and the Origins of Molecular Biology* (New Haven, Conn: Yale University Press, 1999).

phages with different physical and biological properties. Phages were soon associated with the emerging field of molecular biology as they were ideal tools to investigate the nature of genes and heredity.[203] Researchers separated the viral nucleic acid from the proteins, providing molecular biologists a means to examine the viral structure.[204] In this way, phage science played a role in unravelling the structure of DNA in the 1950s.[205]

Researchers knew that the viral genetic code material had to be either its DNA or its protein capsid. In 1952, Alfred Hershey and Margaret Chase performed an experiment on a phage that attacked the *E. coli* bacterium. They used radioactive chemicals to distinguish between the protein capsid and the DNA.[206] Their experiments revealed that the viral DNA or RNA, not the protein, is its genetic code material. This was the point at which scientists acknowledged that DNA was the genetic material and the race was on to be the first to discover its chemical structure.[207] In this way, the technical arm of the phage effort provided impetus for the formation of molecular biology and the eventual elucidation of the structure of DNA.[208] In fact, the year after the Hershey-Chase experiment, using Rosalind Franklin's data, Watson and Crick published a paper in which they proposed and described a hypothetical double helix structure for DNA.[209]

By the mid-1950s, the nature of the virus was no longer a mystery. By then, researchers understood that viruses were parasites that depended on their host for metabolism

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[203] Flint et al., *Principles of Virology*.
[204] Angela N. H. Creager and Gregory J. Morgan, "After the Double Helix," *Isis* 99, no. 2 (June 2008): 239–72.
[205] Hirst, "Development of Virology as an Independent Science"; Keller, *A Feeling for the Organism*; Morse, *Emerging Viruses*; Van Helvoort, "When Did Virology Start?"; Crawford, *The Invisible Enemy*; Norrby, "Nobel Prizes and the Emerging Virus Concept."
[206] This could be either DNA or RNA.
[207] Flint et al., *Principles of Virology*.
[208] Hughes, *The Virus*, 91.
[209] J. D. Watson and F. H. Crick, "Molecular Structure of Nucleic Acids; a Structure for Deoxyribose Nucleic Acid," *Nature* 171, no. 4356 (April 25, 1953): 737–38.

and reproduction and that viruses contained genes.[210] Cell and tissue cultures led to the discovery of many new viruses.[211] Introduced by Renato Dulbecco in 1952, the plaque technique facilitated research in viral infection, reproduction, and immunity at the cellular level.[212] It was during this mid-century period that virology split off from the field of bacteriology and developed as a separate discipline. Techniques for detecting viruses and the desire to conceptualize viruses as objects were part of the legacy of bacteriology. The fields of molecular biology, bacteriology, and virology were all descendants of microbiology.

During the 1960s, virus classification was the subject of controversy based on those who wanted to classify viruses by their similarities ("lumpers") or their differences ("splitters").[213] In 1962, Lwoff et al. advanced a comprehensive scheme for the classification of all viruses that grouped viruses according to their shared properties rather than the properties of the cells they infected. These shared properties included type of nucleic acid (RNA or DNA), symmetry of the capsid, and dimensions of the virion and capsid.[214] With the development of nucleic acid sequencing technologies in the 1970s, genomics has played an increasingly important role in taxonomy. The Baltimore Classification Scheme for viruses combined genetic information with morphological features.[215] The Baltimore Scheme, encompassing seven classes of viral genome, takes into account the nature of the viral nucleic acid.[216] Classifying viruses according to their genome type offered investigators some indication of how to proceed with further experiments.

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[210] Creager, *The Life of a Virus*, 1.
[211] Waterson and Wilkinson, *An Introduction to the History of Virology*.
[212] Hughes, *The Virus*, 98. Plaque-based assays are the standard method used to determine virus concentration in terms of infectious dose.
[213] The lumper vs. splitter dialog is not confined to virology.
[214] A. Lwoff, R. Horne, and P. Tournier, "A System of Viruses," *Cold Spring Harbor Symposia on Quantitative Biology* 27, no. 0 (January 1, 1962): 51–55.
[215] D. Baltimore, "Expression of Animal Virus Genomes," *Bacteriological Reviews* 35, no. 3 (September 1971): 235–41.
[216] Flint et al., *Principles of Virology*, 21.

Today, rapid gene isolation technology and automated DNA sequencing has opened new windows into the world of viruses. Surprises include a virus of unprecedented size reactivated from Russian permafrost. The estimated age of this virus is 30,000 years; it apparently does not cause harm to mouse or human cells.[217] These new discoveries challenge the exclusion of viruses from the tree of life and suggest that the classical definition of species may need reworking.[218] Although viruses are not alive (at least not as virions), some experts now call for viruses to be included in a fourth domain of life.[219]

The development of deep sequencing methods has made it possible to study the quasi-species. The quasi-species theory predicts, according to virologist Racaniello, that viruses are an interactive group of variants. [220] Diversity of the population is critical for propagation of the viral infection. The viral infection produces viruses that operate inside the infected host. Virions that go on to infect a new host must pass through a different set of selective forces.

Today, there are more than 5,000 species of viruses known that may or may not be harmful to host species.[221] Researchers estimate there may be hundreds of thousands of viruses not yet discovered in mammals.[222] Some experts believe that most of the uncharacteristic genomic biodiversity on Earth is in viruses. Others argue that every cellular form of life on earth supports at least one RNA virus.[223] According to biologist Jonathan

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[217] Matthieu Legendre et al., "Thirty-Thousand-Year-Old Relative of Giant Icosahedral DNA Viruses with a Pandoravirus Morphology," *Proceedings of the National Academy of Sciences*, March 3, 2014.
[218] The three-domain system, established in 1977, divides cellular life forms into archaea, bacteria, and eukaryote domains. It emphasizes the separation of prokaryotes into two groups, originally called *Eubacteria* (now *Bacteria*) and *Archaebacteria* (now *Archaea*).
[219] O'Malley, *Philosophy of Microbiology*, 55.
[220] Racaniello, "The Quasispecies Concept."
[221] Torrey and Yolken, *Beasts of the Earth*.
[222] Kai Kupferschmidt, "Sizing Up the Viral Threat | Science/AAAS | News," *Science* 341, no. 6150 (September 6, 2013): 1049.
[223] Edward C. Holmes, *The Evolution and Emergence of RNA Viruses* (Oxford ; New York: Oxford University Press, 2009).

Eisen, if researchers were able to integrate viral history with its function, genomes, and biogeography, they could create a field guide of viruses, something known to be useful in other scientific endeavors.[224]

Scientific understanding of this abundance of viruses on Earth is in a nascent stage and questions abound - how do viruses evolve in nature, in populations, and in hosts occupying all extremes and all possible environmental niches? Viruses not only have the capacity to shape knowledge about disease but also to redirect the work of researchers as new discoveries come into focus.

In summary, researchers have good evidence for the origins of some viruses, plausible hypotheses for others, and no information for the majority.[225] As the study of viruses is well into its second century, they continue to outstrip our expectations and flout the boundaries between scientific disciplines. Yet, contrary to the notion expressed by biologist Medawar that a virus is "…a piece of bad news wrapped in a protein coat," many researchers look upon viruses not as something to fear but as a source of wonder.[226] For these scientists, viruses unlock some of the most profound secrets of life. Knowledge about viruses is partial, always changing.

Due to the human immune system, the vast majority of viruses have little or no consequence for humans. While many zoonotic pathogens (those that pass from animals to humans) periodically infect humans, few can transmit to a new host. However, human

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[224] Jonathan A. Eisen, "Genomic Evolability and the Origin of Novelty: Studying the Past, Interpreting the Present, and Predicting the Future," in *Microbial Evolution and Co-Adaptation*, Forum on Microbial Threats (Washington D.C.: The National Academies Press, 2009).
[225] Mark Woolhouse and Eleanor Gaunt, "Ecological Origins of Novel Human Pathogens," in *Microbial Evolution and Co-Adaptation: A Tribute to the Life and Scientific Legacies of Joshua Lederberg*, ed. David A Relman et al., Forum on Microbial Threats (Washington D.C.: The National Academies Press, 2009).
[226] Drexler, *Emerging Epidemics*, 9.

activity is creating efficient pathways for viral transmission from new sources.[227] The following section discusses these ecological pathways for viral disease.

3.2 Virus, Environment, and Host

As discussed, there is an essential relationship between the virus and its host organism. Every explanation about the replication and infectious cycle of a virus must also reveal something about the host.[228] This section explores how viral ecology incorporates the host's biological and physical environment. It provides a foundation for answering my research question: what are the shifting dynamics in both nature and society that provide opportunities for viruses such as avian flu to jump from their animal hosts to humans?

Zoonoses: Diseases transmitted among Animals and Humans

A zoonotic disease refers to an infectious organism that can move between people and animals, often in a bidirectional manner.[229] Zoonotic infections are not new and encompass a wide range of human diseases including anthrax, plague, yellow fever, and influenza. Most of these diseases have come from domestic animals, poultry and livestock. Measles and smallpox emerged when diseases in domesticated wildlife led to a "spillover" (diseases that pass from one species to another species) of their pathogens that became human adapted strains.[230] This process has repeated throughout human history.

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[227] David A Relman et al., eds., *Microbial Evolution and Co-Adaptation: A Tribute to the Life and Scientific Legacies of Joshua Lederberg*.
[228] Racaniello, *What Is a Virus?*
[229] World Health Organization's definition of zoonoses is "diseases or infections which are naturally transmitted between vertebrate animals and humans."
[230] A.P. Dobson, E.Carper, "Infectious diseases and human population history," *Bioscience*, 1996; 115–126.

As these episodes of disease emergence suggest, one predictor of infectious disease emergence is human mobility to new geographic regions. With an expanding geographic range, pathogens encountered new sources of susceptible hosts. Pandemics occurred as pathogens adapted and became transmissible among humans. It is rare to reach this pandemic stage. However, when a pandemic does occur it can lead to severe impact due to high mortality (e.g., HIV/AIDS) as well as economic impact.[231]

Outbreaks of zoonoses have been increasing since the 1950s with a quickening pace since the 1970s.[232] Until this period, regional-scale geographic distances ensured a limited reach for most infectious agents. Rapid, long distance movement of people and goods allowed for rapid transport of infectious agents as well.[233] The human population grew exponentially throughout the twentieth century, now at seven billion people. The increase in zoonotic disease is associated with anthropogenic drivers such as encroachment into wild animal habitats; deforestation; agricultural expansion; farming practices; natural resource exploitation; urbanization; climate change; and global travel and trade.[234] Thus, human advancement into new habitats has provided greater exposure to previously isolated viral sources. Changes in human demography and mobility, and increased environmental disruption have led to increases in new and resurgent infectious diseases.[235]

In a systematic review of 1,415 pathogens known to infect humans since 1980, the majority (75%) were zoonotic.[236] Animals and birds are perhaps the largest reservoir for

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[231] Daszak, "Can We Predict Future Trends in Disease Emergence?" 253.
[232] Jones et al., "Zoonosis Emergence Linked to Agricultural Intensification and Environmental Change."
[233] Joan L. Aron and Jonathan A. Patz, eds., *Ecosystem Change and Public Health: A Global Perspective*. (Baltimore: The Johns Hopkins University Press, 2001).
[234] Deforestation creates new habitats for pathogens and vectors. Institute of Medicine, *The Influence of Global Environmental Change on Infectious Disease Dynamics: Workshop Summary* (Washington D.C.: The National Academies Press, 2014), 13.
[235] McMichael, *Human Frontiers, Environments and Disease*.
[236] L. H. Taylor, S. M. Latham, and M. E. J. Woolhouse, "Risk Factors for Human Disease Emergence," *Philosophical Transactions of the Royal Society B: Biological Sciences* 356, no. 1411 (July 2001): 983–89.

these diseases. Zoonotic diseases can be caused by bacteria (e.g., anthrax), protozoans (e.g., giardia), fungi, or viruses carried by animals and insects.[237] During the past two decades, viruses have had a substantial role in "emerging" diseases, defined as those with increasing incidence in human populations. These emerging diseases are statistically more likely to be from viruses associated from a nonhuman animal source.[238] In other words, they are viral zoonoses. These include avian influenza, Ebola, West Nile Fever, Dengue, and others with an increasing impact on both wildlife, domestic animals, and human populations.

Perhaps finding more of these spillover outbreaks may mean that the world is looking harder for them. However, experts claim that even after accounting for more researchers and improved disease surveillance methods, the number of viral zoonotic events has escalated in the past few decades.[239] Humans and their domestic animals are making increased contact with wildlife and providing new opportunities for viral transmission. With this knowledge, disease ecologists have recommended that research focus on ecological interactions between wildlife hosts and zoonotic viruses.[240] This is not a new argument. In the 1930s, ecologist Aldo Leopold championed the idea that wildlife disease is an ecological issue influenced by human activities.[241]

An important aspect of viral zoonoses is the concept that the reservoir or persistent source for viruses resides in the animal world including wild and domestic animals. A reservoir host (also known as "natural" host) is an organism that carries the pathogen while suffering little or no illness.[242] For example, water birds harbor the widest diversity of flu

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[237] Jones, *Death in a Small Package*.
[238] Woolhouse and Gaunt, "Ecological Origins of Novel Human Pathogens."
[239] Daszak, "Can We Predict Future Trends in Disease Emergence?"
[240] Ostfeld and Eviner, *Infectious Disease Ecology the Effects of Ecosystems on Disease and of Disease on Ecosystems*.
[241] Aldo Leopold, *Game Management* (Madison, Wis.: University of Wisconsin Press, 1986).
[242] Quammen, *Spillover*, 2012, 23.

strains; however, the birds are asymptomatic.[243] As we have seen, some viruses have more than one reservoir host. Influenza viruses, for example, circulate among humans, wild and domestic birds, horses, and pigs.

Prominent zoonotic diseases include Ebola from cave-dwelling bats, and SARS coronavirus from bats to civets and ultimately to humans in southern China.[244] HIV started as a zoonosis from chimpanzees. The World Health Organization and most disease experts agree that the source of the next pandemic is likely to be zoonotic with wildlife as the primary source.[245]

Viral zoonoses are either directly transmitted (physical contact or droplets) or indirectly transmitted (food, water, or a vector, such as mosquito). Directly transmitted zoonoses have three components: microbe, animal reservoir, and human. Indirectly transmitted zoonoses encompass four components: microbe, vector, animal reservoir, human (e.g., SARS virus with a civet as the vector and bats as the animal reservoir). Vector-borne viruses are more ecologically complex compared to directly transmitted agents and are thus much more difficult to track and predict.[246]

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[243] Lam et al., "Reassortment Events among Swine Influenza A Viruses in China."
[244] LF Wang and Crameri, "Emerging Zoonotic Viral Diseases.," *Revue Scientifique et Technique (International Office of Epizootics)* 33, no. 2 (August 2014): 569–81.
[245] Aron and Patz, *Ecosystem Change and Public Health*.
[246] Aron and Patz, *Ecosystem Change and Public Health*.

Table 1 provides examples of the interrelationships between human viral disease and the animal reservoirs from which they arise.[247]

Viral disease in Humans	Viral disease reservoir
Colorado Tick Fever	Ground squirrels, chipmunks, porcupines, small rodents
Dengue	Monkeys; through mosquito bites
Eastern equine encephalomyelitis	Wild birds, domestic fowl, horses, mules, donkeys
Ebola	Bats
Hantavirus	Rodents
HIV	Chimpanzees and monkeys
Influenza type A	Swine, domestic and wild aquatic birds
Lassa Fever	Rodents
Marburg	Bats
Nipah	Bats; through pigs
SARS	Bats; through intermediate host
Rabies	Bats, dogs, foxes; through bites
Rift Valley Fever	Sheep, goats, cattle, camels; through mosquito bites
West Nile fever	Wild birds, horses; through mosquito bites
Yellow fever	Monkeys, Baboons; through mosquito bites

Table 1 Viral Disease Reservoirs. Data from Forum on Microbial Threats and Institute of Medicine; Venkatesan et al.; Bidaisee et al.[248]

Virologists Woolhouse and Gaunt argued that four characteristics are particularly important for emerging viruses: RNA viruses; non-human animal reservoir; a broad host range; and some potential for transmission between humans, perhaps limited at first.[249] Most

[247] Definitions of a zoonosis, animal reservoir, and host organism vary according to specialization and field.
[248] Forum on Microbial Threats, Board on Global Health, and Medicine, *Emerging Viral Diseases:The One Health Connection: Workshop Summary* (National Academies Press, 2015); G. Venkatesan et al., "Viral Zoonosis: A Comprehensive Review," *Asian Journal of Animal and Veterinary Advances* 5, no. 2 (February 1, 2010): 77–92; Satesh Bidaisee, Cheryl Cox Macpherson, and Calum N.L. Macpherson, "Human Behavior and the Epidemiology of Viral Zoonoses," in *Viral Infections and Global Change*, ed. Sunit K. Singh (John Wiley & Sons, Inc, 2013), 87–109.
[249] P Daszak, A Cunningham, and A D Hyatt, "Emerging Infectious Diseases of Wildlife--Threats to Biodiversity and Human Health," *Science (New York, N.Y.)* 287, no. 5452 (January 21, 2000): 443–49;

of the emerging pathogens listed in **Table 1** are RNA viruses known to replicate and mutate quickly.

One example that illustrates the pathway and outcome of a zoonotic virus passing from an animal to a human is the HIV virus. Infectious disease specialist Jacques Pepin gathered pieces of the HIV puzzle from archival samples of blood, phylogenetic analyses of HIV viruses, and colonial medical archives in Africa. Pepin argued that HIV-1 and its subtypes originated from central Africa in about 1921, a region that corresponds to the habitat of a population of chimpanzees. This species carried a simian virus, a strain genetically very close to the HIV virus that ultimately showed up in humans. Pepin proposed that when hunters killed chimps, they were exposed to the simian virus as the hunters dressed their kill in the field and had direct contact with the chimp's blood. During the first decades of the twentieth century, four different subtypes of HIV-1 emerged in Africa. Yet, the virus remained confined with little evidence of epidemic spread until mid-century.[250]

During the "scramble for Africa," French and Belgian colonial administrations launched mass health campaigns to treat local populations for a variety of tropical diseases and sexually transmitted infections. Laboratory practices were rudimentary and it was common to reuse needles and glass syringes. Pepin argued that these medical injections jump-started the HIV epidemic in Africa, building up a critical mass of HIV-infected individuals. By mid-century, Leopoldville (now Kinshasa) became an urban area with high levels of prostitution. By the 1980s, ninety percent of sex workers in Central Africa had

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William B Karesh et al., "Ecology of Zoonoses: Natural and Unnatural Histories," *The Lancet* 380, no. 9857 (December 7, 2012): 1936–45.

[250] Pepin, *The Origins of AIDS*, 18.

HIV-1 infections. Pepin became convinced that, as health care expanded in the Congo, well-intentioned health workers re-used needles that, in turn, spread the HIV viruses.[251]

Pepin has argued against the theory that HIV/AIDS was the result of contamination of an oral polio vaccine with a simian virus from chimpanzee cells during vaccine production.[252] Based on Pepin's phylogenetic analysis, a simian-like virus emerged in human populations at least twenty-five years prior to the oral polio trials in Africa. There is no documentary evidence, according to Pepin, that chimpanzee cells were ever used, anywhere in the world, to produce oral polio vaccine.[253]

The HIV example highlights the interplay of ecological, virological, and social aspects of the emergence of viral zoonoses. Typically, the emergence of zoonotic disease is multifactorial. It is true that the social and economic burdens are much higher from non-zoonotic infectious diseases (e.g., typhoid, cholera, tuberculosis) as well as from chronic human diseases (cancer, heart disease). However, zoonotic diseases receive attention because of their potential to lead to unpredictable global pandemics like HIV-AIDS.[254]

Despite the lessons learned from the emergence of HIV viruses, experts do not know the animal host range for many pathogens. Described by Morse as the "zoonotic pool" of pathogens, the global distribution of this zoonotic pool is unknown, as is the diversity of microbes able to emerge as disease in the future.[255] Another factor in emerging infectious disease is how environmental disruption sets the stage for viruses to spill over to new host organisms. The next section discusses the environmental drivers for zoonotic disease.

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[251] Pepin, *The Origins of AIDS*.
[252] Edward Hooper, *The River: A Journey to the Source of HIV and AIDS*, (Boston, MA: Little, Brown and Co, 1999).
[253] Pepin, *The Origins of AIDS*, 51, 53.
[254] Quammen, *Spillover*, 381.
[255] Morse, *Emerging Viruses*.

Environmental Drivers for Zoonoses

Until recently, researchers did not believe that ecological degradation had much to do with understanding patterns of infectious disease.[256] Yet, research into disease ecology revealed that some of the same factors that cause environmental disruption also drive the emergence of infectious diseases.[257] Ecological changes including deforestation, dam building, and shifting land use can precipitate viral emergence. Thus, as the result of environmental disruption, the nidus for the emergence of viral strains that threaten human health will most likely be in locations where humans have altered the ecology of the host, virus, or environment.[258]

In other words, infectious disease typically results from a natural or anthropogenic change in the ecology of the host and pathogen. **Table 2** provides examples of viral zoonoses and potential pathways of environmental effect that can lead to a viral zoonosis.

Environmental Change	**Potential Pathway of Effect**	**Viral Disease**
Dams, canals, irrigation Deforestation Urban Crowding	Breeding sites for mosquitos	Dengue
Agricultural intensification	Overlap of wild and domestic bird habitat	Avian Influenza
Deforestation	Breeding sites and bats as vectors	Ebola
Deforestation Urban crowding	Bush meat – hunting wild primates for food	HIV
More rain, climate change	Mosquito breeding habitat, rodent food	Hantavirus

Table 2 Viral Zoonoses – Environmental Pathways. B. Canavan**,** modified from Aron and Patz.[259]

[256] Rapport, "Avian Influenza and the Environment: An Ecohealth Perspective."
[257] Kevin J. Olival, Robert L. Hoguet, and Peter Daszak, "Linking the Historical Roots of Environmental Conservation with Human and Wildlife Health," *EcoHealth* 10, no. 3 (September 1, 2013): 224–27.
[258] Walter M. Boyce et al., "Avian Influenza Viruses in Wild Birds: A Moving Target," *Comparative Immunology, Microbiology and Infectious Diseases* 32, no. 4 (July 2009): 275–286; Daszak, Cunningham, and Hyatt, "Emerging Infectious Diseases of Wildlife.
[259] Aron and Patz, *Ecosystem Change and Public Health*.

Known as "viral traffic," the flow of viruses precipitated by environmental factors often creates new opportunities for a virus to spread to different host populations. Environmental disruptions provide a trigger for viruses to move from one species to another. Disease ecologist Richard Ostfield took this argument further and emphasized that a zoonosis might spill over from one species to another more readily within a disrupted, fragmented ecosystem than within an intact, diverse ecosystem.[260] The recent re-emergence of Ebola virus may provide the best example of this dynamic. Deforestation provides many opportunities for the bat, the likely reservoir of Ebola, to move into human habitat. To address this problem, Morse recommended an approach to virus research that includes the science of "viral traffic" patterns: part biology and part social science.[261]

Although researchers generally agree about the broad impact of environmental change on emerging pathogens, there are many uncertainties. Experts disagree about the precise site of origin (nidus) for future viral zoonoses. Some ecologists contend that most emerging disease hotspots (specific geographical locations) are located in tropical countries.[262] However, Woolhouse and Gaunt claim that there is no striking tendency for new pathogens to emerge from tropical rather than temperate regions or from less developed regions compared to more densely populated regions.[263] Indeed, the dissertation case study takes place at the remote Qinghai Tibet Plateau, hardly a tropical, densely populated place for human habitation.

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[260] Ostfeld, Keesing, and Eviner, *Infectious Disease Ecology the Effects of Ecosystems on Disease*.
[261] Morse, *The Evolutionary Biology of Viruses*; Morse, "Examining the Origins of Emerging Viruses," 388; Morse, "Emerging Viruses."
[262] Kate E. Jones et al., "Global Trends in Emerging Infectious Diseases," *Nature* 451, no. 7181 (February 2008): 990–993.
[263] Woolhouse and Gaunt, "Ecological Origins of Novel Human Pathogens."

Despite the growing awareness of the links between disease emergence and ecological change, few studies can confirm or refute precisely how ecological change plays this role. Environmental phenomena are difficult to study, because they are complex and occur over very large scales that defy experimental manipulation. In addition, there are inherent difficulties of studying gaps in baseline data concerning prevalence of diseases in natural systems.[264] Some researchers suggest that it is necessary to focus on upstream causes of emerging diseases such as ecosystem degradation.[265]

Fuller et al. analyzed the interconnections between the environment and the emergence of bird flu.[266] They argued that the dynamics of both pathogens and hosts are likely to shift because of global warming. Evolutionary biologist Harvell has argued for fifteen years that climate change can increase pathogen development and survival rates, disease transmission, and host susceptibility.[267] This is of particular relevance for the dissertation case study, as the Qinghai-Tibet Plateau is experiencing significant warming.

In summary, as human intervention in the global environment and its life processes intensifies, we need a better understanding of the effects of ecological disruptions on health and disease.[268] For avian flu in particular, the increase in bird flu epidemics and the continued human cases may be the biological fallout of a changing climate. As Qinghai is a place subject to intense climate shifts, this is certainly a place to watch for these early signals of climate change.

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[264] Samuel S. Myers and Jonathan A. Patz, "Emerging Threats to Human Health from Global Environmental Change," *Annual Review of Environment and Resources* 34, no. 1 (Nov 2009): 223–252.
[265] Rapport, "Avian Influenza and the Environment: An Ecohealth Perspective."
[266] Trevon Fuller et al., "The Ecology of Emerging Infectious Diseases in Migratory Birds: An Assessment of the Role of Climate Change and Priorities for Future Research," *EcoHealth* 9, no. 1 (Mar 2012): 80–88.
[267] Harvell, "Climate Warming and Disease Risks for Terrestrial and Marine Biota."
[268] McMichael, *Human Frontiers, Environments and Disease*, xiv.

Avian influenza research is at the forefront of a reinvigorated ecological tradition in viral research. In the next section, I rewind back to the 1930s to explore in greater depth the path of an ecological perspective to viral research, how this approach faded for many decades, and now holds promise for understanding the nexus of the virus, the environment, wildlife, and humans.

3.3 Historical Perspectives: Ecological Approaches to Microbes

In this section, I trace how an ecological dimension emerged within viral research in the 1930s; why it shifted and disappeared for decades; and what factors are involved in the return of a deeper ecological perspective in the contemporary study of viruses. What are the recurring themes for an ecological approach to the study of viruses? What have we gained and lost from a reductionist perspective to viral research?

Pendulum Swings: Ecological Approach to Reductionism and Back Again

Physician/historian Warwick Anderson described disease ecology as a natural history approach to disease, one that considers evolutionary time scales and a global scope.[269] I extend this definition to include the history of the ecological tradition within viral research, one that considers the relationship among the virus, the host, and the host's environment.

In the decades prior to World War II, traditions of viral research produced many works that encouraged viewing viruses as biological entities functioning within an ecological context. Early supporters of an ecological or natural history perspective used microbiology as a way to describe relationships between host, virus, and environment. According to

[269] W. Anderson, "Natural Histories of Infectious Disease: Ecological Vision in Twentieth-Century Biomedical Science," *Osiris*, 2004, 39–61.

Anderson, two pioneering supporters of disease ecology in the 1930s and 1940s were Australian microbiologist MacFarlane Burnet and Rockefeller microbiologist René Dubos. Describing their texts as the "nexus of microbiology and general biology," Anderson contended that Burnet and Dubos characterized the interplay of disease, environment, and evolutionary processes in "newly fashionable ecological terms."[270] With differing styles, working on different continents, Burnet and Dubos found a common conceptual framework and integrative approach for their study of microbes and disease.

For Burnet, known for isolating influenza virus strains in the 1930s, ecology suggested an appreciation of natural complexity and the transcendence of mere physicochemical mechanism.[271] Burnet was interested in disease as the interplay of "living beings" in a changing environment.[272] Through the 1970s, Burnet viewed ecology as an appreciation of the complexity in natural systems.[273] Dubos admired Burnet's views on disease ecology, although the two scientists never met.

Dubos' investigations of soil microbiology in the 1930s led him to appreciate how microbes responded to their biogeochemical surroundings.[274] He was the first to show that bacilli could produce antibiotics.[275] Dubos' findings shifted the discussion of the microbe from purely pathogenic terms to ecological terms. For example, Dubos showed that various environmental stresses affect the development of the whole organism. He was one of the first to insist that the mere introduction of the microbial agent is rarely sufficient to establish an

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[270] Ibid., 40.
[271] Ibid., 43
[272] Burnet, *Biological Aspects of Infectious Disease*, 23.
[273] Burnet and White, *Natural History of Infectious Disease,*.
[274] Dubos, *The Bacterial Cell*.
[275] For reasons that are not clear, Dubos' discovery of the antibiotic properties of bacilli attracted little notice with the exception of Joshua Lederberg, greatly influenced by Dubos. When the genome of *Bacillus subtilis* was uncovered in 1997, it came as a surprise that the organism produced several antibiotics. Dubos's contribution never received the recognition it deserved. Personal Communication with Stephen Morse, November 2014.

epidemic state, and that every epidemic develops within a social factor. Ultimately, Dubos would suggest that a method of public health that did not engage with the ecological aspects of disease was inadequate and misguided.[276]

Evolutionary biologist Ernst Mayr offered his own opinion about scientists who emphasized interactions between virus and host. Mayr's admired virologists included Burnet along with bacteriologist Theobald Smith and influenza virologists Richard Shope and Christopher Andrewes. Mayr argued that Shope's approach to swine flu was ecological, one in the naturalist tradition in which the virus exists as part of the host's environment.[277] Andrewes' role in influenza research included his contribution to isolate the first human influenza virus in 1933 and his later role in tracking flu as it appeared around the globe.[278]

In the decades following the introduction and use of the electron microscope in the 1930s, newer technologies emerged that provided researchers an even closer look at the submicroscopic world of viruses. Electron microscopy permitted the measurement of viral size.[279] Techniques included X-ray crystallography, cell-culture, and recombinant DNA technology that exposed the immense variety of viruses. Hughes described how experimental techniques emphasized variation of viral shape, structure and components, biochemical composition, and viral replication.[280] However, virologist Morse claimed that there was little clarity among virus researchers about what this variation in shape, structure, and composition really meant.[281]

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[276] Dubos, *So Human an Animal*; Dubos, *Man Adapting*; Dubos, *Mirage of Health.*
[277] Ernst Mayr, "Driving Forces in Evolution: An Analysis of Natural Selection," in *The Evolutionary Biology of Viruses*, ed. Stephen S Morse (New York: Raven Press, 1994).
[278] Wilson Smith, C.H. Andrewes, and P.P. Laidlaw, "A Virus Obtained from Influenza Patients," *The Lancet* 222, no. 5732 (July 1933): 66–68.
[279] Hughes, *The Virus*, 96.
[280] Ibid., xviii.
[281] Morse, *The Evolutionary Biology of Viruses*.

Changes in bioscience after the 1950s challenged the methods researchers used for investigations of viruses and disease. Historian Paul Forman argued that the revolution in the biomedical sciences led to growth of more specialization of disciplines, considered crucial to the production of new knowledge.[282] But virologist Ewald lamented this emphasis on new disciplines in science, an emphasis that put pressure on researchers to study individual "leaves on the tree" and ignore the metaphorical forest.[283] Burnet also protested that a new generation of researchers had little interest in the ecological aspects of microbes or disease.

New technology had provided a ready means for reductionist experimentation - a way to reduce complex interactions and entities to the sum of their constituent parts in order to make them easier to study. Methodological reduction was the idea that biological systems are most fruitfully investigated at the lowest possible organizational level, and that experimental studies should uncover molecular and biochemical causes.[284] Although successful in the early days of molecular biology, some experts argued that biological systems are too complex to understand by studying their individual parts.[285] Yet, some researchers argued that a reductionist approach was the only way to get anything done. In one example, virologist Renato Delbecco declared that without a reductionist approach, advances in cell biology or DNA replication would not have been possible.[286] In most cases, both approaches are necessary to understand how the individual components work and to appreciate how the parts work together.

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[282] Paul Forman, "On the Historical Forms of Knowledge Production and Curation: Modernity Entailed Disciplinarity, Postmodernity Entails Antidisciplinarity," *Osiris* 27, no. 1 (January 2012): 56–97.
[283] Ewald, *Plague Time*, x.
[284] Brigandt and Love, "Stanford Encyclopedia of Philosophy."
[285] Marc H.V. Van Regenmortel, "Reductionism and Complexity in Molecular Biology," *EMBO Reports* 5, no. 11 (November 2004): 1016–20.
[286] Natalie Angier, *Natural Obsessions: Striving to Unlock the Deepest Secrets of the Cancer Cell* (Boston: Mariner Books, 1999), 16.

By mid-century, researchers learned to study the virus in relative isolation, no longer as part of an integrated system with its host and environment. Burnet contrasted these reductionist methods of viral research with his preferred ecological approach that studied organisms within their natural milieu.[287] He was especially reluctant to accept the reductionism of examining DNA. Scientists sliced the delicate network traced by the virus into tidy compartments that removed its context within the host and environment.[288] Mayr complained that the host organism often served as a mere substrate for viral growth rather than as an active participant in the viral-host ecology.[289]

Ernest Rutherford famously said, "All science is either physics or stamp collecting."[290] Many researchers considered the ecological approach as mere "stamp collecting," particularly since it was difficult to predict which viruses had the greatest human disease potential.[291] By the 1960s, from being highly influential, there was a trend away from the ecological aspects of infectious diseases in general and viruses in particular.[292] According to Mayr, funds shifted from an ecological to a reductionist approach by the mid-1960s.[293] This was a period of over-optimism and complacency about infectious disease.

Confidence in antibiotic and vaccine development in 1960s and 1970s led to further neglect of ecological understanding of microbes and disease. In 1967, there were reports that the U.S. Surgeon General stated it was "…time to close the book on infectious disease" and turn scientific attention on chronic diseases of humans.[294] By 1972, even Burnet and White

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[287] van Helvoort, "History of Virus Research in the Twentieth Century."
[288] Latour, *We Have Never Been Modern*, 2.
[289] Mayr, "Driving Forces in Evolution: An Analysis of Natural Selection."
[290] John Betteley Birks, *Rutherford at Manchester* (London: Heywood, 1962).
[291] Morse, *The Evolutionary Biology of Viruses*.
[292] Burnet and White, *Natural History of Infectious Disease,*.
[293] Ernst Mayr, "Driving Forces in Evolution: An Analysis of Natural Selection," in *The Evolutionary Biology of Viruses*, ed. Stephen S Morse (New York: Raven Press, 1994).
[294] Spellberg and Taylor-Blake, "On the Exoneration of Dr. William H. Stewart." The authors claim that attribution to Dr. Stewart of a belief that it was time to close the book on infectious diseases is an urban

wrote that the future of infectious disease would be very dull.[295] The Rockefeller Foundation Virus Program, perhaps the strongest impetus for the ecological tradition in viral research, closed its operations in the 1970s.

However, by 1981, the emergence of HIV/AIDS jolted scientists who had become complacent about viruses in the developed world. According to Lederberg, this discovery sparked the most concentrated program of biomedical research in history that, in turn, transformed diagnostic virology.[296] The crisis especially prompted a re-thinking of viruses. Lederberg urged fellow scientists to adopt an ecological perspective to replace the twentieth century metaphor of "war on disease" to describe the relationship between people and infection.

Within a decade following the early AIDS crisis, a new paradigm unfolded for understanding the biological, environmental, and social aspects of virus ecology. Morse and other leaders within the virology community encouraged integrative thinking about viral evolution in order to bridge the gaps among separate disciplines.[297] In one example, during the 1990s, epidemiologists Roy Anderson and Robert May developed a theoretical model of parasite-host interactions that took into consideration both the medical and ecological.[298] Although Burnet and Dubos received credit for "inventing" an ecological approach to disease, May and Anderson quantified it with a basic reproduction rate of the infection.[299]

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legend. Dr. Stewart was associated with reports from 1967 and 1968 that called attention to a shift in attention from infectious diseases to chronic disease. However, people in academia and public health adopted this belief. See Garrett *The Coming Plague*, p. 33; also, "A Mandate for State Action," in Proceedings of the 65th Annual Meeting of the Association of State and Territorial Health Officers, 1967.

[295] Burnet and White, *Natural History of Infectious Disease.*

[296] Lederberg, "Infectious History."

[297] Morse, *Emerging Viruses*, 1993; Morse, *The Evolutionary Biology of Viruses*.

[298] Roy M. Anderson, *Infectious Diseases of Humans Dynamics and Control*, (Oxford; New York: Oxford University Press, 1992).

[299] Quammen, *Spillover*, 304.

Viral ecology, according to historian Anderson, attracted more attention for shedding light on emerging disease, bioterrorism, and the health impacts of climate change.[300]

Yet, leading investigators of an ecological approach to microbes continued to protest that their views were marginalized in biomedical science.[301] Anderson argued that historians have neglected the ecological traditions in biomedical science to emphasize the development of laboratory models. Experts in disease ecology argued that most biomedical scientists have not considered the broader ecological contexts of disease.[302] In stronger terms, Lederberg claimed that the pioneering ecological approaches were largely ignored.[303]

This dissertation seeks to close some of these gaps by linking the early ecological contexts of disease to its resurgence in avian influenza science. Beginning in the 1990s, a deeper understanding of the interconnected nature of human, animal, and environmental health would emerge. The next section traces how scientists have come to a new understanding of these interconnections.

Toward a New Paradigm

This section discusses contemporary strategies and programs that address an integrated approach to understanding human, animal, and environment health. No single approach has come to the fore; however, a variety of methods and tools help to advance common goals to identify and control emerging infectious diseases.

With the HIV/AIDS crisis beginning in the 1980s, it became imperative to track the sources of the pathogens in order to understand the ecological causes of disease in human and

[300] Anderson, "Natural Histories of Infectious Disease," 31.
[301] Ibid., 61.
[302] Keesing, Ostfeld, and Eviner, *Infectious Disease Ecology*.
[303] Lederberg, "Viruses and Humankind: Intracellular Symbiosis and Evolutionary Competition."

animal populations.[304] Determining the source of HIV infections could provide insight in preventing future zoonoses. Some approaches spanned basic and applied biomedical research as well as public health response within wildlife, veterinary, and human disciplines.[305]

Using the broad term "ecohealth," ecological approaches to health emerged as a defined field of inquiry and application by the 1990s. The term "ecohealth" has various definitions but the term has some resonance among researchers in various fields of scholarship (e.g., Conservation Medicine, Social Medicine) or different collaborative initiatives (e.g., One Health movement, Resilience Alliance).[306] An "ecohealth" approach focuses on human beings within their environment. From this broad definition the more formal approach of EcoHealth emerged, one of two approaches from the plethora of ideas and movements at the intersection of human disease and environment. The other approach is known as One Health.

The EcoHealth and One Health approaches had similar founding principles and a shared vision that the global problem of disease emergence required an integrated approach. The common ground for both EcoHealth and One Health is in the study of zoonotic disease and pandemic threats; both approaches champion systems thinking and transdisciplinary research to achieve a greater understanding of health problems. Founded in the late 1990s, both organizations emphasized a holistic understanding of health that went "…beyond the purely biomedical."[307]

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[304] A. Alonso Aguirre, ed., *Conservation Medicine: Ecological Health in Practice* (Oxford ; New York: Oxford University Press, 2002).
[305] Sandrock, "Editorial."
[306] Johanne Saint-Charles et al., "Ecohealth as a Field: Looking Forward," *EcoHealth* 11, no. 3 (September 2014): 300–307.
[307] Jakob Zinsstag, "Convergence of Ecohealth and One Health," *Ecohealth* 9, no. 4 (Dec 2012): 371–73.

Although EcoHealth and One Health share this common ground, they do come from different traditions.[308] EcoHealth has its roots in environmental health and One Health focuses on emerging diseases arising at the intersection of human and animal domains.[309] As we have seen from discussions of the animal and environmental drivers of emerging infectious diseases, it is clear that both approaches are important.

After a decade of international conferences in North America and Australia under the umbrella of "ecosystem health," the first formal EcoHealth forum was held in Montreal in 2003. At that time, EcoHealth adopted a broad perspective informed by geography, systems sciences, philosophy, and public health.[310] The EcoHealth perspective presumed that human survival depends on healthy ecosystems that are now under threat.[311] Since 2003, the International Association for Ecology and Health (IAEH) and the journal *Ecohealth* have established EcoHealth as a legitimate scholarly activity.

Alternatively, One Health has a focus on the emergence of zoonotic disease within the human-animal interface with little emphasis on the ecosystem.[312] While One Health is expanding to include new disciplines, veterinarians and public health practitioners form the majority of the field.[313] In 2004, the Wildlife Conservation Society convened a meeting of human and animal health experts who called for an interdisciplinary approach to prevent disease and formed the basis of the "One Health, One World" concept. Although One Health is a contemporary approach, scientists since the nineteenth century have noted the similarity

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[308] Zee Leung, Dean Middleton, and Karen Morrison, "One Health and EcoHealth in Ontario: A Qualitative Study Exploring How Holistic and Integrative Approaches Are Shaping Public Health Practice in Ontario," *BMC Public Health* 12, no. 1 (May 16, 2012): 358.
[309] Trevon L. Fuller et al., "Predicting Hotspots for Influenza Virus Reassortment," *Emerging Infectious Diseases* 19, no. 4 (April 2013): 581–88.
[310] Leung, Middleton, and Morrison, "One Health and EcoHealth in Ontario."
[311] Zinsstag, "Convergence of Ecohealth and One Health."
[312] Andrew Papadopoulos and Sarah Wilmer, "One Health: A Primer" (Vancouver, BC, Canada: National Collaborating Center for Environmental Health, 2011).
[313] Zinsstag, "Convergence of Ecohealth and One Health."

in disease processes among animals and humans. In fact, Rudolf Virchow in 1855 coined the term "zoonosis" to indicate an infectious disease that passes between humans and animals.[314]

By the end of the twentieth century, the surprising spillover of highly pathogenic avian influenza from poultry to humans galvanized international health agencies to gather scientists across disciplines to address threats from influenza and other emergent diseases. Through a consolidated effort under One Health, experts were able to influence the world authorities on animal (World Organization for Animal Health), agricultural (Food and Agriculture Organization), and human (World Health Organization) health threats.[315] A major outcome of the One Health effort was the 2009 formation of a One Health Office as part of The Centers for Disease Control and Prevention (CDC). This office specifically addresses the convergence of human and animal health. The first One Health international conference was in Africa in 2011. The American Society for Microbiology organized One Health sessions at the annual meetings of the American Association for the Advancement of Science in 2010, 2011, and 2012.[316] Thus, the One Health collaborative is in better alignment with the goals of large health institutions compared to the EcoHealth initiative.

Yet, achieving integrated approaches for disease detection has been difficult because of the traditional boundaries of medical and veterinary practice.[317] Some experts in the fields of human medicine see One Health as a field championed primarily by veterinarians and object to the term “holistic medicine” used to describe to One Health. In addition, One

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[314] Corrie Brown, “Virchow Revisited: Emerging Zoonoses,” *ASM News (American Society for Microbiology)* 69, no. 10 (2003): 493–97.
[315] Anderson et al., “FAO-OIE-WHO Joint Technical Consultation on Avian Influenza at the Human-Animal Interface.”
[316] Ronald M. Atlas, “One Health: Its Origins and Future,” in *One Health: The Human-Animal-Environment Interfaces in Emerging Infectious Diseases*, ed. John S. Mackenzie et al., vol. 365 (Berlin, Heidelberg: Springer Berlin Heidelberg, 2012), 1–13.
[317] Ibid.

Health does not have a formal organizational structure or its own research journal.[318] However, by collaborating with the IAEH and its *Ecohealth* journal and with communities of practice in EcoHealth around the world, those who identify with One Health are able to gain platforms for interaction and outreach.

Both One Health and EcoHealth are still relatively unknown within the public sphere.[319] Those who are aware include many skeptics. Some argue that One Health and EcoHealth have goals that are too idealistic, too costly, and their expectations of interdisciplinary collaboration are too high. In addition, the scope and boundaries of each approach are not clearly defined.[320] There are likely multiple benefits gained by bringing together One Health and EcoHealth but, according to veterinarian Zinsstag, many individuals working in either field are unaware of the potential for collaboration.[321]

Whatever triggers emerging infectious diseases, one of the biggest challenges is to establish whether and how researchers can intervene before a pathogen reaches the human population. To identify a pathogen at its source is an "upstream" approach.[322] The Emerging Pandemic Threats program, a project initiated in 2009 by USAID, was designed to rapidly identify (and "eventually predict") new public health threats and increase capacities to lessen the potential effects of these threats.[323] Drawing from efforts to address the H5N1 avian flu threat, the Emerging Pandemic Threats program specifically promotes a One Health approach that spans the animal health, public health, and environmental communities.[324] Through its PREDICT component, the Emerging Pandemic Threats Program seeks to identify the

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[318] Zinsstag, "Convergence of Ecohealth and One Health."
[319] Leung, Middleton, and Morrison, "One Health and EcoHealth in Ontario."
[320] Ibid.
[321] Zinsstag, "Convergence of Ecohealth and One Health."
[322] Morse et al., "Prediction and Prevention of the next Pandemic Zoonosis."
[323] Daszak, "Can We Predict Future Trends in Disease Emergence?"
[324] W. B. Karesh and R. A. Cook, "One World - One Health," *Clinical Medicine* 9, no. 3 (June 1, 2009): 259–60.

regions, wildlife hosts, and human–animal interfaces most likely to circulate the next emerging zoonosis.[325] The focus is on building a global early warning system for emerging diseases that move between wildlife and people.

Biologist Raina Plowright argued that the course of the next pandemic may very well depend on the work of the PREDICT project for identifying how people alter the landscape and where the next diseases are likely to spill over to humans.[326] Relevant for this dissertation, the Emerging Pandemic Threats program of USAID helped to lead and fund investigations of avian influenza emerging from Qinghai.[327]

Another program, initiated through the Smithsonian Conservation Biology Institute, focuses on migratory connectivity as critical for predicting disease transmission among domestic animal, wildlife, and human populations. Their overall goal is to preserve important migration routes and to prevent high infection rates among wildlife populations. For example, densely populated stopover points for waterfowl may have a higher likelihood of disease transfer among the birds.[328] Scientists used Movement Ecology methods at Qinghai to determine the patterns of migratory birds, their links to domestic birds, and the spread of avian influenza to many countries.

One of the very first coordinated efforts for tracking potential pandemics was ProMED (the Program for Monitoring Emerging Diseases), established in 1994 with the support of the Federation of American Scientists. Virologist Morse and colleagues proposed ProMED as a demonstration project to create an early warning system for infectious diseases

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[325] Morse et al., "Prediction and Prevention of the next Pandemic Zoonosis."
[326] Raina K Plowright et al., "Causal Inference in Disease Ecology: Investigating Ecological Drivers of Disease Emergence," *Frontiers in Ecology and the Environment* 6, no. 8 (October 2008): 420–29.
[327] Newman, *Niche Mapping, Multi-Criteria Decision Analysis and Animal Movement Data for Mapping the Risk of Avian Influenza Emergence in Asia*.
[328] Fergus et al., "Migratory Birds and Avian Flu"; Gilbert et al., "Anatidae Migration in the Western Palearctic and Spread of Highly Pathogenic Avian Influenza H5NI Virus"; Rappole, *The Avian Migrant the Biology of Bird Migration*; Reed et al., "Birds, Migration and Emerging Zoonoses."

in humans, animals and plants worldwide. It is the only organization to include plants as part of an integrated warning system for emerging infectious disease. The rationale for creating ProMED was the increasing risk of emerging diseases based on population growth as well as environmental triggers that increase human exposure to zoonotic or vector-borne infections.[329]

As an internet-based reporting system, ProMED-mail promotes communication among the international infectious disease community on a global scale. A team of human, plant, and animal disease experts review and investigate reports of emerging disease before posting to ProMED-mail. The sources include social media reports, official reports, local observers, and others. ProMED-mail distributes regular (weekly) email reports to nearly 100,000 subscribers in about 185 countries, posting immediately on the ProMED web site.[330]

Another widely accessible web-based program is HealthMap. Founded in 2006 by a team of researchers, epidemiologists and software developers, HealthMap utilizes online sources for disease outbreak monitoring and real-time surveillance of emerging public health threats. It is a freely accessible, automated electronic information system.[331] HealthMap brings together disparate data sources, including online news aggregators, eyewitness reports, expert discussions and official reports, to achieve a unified and comprehensive view of the current global state of infectious diseases and their effect on human and animal health. In March 2014, HealthMap tracked early press and social media reports of a hemorrhagic fever

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[329] Morse, Rosenberg, and Woodall, "Health Policy," *Health Policy*, 38 (1996) 135-153. Current funders for ProMED include corporations, universities, non-profit organizations, governmental organizations as well as individual donors. Recent financial support has come from the Wellcome Trust, Skoll Global Threats Fund, The Gates Foundation, the Rockefeller Foundation, the Oracle Corporation, the Nuclear Threat Initiative and others.

[330] Yu and Madoff, "ProMED-Mail"; Woodall and Calisher, "ProMED-Mail." http://www.promedmail.org/

[331] Funders for HealthMap include Skoll Global Threats Fund, the U.S. Defense Global Threat Reduction Agency, U.S. Office of the Director of National Intelligence, Bill & Melinda Gates Foundation, USAID, the National Library of Medicine, The Centers for Disease Control and Prevention, Canadian Institutes of Health Research, Amazon.com, Merck, Unilever, and individual donors.

in West Africa, subsequently identified by WHO as Ebola. HealthMap sources include ProMED-mail, World Health Organization, and World Organization for Animal Health, Food and Agriculture Organization of the United Nations, EuroSurveillance, Google News, and the Wildlife Data Integration Network.[332]

In summary, integrating health studies across species is gaining support and attention from global health organizations as well as "threat reduction" organizations such as the U.S. Defense Global Threat Reduction Agency. It is clear that collaboration among veterinary, medical, and public health professionals can facilitate a better understanding of the ecological interactions of environment, animal, and human health. There are obstacles, many of which are economic, to the acceptance of the benefits gained from a transdisciplinary approach. These range from understanding the determinants of zoonoses to the response when diseases occur in animals compared to when they occur humans.[333] To predict the next zoonotic pathogen, if such a thing is even possible, would require a fusion of expertise from many disciplines including evolution, ecology, virology, microbiology, social science, and history.

Analyses of the historical patterns and frequency of avian influenza epidemics are critical for shedding light on the interaction between a virus and its host. This is particularly true for avian viruses because their host range is so extensive. The next chapter includes historical perspectives on the history of avian influenza in both birds and humans.

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[332] Hsinchun Chen, Daniel Zeng, and Ping Yan, "HealthMap," in *Infectious Disease Informatics*, by Hsinchun Chen, Daniel Zeng, and Ping Yan, vol. 21 (Boston, MA: Springer US, 2010), 183–86,
[333] Zinsstag et al., "Mainstreaming One Health."

Chapter Four: Avian Influenza
Biography of a Cross-Species Virus

As discussed, viruses hijack the cells of a living organism and commandeer its functions for their own replication cycle. Viruses circulate globally among multiple hosts in a wide range of physical environments. Among viruses known to affect humans, the influenza virus is unique. It is not only highly transmissible among people but also circulates each year in a modified form as the virus mutates. On an irregular basis, influenza viruses cause epidemics or pandemics in humans and epizootics in animals. The history of avian influenza reveals a remarkable interconnected viral web among many species. All human and animal influenza viruses originated, at some point in the distant past, from aquatic waterfowl.

Describing the physical attributes of the flu virus, the first section of this chapter outlines what is known and unknown about its transmission. The next section documents how scientists came to the realization that wild birds are the primordial source of all influenza viruses. The chapter than turns to the history of avian influenza outbreaks among birds since the late nineteenth century, followed by a section that explores potential links among commercial factory farms and escalating bird flu outbreaks. The final section discusses the first known avian flu infections transmitted, since at least 1997, from birds to humans. Throughout, the emphasis is on the critical changes over time in the scientific understanding of avian influenza.

4.1 Influenza Virus: Anatomy and Species Range

Influenza is a member of the Orthomyxoviridae family of RNA (ribonucleic acid) viruses, measuring 80 to 120 nanometers in diameter. There are three types of influenza, designated as A, B, and C. Type C rarely causes human infection, type B can cause mild epidemics but with far less impact on human society. In contrast, type A poses the greatest threat to health across species. All influenza viruses affecting animal species (including horses, pigs, birds, and humans) belong to subtype A, at least as far as scientists know. All further references to flu or influenza in this dissertation refer to influenza A.[334]

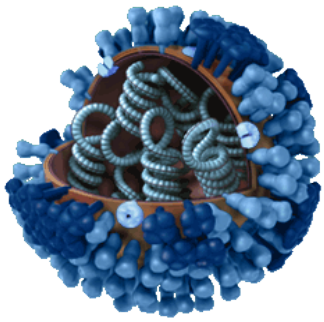

Figure 6. Influenza Virus Structure. Source: The Centers for Disease Control and Prevention, August 15, 2014.

The structure of the flu virus provides insights into how it functions. Researchers classify flu viruses by their two surface proteins: hemagglutinin (HA) and neuraminidase (NA) as depicted in light and dark shades in **Figure 6**. HA enables the virus to bind to the host cell and NA enables the virus to release itself from the host cell to seek a new cell.[335] The RNA is the ribbon-like material inside the sphere. All flu virus subtypes are a numbered combination of HA and NA proteins.

Different influenza viruses infect different animals and remain endemic in those populations: humans (H1, H2, and H3), pigs (H1 and H3), horses (H3, H7), and seals (H7). Based on current scientific understanding, human influenza pandemics with sustained transmission from person-to-person are of subtypes H1, H2, and H3 in combination with N1 or N2. Of the seventeen HA and nine NA subtypes of influenza discovered so far, many

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[334] Karl G. Nicholson, Robert Webster, and Alan Hay, eds., *Textbook of Influenza* (Wiley-Blackwell, 1998).
[335] Institute of Medicine, *Perspectives on Research with H5N1 Avian Influenza: Scientific Inquiry, Communication, Controversy: Summary of a Workshop* (National Academies Press, 2013).

occur only in various species of waterfowl.[336] Wild aquatic birds are the hosts of flu viruses, a viral reservoir that includes hundreds of known avian species.

Figure 7 is a conceptual diagram to illustrate the overlap of some of the major flu virus subtypes. Pigs, birds, and humans share many flu viruses; birds and horses share far fewer. Note that H5N1 and other avian flu viruses reside at the point of greatest overlap among those species that get influenza.

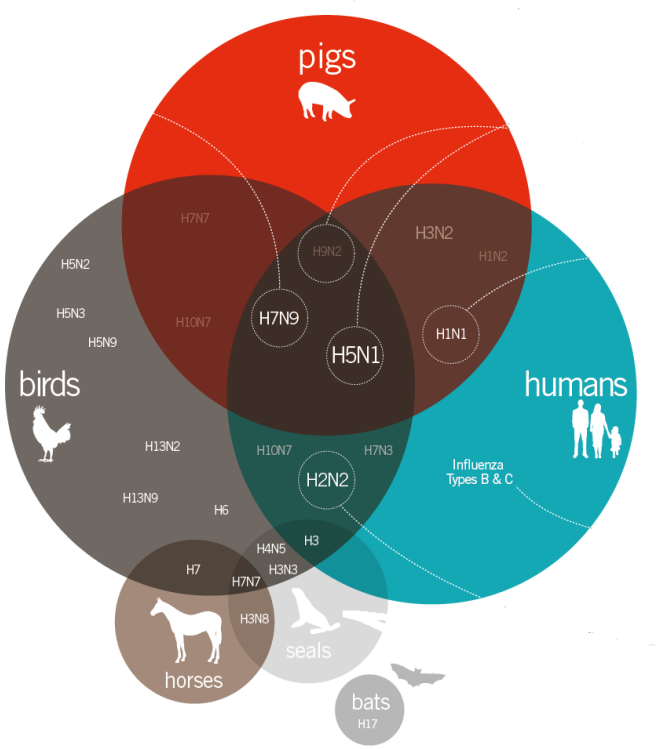

Figure 7 Influ-venn-za. David McCandless, 2013. Used with permission.

[336] Krauss et al., "Influenza A Viruses of Migrating Wild Aquatic Birds in North America"; Munster and Fouchier, "Avian Influenza Virus"; Webster et al., "Evolution and Ecology of Influenza A Viruses."

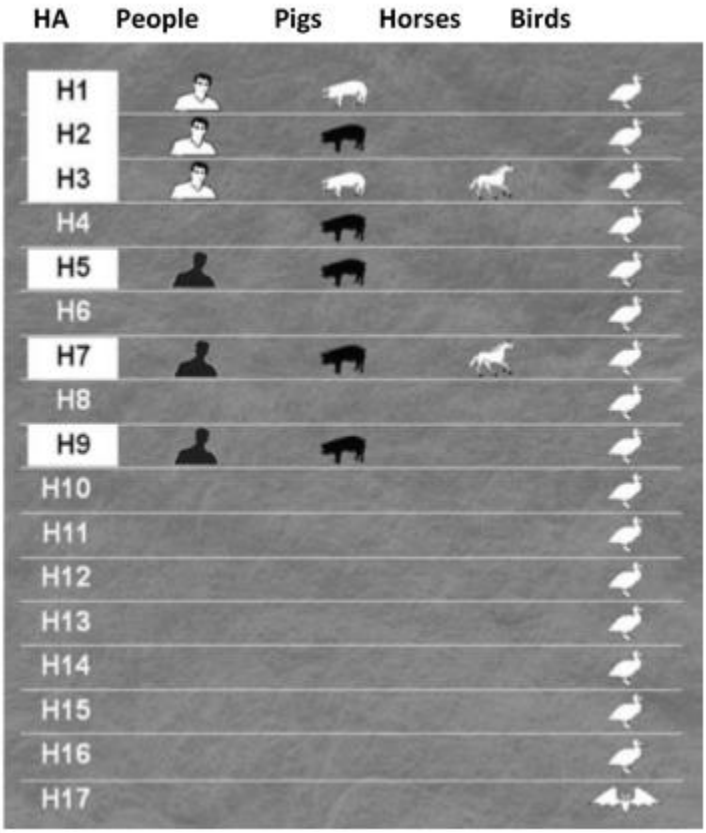

Figure 8. Influenza A Viral Host Range. Source: Courtesy of Robert G. Webster, as cited in Institute of Medicine Report 2013.

To illustrate the host ranges for influenza viruses, **Figure 8** demonstrates flu HA designations and their animal host ranges. Hemagglutinin (HA) is most important for binding the virus to host cells in the crossover of the virus from waterfowl to other hosts. White symbols indicate flu viruses that have established permanent lineages in the host. Black symbols indicate sporadic viral infection.

For example, subtypes H5, H7, and H9 transmit only sporadically to humans unlike H1, H2, and H3 that have an entrenched lineage within the human population. The H7 subtype established a permanent lineage in horses suggesting that H7 influenza viruses have a successful lineage in mammals. The H3 viruses are the only viruses known, so far, to have an enduring place in the viral web of humans, pigs, horses, and birds.[337] Note that all HA designations from H1 through H17 have an established lineage in birds, mostly waterfowl.

In addition to birds, recent studies reveal that the H17 subtype of the flu virus has been described in bat species, a mammal, since 2012.[338] According to the CDC, the

[337] Institute of Medicine, *Perspectives on Research with H5N1 Avian Influenza*.
[338] Tong et al., "New World Bats Harbor Diverse Influenza A Viruses."

discovery of bat flu is important for public health because these viruses represent a newly identified animal species that may act as a source of flu viruses in ways we do not yet understand.[339] It is also possible that genes of bat influenza viruses are descendants of flu viruses that are now extinct – or yet to be discovered.

As a human pathogen, the influenza virus has a very high potential for adaptive change.[340] The structure of the influenza virus genome consists of eight separate segments of single-stranded RNA. One analogy is to compare a viral genome to a computer byte, another entity with eight segments. Since a byte contains eight bits, each with two possible values, a single byte may have 2^8 or 256 different values. A virus also has eight segments but, unlike a computer byte, viruses have a far greater number of combinations possible.

During the 1970s, the reassortment theory of viruses, in which crossbreeding can occur between human and animal strains, came to the fore.[341] Avian flu expert Robert Webster explained that when two different influenza viruses infect the same host, the segments from the two viruses could swap in many different ways. Two or more different strains of a virus combine in random ways to form a new viral subtype, a process known as antigenic shift.[342] The antigenic properties of the virus' surface proteins determine the host's ability to fight off infection of that particular strain.

Passage of viruses among non-human animal species occurs with sufficient regularity to allow infection by two or more strains in the same host individual. For example, pigs are prone to infection with both avian and human influenza strains (in addition to their own

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[339] CDC, "Bat Influenza (Flu) | Seasonal Influenza (Flu) |.".
[340] Douglas Causey and Scott V. Edwards, "Ecology of Avian Influenza Virus in Birds," *The Journal of Infectious Diseases* 197, no. s1 (February 15, 2008): S29–33.
[341] Wolfe, *The Viral Storm*.
[342] An antigen is a toxin or virus that induces an immune response in the body, especially the production of antibodies. Antigenic variation refers to the mechanism by which virus alters its surface proteins in order to evade a host immune response.

swine flu strains), and are thus a "mixing vessel" for flu viruses with pandemic potential for humans.[343] This antigenic shift can lead to a virus so novel that humans have little or no immunity to it. In this way, the virus no longer resembles influenza viruses that had previously been in circulation. Some pandemics are the direct result of antigenic shift.[344] For example, the pandemic strain of 2009 was a reassortment of three flu strains – avian, human, and swine - that had been circulating individually in the U.S., Europe, and Mexico.[345] However, antigenic drift is a different process. It is the natural mutation of an influenza virus strain with minor changes over time.

Another reason for the adaptive nature of the flu virus is that influenza viruses lack proofreading ability during replication. This is true for all RNA viruses because it is single-stranded, unlike the double strands of DNA. Thus, the "code" in RNA viruses is only written once rather than in duplicate. RNA viruses have the highest mutation rate of any group of organisms, averaging one mutation per genome per replication. Virologist Racaniello emphasized the importance of error-prone synthesis in RNA viral evolution and disease production. Flu viruses are adaptive and successful because they make many mistakes in their replication cycle.[346] Viral mutation quickly produces multiple lineages of viruses within any given subtype.[347] In this way, each virus has its own unique evolutionary history.

This natural potential for viruses to swap their genetic material with each other underscores that flu viruses are part of an interconnected viral web among many species. Nature has provided a powerful and flexible architecture to ensure its replication in many

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[343] Webster et al., "Evolution and Ecology of Influenza A Viruses."
[344] Horimoto and Kawaoka, "Pandemic Threat Posed by Avian Influenza A Viruses"; Perdue and Swayne, "Public Health Risk from Avian Influenza Viruses"; Henry Nicholls, "Pandemic Influenza: The Inside Story," *PLoS Biol* 4, no. 2 (February 14, 2006): e50.
[345] Webster, "Influenza: Lessons Learned from Pandemic H1N1…Can We Now Ignore H5N1?"
[346] Racaniello, "The Error-Prone Ways of RNA Synthesis."
[347] Chen et al., "Establishment of Multiple Sublineages of H5N1 Influenza Virus in Asia."

hosts and environments. Influenza viruses, in particular, have evolutionary flexibility that reaches across species.

For a human flu virus, "lungs are the easy way in."[348] Aerosol transmission is person-to-person transmission of viruses through the air by means of inhalation of infectious particles. Mutation and reassortment of influenza viruses circulating within the human population ensures that new outbreaks of epidemic influenza will occur every year without any new introductions of viruses or genetic elements from birds or other species. The influenza viruses causing seasonal epidemic influenza among humans are variants of previous pandemic viruses.

Once initiated, flu epidemics or pandemics perpetuate by sustained human-to-human transmission of the virus drawn from the human, not avian, viral reservoir.[349] Because influenza can kill 250,000–500,000 people each year, the World Health Organization (WHO) makes vaccine recommendations based on which flu viruses are circulating and which viruses are the most likely to circulate during the coming season.[350] This process occasionally results in a vaccine that is not optimal for inducing human immunity against the circulating flu strains. It is a process based in science but the path of the influenza virus is unpredictable, even over short periods.

The Institute of Medicine argued that the virulence (severity of the virus as measured by disease in the host) of some viral strains is often much higher on the other side of the species barrier.[351] This has been the case with avian H5 and H7 influenza subtypes,

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[348] Michael Greger, *Bird Flu: A Virus of Our Own Hatching* (New York: Lantern Books, 2006).
[349] Boyce et al., "Avian Influenza Viruses in Wild Birds"; L. P. Shu et al., "Genetic Reassortment in Pandemic and Interpandemic Influenza Viruses," *European Journal of Epidemiology* 12, no. 1 (February 1, 1996): 63–70.
[350] CDC, "Selecting the Viruses in the Seasonal Influenza (Flu) Vaccine | Health Professionals | Seasonal Influenza (Flu)."
[351] Institute of Medicine, *Perspectives on Research with H5N1 Avian Influenza*.

transmitted from wild birds to domesticated poultry and occasionally to people. The H5N1 avian virus is the focus of the dissertation case study.

Figure 9 illustrates what is known and unknown about the natural history of the H5N1 avian virus. Arrows show the transmission of the H5N1 virus among different host reservoir groups and circulation among species within each group. Dotted lines represent sporadic transmission; solid lines represent sustained transmission between different species. Question marks indicate unknown or unresolved transmission patterns.[352] Based on this diagram, it is clear that many questions remain in this complex ecology. The next section highlights the origins and key events in the history of avian influenza among birds.

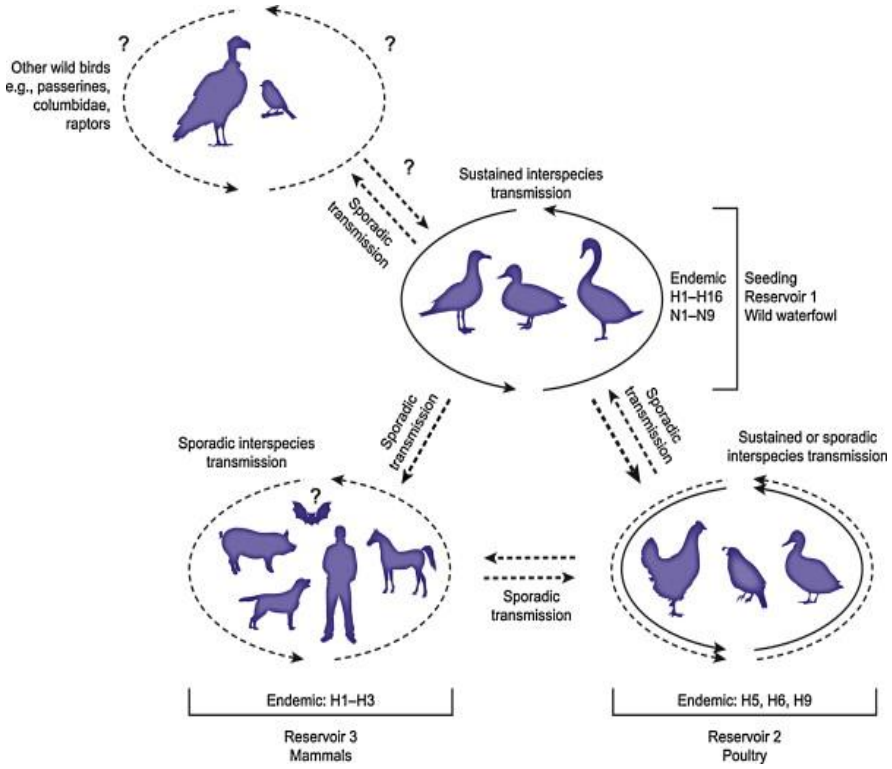

Figure 9: Natural History of HPAI H5N1, Sonnberg, Webby,Webster, 2013.

[352] Sonnberg, Webby, and Webster, "Natural History of Highly Pathogenic Avian Influenza H5N1."

4.2 Influenza: Origins of a Cross-Species Virus

As discussed previously, influenza has a wide diversity of hosts including humans, horses, pigs, domestic poultry, and aquatic waterfowl. Regardless of host organism, the primordial source of all these influenza viruses is aquatic birds. Consequently, each influenza virus received some portion of its genetic material from a bird virus in its long and circuitous history. Ultimately, understanding how influenza viruses evolve and move among birds, and from birds to people, is significant for understanding the role of birds in the emergence and spread of influenza in humans. This section provides a foundation for such understanding.

Birds have existed on earth in vast numbers for more than fifty million years. Humans are the relative newcomers. Avian influenza experts reported that influenza viruses have existed for millions of years as a harmless intestinal infection of aquatic birds such as ducks and geese.[353] According to virologists Causey and Edwards, such birds dwell in nearly every terrestrial and aquatic habitat throughout the world.[354]

Virologist Webster has long argued that flu viruses are in evolutionary equilibrium in waterfowl, infecting a high proportion of the host population, yet causing minimal damage to the host.[355] Thus, in wild birds, the avian infection is ubiquitous and infection asymptomatic.[356] In humans, however, influenza comes under ferocious attack from immune systems that generate intensive selective pressures on the virus. Under these circumstances, viral evolution escalates.

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[353] R J Webby and R G Webster, "Emergence of Influenza A Viruses," *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 356, no. 1416 (December 29, 2001): 1817–1828 ; Drexler, *Secret Agents*; Mohammad Yousaf, "Avian Influenza Outbreak Hits the Industry Again," *World Poultry* 20, no. 3 (2004): 22–25.
[354] Causey and Edwards, "Ecology of Avian Influenza Virus in Birds."
[355] Nicholson, Webster, and Hay, *Textbook of Influenza*. from p. 117 "…the long-term survival of the avian viruses appears to favor those that have not changed, and selection is primarily negative."
[356] Webster et al., "Evolution and Ecology of Influenza A Viruses."

According to virologist Shortridge, human influenza likely emerged about 4,500 years ago with the domestication of ducks, perhaps the original source of all influenza viruses.[357] Duck farming spread and intensified over the last 500 years, beginning with the Qing Dynasty in China in the middle of the seventeenth century.[358] Farmers moved ducks from rivers onto flooded rice fields as an adjunct to rice farming. Shortridge argued that it is possible this led to a permanent gene pool of avian influenza viruses in close proximity to humans.[359] Recent studies by Gilbert et al. confirmed an association between the H5N1 virus and duck populations, human populations, and rice production in Vietnam and Thailand.[360]

The gregarious nature of many bird species, coupled with migratory and scavenging instincts, offers an indication of how viral mixing may occur. The wide geographic distribution of wild birds presents countless opportunities for contact of a wild bird with a domestic bird species such as a chicken. However, influenza in birds is very different from its manifestations in humans and other species. For birds, flu is typically not a respiratory disease but a gastrointestinal disease. Viruses replicate in the gut of the bird, and birds excrete the viruses in great quantities into the environment. Migrating waterfowl thus expose large numbers of domestic fowl (such as chickens) to avian influenza viruses. Webster has argued for decades that this contact provides opportunities for flu viruses to cross the host barrier and initiate local or widespread epidemics.[361]

In addition, there are differences in avian viruses found among wild birds from different geographic regions. For example, Ito et al. claimed there are substantial genetic

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[357] Kennedy F Shortridge, "Severe Acute Respiratory Syndrome and Influenza: Virus Incursions from Southern China," *American Journal of Respiratory and Critical Care Medicine* 168, no. 12 (December 15, 2003): 1416–1420.
[358] Wallace, "Breeding Influenza," 929; Schrijver and Koch, *Avian Influenza*.
[359] Greger, *Bird Flu*.
[360] Gilbert et al., "Mapping H5N1 Highly Pathogenic Avian Influenza Risk in Southeast Asia."
[361] Webster et al., "Evolution and Ecology of Influenza A Viruses."

differences between avian influenza viruses found in Eurasia and North America but limited differences found among viruses from birds in different flyways within the same continent.[362] The reason for this, virologist Wolfe argued, is that despite their wings, most bird and bat species live close to where they were born. Only a few species, such as the arctic tern, have evolved to move great distances.[363] Highly mobile species, particularly ones that congregate in large colonies, are of particular importance for the spread of avian viruses. One of those long-distance flyers is the object of investigation in this dissertation – the bar headed goose is a key actor in the Qinghai case study.[364]

In birds, there is an important distinction as to whether a flu virus subtype is low pathogenic (LP) or high pathogenic (HP). Researchers have found that the vast majority of viruses detected in wild birds (e.g. ducks, geese, shorebirds, etc.) are LP viruses, typically asymptomatic.[365] In poultry (defined here as domesticated chickens, turkeys, ducks, and geese), LP flu viruses cause mild disease, often decreasing egg production, while HP forms are fatal.

However, virologists Kim et al. reported that H5 and H7 subtypes could convert from LP to HP in their natural hosts such as ducks and geese.[366] When H5 and H7 viruses convert (mutate) from LP to HP, they can cause illness in both avian and mammalian hosts including humans. The first documented conversion of an LP avian virus to an HP form was during the Pennsylvania epizootic among chickens in 1983.[367] One hypothesis presented by virologist

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[362] T. Ito et al., "Perpetuation of Influenza A Viruses in Alaskan Waterfowl Reservoirs," *Archives of Virology* 140, no. 7 (July 1, 1995): 1163–72.
[363] Wolfe, *The Viral Storm*.
[364] See chapter five.
[365] Boyce et al., "Avian Influenza Viruses in Wild Birds"; Olsen et al., "Global Patterns of Influenza a Virus in Wild Birds."
[366] Kim et al., "Ducks: The 'Trojan Horses' of H5N1 Influenza."
[367] D. A. Halvorson, "Prevention and Management of Avian Influenza Outbreaks: Experiences from the United States of America," *Revue scientifique et technique (International Office of Epizootics)* 28, no. 1 (April 2009): 359–69.

Van Reeth is that after the introduction of LP viruses from wild ducks to poultry, influenza viruses then mutate to their more pathogenic form. Yet, viruses that are HP for poultry replicate poorly in wild birds, indicating that the ecological pathway from wild bird to and from poultry may not be smoothly two-way.[368] While scientists understand the molecular transformations in the conversion of H5 or H7 from LP to HP, the factors that trigger this conversion are not clear.[369]

Until the past few decades, it was rare to isolate an HP avian virus from wild birds. Since 1997, however, highly pathogenic H5N1 virus in both wild birds and chickens has persisted in Asia. Prior to this time, there was only one historic case of wild bird mortality associated with a highly pathogenic AIV. In the 1960s, Becker isolated an H5N3 virus that caused mortality in common terns in South Africa.[370] Of course, it is likely that we are looking harder and have better tools to discover these events as they occur.

In an interesting complication, Kim et al. found that some duck species are resistant to the HP form of H5N1. These ducks can shed and spread viruses while showing no signs of disease. Thus ducks, as silent spreaders infected with H5N1, are shedding more viruses for longer periods without showing symptoms of disease.[371] While HP H5N1 viruses are always lethal to chickens, the absence of disease symptoms in ducks has led to their designation as the "Trojan Ducks" of H5N1.[372]

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[368] Kristen Van Reeth, "Avian and Swine Influenza Viruses: Our Current Understanding of the Zoonotic Risk," *Veterinary Research* 38, no. 2 (April 2007): 243–60, 248.
[369] FAO, *Influenza and Other Emerging Zoonotic Diseases at the Human-Animal Interface*.
[370] W. B. Becker, "The Isolation and Classification of Tern Virus: Influenza A-Tern South Africa—1961." *The Journal of Hygiene* 64, no. 3 (September 1966): 309–20.
[371] Scoones, *Avian Influenza*, 8.
[372] Kim et al., "Ducks."

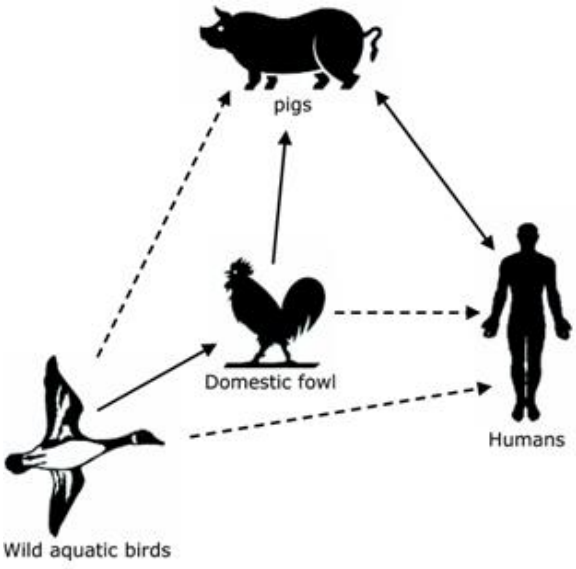

Figure 20. Transmission Cycle for Bird Flu. U.S. National Library of Medicine, Open-Access License, 2015. Solid lines: frequent or confirmed transmission events. Dotted lines: possible or occasional transmission.

The ability of LP viruses to mutate into HP viruses in poultry emphasizes the importance of domestic birds as a source of avian influenza in human populations.[373] HP viruses can transmit directly to humans (**Figure 10**) through their contact with chickens, sometimes with deadly results. Live bird markets have played an especially important role in the spread of epidemics through direct contact with infected poultry.[374] Transmission of influenza viruses from birds to humans has occurred most often through contact with sick poultry.

The World Health Organization provided statistics of human deaths from bird flu since 1997 (844 laboratory confirmed cases with 449 deaths effective 7/17/2015) with a majority of deaths in Indonesia and Egypt.[375] Virologist Kawaoka has confirmed that H5N1 infections that were lethal for humans were all of the HP form.[376]

Yet, many virologists claim that avian viruses are not very good at passing from person to person. In one example, Boyce et al. argued that even if humans acquire the disease from birds, humans generally are dead-end hosts for such avian influenza viruses.[377]

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[373] Causey and Edwards, "Ecology of Avian Influenza Virus in Birds."
[374] Boyce et al., "Avian Influenza Viruses in Wild Birds"; Webster et al., "Evolution and Ecology of Influenza A Viruses"; Horimoto and Kawaoka, "Pandemic Threat Posed by Avian Influenza A Viruses."
[375] Source: WHO/GIP, data in HQ as of 17 July 2015.
[376] Kawaoka, *Homeland Virology - 2/2/2014*.
[377] Boyce et al., "Avian Influenza Viruses in Wild Birds."

The virus must undergo subtle changes, usually passing through an intermediate mammal host such as a pig, before it can reliably infect humans.[378] As noted earlier, only three subtypes of influenza viruses are currently transmissible among humans: H1N1, H1N2, and H3N2.[379] Thus far, no avian influenza is transmissible among humans.

Knowledge regarding the epidemiology of avian influenza in wild birds is extensive but not complete, particularly regarding immune mechanisms in birds. Unanswered questions include can H5N1 HP viruses be carried back to waterfowl breeding areas to infect the next generation? Why has H5N1 not spread to susceptible hosts in Australia or the Americas, both with major flyways of migratory waterfowl? Comprehensive surveillance of wild birds in Alaska has not detected any H5N1 viruses.[380]

Humans have provided ample pathways for avian viruses to test their prodigious skills of evolutionary adaptation. The next sections discuss the history of influenza viruses that have jumped from wild waterfowl to chickens and, ultimately, to humans.

4.3 Historical Perspectives: Fowl Plague

Veterinarians, infectious disease specialists, and historians have documented the natural history of AIVs over the past 137 years.[381] However, most histories of influenza in

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[378] Beveridge, *Influenza*, 1978, x.
[379] Krauss et al., "Influenza A Viruses of Migrating Wild Aquatic Birds in North America"; Munster and Fouchier, "Avian Influenza Virus"; Webster et al., "Evolution and Ecology of Influenza A Viruses."
[380] Kim et al., "Ducks."
[381] Dennis J. Alexander, "Avian Influenza: Historical Aspects," *Avian Diseases* 47 (January 1, 2003): 4–13; Alexander and Brown, "History of Highly Pathogenic Avian Influenza."; Dennis J. Alexander, "An Overview of the Epidemiology of Avian Influenza," *Vaccine* 25, no. 30 (July 26, 2007): 5637–44; D J Alexander, "Ecological Aspects of Influenza A Viruses in Animals and Their Relationship to Human Influenza: A Review," *Journal of Royal Society of Medicine* 75 (October 1982): 799–811; David M. Morens, Jeffery K. Taubenberger, and Anthony S. Fauci, "Pandemic Influenza Viruses — Hoping for the Road Not Taken," *New England Journal of Medicine* 368, no. 25 (June 20, 2013): 2345–48; Lupiani and M Reddy, "The History of Avian Influenza." Boyce et al., "Avian Influenza Viruses in Wild Birds"; Morens and Taubenberger, "Historical Thoughts on Influenza Viral Ecosystems"; Waterson and Wilkinson, *An Introduction to the History of Virology*.

humans and in birds had separate and distinct contexts – one was a human concern and the other was a veterinary issue.

The earliest date for the beginning of avian influenza history is 1878. This outbreak was the first to distinguish between "fowl plague," ultimately known as avian influenza, and fowl cholera, a very different chicken disease caused by a bacterium.[382] Italian veterinarian Perroncito described this "fowl plague" as a disease causing high mortality in chickens in Italy at that time.[383] In a historical search completed in the 1880s and covering centuries, Scottish veterinarian Fleming found no bird epidemics consistent with the symptoms of avian flu.[384] Despite Fleming's efforts, it seems possible that avian influenza could have existed for centuries without detection. Most notably, references to birds in Greek literary traditions attribute avian deaths to human epidemics.[385]

Six years prior to the recognition of the first official fowl plague in 1878, veterinarians Law and Judson reported a strange chicken disease. The 1872 outbreak was an explosive epizootic in poultry, turkeys, ducks, and geese that occurred across the United States.[386] The epidemic centered in the Northeast and Midwest, spreading from the upper Hudson River area of New York. There was no organized poultry industry in the United States at that time and no mention of these events in the literature. Virologists Morens and Taubenberger accessed untraditional historical sources (agricultural and poultry reports, archived newspaper reports) and used molecular biology to speculate on these reports of an early fowl plague in North America.[387]

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[382] Alexander, "Avian Influenza: Historical Aspects"; Perroncito, *Ann. Accad. Agric. Torino* 21 (1878): 87–126.
[383] Perroncito, "Epizoozia Tifoide Nei Gallinacei."
[384] Fleming, *Animal Plagues Their History, Nature, and Prevention.*
[385] Morens and Taubenberger, "Historical Thoughts on Influenza Viral Ecosystems".
[386] Law, "Influenza in Horses"; Judson, "A Report on the Origin and Progress of the Epizootic among Horses in 1872."
[387] Morens and Taubenberger, "An Avian Outbreak Associated with Panzootic Equine Influenza in 1872"

According to Morens and Taubenberger, all "chicken disease" outbreaks in 1872 occurred in areas that were having, or had within the previous weeks, widespread equine flu. Circumstantial evidence for equine influenza included clinical signs and geographic proximity to human influenza.[388] Newspapers from New York to Chicago reported that prominent features of the "henfluenza" included signs of "a cold or influenza," "dizziness" or "staggering fits," and death within a day.[389] Some press reports suggested that outbreaks in poultry occurred soon after chickens pecked in stables that held sick horses.[390] This is interesting but speculative.

However, following the first officially reported event in 1878, a number of fowl plague outbreaks in poultry occurred throughout the world. There were subsequent outbreaks of fowl plague in 1894 and 1901 that eventually spread to Austria, Germany, Belgium, and France.[391] Yet, according to Lupiani and Reddy's history, most people did not link the severity of the symptoms to human influenza viruses.[392] By the early twentieth century, researchers recognized fowl plague as a distinct microbe, a filterable agent.[393]

During the first third of the twentieth century, outbreaks of fowl plague appeared in many countries throughout the world including Austria, Hungary, Switzerland, France, Belgium, Holland, England, Egypt, China, Japan, U.S., Argentina and Brazil.[394] Based on reports in veterinary journals, the 1924 fowl plague outbreak spread halfway across the U.S.

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[388] Morens and Taubenberger, "Historical Thoughts on Influenza Viral Ecosystems," 6.
[389] "Unhappy Hendom"; "The Epizootic among the Chickens"; "The Epizootic among the Poultry."; "Epihippo Notes."
[390] "The Poultry Disease"; "The Epizootic Killing Hogs and Chickens."
[391] L Wilkinson, "The Development of the Virus Concept as Reflected in Corpora of Studies on Individual Pathogens," *Medical History* 18, no. 3 (July 1974): 211–21; E.L. Stubbs, "Fowl Pest," *Journal of the American Veterinary Medical Association* 21 (1926): 561–69.
[392] Lupiani and Reddy, "The History of Avian Influenza," July 2009.
[393] Waterson and Wilkinson, *An Introduction to the History of Virology*.
[394] Todd and Rice, "Fowl Plague."

via contaminated rail cars and poultry crates.[395] In New York City, fowl plague resulted in substantial losses in live bird markets.[396] The disease then spread to ten neighboring states.[397]

The degree and variety of clinical signs for different viruses among various hosts suggests that many reports of fowl plague outbreaks were unconfirmed. One reason was that considerable problems existed in distinguishing outbreaks of influenza from other viral bird infections and even bacterial infections.[398] Until developments in the 1950s in isolation, culture and serological identification of the viruses, fowl plague could be confused with the bacterial Newcastle disease and the term described outbreaks of either virus or bacteria.[399]

By 1955, German virologist Schaefer's research revealed the kinship of the 1901 fowl plague with viruses causing influenza in humans.[400] This was the beginning of a period of intense study of the possible links among flu viruses across species. As early as 1958, the World Health Organization promoted studies on the ecology of flu viruses in wild animals but it would be years before research would commence.[401]

Thus, by mid-century, the scientific understanding of fowl plague shifted from an animal-only disease to one that had possible implications for human health. The first isolation of an influenza virus from a wild bird population was in 1961 from terns in South

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[395] Halvorson, "Prevention and Management of Avian Influenza Outbreaks."
[396] Mohler, "Fowl Pest in the United States."
[397] Ibid.; Baudette, "Observations upon Fowl Plague in New Jersey"; Stubbs, "Fowl Plague in Pennsylvania"; Brunett, "A Filterable Virus Disease of Chickens (fowl Plague?)"; Julien, "Fowl Pest in Indiana"; Johnson, "European Fowl Pest in Michigan"; Boughton and Tunnicliff, "European Fowl Pest in Illinois."
[398] Alexander, "Avian Influenza."
[399] Ibid.; Mohler, "Fowl Pest in the United States."
[400] Schaefer, "Comparative Sero-Immunological Studies of the Viruses of Influenza."
[401] Alexander, "Avian Influenza."

Africa.[402] By the late 1960s, serologic surveys of wild birds had demonstrated the presence of avian virus infection in wild birds in the U.S., Canada and Australia.[403]

Following the 1968 flu pandemic, virologists Webster and Laver received a grant from the National Institutes of Health to study the flu viruses among nesting seabirds on the coral islands of the Great Barrier Reef off Australia.[404] They admitted that this was a rather pleasant and fruitful research assignment.[405] The researchers found influenza virus in shorebirds, a strain that appeared similar to human influenza.

When Webster noticed that migrating birds were rife with asymptomatic influenza, his "barnyard theory" suggested that viruses in human pandemics recruited some of their genes from viruses in birds.[406] When Webster proposed a possible link between human and bird viruses, both veterinarians and medical people dismissed this idea. Colleagues told Webster not to waste his time on such a far-fetched theory. Virologist Laver remembers "…scornful remarks about Webster and his obsession with chicken influenza."[407] The scientific community dismissed influenza in birds as irrelevant for human disease.[408] It was, after all, only a bird disease.

However, isolation of avian flu from wild ducks in 1974 led to the ultimate realization that wild aquatic birds are the natural reservoir for all avian influenza viruses.[409]

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[402] Becker, "The Isolation and Classification of Tern Virus: Influenza A-Tern South Africa--1961."
[403] B. C. Easterday et al., "Evidence of Infection with Influenza Viruses in Migratory Waterfowl," *Nature* 219, no. 5153 (August 3, 1968): 523–524; W. G. Winkler, D. O. Trainer, and B. C. Easterday, "Influenza in Canada Geese," *Bulletin of the World Health Organization* 47, no. 4 (1972): 507–513; Dasen and Laver, "Antibodies to Influenza Viruses."
[404] Drexler, *Secret Agents*, 170–73.
[405] Personal communication with Robert Webster, June 2011.
[406] Drexler, *Secret Agents*.
[407] William Graeme Laver, "From the Great Barrier Reef to a 'Cure' for the Flu: Tall Tales, but True," *Perspectives in Biology and Medicine* 47, no. 4 (2004): 590–96.
[408] Webster et al., "Influenza--a Model of an Emerging Virus Disease."
[409] Slemons et al., "Type-A Influenza Viruses Isolated from Wild Free-Flying Ducks in California"; Webster et al., "Evolution and Ecology of Influenza A Viruses."

By 1980, the recognition that viruses related to those of humans, pigs, and horses were present among wild birds led the World Health Organization to develop a unified system of classification for influenza viruses.[410] Since that time, all of the currently recognized subtypes of human influenza A have been isolated from wild aquatic birds.[411]

From 1959 to 1994, avian influenza outbreaks among chickens and other poultry occurred on fifteen occasions, but losses were minimal with one exception. The Pennsylvania epizootic of 1983 spread by transport of live and dead poultry.[412] Avian outbreaks in the United States from the Pennsylvania epizootic resulted in the slaughter of more than 17 million birds and economic losses in the millions of dollars.[413]

Since the 1980s, there have been many more avian flu outbreaks. At first, these outbreaks had narrow geographical spread, generally limited to a single flock of birds. A "stamping-out" program (removing and exterminating sick birds) achieved eradication in some of these epizootics, and chicken vaccination helped to control epizootics when stamping out alone was not effective.[414] The usefulness of vaccination, however, is not clear.[415] In addition, there may be unintended consequences of vaccination in the form of more relaxed biosecurity measures.[416] Many assume that if poultry are vaccinated, there is little need for disinfection in the commercial facility. However, vaccinated birds can still harbor LPAI, especially if the vaccine is a poor match for the virus.

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[410] WHO, "A Revision of the System of Nomenclature for Influenza Viruses."
[411] V. S. Hinshaw et al., "Replication of Avian Influenza A Viruses in Mammals," *Infection and Immunity* 34, no. 2 (November 1, 1981): 354–361.
[412] Halvorson, "Prevention and Management of Avian Influenza Outbreaks."
[413] Robert J. Eckroade and Linda A. Silverman Bachin, "Avian Influenza in Pennsylvania the Beginning," *Avian Diseases* 47 (January 1, 2003): 22–32; Gerald J. Fichtner, "The Pennsylvania/Virginia Experience in Eradication of Avian Influenza," *Avian Diseases. Second International Symposium on Avian Influenza 1986 Proceedings (2003).* 47 (January 1, 2003): 33–38.
[414] Lupiani and Reddy, "The History of Avian Influenza," July 2009; Alexander, "Avian Influenza."
[415] Lee and Suarez, "Application of Real-Time RT-PCR for the Quantitation and Competitive Replication Study of H5 and H7 Subtype Avian Influenza Virus."
[416] Capua and Alexander, "Avian Influenza."

The largest avian flu outbreak within the United States, thus far, occurred in 2015 with the culling of about 48.8 million poultry birds. These H5N2 outbreaks hit hundreds of commercial farms and a handful of backyard poultry holdings, primarily in the spring. The estimated cost to U.S. taxpayers was $950 million. One alarming aspect of this epizootic is that biosecurity standards for industrial poultry farms failed to keep H5N2 out of the factory henhouses. As is true for previous avian strains, it is likely that H5N2 arrived in the U.S. with migratory birds. However, the virus then spread among farms in the Midwest in unforeseen ways, perhaps from ventilation systems, poultry transport or even viruses dispersed by the wind.[417]

Based on Alexander and Brown's history, the avian flu epizootics prior to 1997 pale in comparison to the H5N1 avian virus that has since spread throughout Asia and into Europe and Africa, affecting over 60 countries and causing the loss of hundreds of millions of birds.[418] For the poultry industry, avian influenza is no longer an occasional nuisance. For the chickens, it has been an apocalypse, one with the potential of spillover to humans.

The next section examines the possible links between the global scale of factory farming and the emergence of so many avian influenza outbreaks in the past decades. As illustrated with **Table 3,** there has been a dramatic change over time in the number, frequency, and scale of outbreaks from 1959 through 2015.[419] Current serology tests for avian viruses date back to 1959 with the first confirmed reports of avian flu among a few chicken flocks in Scotland.[420] Most epizootics with poultry deaths over one million have occurred since 1994.

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[417] Fry, "What the Worst Bird Flu Outbreak in U.S. History Means for Farms."
[418] Alexander and Brown, "History of highly pathogenic avian influenza."
[419] Lupiani and Reddy, "The History of Avian Influenza," July 2009; Racaniello, "H5N1 Lecture"; Sonnberg, Webby, and Webster, "Natural History of Highly Pathogenic Avian Influenza H5N1."
[420] Pereira, Tůmová, and Law, "Avian Influenza A Viruses."

Table 3 Major HPAI outbreaks 1959-2015

Virus Name according to WHO Type/species/location/year	Subtype	# of birds dead from disease or slaughter
A/chicken/Scotland/59	H5N1	Two chicken flocks
A/tern/South Africa/61	H5N3	1,300 terns
A/turkey/England/63	H7N3	29K breeder turkeys
A/turkey/Ontario/66	H5N9	8K turkeys
A/chicken/Victoria/76	H7N7	25K, 17K broilers, 16K ducks
A/turkey/England/79	H7N7	3 commercial turkey farms
A/chicken/Pennsylvania/83	**H5N2**	17 million chickens or turkeys
A/turkey/Ireland/83	H5N8	8K turkeys, 28K chickens, 270K ducks
A/chicken/Victoria/85	H7N7	24K breeders, 69K broilers, 118K chickens
A/turkey/England/91	H5N1	8K turkeys
A/chicken/Victoria/92	H7N3	12K broiler breeders, 5K ducks
A/chicken/Queensland/95	H7N3	22K chickens
A/chicken/Mexico/94	**H5N2**	Millions of birds
A/chicken/Pakistan/95	**H7N3**	3.5 million birds
A/chicken/Hong Kong/97	**H5N1**	1.5 million chickens; 18 humans cases
A/turkey/Italy/99	**H7N1**	14 million chickens, turkeys, ducks[421]
A/chicken/Chile/02	H7N3	700,000 chickens, turkeys
A/grey heron/Hong Kong/02	H5N1	Wild birds; 800K domestic birds culled
A/chicken/Netherlands/03	**H7N7**	34 million chickens[422]
A/chicken/Asia, Europe, Africa/03	**H5N1**	100s of millions of chickens and ducks. Hundreds of human deaths, many countries.
A/chicken/Canada/04	**H7N3**	16 million chickens[423]
A/northernpintail/Washington/14	**H5N2**	48.8 million chickens and turkeys culled

Table 3: Global Avian Influenza Outbreaks 1959-2015. Data sources from Lupiani and Reddy; Racaniello; and Sonnberg *et al*. **Bold** entries represent over a million birds slaughtered or dead from disease.

[421] A. Zanella, "Avian Influenza Attributable to Serovar H7N1 in Light Layers in Italy," *Avian Diseases* 47 (January 1, 2003): 1177–1180; Ilaria Capua et al., "The 1999-2000 Avian Influenza (H7N1) Epidemic in Italy: Veterinary and Human Health Implications," *Acta Tropica* 83, no. 1 (July 2002): 7–11.
[422] F. C. Velkers et al., "Outbreak of Avian Influenza H7N3 on a Turkey Farm in the Netherlands," *Veterinary Record* 159, no. 13 (September 23, 2006): 403–405; M. A. Gerritzen et al., "Slaughter of Poultry during the Epidemic of Avian Influenza in the Netherlands in 2003," *Veterinary Record* 159, no. 2 (July 8, 2006): 39–42.
[423] V. A. Bowes et al., "Virus Characterization, Clinical Presentation, and Pathology Associated with H7N3 Avian Influenza in British Columbia Broiler Breeder Chickens in 2004," *Avian Diseases* 48, no. 4 (December 1, 2004): 928–934.

4.4 The Commodification of Poultry

In this section, I examine the role of industrial poultry farming in the unprecedented wave of bird flu epizootics over the past fifteen years. The purpose is to provide background for one of my research questions: what are the shifting dynamics in nature and society that permit avian viruses to flourish? Elucidating relationships among living organisms and human production systems demonstrates how avian flu viruses are able to thrive so well in our global world.

Well into the 20th century, chickens played a relatively minor role in the global economy. Today, there are more than sixteen billion chickens in the world. Factory farming on a global scale represents the chicken's transformation into the food commodity business.[424] According to the World Watch Institute, the majority of the world's poultry meat and eggs is the product of intensive factory farming with tens of thousands of chickens raised in confined areas.[425]

Mass commodification of poultry emerged in the Livestock Revolution in the 1970s when large corporations bought up local chicken producers to consolidate production under one roof.[426] In many respects, industrial agriculture uses chickens, pigs, and cows as a means to transform corn to animal protein. In turn, agribusiness moved company operations to the global South to take advantage of cheap labor and weak regulation.[427] Based on the rebuttable assumption that corporate farms are more efficient, the idea was that markets could expand indefinitely in a global unregulated market.[428] In this scenario, according to historian

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[424] Jerry Adler and Andrew Lawler, "How the Chicken Conquered the World," *Smithsonian*, June 2012.
[425] Worldwatch Institute, *State of the World 2006*, 16.
[426] W. Boyd and M. Watts, "Agro-Industrial Just-in-Time: The Chicken Industry and Postwar American Capitalism.," 1997, 192–225.
[427] McMichael, Woodruff, and Hales, "Climate Change and Human Health: Present and Future Risks."
[428] Ted Steinberg, *Down to Earth: Nature's Role in American History* (Oxford University Press, USA, 2008).

Richard Tucker, the animal becomes a means to extract a commodity, a production unit.[429] Animals used for meat, eggs, and dairy often suffer on factory farms where they are treated as units of production rather than as sentient creatures.[430]

Poultry in such close quarters as factory farms pass diseases such as avian flu easily. The intensive confinement of poultry may facilitate the frequency and scale of avian flu outbreaks. Since about 1990, outbreaks of HP avian virus have increased among farmed birds.[431] As evolutionary biologist Robert Wallace has argued, the "biology of influenza is enmeshed with the political economy of the business of food."[432]

What is the viral connection among wild birds, the reservoir of avian flu viruses, and poultry birds? Avian flu researchers Capua and Alexander argued that low pathogenic (LP) influenza in wild birds develop greater virulence only in contact with populations of domestic birds.[433] In other words, the LP forms of H5 and H7 viruses in wild birds mutate only after introduction to poultry.[434] Evidence strongly suggests that HP avian flu viruses are not normally present in wild bird populations.

Theories about viral evolution help to explain the expansion of HP avian influenza subtypes within factory farms. In epidemiology a "susceptible" is a member of a population, human or other animal, who is at risk of infection by a disease due to lack of immunity to that disease. Biologists Lipsitch and Nowak examined the evolution of viruses to a more pathogenic form (virulence). They concluded that the key to virulence is the supply of

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[429] Richard P. Tucker, *Insatiable Appetite: The United States and the Ecological Degradation of the Tropical World, Concise* (Rowman & Littlefield Publishers, 2007).
[430] Humane Society of the United States, http://www.humanesociety.org/news/publications/whitepapers/farm_animal_welfare.html
[431] Peiris, de Jong, and Guan, "Avian Influenza Virus (H5N1)"; Capua and Alexander, "Animal and Human Health Implications of Avian Influenza Infections."
[432] Wallace, "Breeding Influenza," 928.
[433] Capua and Alexander, "Avian Influenza."
[434] Ibid.; Perdue and Swayne, "Public Health Risk from Avian Influenza Viruses."

susceptibles.[435] Industrial livestock production provides a continually "…renewed supply of susceptibles, the fuel for the evolution of virulence," according to Wallace.[436] In addition, genetic uniformity of poultry worldwide may increase the susceptibility of the flocks to disease.[437]

In the case of intensive and crowded chicken farms, a virus can afford to be virulent because it is so easy to infect the next susceptible before the virus kills the host. If the transmission of a virus to a new host is very fast, the evolutionary cost of virulence is lower.[438] Without a supply of susceptibles, influenza epidemics tend to burn out in all species. In addition, Ewald has argued that pathogens do not necessarily become less virulent over time. He posited that it is a mistaken conclusion that the coevolution of microbes with their hosts will inevitably lead to benign coexistence.[439]

Theories about alternative pathways for H5N1 between wild and domestic birds are controversial largely because large corporations seek to protect their interests and investments in commercial poultry farms. Yet, the WHO, OIE, and FAO, respectively the world's leading medical, veterinary, and agricultural authorities, have all implicated industrial poultry production as playing a role in the current global bird flu crisis. Their joint report advised that wild birds are the reservoir for bird flu, including human influenza; that mixing of wild and domestic bird populations resulted in the spread of viruses to poultry; and that wild and domestic birds in close proximity to pigs and humans increased the risk of infectious disease across species barriers.[440] The WHO concluded that avian flu requires a

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[435] Lipsitch and Nowak, "The Evolution of Virulence in Sexually Transmitted HIV/AIDS."
[436] Wallace, "Breeding Influenza," 922.
[437] Parker, National Defense University, and Institute for National Strategic Studies, *Agricultural Bioterrorism*.
[438] Ibid., 921.
[439] Ewald, *Plague Time*, 11.
[440] Hepworth, "Avian Influenza and Wild Birds."

multifactorial approach that considers the interaction of both wild bird migration and domestic poultry.[441]

Yet, FAO has claimed that there was no evidence that the Asian H5N1 emerged from an intensive poultry farm in Asia. They argued that circulation of LP influenza in industrial poultry operations may be a factor but not a prerequisite for viral conversion to a highly pathogenic form.[442] Researchers asserted that rigorous biosecurity measures to protect poultry farms are the only solution presently available to mitigate risk.[443] After the Qinghai outbreaks in 2005, WHO and FAO reversed their policy of encouraging small-scale poultry farming to one of encouraging biosecure factory farms.[444]

According to FAO guidelines, the basics of a biosecure poultry operation include barriers to keep infected animals or materials out; cleaning all visible dirt from all vehicles that enter or leave a farm site; disinfection to inactivate any virus present on materials, including those already thoroughly cleaned. A critical component of biosecurity is to provide food and water to animals indoors and to strictly limit and control access to poultry flocks. In most commercial facilities, poultry birds are not allowed outside. These guidelines can vary with the type of poultry production unit.[445]

For small village farms, the emphasis is on bio-exclusion, keeping disease agents out. For larger operations with greater than ten thousand birds, the emphasis is on biocontainment, keeping disease agents contained within the facility. Yet, experience has

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[441] Nick Bingham and Stephen Hinchliffe, "Mapping the Multiplicities of Biosecurity," in *Biosecurity Interventions*, ed. Andrew Lakoff and Stephen J. Collier (New York: Columbia University Press, 2008), 173–93.
[442] Les Sims and Clare Narrod, "Understanding Avian Influenza - Chapter 2," Avian Influenza (Rome: FAO, last updated 2015)
[443] Artois et al., "Outbreaks of Highly Pathogenic Avian Influenza in Europe."
[444] Bingham and Hinchliffe, "Mapping the Multiplicities of Biosecurity." This policy shift took place following the Qinghai avian flu outbreaks in 2005.
[445] FAO, "Approaches to Controlling, Preventing and Eliminating H5N1."

shown that large farms can have inadequate biosecurity and some small-scale farms have biosecurity that is sufficient for their level of risk.[446]

Most biosecurity measures apply to large-scale commercial systems that have strong incentives, some of which are regulatory, to adopt biosecurity protocols. However, the more complex the production and marketing chain, the harder it is to control and eradicate avian influenza agents such as H5N1. In addition, there is a growing trend towards free-range systems in the commercial sector, both for laying hens and broilers. Under these circumstances, it is almost impossible to prevent poultry contact either with wild birds or with an environment contaminated with avian flu viruses. When a poultry farm becomes infected with H5N1, birds quickly transform from food machines to virus carriers.[447] At that point, they are exterminated (culled).

Few of these biosecurity measures are appropriate for small-scale commercial systems, village or backyard production with birds or products consumed locally. Referred to as scavenging poultry in most developing countries, they are the most numerous type of poultry flock. For these smaller operations, the challenges include how to balance incentives and penalties and who pays for biosecurity. While it is difficult to impose biosecurity on these flocks, it is neither feasible nor desirable to limit scavenging poultry as a livelihood option for the poor. Culling disproportionately harms the poor while large-scale poultry farms are assumed to be biosecure.[448] Social scientist Scott Naysmith argued that lack of

[446] FAO, "Approaches to Controlling, Preventing and Eliminating H5N1."
[447] Frederic Keck, "From Mad Cow Disease to Bird Flu," in *Biosecurity Interventions*, ed. S. J. Collier and A. Lakoff (New York: Columbia University Press, 2008), 7–32.
[448] Collier and Lakoff, "The Problem of Securing Health."

effective compensation schemes for affected poultry flocks in small farms most likely leads to the underreporting of avian disease.[449]

For all commercial flocks, of whatever size, FAO recommends an all-in, all-out (AIAO) system - all birds must enter together and leave together – to allow for cleaning of buildings and equipment. AIAO is not practical for scavenging poultry flocks that mix with other birds from other flocks on a daily basis. In addition, duck keepers must implement the same bio-exclusion measures as other poultry keepers. Yet, ducks can remain asymptomatic for long periods and applying effective biosecurity in this system is problematic. Free-range duck keeping is an integral part of the "rice/duck" cultivation system; the consequences of banning the rice/duck system might be worse than the possible gains.[450]

Bird conservation organizations have their own perspectives about bird flu. According to Gauthier-Clerc et al. at the French Office National de la Chasse et de la Faune Sauvage, avian influenza outbreaks were not tied to bird migration at all and wild birds were not the primary vectors.[451] GRAIN is a non-profit organization that works to support small farmers in their struggles for community-controlled food systems. While authors of the GRAIN report concurred that migratory birds transported H5N1 to Europe, they argued that the H5N1 strain of bird flu points to the international poultry industry as the main vector of avian flu.[452] BirdLife International, a non-governmental global partnership of bird conservation organizations, argued that although there was some evidence that wild migratory birds can transmit avian influenza to domestic poultry, there was no direct

[449] Peiris, de Jong, and Guan, "Avian Influenza Virus (H5N1)"; Naysmith, "Observations from a Live Bird Market in Indonesia Following a Contained Outbreak of Avian Influenza A (H5N1)."
[450] FAO, "Approaches to Controlling, Preventing and Eliminating H5N1."
[451] Gauthier-Clerc, Lebarbenchon, and Thomas, "Recent Expansion of Highly Pathogenic Avian Influenza H5N1."
[452] GRAIN, "Fowl Play: The Poultry Industry's Central Role in the Bird Flu Crisis."

evidence of their role on factory farms that contained birds with no outside access. The latter organization also argued that the most efficient control techniques for the spread of the disease involve improved biosecurity.[453]

Yet, as we have seen during the 2015 avian flu epizootic in the United States, biosecurity is not impenetrable. Hinchliffe and Bingham posited their own theory that the spread of avian flu is traceable to the circulation of poultry and to industrial poultry production.[454] At its core, their argument is about whether biosecurity of factory-farmed poultry is sufficient. They wrote "…there are reasons to doubt that a worldwide culture of safety can be engineered."[455] They argued it is unwise to presume that systems involving such a variety of living and dynamic things (e.g., people, technologies, viruses) can be secured now or in the future. It turns out that poultry biosecurity is not so secure.[456] Once again, avian influenza is changing the rules.

Other environmental pathways for the transmission of avian viruses include contamination of shipping containers, open transport of animals between farms and processing plants, and ventilation systems that flow animal materials directly into the environment. The role of wind and ventilation systems, transmission routes that current biosecurity strategies do not address, are now the subject of intense study. Based on the research of historian Jacob Darwin Hamblin, U.S. military scientists during the Cold War "…determined that birds would make good biological warfare agents because their feathers could be dusted with cereal rust spores to infect oat crops over a wide area."[457] U.S.

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[453] Birdlife International, "Update on Avian Influenza."
[454] Bingham and Hinchliffe, "Mapping the Multiplicities of Biosecurity."
[455] Ibid., 189.
[456] Wallace, "Breeding Influenza."
[457] Jacob Darwin Hamblin, *Arming Mother Nature: The Birth of Catastrophic Environmentalism* (Oxford University Press, USA, 2013), 43.

bioterrorism experts learned about these "feather bombs" from their Japanese counterparts.[458] Thus, evidence reaches back many decades that birds can carry pathogens and that the wind can disperse such pathogens.

Emerging diseases that arise as the result of changes in livestock production, such as highly pathogenic avian influenza, are becoming more difficult to trace and combat in the newly globalized marketplace. Despite biosecurity measures, bird flu finds a way in, as seen in massive outbreaks in the United States in 2015. As Wallace suggested, influenza may be the "inadvertent biotic fallout" of steering animal ecology to multinational profitability.[459]

In another historical episode of attempting to control microbes, Susan Jones recounted how humans domesticated the anthrax bacillus, inviting the organism to intermingle through close contact with soil and animals. Ultimately, people transformed anthrax bacilli into something for nefarious purposes, a bioterror weapon. Yet, during this transformation, *B. anthracis* retained its own life cycle and nutritional requirements, often escaping the confines of the laboratory.[460] In similar ways, the avian flu virus resists control through the human-animal cycle.

People developed industrial factory farms to raise poultry for food, but we also have a use for all those chicken eggs. The majority of influenza vaccines for humans are produced in embryonated chicken eggs. It is ironic that we need eggs from chickens to culture vaccine to protect us from a virus that infects us through contact with chickens. Future experts may shake their heads in wonder at our current dependence on egg-based vaccine production.

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[458] Ibid.; Congressional Record: November 10, 1999 (Senate) Page S14533-S14571
[459] Wallace, "Breeding Influenza," 919.
[460] Jones, *Death in a Small Package*, 267–68.

Energetic debate continues about the principal method of geographical spread for avian viruses.[461] Some scientists emphasize the role of wild migratory birds and others stress the role of poultry trade routes. It is likely that both are important individually and, at times, in combination. Wild birds can introduce the virus to new areas but it is likely through human actions that the disease spreads locally. Many observers protest that wild birds are the victims, not the vectors of disease.[462] This dissertation argues that they are both.

4.5 Jumping the Species Barrier

Southern China has a unique agricultural ecosystem, interwoven with numerous lakes, rivers, creeks and ponds. It is a region with an animal agricultural system that includes chickens, geese, and ducks. In 1982, based on the wide diversity of avian influenza viruses in domestic poultry raised in close proximity to humans, virologists Shortridge and Stuart-Harris suggested this region of southern China as a hypothetical epicenter for pandemic influenza viruses.[463] Guangdong Province is at the heart of the southern China agricultural system.

In Guangdong Province during 1996, an H5N1 virus (A/goose/Guangdong/1/1996) emerged in farmed geese within a rural area. The virus caused a moderate number of deaths in geese and attracted very little attention.[464] Surveillance of the Guangdong chicken population during 1996 and 1997 failed to detect any additional H5N1 virus. However, a

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[461] Rapport, "Avian Influenza and the Environment: An Ecohealth Perspective"; Normile, "Avian Influenza. Evidence Points to Migratory Birds in H5N1 Spread"; Butler, "Doubts Hang over Source of Bird Flu Spread."
[462] John Y. Takekawa et al., "Victims and Vectors: Highly Pathogenic Avian Influenza H5N1 and the Ecology of Wild Birds," *Avian Biology Research* 3, no. 2 (June 10, 2010): 51–73.
[463] Wan, "Lessons from Emergence of A/Goose/Guangdong/1996-Like H5N1 Highly Pathogenic Avian Influenza Viruses and Recent Influenza Surveillance Efforts in Southern China"; Shortridge and Stuart-Harris, "An Influenza Epicentre?"
[464] Xu et al., "Genetic Characterization of the Pathogenic Influenza A/Goose/Guangdong/1/96 (H5N1) Virus."

year later, viral reassortants of the Guangdong strain emerged in Hong Kong with high mortality among domestic poultry.[465] According to Guan et al., by 1997 the H5N1 virus acquired genetic material from a co-circulating H9N2 virus typically found in domestic quail.[466]

Significantly, the Hong Kong H5N1 avian flu virus claimed its first human victims of a bird flu. Before 1997, there had never been reports of avian influenza transmitted directly from birds to humans. Researchers believed that pigs (or other mammals) were necessary as viral mixing vessels to combine genetic segments from human and avian flu viruses. Yet in Hong Kong in 1997, the H5N1 flu virus transmitted from sick chickens to eighteen people, six of whom died.[467] Until this time, researchers believed that influenza H5N1 was avian only, strictly a disease for the birds.

This was the first documented case of a purely avian virus causing a disease in humans. Molecular analysis from Subbarao et al. revealed that all gene segments were of avian origin, suggesting direct avian to human transmission in Hong Kong.[468] The influenza virus had managed to open the lock on human cells. It was a staggering discovery. Researchers had to recalibrate what they thought they understood about avian flu viruses.[469]

These first documented cases of bird flu in humans alarmed public health authorities around the world. The slow recognition that wild aquatic birds are the disease reservoir for influenza viruses suddenly turned into a high alert for global health. Influenza researchers

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[465] Sims et al., "Avian Influenza in Hong Kong 1997–2002."
[466] Guan et al., "H9N2 Influenza Viruses Possessing H5N1-like Internal Genomes Continue to Circulate in Poultry in Southeastern China."
[467] Claas et al., "Human Influenza A H5N1 Virus Related to a Highly Pathogenic Avian Influenza Virus."
[468] Subbarao et al., "Characterization of an Avian Influenza A (H5N1) Virus Isolated from a Child with a Fatal Respiratory Illness."
[469] Mike Davis, *The Monster at Our Door: The Global Threat of Avian Flu* (New York: Henry Holt, 2006).

from around the world converged in Hong Kong, among them avian influenza expert Robert Webster.

At first, Webster thought there must have been some lab contamination. H5N1 had never crossed over to humans. If H5N1 was in the poultry markets, as Webster suspected, the virus could mutate in the chickens and perhaps other animals. Webster's research had shown that ducks could transmit flu viruses quite easily to chickens. Webster noted that it was always shocking to see thousands upon thousands of dead birds inside a poultry facility that had experienced an H5N1 virus outbreak.[470] While domestic birds with bird flu die, many ducks do not get sick at all.

Within three days of arriving in Hong Kong, researchers located the H5N1 virus in the live poultry markets. Hong Kong officials reacted by destroying its entire poultry population of 1.5 million birds. Many believed that this action prevented a pandemic by removing opportunities for further human exposure.[471] For a time, there were no new cases of H5N1. By 2002, scientists diverted their attention to the first alarms of SARS in Hong Kong, a very different virus.[472]

Yet, H5N1 viruses continued to circulate in the wider region among ducks and geese.[473] Virologists Guan et al. discovered a number of viral reassortments. However, there was no evidence of infection in wild birds, at least not with the HP form of the virus.[474] Retrospective genetic analysis by Wang et al. showed that H5N1 viral strains spread from southern China to Thailand, Vietnam, and Indonesia during 2002 and 2003.[475] Researchers Li

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[470] Personal communication with Robert Webster, June 9, 2011.
[471] Webster and Hulse, "Controlling Avian Flu at the Source."
[472] Quammen, *Spillover*, 2012, 509.
[473] Kaplan and Webby, "The Avian and Mammalian Host Range of Highly Pathogenic Avian H5N1 Influenza."
[474] Guan et al., "Emergence of Multiple Genotypes of H5N1 Avian Influenza Viruses in Hong Kong SAR."
[475] Wang et al., "Identification of the Progenitors of Indonesian and Vietnamese Avian Influenza A (H5N1) Viruses from Southern China."

et al. argued that H5N1 had found a new ecological niche in poultry, but the virus had not yet fully adapted to this host.[476]

By the end of 2003, tigers and leopards that fed on chicken carcasses began dying unexpectedly of highly pathogenic H5N1 flu at a zoo in Thailand. Research revealed that domestic cats experimentally infected with H5N1 developed severe disease and spread infection to other cats.[477] A second outbreak of H5N1 resulted in the death of 147 tigers at a Thailand zoo including more than eighty Bengal tigers.[478] It appeared to researchers that H5N1 had become progressively more lethal for mammals and could even kill wild waterfowl, long considered a disease-free natural host.[479] Soon, Vietnam and Thailand reported their first H5N1 outbreaks in poultry and identified the first human cases in their respective countries. These outbreaks caused alarm and galvanized the scientific community to conduct even more research.

In April of 2005, wild birds began dying when hundreds of thousands of migratory birds congregated at Qinghai Lake in China.[480] This was the first reported instance of any highly pathogenic avian influenza causing mass die-offs in wild birds. Liu et al. isolated viruses from dead birds at Qinghai, discovering a new variant of the H5N1 virus. This variant of H5N1 was lethal to wild birds and to experimentally infected mice.[481] Additional research by Chen et al. demonstrated transmission of the virus among migratory geese and suggested, for the first time, that migratory birds might carry the H5N1 virus. Soon

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[476] Li et al., "Genesis of a Highly Pathogenic and Potentially Pandemic H5N1 Influenza Virus."
[477] Kuiken et al., "Avian H5N1 Influenza in Cats."
[478] Davis, *The Monster at Our Door*, 122.
[479] Chen et al., "The Evolution of H5N1 Influenza Viruses in Ducks in Southern China."
[480] Chapter five is a case study that focuses on the H5N1 outbreaks at Qinghai Lake.
[481] Liu et al., "Highly Pathogenic H5N1 Influenza Virus Infection in Migratory Birds."

thereafter, researchers reported pathogenic H5N1 in wild birds in Mongolia and Russia. The H5N1 virus then spread west across Russia and onward to Turkey, Europe, and Africa.[482]

Based on data from WHO and FAO, during the period of November 2005 to April 2006, the number of countries with confirmed cases of H5N1 in wild birds or poultry increased from 16 to 55 countries, nine of which had human fatalities. By December 2007, H5N1 outbreaks in wild birds or poultry increased to at least 61 countries, genetically traced to the virus that emerged at Qinghai.[483]

In 2008, experimental studies at the Erasmus Medical Center in The Netherlands revealed that some species of wild ducks could survive infections with H5N1 that are pathogenic to poultry. Thus, it was possible that these ducks could serve as long-distance vectors under some circumstances.[484] However, intensive wild bird surveillance programs conducted by FAO in Europe failed to detect any cases of H5N1 among wild birds.[485] Researchers from Eurosurveillance suggested the possibility of other routes of infection such as poultry supply and distribution chains.[486]

Fortunately, human-to-human airborne flu transmission, normally seen in the annual flu outbreaks, has not occurred with H5N1. In other words, H5N1 is not a human influenza, at least not at this time. It is a zoonotic disease and theoretically, each human case is the result of contact with an infected animal, usually poultry.[487] A study describing the epidemiology of 54 human cases of H5N1 infection in Indonesia concluded that 76% of cases

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[482] Kilpatrick et al., "Predicting the Global Spread of H5N1 Avian Influenza."
[483] FAO/OIE/WHO *Influenza and Other Emerging Zoonotic Diseases at the Human-Animal Interface*.
[484] Keawcharoen et al., "Wild Ducks as Long-Distance Vectors of Highly Pathogenic Avian Influenza Virus (H5N1)."
[485] Newman, Mundkur, and Harris, *Wild Birds and Avian Influenza*.
[486] Needham, "H5N1 in Wild and Domestic Birds in Europe – Remaining Vigilant in Response to an Ongoing Public Health Threat," *12* 49 (June 12, 2007).
[487] Kaplan and Webby, "The Avian and Mammalian Host Range of Highly Pathogenic Avian H5N1 Influenza," 5.

were associated with poultry contact; researchers could not identify the source of infection in 24% of cases.[488]

Findings from two research groups explained why the H5N1 virus does not easily infect humans as seasonal influenza spreads. Whereas human influenza viruses attach themselves to cells lining the nose and throat, avian viruses bind to cells located deep in the lungs in humans. Such findings are consistent with the clinical picture of H5N1 infection, in which most patients present with symptoms of infection in the lower respiratory tract.[489]

Fatal cases of H5N1 in humans have accumulated into the hundreds since 1997 with a case fatality rate as high as 60%. Critics of the method used to establish this rate have claimed that it is highly selective (biased) and may overstate the genuine human mortality rate from bird flu.[490] The case fatality rate is the number of deaths divided by the number of confirmed cases. Yet, investigators know little about the case fatality rate in the wider community of exposed people including possible asymptomatic individuals. The WHO does not include asymptomatic infections in their avian flu case definition. A more accurate measure of the impact of avian flu disease on humans would be a mortality rate - number of deaths divided by the number of infections that include unapparent infections. Unfortunately, the number of unapparent infections is unknown and this information is difficult to obtain.

After nearly two decades since Hong Kong in 1997, the spillover of H5N1 to humans has not become a global pandemic but has sparked energetic debates, dead poultry, hundreds of human deaths, and fears of a global pandemic.[491] Fundamental questions remain about

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[488] Sedyaningsih et al., "Epidemiology of Cases of H5N1 Virus Infection in Indonesia, July 2005-June 2006."
[489] Shinya et al., "Avian Flu"; van Riel et al., "H5N1 Virus Attachment to Lower Respiratory Tract."
[490] Peter Palese and Taia T. Wang, "H5N1 Influenza Viruses: Facts, Not Fear," *Proceedings of the National Academy of Sciences* (January 25, 2012): 201121297.
[491] Morens and Taubenberger, "Historical Thoughts on Influenza Viral Ecosystems."

how flu viruses switch hosts, from wild bird to chicken to human. Particularly concerning are HP H5N1 strains that are asymptomatic in waterfowl that may mask the spillover of avian disease to poultry. It appears that the zoonotic pool of avian viruses to which humans are exposed is expanding. However, Taubenberger and Morens emphasized there is limited data to suggest that H5N1 is evolving in the direction of human adaptation.[492]

In summary, according to the World Health Organization, the current H5N1 panzootic has become the most extensive animal disease ever recorded, complicated by the fact that it can be fatal in humans, other mammals, and birds.[493] The next chapter, the Qinghai case study, brings forward the diverse threads of the avian flu puzzle.

[492] Taubenberger and Morens, "Pandemic Influenza – Including a Risk Assessment of H5N1."
[493] Dudley, "Public Health and Epidemiological Considerations for Avian Influenza Risk Mapping and Risk Assessment."

Chapter Five: Qinghai Case Study

5.1 Introduction

Qinghai is a story of environmental history, of longstanding culture and new technology, and of the health of many species. The Qinghai case study examines the nature and significance of relationships among phenomena that occur in the same place. The focus is on the integrated nature of systems at a particular place and unintended consequences due to this interconnectedness. This dissertation argues that avian flu events at this specific place, the Qinghai-Tibet Plateau, are significant within the historical context of emerging infectious diseases. According to historian of science Michael Osborne, place is not just a point on the map but is also a site of meaning, history, and relationships.[494]

The case study tracks the avian viruses within the context of biological, environmental, social, and geopolitical factors. Using Actor Network Theory as a descriptive method, the case study actors include a wild goose; a vast permafrost plateau; a high-altitude railroad to Tibet that traverses the plateau; an avian virus; and bioscience and geopolitics.

Events at Qinghai stimulated new science and knowledge about avian influenza, with research results fragmented across many disciplines. The case study provides a glimpse into remarkable science undertaken at the intersection of diverse disciplines: historical ecology, climate science, high altitude medicine, wildlife biology, remote sensing technology, bioscience, and global health.

William Summers, a microbiologist and historian, examined the role of railroads and agricultural markets as key features in the spread of disease in Manchuria in 1910-11. He argued that the story of Manchuria is a story of railroads and geopolitics on a grand scale. In

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[494] Michael A. Osborne, *The Emergence of Tropical Medicine in France* (Chicago: University of Chicago Press, 2014), 4.

this way, Summers' approach became a model for this dissertation's case study, one that includes a very different railway and agricultural market.[495]

First, I narrate the overall story of Qinghai from the perspective of the new high altitude train that races across the Qinghai-Tibet Plateau, the Qinghai-Tibet Railway (QTR). I envision the railway as a contemporary metaphor for a post-industrial world where nature, culture, and technology interact in increasingly complex ways. As the technological agent of landscape disorder, the QTR captures the environmental, technological, and geopolitical context of a changing world. As portrayed in Leo Marx's *Machine in the Garden*, a locomotive bursts onto the scene almost from nowhere, forever spoiling a pastoral ideal.[496]

In the case of the QTR, the "spoiling" is at the scale of the world's highest and largest plateau, a place drawing intense scientific interest for its rapid climate change. While the avian flu events at Qinghai do not draw as much interest as climate change, bird flu exists at this place as a kind of unseen background radiation, only interesting for those willing to take a closer look. The purpose of this chapter is to take that closer look and to untangle the web of causality for the startling and repeated emergence of bird flu at such an unlikely place.

Following a discussion of Qinghai-Tibet Railway, I examine events at Qinghai from the perspectives of the other actors: a virus, a migratory bird, and a fragile environment that is at the leading edge of global climate change.

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[495] Summers, *The Great Manchurian Plague of 1910-1911*.
[496] Leo Marx, *The Machine in the Garden: Technology and the Pastoral Ideal in America* (New York: Oxford University Press, 2000).

5.2 Riding the Permafrost Rooster

"Iron rooster" is a Chinese phrase for a stingy bird, one so difficult to pluck it might as well be made out of iron. Paul Theroux borrowed this phrase in *Riding the Iron Rooster* to describe his arduous train travels across China during the 1980s.[497] Theroux did not travel to the Tibet Autonomous Region, a place difficult to reach by road and impossible by rail. Tibet has long retained an exotic allure for travelers crossing to China's western region. Until recently, this mountainous region, a natural and political buffer between China and India, had been impossible to reach by rail. For a time, physical and transportation barriers protected Tibet from the sweep of globalization. This would soon change.

Technology, Culture, and Environment: Building a Railway on Permafrost

Today, travelers no longer have to possess the resolve of adventurous backpackers to get to Tibet. Beginning in 2006, rail passengers could cross the vast permafrost environment of the Qinghai-Tibet Plateau (Roof of the World) from Golmud into Lhasa via the longest high-elevation railway in the world (**Figure 11**).

Figure 11. Qinghai-Tibet Railway Map. Map Credit: Ben Newell. Source: Journal of the American Enterprise Institute.

Passenger carriages include enriched-oxygen systems, UV-protection and luxury sleeper cars that traverse the frozen ground at speeds of up to 100 kilometers per hour. The

[497] Theroux, *Riding the Iron Rooster*.

Qinghai-Tibet Railway (QTR) has firmly established China's technological prowess and has provided a strategic connection to the plateau for natural resources as well as for geopolitical advantages. For China, these achievements are as momentous as they are controversial.

The potential for a railway across the Roof of the World provided a powerful incentive for the Chinese to study permafrost regions of the Qinghai-Tibet Plateau beginning in the 1950s. According to environmental journalist Abrahm Lustgarten, as soon as the Chinese army entered Lhasa in 1951, building a railway became a top priority.[498] The government planned and ran scientific studies but had to wait for advances in technology to be able to tunnel through ice and lay track on shifting permafrost. By 2001, the ambitions of the late fifties had the backing of science, funding, and political will.[499] At a cost of $4.3 billion, it was an audacious project.

Lustgarten provided first-hand accounts as well as historical perspectives of the railway construction. From his perspective, China's grip on the remote frontier promises to give that nation rich resources and geographic supremacy over South Asia.[500] Erling Hoh, a scholar in Chinese culture and history, also highlighted the military and geopolitical implications of the railway.[501] Hoh argued that China is counting on the rail to reduce the cost of transport to Tibet, speed economic development, and stimulate tourist business in Tibet.[502] Critics claim that the railway's real aim is to be a symbol of China's administrative and military control over a contested border region.

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[498] Lustgarten, *China's Great Train*, 7.
[499] Ibid., 52
[500] Lustgarten, *China's Great Train*.
[501] Erling Hoh, "Railway to the Top of the World," *New Internationalist*, August 1, 2005.
[502] Ibid.

Figure 12 Qinghai-Tibet Railway Tourist. Photo credit: IntoWestChina Holiday (2006).

By the end of the first year of operation in 2006, 2.5 million tourists **(Figure 12)** had visited Tibet, half of whom arrived via the QTR. Yet, from a cultural perspective, there are deep concerns that the railway will expedite a transfer of population that will make Tibetans a minority group in their own land.[503] The problem, according to the Mongolian and Tibetan Affairs Commission, is that the railway expedites the transfer of population that will make Tibetans a minority group in their own land.[504] As Lustgarten explained, the Tibetans already feel the "…drip, drip, drip process of cultural dilution."[505]

From a geographical and environmental perspective, The QTR travels through some of the most difficult terrain on earth. The railway crosses terrain that highlights China's environmental challenges outside the industrial pollution of its populous cities. In western China, dry high plateaus give way to large permafrost regions and impassable mountain ranges as elevation increases. The high plateaus possess fragile grassland ecosystems. Home to ethnic Tibetan herders, the lower elevations of the plateau were legendary for grasses that

[503] Jung-sung Hsu, "The Qinghai-Tibet Railway's Impact on Tibet" (Mongolian and Tibetan Affairs Commission, September 19, 2005).
[504] Hsu, "The Qinghai-Tibet Railway's Impact on Tibet."
[505] Lustgarten, *China's Great Train*, 132.

reached "high as a horse's belly."[506] When discovered by travelers in the Middle Ages, the dazzling horns of rare antelopes "prompted tales of unicorns."[507]

Figure 13. Woman with yak at Qinghai Lake. Photo credit: Bengchye Loo, 2007. (CC BY 2.0)

The Qinghai-Tibet Plateau is a fragile environment sensitive to both natural and human forces. Today, people, yaks, and sheep contribute to erosion and grassland degradation following decades of warming temperatures and overgrazing (**Figure 13**). Researchers from the Chinese Academy of Sciences reported that grassland degradation is now so extensive that rats have invaded the fragile wetlands and have chewed through one third of the lower elevation grasslands.[508]

The engineering challenges of railway construction at the highest altitude region of the Qinghai-Tibet Plateau were even more profound. Drawing on three decades of study, the Chinese Academy of Sciences reported that the instability of the permafrost on the Qinghai-Tibet Plateau causes grave geotechnical problems beneath major roads and rails.[509]

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[506] Eckholm, "Drought Creates New Chinese Desert: Chinese Farmers See a New Desert Erode Their Way of Life." Charles Darwin may have coined the phrase "high as a horse's belly" in *Works of Charles Darwin: Journal of Researches into the Natural History and Geology of the Countries Visited during the Voyage of H.M.S. Beagle Round the World* (D. Appleton, 1915).
[507] David Suzuki, "Wild China: The Tibetan Plateau," *The Nature of Things* (Canadian Broadcasting Company, June 29, 2008).
[508] Zhou et al., "Alpine Grassland Degradation and Its Control in the Source Region of the Yangtze and Yellow Rivers, China."
[509] Chen et al., "The Impacts of Climate Change and Human Activities on Biogeochemical Cycles on the Qinghai-Tibetan Plateau."

Permafrost is perennially frozen earth with a temperature below 0° C continuously for two years or more. The permafrost deep in the ground is not the critical problem. The dilemma is that the active layer on top freezes in winter and thaws in summer, causing the ground to become more like a bog or swamp. This active layer of permafrost slumps when it thaws, causing the soil to collapse, and anything constructed on top of it to shift. Some of the best railway engineers in the world, many of whom are Chinese, protested that it was impossible to solve the permafrost problem.[510] This was not an easy place to build an infrastructure meant to last for many decades. Despite the fact that the plateau is at the leading edge of global climate change, China persisted in its ambitions.[511]

The signals of climate warming on the Qinghai-Tibet Plateau are intense. The Chinese Academy of Sciences reported that the Qinghai-Tibet Plateau has experienced "statistically significant warming" since the mid-1950s, exceeding rates for the northern hemisphere at the same latitude.[512] In addition, the IPCC argued that a retreat of permafrost with rising global temperatures is virtually certain.[513] Experts from the Chinese Academy of Sciences predicted that one-third to one-half of the permafrost on the Qinghai–Tibet Plateau would degrade by 2100.[514] A joint research project of Chinese and American scientists argued that large carbon pools sequestered in permafrost, if released, would increase atmospheric carbon and create accelerated global warming.[515]

Although engineers utilized climate change models prior to building the QTR, early models were overly optimistic. Recent experiments revealed that the ice-rich soil of the

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[510] Lustgarten, *China's Great Train*, 20.
[511] Wang et al., "Climate Changes and Its Impact on Tundra Ecosystem in Qinghai-Tibet Plateau, China."
[512] Huang et al., "Changing Inland Lakes Responding to Climate Warming in Northeastern Tibetan Plateau."
[513] Stocker et al., *Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*, 92.
[514] Li et al., "Cryospheric Change in China."
[515] Yang et al., "Permafrost Degradation and Its Environmental Effects on the Tibetan Plateau."

plateau is sensitive to both load-induced and temperature-induced melting, threatening the railway as it crosses permafrost regions.[516] Inconsistent geophysical cycles have left regions of the plateau frozen in places and melting in others. The QTR can cope with a three-degree rise in temperature but the steady rise in temperature over decades may well pass this limit. These issues, of course, have a direct impact on railway operations now and into the future.

Figure 14 QTR Embankments. Photo credit: Jan Reurink, 2008. (CC BY 2.0).

In response to these challenges, Chinese engineers used state-of the-art technology to cool and stabilize the soil layers under the railroad embankment **(Figure 14)**.[517] The goal was to maintain the frozen state of the land under the railway. Experiments that began as early as the 1970s placed large concrete tubes beneath test railway embankments to allow air flow. The embankments stayed frozen. Beginning in 2001, thousands of Chinese workers travelled to the plateau to use local materials to build these rocky embankments.

However, in warmer permafrost regions, the crushed rock did not produce enough cooling. Cold regions experts recommended other solutions included shading boards, ventilation ducts, and thermosyphons.[518] The latter are cooling sticks that look like

[516] Qin and Zheng, "The Qinghai–Tibet Railway."
[517] Zhang et al., "The Qinghai–Tibet Railroad: A Milestone Project and Its Environmental Impact."
[518] Mu et al., "Comparative Analysis of Cooling Effect of Crushed Rock Embankment along the Qinghai-Tibet Railway."

stovepipes jutting out of the ground. They are about 10 meters deep and 20 centimeters in diameter with 9 liters of ammonia in the bottom layer.[519] The ammonia boils at low temperature, drawing heat from the surrounding earth. Engineers cooled 34 kilometers of the QTR track in this way.

Figure 15 Qinghai-Tibet Railroad Bridge. Photo credit: T.CSH, 2008. (CC BY-NC-ND 2.0)

Yet, even thermosyphons are not enough in the most fragile areas of warming permafrost. The solution was to treat these warmer sections as waterways and elevate the rail with bridges secured to deeper permafrost. This extraordinary measure introduced its own challenges. The concrete piers heated the soil around the bases when first poured, enough to cause concerns about stability. The answer was to pour the concrete in the dead of winter. Lustgarten observed that elevated bridges **(Figure 15)** across the slumping soil looked like "…a Disney monorail running across the surface of the moon."[520]

Tens of thousands of workers converged at the project's highest altitudes in winter periods to build over 165 kilometers of elevated sections for the QTR. New challenges then followed such an influx of workers to this remote, high altitude region. With this influx of people, another dimension of the story unfolded.

[519] Lustgarten, *China's Great Train*, 173.
[520] Ibid., 180–81.

Living and Working at High Altitude

In 1959, when Chinese engineers built the Old Tibetan Highway, over three thousand workers died of exposure and altitude sickness.[521] With this history in mind, the Chinese Ministry of Railroads created a plan for the QTR that considered the health risks that workers would face.[522] Medical specialists became part of the construction project with infirmaries built beside the railway at every eighteen kilometers. As part of the QTR construction from 2001 to 2006, researchers screened thousands of workers who traveled from lowland habitat to altitudes up to 5,100 meters to work at the construction site. Although workers' ascent to the peak mountainous regions was gradual, the incidence of altitude sickness upon first-time exposure was 51%.[523] Work on the railroad was limited to young and healthy individuals who did not show symptoms of altitude sickness. However, one might consider bias in such a study as the workers may conceal moderate discomfort from altitude sickness in order to stay on the job.

While about 90% of the workers for the QTR were Han Chinese, hiring Tibetans might have mitigated the health concerns of working at such high altitude. The Tibetan people, who have a history of living at high altitudes for thousands of years, have a distinctive set of physiological traits that enable them to tolerate lower oxygen levels. In a collaborative study by Chinese and Tibetan researchers, Yi et al. found that Tibetans breathe air that has forty percent less oxygen than is available at sea level, yet they suffer very little mountain sickness.[524]

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[521] *National Geographic - Extreme Railway: Qinghai Tibet Railway* [Video], 2014.
[522] Lustgarten, *China's Great Train*, 102, 111.
[523] Wu, "The Qinghai–Tibetan Plateau: How High Do Tibetans Live?"
[524] Yi et al., "Sequencing of 50 Human Exomes Reveals Adaptation to High Altitude."

Comparing the genomes of Tibetans and Han Chinese, biologists found at least thirty genes that were rare among the Han but common among the Tibetans. Such differences suggest that the genetic variant typical among Tibetans is the result of natural selection. Beall has argued that Tibetan women with genotypes for high oxygen saturation of hemoglobin have higher offspring survival.[525] Julian et al. also claimed that the differences in infant mortality observed between migrant and native high-altitude Tibetan populations support the conclusion that protected fetal growth at high-altitude is the result of human genetic adaptation.[526]

Studies related to the QTR operations confirm these findings. Two million passengers ride the QTR each year, many of whom are not acclimated to high latitudes. For this reason, the PRC Ministry of Railroad studied the occurrence of altitude illness on the QTR. There were three subject groups: Han lowlanders, Han immigrants living at 2200 to 2500 meters, and Tibetans living at 3700 to 4200 meters. Acute Mountain Sickness incidence was 31% in non-acclimatized Han, 16% in the Han high altitude residents, and 0% in Tibetans.[527] Genetic differences between Tibetans and Chinese are a potentially delicate issue, given Tibetan aspirations for political autonomy.

Controversy remains over which population groups benefit from the QTR. Asian Affairs specialist Kerry Dumbaugh reported to the U.S. Congress that the promised economic development does not benefit Tibetans. The QTR does however benefit Han Chinese, many of whom converged at the plateau to build the railway linking Lhasa to the rest of China.[528] In many cases, financial advantages accrue to Chinese corporations that are outside of

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[525] Beall, "From the Cover: Higher offspring survival among Tibetan women with high oxygen saturation genotypes residing at 4,000 m."
[526] Julian et al., "Evolutionary Adaptation to High Altitude: A View from in Utero."
[527] Wu et al., "Altitude Illness in Qinghai–Tibet Railroad Passengers."
[528] Dumbaugh, "Tibet: Problems, Prospects, and U.S. Policy."

Tibet.[529] Alternatively, the Tibetans engaged with new agricultural and animal husbandry projects, such as farms to raise captive-bred geese, on the Qinghai-Tibet Plateau. The rationale was to expand agricultural practices to prepare for the influx of new visitors and workers in advance of the QTR opening in 2006. Significantly, these goose farms were to become a prominent feature during the hunt for the Qinghai avian virus.

Avian Influenza: Opening Pandora's Box at The Roof of the World

As millions take advantage of the QTR for the journey to Lhasa, travelers stop at scenic spots along the rail line, including the nature reserve at Qinghai Lake, the largest inland saltwater lake in China. The lake sits between snowy mountains above 3,600 meters in elevation, surrounded by regions of grasslands and permafrost. Qinghai Lake draws many travelers, both Chinese and international, to the austere beauty of the lake and a chance to visit the nearby Ta'er Monastery, a famous Tibetan lamasery.

It is not only people and their technology that converge at Qinghai Lake but also birds migrating from across Asia. Qinghai Lake is a crucial stopover and breeding site for migratory birds that overwinter in Southeast Asia, Tibet, and India.[530] *Niao Dao* (Bird Island) on the lake's western shore is a breeding ground for sandpipers, cormorants, bar-headed geese, and the black-necked crane. The bar-headed goose (*Anser indicus*) has an extensive range with many breeding populations at Qinghai Lake. This goose is one of the highest-flying birds in the skies and can reach heights of over 8,000 meters while crossing the Himalayas.

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[529] "Politics Travel the China-Tibet Railway," *Marketplace World* (American Public Media, June 3, 2008).
[530] Xiao et al., "Remote Sensing, Ecological Variables, and Wild Bird Migration Related to Outbreaks of Highly Pathogenic H5N1 Avian Influenza."

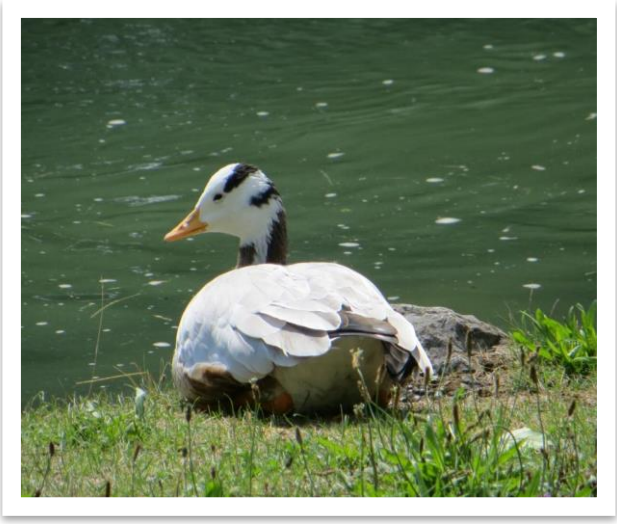

Figure 16 Bar-headed Goose in Munich (*Anser indicus*). Photo Credit: Canavan, 2013.

In the spring of 2005, Qinghai Lake was the scene of an extraordinary event that has far-reaching implications for the global health of multiple species. According to the Chinese Academy of Sciences, thousands of migratory birds died at the lake from an avian influenza infection (subtype H5N1).[531] The majority of the dead birds were bar-headed geese (**Figure 16**). Journalist Li Jiao claimed that the 2005 Qinghai Lake die-off as the single largest H5N1 wild bird mortality event ever recorded.[532] Subsequently, the virus spread from western China to Europe and Africa.

Virologists from the Chinese Academy of Sciences tracked additional outbreaks of bird flu involving bar-headed geese and other waterfowl. Avian influenza outbreaks at Qinghai Lake occurred separately or in conjunction with outbreaks in Mongolia and Russia during 2006, 2007, 2009, and 2010.[533] According to virologist Yoshi Kawaoka, one of the most dominant H5N1 strains in circulation is the one that first emerged in 2005 from Qinghai.[534]

The significance of the spread of H5N1 by migratory birds remains a topic of energetic debate, as does the role of wild birds in the perpetuation of avian flu. Wildlife

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[531] Liu et al., "Highly Pathogenic H5N1 Influenza Virus Infection in Migratory Birds."
[532] L. Jiao, "In China's Backcountry, Tracking Lethal Bird Flu," *Science* 330, no. 6002 (October 2010): 313–313.
[533] Li et al., "Persistent Circulation of Highly Pathogenic Influenza H5N1 Virus in Lake Qinghai Area of China."
[534] Kawaoka, *Homeland Virology - 2/2/2014*, This Week in Virology.

experts and virologists argued that the detection of viruses in migrating aquatic birds does not necessarily mean these viruses have been, or will be, successfully introduced into a new geographic area.[535] Nevertheless, events at Qinghai sparked intensive interest among avian flu researchers and raised questions about the natural environment at Qinghai Lake and the surrounding plateau.

How is the timing of the construction of the QTR and the bird flu outbreaks at Qinghai Lake connected? With tens of thousands of workers temporarily living in rugged high-altitude conditions to work on the QTR, the Chinese government had to shelter and feed them. Based on personal communications with scientists, they found that captive bar-headed geese were raised in the Lhasa Valley as food for the QTR workers.[536] Joint research funded by the FAO, USGS, the National Science Foundation, and the Chinese Academy of Sciences suggested that captive breeding of bar-headed geese, including attempts to interbreed them with domestic geese, represents a plausible route for the evolution of the avian virus to a more dangerous and deadly form.[537] This is the Pandora's Box of Qinghai, one that opened a novel pathway for the spread of an infectious virus to poultry and wild birds and occasionally to people. The next section describes how the scientific community responded to the threat of avian influenza via winged migration, deemed by some to be a biosecurity hazard.

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[535] Boyce et al., "Avian Influenza Viruses in Wild Birds"; Hulse-Post et al., "Role of Domestic Ducks in the Propagation and Biological Evolution of Highly Pathogenic H5N1 Influenza Viruses in Asia."
[536] Butler, "Blogger Reveals China's Migratory Goose Farms near Site of Flu Outbreak."; Personal communication with R. Webster, June 9, 2011.
[537] Newman et al., "Eco-Virological Approach for Assessing the Role of Wild Birds in the Spread of Avian Influenza H5N1 along the Central Asian Flyway."

5.3 Natural History of an H5N1 Virus

The Qinghai case study is a natural experiment in the study of an avian virus that circulates among many animals, including humans. Each virus has a legacy of its own, a history that matters, particularly for this case study.[538] This dissertation examines genetic markers of viruses as a way of historical truth telling.

As virologist Jacques Pepin described, phylogenetic analyses use genetic sequences to reconstruct the evolutionary history of various forms of life, including viruses and other pathogens.[539] The phylogenetic information garnered from Qinghai represents an unprecedented opportunity to answer questions about the evolutionary diversity of a virus.[540] Phylogenetic trees describe the relatedness among living organisms rather than their ancestry. They measure the genetic distance between organisms and identify their nearest relatives.[541] Drawing from documentation of Qinghai phylogenetic trees, it is possible to examine how avian viruses have evolved over a relatively short time span. In this respect, one can use a tool of the scientist as a tool of the historian.[542]

The natural history of this specific virus began with the ancestor of all currently circulating H5N1 viruses, the Goose/Guangdong lineage that emerged in the early 1990s in Southern China.[543] At that time, researchers believed that a migratory waterfowl introduced a

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[538] Here I focus on how and when the Qinghai-lineage of H5N1 virus emerged (A/bar-headed goose/Qinghai/3/05) (clade 2.2 and clade 2.3.2).
[539] Pepin, *The Origins of AIDS* (New York: Cambridge University Press, 2011), 22.
[540] Jessica Green, "Lady Lump's Mouthguard," in *Microbes and Evolution: The World That Darwin Never Saw*, ed. Roberto Kolter and Stanley Maloy (Washington, DC: ASM Press, 2012), 29.
[541] A phylogenetic tree or evolutionary tree is a branching diagram showing the inferred evolutionary relationships among various biological species or other entities - their phylogeny - based upon similarities and differences in their physical or genetic characteristics.
[542] See Appendix A for the Qinghai phylogenetic tree.
[543] Xu et al., "Genetic Characterization of the Pathogenic Influenza A/Goose/Guangdong/1/96 (H5N1) Virus"; Alexander, "Avian Influenza"; Capua and Alexander, "Animal and Human Health Implications of Avian Influenza Infections"; Sonnberg, Webby, and Webster, "Natural History of Highly Pathogenic Avian Influenza H5N1."

low pathogenic avian influenza virus (LPAI) to a chicken. According to virologists Duan et al., that LPAI virus was the result of viral mixing (reassortment) between LPAIs of several subtypes.[544] After this viral matrimony, the novel virus circulated among chickens, its new host, for a few years.

According to Sonnberg and Webster, this novel LPAI virus established a new host reservoir in Hong Kong chickens.[545] Eventually, under conditions not known, the virus became highly pathogenic (HPAI) to domestic fowl including chickens. As the avian virus adapted to its new host, it somehow acquired the ability to infect cells throughout the bird's entire body. In 1996, this novel virus caused an outbreak in farmed domestic geese in Guangdong Province. Researchers from CDC characterized the HPAI virus as an H5N1 subtype.[546] A phylogenetic analysis (the evolutionary history of an organism) revealed that this virus had only recently evolved in geese.[547] However, in contrast to the geese, experimentally infected ducks showed no clinical signs of illness.[548] Researchers claim that these evolutionary events demonstrate instability in the H5N1 virus that is the hallmark of a virus adapting to a new host.[549] Other viral characteristics were no doubt in play including the natural mutability of RNA viruses and the large reservoir of LPAI viruses circulating in poultry.[550]

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[544] Duan et al., "Characterization of Low-Pathogenic H5 Subtype Influenza Viruses from Eurasia."
[545] Sonnberg, Webby, and Webster, "Natural History of Highly Pathogenic Avian Influenza H5N1."
[546] Xu et al., "Genetic Characterization of the Pathogenic Influenza A/Goose/Guangdong/1/96 (H5N1) Virus."
[547] Guan et al., "H5N1 Influenza Viruses Isolated from Geese in Southeastern China"; Xu et al., "Genetic Characterization of the Pathogenic Influenza A/Goose/Guangdong/1/96 (H5N1) Virus."
[548] Webster et al., "Evolution and Ecology of Influenza A Viruses."
[549] J. Holland, "Transitions in Understanding of RNA Viruses: A Historical Perspective," in *Quasispecies: Concept and Implications for Virology*, ed. Esteban Domingo, vol. 299, Current Topics in Microbiology and Immunology (Springer Berlin Heidelberg, 2006), 371–401.
[550] Alexander, "Ecological Aspects of Influenza A Viruses in Animals and Their Relationship to Human Influenza: A Review"; Webster et al., "Evolution and Ecology of Influenza A Viruses."

The catastrophic 1997 avian flu outbreak among Hong Kong's chickens heralded the appearance of a starkly different AIV.[551] Researchers characterized the virus isolated from a child who died because of an H5N1 avian influenza.[552] This was the first-ever human case and death from an avian virus. Researchers suggested that the H5N1 Guangdong ancestor virus co-circulated among poultry in Hong Kong with an H9N2 virus from quail. Quail and pheasants carry viral receptors for both avian and mammalian viruses.[553] Thus, reassortment had generated a new viral lineage that combined genetic elements from an H5N1 and an H9N2 virus.[554] Outbreaks of H5N1 avian influenza in poultry and humans continued for a short time until Hong Kong eradicated its entire poultry population of millions of chickens. For the first time, avian flu was a disease not just for birds and the scientific community took notice.

While all appeared quiet on the virological front after the mass culling of poultry in Hong Kong, the H5N1 virus continued to circulate.[555] In 2002, there were two outbreaks of the Guangdong H5N1 variant among wild birds in Hong Kong. According to virologists Guan et al., the re-introduction of the H5N1 viruses to wild waterfowl was likely from Hong Kong chickens that harbored the viruses.[556] Thus, there appeared to be something resembling a bi-directional flow of viruses between chickens and wild waterfowl. During 2002, H5N1

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[551] Shortridge et al., "Characterization of Avian H5N1 Influenza Viruses from Poultry in Hong Kong."
[552] Subbarao, "Characterization of an Avian Influenza A (H5N1) Virus Isolated from a Child with a Fatal Respiratory Illness"; Claas et al., "Human Influenza A H5N1 Virus Related to a Highly Pathogenic Avian Influenza Virus"; Yuen et al., "Clinical Features and Rapid Viral Diagnosis of Human Disease Associated with Avian Influenza A H5N1 Virus"; Shortridge et al., "Characterization of Avian H5N1 Influenza Viruses from Poultry in Hong Kong"; Suarez et al., "Comparisons of Highly Virulent H5N1 Influenza A Viruses Isolated from Humans and Chickens from Hong Kong."
[553] Simms and Jeggo, "Avian Influenza from an Ecohealth Perspective."
[554] Duan et al., "Characterization of Low-Pathogenic H5 Subtype Influenza Viruses from Eurasia"; Guan et al., "Molecular Epidemiology of H5N1 Avian Influenza"; Xu et al., "Genetic Characterization of the Pathogenic Influenza A/Goose/Guangdong/1/96 (H5N1) Virus"; Sonnberg, Webby, and Webster, "Natural History of Highly Pathogenic Avian Influenza H5N1."
[555] Culling refers to the unsavory practice of disposing of poultry through gassing or incinerating.
[556] Guan et al., "H5N1 Influenza."

was responsible for avian influenza outbreaks in Southern China and the expansion of HPAI into South East Asia and to Indonesia.[557] Millions of chickens were culled. The human fatalities were sporadic but slowly accumulated to hundreds across many countries.

During 2003-2004, outbreaks of H5N1 occurred frequently in South East Asia as different H5N1 viral strains expanded their geographic range. In 2003, H5N1 emerged in eight Asian countries almost simultaneously, and then continued to circulate regionally in 2004.[558] During this period, the ability of wild birds to disseminate the Guangdong lineage of H5N1 viruses remained unclear.[559] No one except perhaps Robert Webster and his colleagues considered wild migrating birds a factor in the spread of AIVs. However, based on spatiotemporal analyses from numerous studies, researchers retrospectively concluded that migratory bird movement might have been a contributing factor to the expansion of HPAI in Indonesia and East Asia in the 2003-2005 period.[560]

In summary**,** the natural history of HPAI H5N1 includes the ability to persist in geese, noted from at least the early 1990s. The Guangdong-lineage H5N1 then diversified into sublineages and adapted to domestic ducks as the host reservoir. The viral pathogen amplified in the poultry hosts and spilled back into the wild bird population.

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[557] Li et al., "Genesis of a Highly Pathogenic and Potentially Pandemic H5N1 Influenza Virus in Eastern Asia."
[558] Prosser, *Examining Movement Ecology of Wild Birds and Their Role in Disease Transmission*.
[559] Sonnberg, Webby, and Webster, "Natural History of Highly Pathogenic Avian Influenza H5N1."
[560] Gaidet et al., "Potential Spread of Highly Pathogenic Avian Influenza H5N1 by Wildfowl"; Gilbert et al., "Anatidae Migration in the Western Palearctic and Spread of Highly Pathogenic Avian Influenza H5NI Virus"; Liang et al., "Combining Spatial-Temporal and Phylogenetic Analysis Approaches for Improved Understanding on Global H5N1 Transmission"; Si et al., "Spatio-Temporal Dynamics of Global H5N1 Outbreaks Match Bird Migration Patterns"; Webster et al., "The Spread of the H5N1 Bird Flu Epidemic in Asia in 2004."

5.4 Chronology: Events at Qinghai

Late April of 2005 marked the most significant shift in the ecology of the Guangdong lineage of H5N1. There was a large-scale influenza outbreak detected in several wild bird species at the Qinghai Lake Nature Reserve. The reserve is a major breeding site for migratory waterfowl from the Central Asian Flyway and the East Asian Flyway and, according to Olsen et al., hosts about 150,000 birds from 180 species in spring and summer.[561] Bar-headed geese breed in the mountainous regions of central Asia north of the Himalayas, most notably at Qinghai Lake.[562] They migrate to the Indian subcontinent in fall and return to Qinghai Lake in April for the summer.

The initial 2005 H5N1 outbreak at Qinghai Lake was at one location. More than six thousand wild birds died within a two-week period. The bar-headed geese were the first to become symptomatic with H5N1 and represented the majority of the fatal cases. Afflicted birds staggered around for a day or so, then fell over and died.[563] Wild bird experts were rather shocked at the news of so many birds dying at once, at a single location. An event of this magnitude is rare and, at first, most observers shrugged it off as an unusual event for wildlife.[564]

Isolation of virus from dead birds in 2005 revealed a new strain of H5N1, designated as 2.2, a reassortant virus.[565] This viral strain caused 100% mortality in chickens and mice and 80% mortality in migratory waterfowl.[566] The independent investigations of virologists

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[561] Olsen et al., "Global Patterns of Influenza a Virus in Wild Birds."
[562] Hawkes et al., "The Trans-Himalayan Flights of Bar-Headed Geese (Anser Indicus)"; Hawkes et al., "The Paradox of Extreme High-Altitude Migration in Bar-Headed Geese Anser Indicus."
[563] Alan Sipress, *The Fatal Strain: On the Trail of Avian Flu and the Coming Pandemic* (New York: Viking, 2009).
[564] Ruth Cromie, personal communication, Aug. 2014
[565] Anderson et al., "FAO-OIE-WHO Joint Technical Consultation on Avian Influenza at the Human-Animal Interface." See Appendix 1 for the phylogenetic tree of this virus.
[566] Zhou et al., "Characterization of a Highly Pathogenic H5N1 Influenza Virus Derived from Bar-Headed Geese in China."

H. Chen and J. Liu and their subsequent publications in 2005 caused quite a stir within the scientific community.[567] A subset of the viruses at Qinghai Lake carried a marker for mammalian adaptation.[568] According to bird ecologist Chris Feare, mammalian adaptation suggested that the Qinghai virus originated, at some point, in a mammal that subsequently transmitted the virus to wild birds.[569] Initially, the directionality of virus transmission between domestic and wild birds was difficult to ascertain.[570]

Months later, researchers discovered that H5N1 viruses isolated from dead birds in Russia and Mongolia were of the Qinghai-lineage.[571] Mongolia and the surrounding region are vast, sparsely populated areas that contain major breeding and stopover areas for migratory waterfowl including geese, swans, and ducks. There is minimal commercial or backyard poultry in this region.

By late 2005 and throughout 2006, the Qinghai-lineage H5N1 expanded across Eurasia, into the Indian subcontinent, and to Africa.[572] Experts from multiple countries and organizations claimed that this geographic spread correlated in time and space with annual bird migration movements along the overlapping flyways spanning Eurasia.[573]

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[567] Chen et al., "Avian Flu: H5N1 Virus Outbreak in Migratory Waterfowl"; Liu et al., "Highly Pathogenic H5N1 Influenza Virus Infection in Migratory Birds," August 19, 2005.
[568] Liu et al., "Highly Pathogenic H5N1 Influenza Virus Infection in Migratory Birds."
[569] Feare, "Role of Wild Birds in the Spread of Highly Pathogenic Avian Influenza Virus H5N1 and Implications for Global Surveillance."
[570] Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau," 2011.
[571] Chen et al., "Properties and Dissemination of H5N1 Viruses Isolated during an Influenza Outbreak in Migratory Waterfowl in Western China."
[572] Organization, Nations, and Health, "FAO/OIE/WHO Joint Scientific Consultation on Influenza and Other Emerging Zoonotic Diseases at the Human-Animal Interface, 27-29 April, 2010, Verona, Italy."
[573] Artois et al., "Outbreaks of Highly Pathogenic Avian Influenza in Europe"; Gaidet et al., "Potential Spread of Highly Pathogenic Avian Influenza H5N1 by Wildfowl"; Gilbert et al., "Anatidae Migration in the Western Palearctic and Spread of Highly Pathogenic Avian Influenza H5NI Virus"; Liang et al., "Combining Spatial-Temporal and Phylogenetic Analysis Approaches for Improved Understanding on Global H5N1 Transmission"; Si et al., "Spatio-Temporal Dynamics of Global H5N1 Outbreaks Match Bird Migration Patterns."

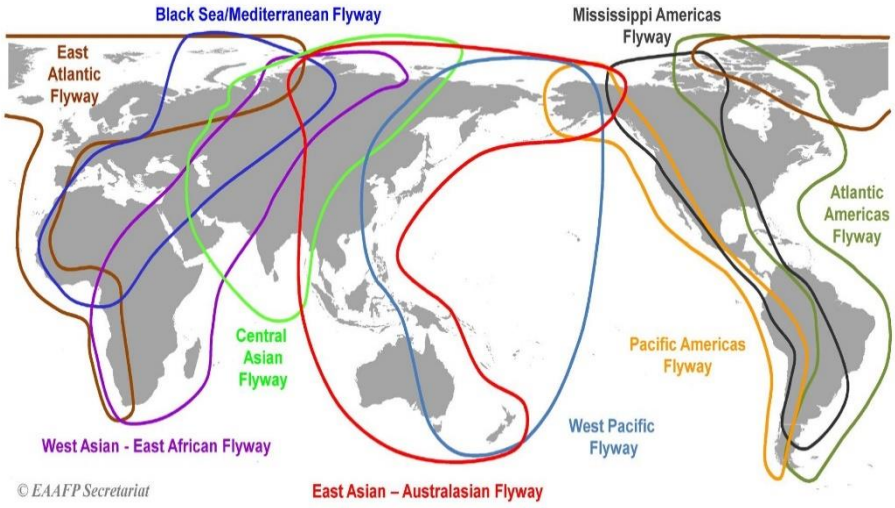

Figure 17. Flyways for Water Birds. Wetlands International, 2012.

As shown in **Figure 17**, three migratory bird flyways intersect at the Qinghai-Tibet Plateau: the East Asia-Australian flyway, the Central Asia flyway, and the West Asia-East African flyway.

Soon, the virus isolated at Qinghai showed up in chicken flocks in many countries in Eastern Europe and, in some cases, sickened humans who handled the chickens. Because Qinghai Lake sits within the eastern portion of the Central Asian Flyway that reaches from India and Bangladesh to Russia, experts were concerned that it had become a focal point of viral transmission. Other experts, particularly wild bird enthusiasts, disagreed and argued that the virus had traveled by road or rail.[574]

In the spring of 2006, more waterfowl, mostly bar-headed geese, died of H5N1 at four sites in Qinghai province and three sites in Tibet.[575] Phylogenetic analyses revealed that

[574] M. Gauthier-Clerc, C. Lebarbenchon, and F. Thomas, "Recent Expansion of Highly Pathogenic Avian Influenza H5N1: A Critical Review," *Ibis* 149, no. 2 (March 20, 2007): 202–14.
[575] Feare, Kato, and Thomas, "Captive Rearing and Release of Bar-Headed Geese (Anser Indicus) in China."

these viruses were also from Qinghai-lineage dating to 2005.[576] Researchers from the Chinese Academy of Sciences suggested that avian viruses originating at Qinghai Lake might travel back via migratory birds, though not ruling out the possibility of local circulation of viruses.[577]

By this time in 2006, wildlife groups and the general population were alarmed. In Europe, routine bird watching was recast as something of a border patrol.[578] Some citizen groups even demanded that officials drain wetlands to keep wild birds out of their region.[579] Virologists maintained that the role of wild birds in the spread of avian influenza virus was uncertain and an understanding of the ecology of influenza viruses was in its nascent stages. There had been many research studies about diseases of poultry but very few studies about diseases of migratory birds.[580]

In 2007, virologists from the Chinese Academy of Sciences isolated H5N1 viruses from another dead bar-headed goose at Qinghai Lake.[581] By this time, there was increased urgency to track the spread of avian influenza strain from domestic poultry to free-ranging wild birds, including migratory birds.[582] Recognizing that this research would require different tools, in 2007 the Food and Agriculture Organization of the United Nations (FAO)

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[576] See Appendix 1 for the phylogenetic tree of the Qinghai H5N1 lineage.
[577] Wang et al., "H5N1 Avian Influenza Re-Emergence of Lake Qinghai."
[578] Chris Wilbert, "The Birds, the Birds: Biopolitics and Biosecurity in the Contested Spaces of Avian Flu.," *Forum on Contemporary Art and Society* 8 (2007): 102–23.
[579] Personal communication with Ruth Cromie, Director of Britain's Wildlife and Wetlands Trust, August 2014. Cromie sits on the UN Scientific Task Force on Avian Influenza and Wild Birds and the Scientific Task Force on Wildlife and Ecosystem Health, both convened through the Convention of Migratory Species and the U.N. Food and Agriculture Organization.
[580] Simianer, "Decision Making in Livestock Conservation."
[581] Li et al., "Persistent Circulation of Highly Pathogenic Influenza H5N1 Virus in Lake Qinghai Area of China."
[582] Newman, Mundkur, and Harris, *Wild Birds and Avian Influenza*.

produced an applied field research and disease sampling manual including techniques for monitoring and testing wild birds.[583]

Highly pathogenic H5N1 was again isolated from dead wild birds at Qinghai during May-June 2009. Phylogenetic analyses showed that this outbreak was clearly distinguishable from the 2005 Qinghai clade 2.2 viruses and belonged to clade 2.3.2.[584] In all, there were sixteen outbreaks reported on the Qinghai-Tibet Plateau from 2003–2009, nine in wild birds and seven in poultry. According to Prosser et al., all poultry outbreaks of H5N1 occurred near Lhasa.[585] The bar-headed goose was the primary species infected during the outbreaks. There were no human cases of avian flu reported from this region. The official designation for the 2005 isolates from bar-headed geese is influenza A/bar-headed goose/Qinghai/3/05 (clade 2.2).

In early July of 2015, OIE reported a die-off of over 2,000 great black-headed gulls at Qinghai Lake.[586] For the past ten years, alternative and overlapping theories suggested that bird flu at Qinghai was from migrating birds, poultry trade and industrial production, viruses in rapidly melting permafrost, impacts from climate change, shrinking waterways, or agricultural practices. Theories emerged from a variety of diverse scientific disciplines and most considered that a multifactorial explanation was likely. Methods to control the outbreaks in poultry appeared to be unsuccessful on the larger scale.[587]

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[583] Ibid.
[584] Li et al., "New Avian Influenza Virus (H5N1) in Wild Birds, Qinghai, China"; Wang et al., "H5N1 Avian Influenza Re-Emergence of Lake Qinghai." See Appendix 1 for phylogenetic tree.
[585] Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau," 2011. Prosser, a wildlife biologist with the USGS Patuxent Wildlife Research Center, has first-hand knowledge of bird migration routes from Qinghai Lake, and the transmission risk between of AIV between domestic and wild birds. She completed her dissertation on this topic in 2012.
[586] CIDRAP, "Flu Scan for Jul 21, 2015."
[587] Capua and Alexander, "Avian Influenza Infection in Birds."

Whatever the cause, it became imperative to find the H5N1 transmission route and determine the environmental factors that affect the prevalence of avian influenza virus. Since 2005, previously unprepossessing phenomena, the migration of wild geese, came to rivet the attention of scientists who converged at Qinghai.

5.5 Wild Goose Chase

Despite continued debate about the role of wild bird migration in spreading avian influenza viruses, researchers were able to link the spread of H5N1 beyond Asia and into Europe and Africa to the H5N1 viruses originating at Qinghai.[588] In this section, I examine the putative role of bar-headed geese in the spread of disease as well as the scientific studies to track wild birds along the major flyways of Asia. I commence with a description of the bar-headed goose as a significant actor in the case study.

Bar-Headed Goose: a High Flyer

From a natural history perspective, winged migration evokes a sense of human connection to the web of nature. Environmental historians Wilson and Cronon wrote, "No organisms demonstrate the geographical paradoxes of scale and place better than migratory birds."[589] According to historian/veterinarian Susan Jones, non-human actors such as birds play a vital role in making history and in reshaping scientific knowledge.[590] However, the research norm, according to historian of science Anita Guerrini, has been to relegate animals

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[588] Liu et al., "Highly Pathogenic H5N1 Influenza Virus Infection in Migratory Birds;" Kilpatrick et al., "Predicting the Global Spread of H5N1 Avian Influenza"; Rappole and Hubalek, "Birds and Influenza H5N1 Virus Movement to and within North America"; Dierauf et al., "Avian Influenza Virus and Free-Ranging Wild Birds"; Morgan, "Avian Influenza"; Gilbert et al., "Anatidae Migration in the Western Palearctic and Spread of Highly Pathogenic Avian Influenza H5NI Virus."

[589] Robert Wilson and William Cronon, *Seeking Refuge: Birds and Landscapes of the Pacific Flyway* (Seattle: University of Washington Press, 2012), ix.

[590] Jones, "Body and Place," 47-48.

as part of "animal studies" and to ignore "…animals as historical actors."[591] Environmental historian Brett Walker considers animals as primary sources with natural agency of their own, subject to historical interpretation.[592] This dissertation applies these perspectives to the bar-headed goose, an actor in the case study narrative with a history of its own.

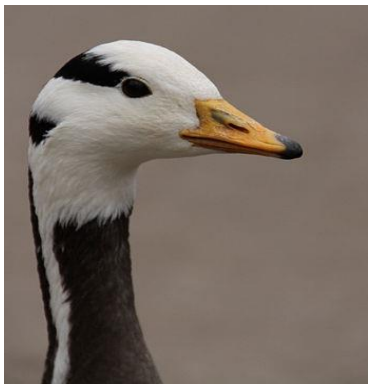

Figure 18. Bar-headed Goose. Photo credit: David Long, London, United Kingdom [CC BY 2.0]

The bar-headed goose makes one of the highest and most iconic trans-mountain migrations in the world. Its gray body, long neck, and short, tapered beak create an elegant S-shaped silhouette. Adults weigh about five pounds and stand about two feet high. Two horizontal black stripes on the back of the bird's white head give the species its name (**Figure 18**). Bar-headed geese use both the Central Asian and the East Asian Flyways with breeding populations in Tibet, Qinghai Lake, and western Mongolia.[593]

According to Lucy Hawkes, a researcher in physiological ecology, bar-headed geese fly over the Himalayan Mountains at altitudes up to 10,175 meters on their migratory route between South and Central Asia.[594] Researchers examined how the bar-headed goose gained its exceptional ability to sustain climbing flight over the highest mountain passes under their own aerobic power.[595] Zoologists Scott and Milson suggested that evolutionary changes in

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[591] Anita Guerrini, *The Courtiers' Anatomists: Animals and Humans in Louis XIV's Paris* (Chicago: University of Chicago Press, 2015), 3.
[592] Brett L. Walker, *Toxic Archipelago: A History of Industrial Disease in Japan* (University of Washington Press, 2011).
[593] Prosser et al., "Satellite-Marked Waterfowl Reveal Migratory Connection between H5N1 Outbreak Areas in China and Mongolia"; Takekawa et al., "Migration of Waterfowl in the East Asian Flyway and Spatial Relationship to HPAI H5N1 Outbreaks."
[594] Hawkes et al., "The Trans-Himalayan Flights of Bar-Headed Geese (Anser Indicus)"; Hawkes et al., "The Paradox of Extreme High-Altitude Migration in Bar-Headed Geese Anser Indicus."
[595] Scott et al., "Evolution of Muscle Phenotype for Extreme High Altitude Flight in the Bar-Headed Goose."

the respiratory system of bar-headed geese enhance oxygen loading into their blood and flight muscles. In addition, their lungs are proportionally larger and bar-headed geese breathe faster at higher elevations than other geese, bringing more air through the lungs.[596]

Humans are not the only species with high altitude adaptations at the Qinghai-Tibet Plateau. Evolutionary biologist Stephen Stearns suggested that it is important to observe signs of evolution across species:

> Research on human evolutionary responses to sudden environmental changes will contribute to cross-species comparisons that will help us understand the role of evolution in a rapidly changing world.[597]

Animal health expert Claire Heffernan also argued that explorations of disease across species might better explain the role and interaction of climate than the current focus on individual diseases.[598]

Long-distance migration is one of the most demanding activities in the animal world. Such prolonged, intense exercise leading to immunosuppression and infections would certainly affect migratory performance in a negative way. For this reason, some researchers maintained that it is unlikely that wild birds can spread the virus along long-distance migration pathways. However, other researchers argued that migratory movement could occur before the virus impaired a bird's ability to migrate.[599] Infected birds can travel considerable distances while harboring the virus. The bar-headed goose, for example, can remain asymptomatic for almost seven days and survive infection.[600] The migration journey from Qinghai Lake to the Lhasa wintering grounds typically takes five days.[601]

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[596] Scott and Milsom, "Control of Breathing and Adaptation to High Altitude in the Bar-Headed Goose."
[597] Stearns et al., "Measuring Selection in Contemporary Human Populations," 622.
[598] Heffernan, "Climate Change and Infectious Disease."
[599] Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau," 2011.
[600] Brown, Stallknecht, and Swayne, "Experimental Infection of Swans and Geese with Highly Pathogenic Avian Influenza Virus (H5N1) of Asian Lineage."
[601] Prosser, *Examining Movement Ecology of Wild Birds and Their Role in Disease Transmission*.

In a study of avian ecology, researchers Reperant et al. found that birds with elevated plasma concentration of corticosterone at the time of migration might be more susceptible to an HPAI infection and shed more virus.[602] Although these results are preliminary, they have interesting implications for the long-distance migration patterns of the bar-headed goose.

The 2005 H5N1 outbreak at Qinghai Lake reduced the global population of bar-headed geese by about ten percent.[603] However, they are not an endangered species, at least not at this time. Bar-headed geese remain popular in captivity, as they are beautiful, breed readily, and get along well with other birds. Some people prize the bar-headed geese for their meat, regarded as a specialty product claimed to have cancer prevention properties.

Legend of the Goose Farms

After the 2005 outbreak of H5N1 at Qinghai Lake, Chinese-language internet bulletins described captive rearing of bar-headed geese on China's high plateau. According to a *Nature* journalist, a local blogger claimed that a captive goose farm was near the site of an avian flu outbreak.[604] Avian ecologists Chris Feare et al. documented these reports and provided insights into the potential links between the goose farms and the emergence of H5N1 at Qinghai.[605]

Apparently, captive breeding of geese commenced on the Qinghai-Tibet plateau during 2003 with the "Lhasa Nida Natural Ecology Development bar-headed Goose Artificial Breeding Company," about 100 km from Lhasa. The company collected hundreds of goose

[602] Reperant et al., "Highly Pathogenic Avian Influenza Virus H5N1 Infection in a Long-Distance Migrant Shorebird under Migratory and Non-Migratory States."
[603] Liu et al., "Highly Pathogenic H5N1 Influenza Virus Infection in Migratory Birds," August 19, 2005.
[604] Butler, "Blogger Reveals China's Migratory Goose Farms near Site of Flu Outbreak."
[605] Feare, Kato, and Thomas, "Captive Rearing and Release of Bar-Headed Geese (Anser Indicus) in China."

eggs from a declining colony at Qinghai Lake. The operation expanded to another facility about 300 km NE of Lhasa where breeders raised bar-headed geese to "meet market demand." There were reports that captive goose farms were close to the Qinghai Nature Reserve with an unknown number of birds released back into the wild. In addition, flocks of geese on the ground are attractive to over-flying birds on their northward journeys from India and southern Tibet.[606] Feare argued that contact between wild bar-headed geese and outdoor grazing captive birds could have occurred as early as 2003.[607]

During 2004, a captive goose-breeding unit opened in Gonggar County (Tibet) as part of a program to boost animal husbandry in association with the opening of the Qinghai-Tibet Railway. Soon, there was large-scale breeding of bar-headed geese in several counties outside Lhasa.[608] Although little reported, some experts argued that the larger goose farms existed primarily to raise geese as food for the Qinghai-Tibet railway workers, a group that numbered in the tens of thousands at the height of construction from 2003-2006.[609] In 2006, officials closed and disinfected one breeding facility in Gonggar County because of concerns of avian influenza. Researchers do not know if there was an avian flu outbreak at this facility, as the results of any viral testing were unavailable.[610] The first confirmed H5N1 outbreak on the plateau was among chickens in Lhasa during 2004 but, once again, the genetic sequence data of the viruses were not available for researchers. The next big event

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[606] Inglis and Isaacson, "The Responses of Dark-Bellied Brent Geese to Models of Geese in Various Postures."
[607] Butler, "Blogger Reveals China's Migratory Goose Farms near Site of Flu Outbreak"; Feare, Kato, and Thomas, "Captive Rearing and Release of Bar-Headed Geese (Anser Indicus) in China."
[608] Feare, Kato, and Thomas, "Captive Rearing and Release of Bar-Headed Geese (Anser Indicus) in China."
[609] Personal communication with Robert Webster, June 9, 2011.
[610] Feare, "The Role of Wild Birds in the Spread of HPAI H5N1."

after the Lhasa poultry outbreaks was the Qinghai Lake wild bird epizootic in the spring of 2005.[611]

Scott Newman, an avian flu researcher/veterinarian from FAO, led and participated in many investigations at Qinghai.[612] FAO engaged with the biosecurity issues for monitoring and surveillance of wild and domestic birds.[613] From 2007-2010, Newman et al. examined the movement of migratory birds from Qinghai Lake by means of satellite-tracked wild birds. According to Newman, most of the U.S. funding for these projects comes through the Emerging Pandemic Threats program of USAID.[614]

As part of this interdisciplinary research effort, in 2007-2008 Prosser et al. travelled to the Qinghai-Tibet Plateau to investigate the links between the goose farms, the wild bird flyways, and H5N1.[615] The researchers wanted to know the bird migration paths, the stopovers, overlap of bar-headed geese with poultry zones of infection and, most of all, whether birds infected with H5N1 can migrate. Until that time, there was little background

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[611] Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau," 2011.
[612] Bourouiba et al., "Spatial Dynamics of Bar-Headed Geese Migration in the Context of H5N1"; Fergus et al., "Migratory Birds and Avian Flu"; Gaidet et al., "Potential Spread of Highly Pathogenic Avian Influenza H5N1 by Wildfowl"; Gaidet et al., "Duck Migration and Past Influenza A (H5N1) Outbreak Areas"; Gilbert et al., "Flying over an Infected Landscape"; Hawkes et al., "The Trans-Himalayan Flights of Bar-Headed Geese (Anser Indicus)"; Newman et al., "Eco-Virological Approach for Assessing the Role of Wild Birds in the Spread of Avian Influenza H5N1 along the Central Asian Flyway"; Ottaviani et al., "The Cold European Winter of 2005–2006 Assisted the Spread and Persistence of H5N1 Influenza Virus in Wild Birds"; Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau," 2011; Prosser et al., "Satellite-Marked Waterfowl Reveal Migratory Connection between H5N1 Outbreak Areas in China and Mongolia"; Takekawa et al., "Migration of Waterfowl in the East Asian Flyway and Spatial Relationship to HPAI H5N1 Outbreaks"; Takekawa et al., "Movements of Wild Ruddy Shelducks in the Central Asian Flyway and Their Spatial Relationship to Outbreaks of Highly Pathogenic Avian Influenza H5N1"; Takekawa et al., "Victims and Vectors"; Tian et al., "Avian Influenza H5N1 Viral and Bird Migration Networks in Asia"; Zhang et al., "Tracking the Autumn Migration of the Bar-Headed Goose (Anser Indicus) with Satellite Telemetry and Relationship to Environmental Conditions."
[613] Wilbert, "The Birds, the Birds: Biopolitics and Biosecurity in the Contested Spaces of Avian Flu."
[614] Newman, *Niche Mapping, Multi-Criteria Decision Analysis and Animal Movement Data for Mapping the Risk of Avian Influenza Emergence in Asia*.
[615] This research was funded by the United States Geological Survey (Patuxent Wildlife Research Center, Western Ecological Research Center, Alaska Science Center, and Avian Influenza Program); the United Nations FAO, Animal Production and Health Division, EMPRES Wildlife Unit; National Science Foundation Small Grants for Exploratory Research; and the Chinese Academy of Sciences.

information available about the ecology and migration of wild birds originating from Qinghai Lake. The researchers used GPS satellite telemetry to track the bird migration patterns. They compared these migration patterns with the path of known H5N1 infections across the Qinghai-Tibet Plateau using phylogenetic analysis.[616]

GPS data revealed that wild geese tagged at Qinghai Lake spent their winters outside of Lhasa via an undocumented migratory pathway between Qinghai Lake and the Lhasa Valley of Tibet. According to Diann Prosser, a USGS wildlife biologist and ecologist, this was a monumental discovery – an undocumented flyway to an area close to confirmed H5N1 poultry outbreaks.[617] During the winter, wild geese used agricultural fields and wetlands near the captive bar-headed geese farm as well as poultry farms. This suggested a path for the virus to move between captive and wild birds.[618] Earlier studies had hypothesized that wild birds transported H5N1 virus to Qinghai from Poyang Lake in China, a theory later disproved.[619]

According to Prosser et al., Lhasa provided a unique situation for the potential transmission of disease between wild and domestic birds. The Lhasa valley location protects the region from intense cold or heat and strong winds. Each winter, the Chinese New Year festival in late January draws concentrations of people and animals to Lhasa when nomadic herders return and chicken production peaks.[620] During this time, about fifty percent of the global population of bar-headed geese winters in sheltered river valleys surrounding Lhasa.[621]

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[616] Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau."
[617] Prosser, *Examining Movement Ecology of Wild Birds and Their Role in Disease Transmission*.
[618] Jiao, "In China's Backcountry, Tracking Lethal Bird Flu."
[619] Chen et al., "Establishment of Multiple Sublineages of H5N1 Influenza Virus in Asia," February 10, 2006; Liang et al., "Combining Spatial-Temporal and Phylogenetic Analysis Approaches for Improved Understanding on Global H5N1 Transmission."
[620] Ibid.
[621] Bishop et al., "Bar-Headed Geese Wintering in South-Central Tibet"; Bishop and Drolma, "Tibet Autonomouse Region January 2007 Survey"; Lang, Bishop, and Le Sueur, "An Annotated List of Birds Wintering in the Llasa River Watershed."

These findings provided new evidence that the Qinghai Lake region was indeed a pivotal point of H5N1 transmission.[622] The described research encompassed not only avian viruses but also the social context in which H5N1 emerged. This is an example of the "local particulars" that Bill Summers deemed so critical for historical analysis of disease epidemics.[623]

By 2010, several research teams concluded that captive goose farms in close proximity to the wintering bar-headed geese at Lhasa were a source for the H5N1 infection.[624] Li et al. from the Chinese Academy of Sciences argued that some of the dead bar-headed geese might have been captive-bred birds. Furthermore, this could explain the apparent persistence of this virus strain in Qinghai Province.[625] In May of 2010, the World Organization for Animal Health (OIE) again reported dead wild birds including bar-headed geese in Tibet. According to OIE, these outbreaks were contemporaneous with or followed by outbreaks in wild birds in Mongolia and southern Russia.[626]

Whatever is to "blame," LPAI and HPAI have continued to co-circulate in poultry and wild waterfowl in Southern China and South East Asia with sporadic outbreaks among sixty countries in Europe, the Middle East, and Africa. Avian influenza has become endemic in Indonesia, Bangladesh, India, and Egypt with repeated emergence in China, Vietnam,

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[622] Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau," 2011.
[623] Summers, *The Great Manchurian Plague of 1910-1911*, 107. Personal communication, May 2013.
[624] Newman et al., "Eco-Virological Approach for Assessing the Role of Wild Birds in the Spread of Avian Influenza H5N1 along the Central Asian Flyway." This team included researchers from FAO, USGS (Western Ecological Research Center, Patuxent Wildlife Research Center, and the Alaska Science Center), University of California Davis, Chinese Academy of Sciences, Mongolian Academy of Sciences, Max Planck Institute for Ornithology, Bombay Natural History Society, Wetlands International. This research was funded by a collaborative of FAO, the USGS, the National Science Foundation, the Biotechnology and Biological Science Research Council of the United Kingdom, and the Chinese Academy of Sciences.
[625] Li et al., "Persistent Circulation of Highly Pathogenic Influenza H5N1 Virus in Lake Qinghai Area of China."
[626] Feare, Kato, and Thomas, "Captive Rearing and Release of Bar-Headed Geese (Anser Indicus) in China."

Thailand, and Mongolia.[627] A major consequence is that both LPAI and HPAI viruses of the H5N1 subtype remained available for reassortment with other, possibly more dangerous, viruses.

Scientific Knowledge: New Modes of Production

In 2005, when H5N1 emerged from Qinghai, there were few prior studies of the movement of wild birds in Asia. However, as shown in the Prosser et al. study, researchers investigated the movement of avian viruses at a scale relevant to the wild bird hosts, the Central Asian Flyway.[628] This approach effectively engaged with both the micro (virus) and macro (flyway) scales of the Qinghai phenomena. The following examples highlight how this mode of research is changing the way that avian flu researchers produce new knowledge.

A study at Poyang Lake, China, was one in which researchers adopted a One Health approach to investigate multispecies ecologies in the transmission of avian flu.[629] The researchers specifically wanted to avoid a reductionist understanding of influenza that focused on the virus alone. They found that the wild bird-domestic poultry interface was, in many ways, shaped by the bird breeders who had blurred the distinction between wild and domestic kinds of birds. While the researchers presumed wild and domestic were two distinct populations, the breeders did not necessarily see them the same way. Farmed wild birds had become a bridge between the wild and the domestic.[630]

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[627] FAO, "EMPRES-I Global Animal Health Information System of FAO's Emergency Prevention Program for Transboundary Animal Diseases."
[628] Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau," 2011.
[629] See chapter three for discussion of One Health.
[630] Lyle Fearnley, "Wild Goose Chase: The Displacement of Influenza Research in the Fields of Poyang Lake, China," *Cultural Anthropology* 30, no. 1 (February 17, 2015): 12–35; Fearnley, "The Birds of Poyang Lake: Sentinels at the Interface of Wild and Domestic"; Takekawa et al., "Victims and Vectors."

Gilbert et al. examined the role of migratory birds in the spread of H5N1 by means of satellite-tracked wild waterfowl along the Central Asia flyway. This was an international team of experts from such diverse organizations as Wetlands International, the Bombay Natural History Society, and the Mongolian Academy of Sciences. Funded by NIH, NASA, FAO, and USGS, data from satellite-tracked birds revealed a spatiotemporal link between potential avian influenza hot spots in India and Bangladesh and wild bird outbreaks during 2009 at the Qinghai Lake region, Mongolia, and Russia. The authors concluded that there were advantages to integrating HPAI risk modeling with waterfowl migration ecology to map and track (and in this case, possibly even predict) hotspots of H5N1 along Asian flyways.[631]

Exploring the eco-virological dimensions of H5N1 at Qinghai, Newman et al. tracked the relationship of migratory birds to local environmental factors. Using phylogeographic mapping to trace the trajectory of the virus outbreaks, the researchers also examined the rate of evolutionary change for different H5N1 virus clades.[632] The viruses were evolving at different rates at different locations, but the specific factors that drive this evolution are not known.[633]

Tian et al. also combined satellite-tracking data with a phylogenetic analysis to examine the spatiotemporal spread of HPAI across Asia. Their study focused on the period 2003-2012, when bird migrations coincided with the peaks of HPAI epidemics. They

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[631] Gilbert et al., "Flying over an Infected Landscape: Distribution of Highly Pathogenic Avian Influenza H5N1 Risk in South Asia and Satellite Tracking of Wild Waterfowl." Project team members were from the Biological Control and Spatial Ecology at the University of Brussels, USGS, FAO, University of Maryland, Bombay Natural History Society, Wetlands International, Chinese Academy of Sciences, Qinghai Lake National Nature Reserve, and the Mongolian Academy of Sciences.

[632] Phylogeographic mapping takes into account publically available genetic information about the HPAI H5N1 clades, maps out the trajectory and distribution of specific virus clades and enables analyses to incorporate virological data as well as other agro-ecological risk factors and migration pathways.

[633] Newman et al., "Eco-Virological Approach for Assessing the Role of Wild Birds in the Spread of Avian Influenza H5N1 along the Central Asian Flyway."

concluded that the HPAI is strongly associated with bird migrations and that "…spatial distance is not a major ecological barrier to gene transfer within a flyway."[634]

From these examples, it is clear that wild bird experts worked alongside virologists, wildlife veterinarians, ecologists, geographers and other experts assessing influenza in the field rather than under a microscope. For avian flu science at Qinghai, this relocation of flu research to the field is changing how scientists produce knowledge about the spread of avian influenza.[635] Today, avian influenza research is as likely to be in wetlands as in "wet" labs. As historians Kuklick and Kohler have argued, field sciences are distinctive because "unlike laboratories, natural sites can never be exclusively scientific domains."[636]

This mode of knowledge production relies on a shared understanding and expertise to explain the phenomena of a viral entity that lives at the boundary of so many living systems. This paradigm of knowledge production is transdisciplinary in nature and emphasizes the ecological relationships at the center of "viral traffic," the place where viruses transfer to new hosts.[637] Thus, the flu virus has moved into what historian/anthropologist Frédéric Keck calls the "frontiers between species."[638] This "frontier" represents the moment when a disease crosses from one species to another. Environmental geographer Sarah Whatmore refers to the domestic-wild boundary as the "bewildering spaces" in reference to the human-animal interface.[639]

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[634] Tian et al., "Avian Influenza H5N1 Viral and Bird Migration Networks in Asia."
[635] Fearnley, "Wild Goose Chase"
[636] Henrika Kuklick and Robert E. Kohler, eds., *Science in the Field*, Osiris, Ser. 2, Vol. 11 (Chicago, Ill: Univ. of Chicago Press, 1996), 4.
[637] Morse, "Emerging Viruses," 1991.
[638] Frédéric Keck, "From Purgatory to Sentinel: 'Forms/Events' in the Field of Zoonoses," *Cambridge Anthropology* 32, no. 1 (March 1, 2014), 59.
[639] Sarah Whatmore, *Hybrid Geographies: Natures, Cultures, Spaces* (London ; Thousand Oaks, Calif: SAGE, 2002).

By taking advantage of USGS expertise in satellite telemetry, geospatial mapping, and waterfowl monitoring, researchers discovered new avian flu transmission links. This is a case in which technological expertise, outside of the virologists' traditional methods, was essential in producing new knowledge. Using satellite telemetry combined with virological analysis, researchers were able to assess the role of bar-headed geese in the transmission of H5N1. However, based on the systematic analysis at the end of this chapter, many studies of disease, environment, and wildlife remain in their disciplinary niches.

Researchers used Movement Ecology methods, a discipline established in 2012, at Qinghai to determine the patterns of migratory birds and their potential links to the spread of avian influenza. The basic principle is that movement is a critical component of almost any ecological process, including processes associated with habitat fragmentation, climate change, biological invasions, and the spread of diseases. This method combines expertise from biology, ecology, botany, environmental science, physics, mathematics, and virology.[640] Specifically, this approach investigates animal navigation and the drivers of inter-continental bird migration.[641]

Spatiotemporal analyses, eco-virological studies, and Movement Ecology are examples of an ecological approach to pathogens and disease, an approach with contemporary roots in the 1930s.[642] Avian influenza science is at the forefront of this revived trend in disease ecology. As a result, the study of avian viruses can happen at scale relevant to the environment of the host organism, even if that environment is a transnational flyway or within a permafrost environment.

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[640] Nathan, "Movement Ecology: Unifying Theory Of How Plants And Animals Move From One Place To Another."
[641] Nathan, "An Emerging Movement Ecology Paradigm."
[642] See chapter three for a discussion of the Ecological Dimensions of Viruses.

In summary, the H5N1 natural experiment mobilized a global community of scientists from diverse fields, stimulated an interdisciplinary approach, and encouraged the use of new technologies and methods to track the virus mutation and spread. The methods and findings of this scientific community are critical to understanding the interplay of landscape scale events with the complex evolution of an avian virus.

Wild Birds as Biological Sentinels

In the context of ecological and health anxiety, the "sentinel" has come to describe living beings or technical devices that provide the first signs of an impending catastrophe. Non-humans have served as environmental sentinels from the beginning of the industrial revolution. Most famously, miners used canaries for more than 75 years in Great Britain as a biological sentinel to detect toxic gases in mines. As long as the bird kept singing, the miners knew their air supply was safe. A dead canary signaled an immediate evacuation. Today, the expression "canary in a coal mine" has become a metaphor for an event that serves as a warning of a potentially detrimental change.[643]

Environmental historian Walker used the term biological sentinel as an early warning sign of industrial poisoning in Japan.[644] In his example of Minamata disease, the "dancing cat," delirious from mercury poisoning, wandered off to die. In most respects, the bar-headed goose fits the description of biological sentinel based on events at Qinghai. Thousands of dead birds certainly attracted attention but did not draw international worry and action until bird flu started to show up in Europe among chicken flocks. However, it is clear that mass

[643] C. Patrick Ryan, "Zoonoses Likely to Be Used in Bioterrorism," *Public Health Reports* 123, no. 3 (May 1, 2008): 276–81.
[644] Walker, *Toxic Archipelago*.

deaths of wild birds can serve as early warning for an avian virus that may have the potential to jump to humans.

It had become quite common to use animals as sentinels of public health to provide early warnings of disease. In the 1970s, Webster and Shortridge proposed that birds, particularly domestic waterfowl, could serve as sentinels for human flu pandemics. The virologists monitored ecological conditions of disease at the wild bird-domestic poultry interface.[645] In 1997, with the emergence of H5N1 in a more deadly form, Keck described how once again the city of Hong Kong served as a sentinel post for pandemic influenza emergence of H5N1 virus in birds.[646]

Yet, current surveillance of apparently healthy wild birds (active surveillance) has not provided early warning of likely infection for the poultry industry, whereas searches for and reports of dead birds (passive surveillance) have provided evidence of environmental presence of the virus, but not necessarily its source.[647] According to Newman et al., there was no HPAI detected as part of FAO's global sampling of more than 750,000 healthy wild birds.[648] This is consistent with studies that show that wild birds cannot perpetuate the avian virus indefinitely.[649]

Currently, it would appear that human avian influenza disease serves as the sentinel for bird disease rather than sick birds being the early warning for humans. It has been very difficult to engineer advance notice of a viral mutation. Although it is not likely that scientists would ignore another large wild bird die-off such as at Qinghai Lake, we cannot

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[645] Shortridge, Peiris, and Guan, "The next Influenza Pandemic."
[646] Frederic Keck and Andrew Lakoff, "Sentinel Devices," *Limn*, June 2013.
[647] Feare, "Role of Wild Birds in the Spread of Highly Pathogenic Avian Influenza Virus H5N1 and Implications for Global Surveillance."
[648] Newman et al., "Eco-Virological Approach for Assessing the Role of Wild Birds in the Spread of Avian Influenza H5N1 along the Central Asian Flyway."
[649] Brown, "Summary of Avian Influenza Activity in Europe, Asia, and Africa, 2006-2009"; Keawcharoen et al., "Wild Ducks as Long-Distance Vectors of Highly Pathogenic Avian Influenza Virus (H5N1)."

count on these rare events as early warning devices. In one example, during 2015, migratory birds died of H5N1 in the Sanmenxia Reservoir Area of China, about 1000 km east of Qinghai Lake. There was fear that this new H5N1 virus had the potential to travel to other regions through bird migration, similar to the Qinghai Lake outbreaks. Researchers monitored, disinfected, and blocked people from entering the reservoir.[650] What else can they do?

The next section examines knowledge about environmental factors on the Qinghai-Tibet Plateau that might explain pathways for avian influenza viruses that are not necessarily at the wild bird-domestic bird interface.

5.6 Ecological Pathways for Avian Viruses

Viruses are inseparable from the broader environmental context in which they occur. According to Newman et al., there are gaps in our knowledge about the environmental persistence of the virus in wetlands, the viral persistence through multiple wildlife hosts, and how climate affects disease ecology for H5N1.[651] A key question is not whether flying birds transport viruses such as H5N1 with them – clearly, they can and do. Rather, an important question is what becomes of these traveling viruses.[652]

Ongoing avian influenza outbreaks present a natural experiment for providing clues about conditions that promote viral persistence. Once again, avian influenza research is at the front line of innovation for integrating environmental and virological disease factors.

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[650] Bi et al., "Highly Pathogenic Avian Influenza (H5N1) Virus Struck Migratory Birds in China in 2015."
[651] Newman et al., "Eco-Virological Approach for Assessing the Role of Wild Birds."
[652] Boyce et al., "Avian Influenza Viruses in Wild Birds"; Hulse-Post et al., "Role of Domestic Ducks in the Propagation and Biological Evolution of Highly Pathogenic H5N1 Influenza Viruses in Asia."

Here, I examine biotic and abiotic factors that might provide a plausible pathway for the persistence of AIVs at Qinghai Lake and elsewhere.

Persistence of Viruses in the Environment

While there is incomplete information about the persistence of AIVs in the environment outside the host, multiple lines of evidence point to the persistence of AIV in water.[653] Water is a likely medium for the transfer of LPAI virus and partially explains the high prevalence of the virus among water birds, shorebirds, and seabirds, species that congregate in large numbers in wetlands.[654] Crowding at breeding or molting locations facilitates disease transmission as demonstrated at Qinghai Lake.[655] Water-borne transmission is a component of the epidemiology of the avian influenza virus.

Roche et al. argued that knowledge of habitat salinity, pH, and temperature is particularly important to identify potential hot spots of aquatic transmission risks of avian flu.[656] Brown et al. also suggested that the pH, temperature, and salinity of natural aquatic habitats could influence the ability of AIVs to remain infective within these environments. For example, pH is an important factor for determining how long virions can exist in the environment.

Brown et al. reported that avian flu viruses are most stable at a basic pH (7.4–8.2), low temperatures (<17 °C), and fresh to brackish salinities (0–20 g/L salinity). Alternatively, AIVs had a much shorter persistence in acidic conditions (pH < 6.6), warmer temperatures

[653] Breban et al., "The Role of Environmental Transmission in Recurrent Avian Influenza Epidemics."
[654] Causey and Edwards, "Ecology of Avian Influenza Virus in Birds."
[655] Li et al., "Persistent Circulation of Highly Pathogenic Influenza H5N1 Virus in Lake Qinghai Area of China."
[656] Roche et al., "Water-Borne Transmission Drives Avian Influenza Dynamics in Wild Birds: The Case of the 2005–2006 Epidemics in the Camargue Area."

(>32 °C), and high salinity (>25 g/L salinity).[657] The typical values at Qinghai Lake are 12.5 g/L salinity and pH of 9.4.[658] The mean value of the highest annual surface water temperatures was 17.3°C, and the lowest annual surface water temperatures was –13.3°C.[659]

Thus, the Qinghai Lake environment is one of nearly ideal conditions for avian flu viruses – not too acidic and not too warm. Ecologist Scoones argued that the "viral soup" existing at Qinghai Lake is one example of the enormous reservoirs of the H5N1 virus in Asia.[660]

Another study by Brown et al. examined the persistence of highly pathogenic AIVs to provide some insight into the potential for these viruses to transmit in the environments of wild bird populations. Viruses were tested at two temperatures (17C and 28C) and three salinity levels (0, 15, and 30 parts per thousand-sea salt). The resulting data demonstrated that H5 and H7 AIVs could persist for extended periods in water; alternatively, the higher the temperature and salinity, the lower the persistence of viruses.[661] According to Stallknecht et al., the overall stability and response of HPAI viruses in water, particularly H5N1, is similar to LPAI viruses, and suggests there was no loss of environmental survivability for HPAI viruses.[662]

Can an avian virus survive a deep freeze? Rogers et al. demonstrated that viruses can remain infective in freshwater lakes for >30 days at 0°C and for even longer periods in ice or

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[657] Brown et al., "Avian Influenza Virus in Water."
[658] Dong et al., "Impacts of Environmental Change and Human Activity on Microbial Ecosystems on the Tibetan Plateau, NW China."
[659] Xiao et al., "Evaluation of Spatial-Temporal Dynamics in Surface Water Temperature of Qinghai Lake from 2001 to 2010 by Using MODIS Data."
[660] Scoones, *Avian Influenza*, 10, 40.
[661] Brown et al., "Persistence of H5 and H7 Avian Influenza Viruses in Water."
[662] Brown et al., "Survivability of Eurasian H5N1 Highly Pathogenic Avian Influenza Viruses in Water Varies between Strains."

frozen ground.[663] However, freeze-thaw experiments show a rapid loss of infectivity.[664] Lake ice and permafrost do not receive much attention, according to biologists, as a potential reservoir of microbes during surveillance activities for human diseases.[665] However, Hu et al. claimed that China's permafrost regions represent a suitable ecological niche capable of colonization by abundant microbes.[666] Given the environment at the Qinghai-Tibet Plateau, additional studies to examine the permafrost on the plateau for persistent viruses would be worthwhile.

An overlooked avian influenza transmission mode is environmental transmission rather than water (or ice) transmission. Researchers know that infectious birds shed large concentrations of virions in the environment, where they may persist for a long time. In addition to direct fecal/oral transmission, birds might become infected by ingesting virions that have long persisted in the environment. Sooryanarain and Elankumaran designed a host-pathogen model that demonstrated environmental transmission of just a few infections per year is sufficient for avian influenza to persist in populations where it would otherwise vanish.[667] It is possible that this could be a factor in the persistent circulation of H5N1 at Qinghai.

Researchers have investigated the ability of highly pathogenic H5N1 to survive on a variety of materials under different environmental conditions. The materials included glass, wood, steel, soil, and chicken feces. They found that H5N1 survived longer (up to two months) at cooler temperatures —about 39 degrees F — but lasted only one day at room

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[663] Stallknecht et al., "Avian Influenza Viruses from Migratory and Resident Ducks of Coastal Louisiana"; Smith, "Ice as a Reservoir for Pathogenic Human Viruses: Specifically, Caliciviruses, Influenza Viruses, and Enteroviruses"; Zhang et al., "Evidence of Influenza a Virus RNA in Siberian Lake Ice."
[664] Stallknecht and Brown, "Tenacity of Avian Influenza Viruses."
[665] Rogers et al., "Recycling of Pathogenic Microbes through Survival in Ice."
[666] Hu et al., "The Microbial Diversity, Distribution, and Ecology of Permafrost in China."
[667] Sooryanarain and Elankumaran, "Environmental Role in Influenza Virus Outbreaks."

temperature. The virus tended to persist at low humidity and no sunlight on many surfaces including glass and steel. At low temperatures and low humidity, the virus actually survived longer on steel, glass, and soil than in chicken feces, a common source for spreading the virus.[668]

Another means of spreading avian viruses is through the bird's feathers. Data from Yamamoto et al. indicated that H5N1 strains are likely to replicate in feathers of domestic ducks and geese.[669] This is not entirely new information. During the Cold War, U.S. military scientists learned about the potential bioterror uses of "feather bombs" from their Japanese counterparts.[670]

Although current research has detected AIV in environmental sources, and experiments have demonstrated the potential for these viruses to remain infectious for long periods under field conditions, research into the extent of AIV environmental contamination is in its early stages. According to Stallknecht and Brown, new knowledge in this area will influence the ability to design and implement effective AIV prevention, control, or eradication strategies.[671]

Climate Change at the Qinghai-Tibet Plateau

As discussed, climate scientists report that the high altitude region of the Qinghai-Tibet Plateau is warming faster than anywhere on earth outside the poles.[672] One reason is that the plateau experiences powerful solar radiation due to both its low latitude and its high

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[668] Joseph P. Wood et al., "Environmental Persistence of a Highly Pathogenic Avian Influenza (H5N1) Virus," *Environmental Science & Technology* 44, no. 19 (October 2010): 7515–20.
[669] Yamamoto et al., "Avian Influenza Virus (H5N1) Replication in Feathers of Domestic Waterfowl."
[670] Hamblin, *Arming Mother Nature*, 43.
[671] Stallknecht and Brown, "Tenacity of Avian Influenza Viruses."
[672] Chen et al., "The Impacts of Climate Change and Human Activities on Biogeochemical Cycles on the Qinghai-Tibetan Plateau."

altitude.[673] The IPCC argued that a retreat of permafrost with rising global temperatures is virtually certain.[674] Melting such a vast region of permafrost could release huge amounts of methane into the environment, amplifying feedback loops for further warming. The Qinghai-Tibet Plateau has a regulating effect on the climate of the entire eastern hemisphere and plays a significant role in global climate change.

Zhao et al. reported that the Qinghai Lake region is experiencing the most significant climate warming on the plateau.[675] Thus, in a region with some of the most rapid climate change on earth, the microenvironment of Qinghai Lake is warming even faster. As a place at the center of the H5N1 spread to over sixty countries beginning in 2005, this may be significant. This dissertation argues that Qinghai is at the global crossroads of avian influenza and climate change.

Examining the historical ecology of the Qinghai-Tibet Plateau provides a broader picture of the accumulated climate effects.[676] The sediment record for Qinghai Lake revealed that change in solar activity is an important trigger for abrupt environmental changes in the region. Li et al. used sediment cores to obtain a record of the Asian monsoon over the past 18,000 years. Their data indicated that since the late glacial period, monsoons are subject to continual and often abrupt cyclic variations. For example, there was the sudden onset of a 2,000-year dry spell that ended 2,300 years ago. The sediment study also highlighted the cold, dry spells of the Dark Ages Cold Period and the Little Ice Age. Warmer and wetter eras included the Roman Warm Period and the Medieval Warm Period.[677] Dong et al. also

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[673] Xiaodong Liu and Baode Chen, "Climatic Warming in the Tibetan Plateau during Recent Decades," *International Journal of Climatology* 20, no. 14 (November 30, 2000): 1729–42.
[674] Stocker et al., *Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*, 92.
[675] Zhao et al., "Changes of Climate and Seasonally Frozen Ground over the Past 30 Years in Qinghai–Xizang (Tibetan) Plateau, China."
[676] Balée, *Advances in Historical Ecology*.
[677] Ji et al., "Palaeoclimatic Changes in the Qinghai Lake Area during the Last 18,000 Years."

conducted a paleoclimate study that suggested the last glacial period (late Pleistocene) terminated with an abrupt warming event about 15,000 years ago. Frequent fluctuations between warm and cold phases characterized the subsequent transition to the Holocene.[678]

Disease emergence is partially a function of shifts in the geographic ranges of pathogens and hosts.[679] Climate change would almost certainly influence the AIV transmission cycle, and directly affect virus survival outside the host. Harvell and McMichael, experts in ecology and evolutionary biology, argued that a warming climate could accelerate pathogen replication and increase animal host susceptibility to infections.[680] Paul Epstein, a Harvard physician who helped alert scientists to the dangers of climate warming on health, noted that the volatility of infectious diseases might be one of the earliest biological expressions of climate instability.[681]

In addition, diminishing biodiversity is a factor in the transmission of viruses from animal species to humans. Studies have shown that increased biodiversity reduces infection levels in natural populations.[682] A zoonosis might spill over from one species to another more readily within a disrupted, fragmented ecosystem than within an intact, diverse ecosystem.[683] For example, forest fragmentation in Africa likely played a role for the expansion of the bat–human interface, increasing the human risk for coming into contact with the Ebola virus.[684] Finding causal pathways, or even good correlational evidence, remain difficult.

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[678] Dong et al., "Impacts of Environmental Change and Human Activity on Microbial Ecosystems on the Tibetan Plateau, NW China."
[679] Scheiner, "The Intersection of the Sciences of Biogeography and Infectious Disease Ecology."
[680] Harvell, "Climate Warming and Disease Risks for Terrestrial and Marine Biota."; McMichael et al., "Climate Change and Human Health: Present and Future Risks."
[681] Epstein, "Climate Change and Infectious Disease: Stormy Weather Ahead?"
[682] Altizer, Harvell, and Friedle, "Rapid Evolutionary Dynamics and Disease Threats to Biodiversity"; Ostfeld, "Biodiversity Loss and the Rise of Zoonotic Pathogens."
[683] Ostfeld, "Biodiversity Loss and the Rise of Zoonotic Pathogens."
[684] Quammen, *Spillover,* 2012.

Tian et al. explored the association between past climate and H5N1 outbreaks attributed to migratory birds from 2005 to 2009. Their findings suggested that due to climate change, H5N1 risk might shift from South East Asia to the western part of the world. They concluded that, by the end of 2030, Europe would be at higher risk for H5N1 outbreaks in January and February.[685] Since the magnitude of climate change in the coming decades will exceed climatic changes in the recent past, the extent to which climate change drives the spread of disease by migrating birds is important.[686]

In the rapidly changing environment of Qinghai, monitoring of water chemistry, ultraviolet radiation, salinity, and temperature will be keys to understanding the impacts of future climate change.[687] At Qinghai Lake, all these factors are undergoing change to some extent.

Shrinking Wetlands

Observers from international health, wildlife, agriculture, and environmental agencies argued that the loss of wetlands around the world might force many wild birds onto alternative sites like rice paddy fields and into direct contact with domestic fowl.[688] Mixing wild migratory species and domestic flocks provides more opportunities for the emergence of novel strains of HPAI.[689] According to journalist Laurie Garrett, human development is the cause in the global shrinkage and fragmentation of wetlands.[690] Acknowledging this ecology,

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[685] Tian et al., "Climate Change Suggests a Shift of H5N1 Risk in Migratory Birds."
[686] Fuller et al., "The Ecology of Emerging Infectious Diseases in Migratory Birds."
[687] Dong et al., "Impacts of Environmental Change and Human Activity on Microbial Ecosystems on the Tibetan Plateau, NW China."
[688] Hepworth, "Avian Influenza and Wild Birds."
[689] Rapport, "Avian Influenza and the Environment: An Ecohealth Perspective."
[690] Laurie Garrett, personal communication at the *Hertog Global Strategy Initiative: The History and Future of Pandemic Threats and Global Public Health*, Columbia University, New York, August, 2011.

engineers detoured around wetlands and lakes during construction of the Qinghai-Tibet Railway. They built bridges rather than surface routes to minimize the impact.[691]

In summary, according to the Millennium Ecosystem Assessment, important drivers for ecosystem disruption include habitat change, climate change, loss of wetlands, invasive species, over-exploitation, and pollution.[692] Based on evidence presented in this chapter, the Qinghai-Tibet Plateau has most of these environmental drivers in play.

5.7 Qinghai: a Black Swan Event?

One of the questions posed at the outset of this dissertation was whether avian flu at Qinghai represented a black swan event according to Taleb's Theory of Black Swan Events.[693] A black swan event is a high profile, difficult-to-predict, and rare event in history. Taleb's thesis is that black swan events have much greater effect than we usually suppose, beyond the realm of normal expectations in history, science, finance and technology. One of Taleb's key arguments is that people are individually and collectively blind to uncertainty and unaware of the massive role of the rare event in historical affairs. Taleb emphasized that one cannot compute the probability of consequential rare events through scientific methods that rely on small probabilities. He deploys the tendency to claim, always after the fact, that a black swan event is predictable.

Historically, the "black swan" problem has its roots in Enlightenment era philosophy and epistemology. From the eighteenth century philosopher David Hume to the twentieth century philosopher Karl Popper, the black swan idea or problem has a long tenure in the

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[691] China through a Lens, "Ecological Protection on the Qinghai-Tibet Railway."
[692] Millennium Ecosystem Assessment, "Millennium Ecosystem Assessment," *Overview of the Millennium Ecosystem Assessment*, 2005.
[693] Taleb, *The Black Swan*, xxi–xxii.

history and philosophy of science. Popper asserted that the sight of one black swan could certify that not all swans are white, but the observation of a trillion white swans does not provide us with certifiable claims.[694] Unlike the earlier philosophical black swan problem, Taleb's theory of black swan events refers only to unexpected events of large magnitude and their dominant role in history.[695]

Taleb claimed that humans have a tendency to ignore silent evidence and look to confirm our pre-existing theories, rather than challenge them. Scientists do not often search for negative or disconfirming evidence, meaning what we see is not necessarily all that is there. In his classic article about multiple working hypotheses, Chamberlain argued over a century ago that there is an unconscious human drive to choose facts that fit a theory.[696] According to Taleb, history hides black swans from us and gives a mistaken idea about the odds of these events: this is the distortion of silent evidence.[697]

Another relevant concept from Taleb's theory is the "toxicity of knowledge" - too much information can be toxic when it inflates the confidence of an "expert" prediction. Taleb is dismissive of prediction and models explicitly in finance and econometrics, and implicitly almost everywhere.[698] As Taleb suggested, predictions are notorious for their inability to forecast financial downturns. This is also true of influenza pandemic predictions, as we shall see.[699]

The concept of black swan events has made its way into world affairs. For example, in 2012, the U.S. National Intelligence Council (NIC) released a report called "Global Trends

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[694] Karl Popper, *The Logic of Scientific Discovery* (Psychology Press, 2002).
[695] Taleb, *The Black Swan*, xxi.
[696] T. C. Chamberlin, "Studies for Students: The Method of Multiple Working Hypotheses," *The Journal of Geology* 5, no. 8 (November 1, 1897): 837–48.
[697] Taleb, *The Black Swan*, 50.
[698] Ibid., 138.
[699] See chapter six of this dissertation.

2030: Alternative Worlds" that anticipates the global shifts that will likely occur over the next two decades. The report conceded that the course of history includes abrupt and unexpected changes by outlier events – black swans – that are simply impossible to predict. As one of seven potential black swans that could cause the greatest disruptive impact in world affairs, the NIC report listed a severe pandemic as first on the list. The basis for this assessment is the unpredictability of exactly which pathogen will emerge, and when or where such a development will occur.[700] But if we can conceive of a severe pandemic, and have evidence of such in the past, is it truly a black swan event?

Thus far, few researchers have applied the theory of black swan events to the world of viruses, as this dissertation attempts to do. However, in 2015 public health experts noted that the West African Ebola epidemic has all the makings of a black swan event.[701] The theory of black swan events is making its way into the realm of global health as a way to characterize events that defy efforts at disease prediction.

Following the 2005 avian flu outbreaks at Qinghai, the number of countries with confirmed cases in wild birds or poultry increased from 16 to 55 countries within six months. Nine of these counties had human fatalities due to bird flu.[702] On the surface, it would appear that Qinghai qualifies as a black swan event for its unpredictability and high impact.

However, my conclusion, based on evidence presented in the dissertation, is that Qinghai was not a black swan event. While there is not a road map pointing to Qinghai phenomena as inevitable, there was ample evidence that viruses would erupt at the human-animal-environment interface in novel ways. First, influenza is a virus that causes disease in

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[700] National Intelligence Council (U.S.), "Global Trends 2030," xi.
[701] Michael T. Osterholm, Kristine A. Moore, and Lawrence O. Gostin, "Public Health in the Age of Ebola in West Africa," *JAMA Internal Medicine* 175, no. 1 (January 1, 2015): 7.
[702] FAO/OIE/WHO, *Influenza and Other Emerging Zoonotic Diseases at the Human-Animal Interface*.

humans and animals every year. Second, for well over one hundred years, avian influenza (formerly known as "fowl plague") had circulated among poultry farms at many locations worldwide. Third, scientists were aware since the 1970s that aquatic waterfowl are a natural host for all known influenza strains in humans. Finally, since 1997, scientists understood that avian flu could pass from poultry to humans, causing disease and death. However, some experts have argued argue that this history is not widely known and that they would not necessarily realize that farming wild and domestic birds together would pose a risk of avian influenza.[703]

5.8 Systematic Mapping of Qinghai Case Study Literature

This section analyzes the results of database searches for major themes from the Qinghai case study. Systematic mapping is a method to identify and describe the nature, volume, and characteristics of research relevant for the case study. This research uses a systematic mapping method as a form of historiography, a way of gathering and interpreting the source material with new findings and insights.

For this dissertation, systematic mapping addresses specific questions about the connections among specialized studies at Qinghai. For example, do studies about the emergence of avian flu at Qinghai Lake draw as much scientific interest as climate change or the Qinghai-Tibet Railroad? With over seven thousand articles produced from a search of "H5N1," what is the distribution pattern across different research categories? For the 111 results specific to "Qinghai" and "H5N1," how does that research align with different categories? What organizations are funding this research and what countries are involved?

[703] Bill Heinrich, personal communication, June 2013. Heinrich is the director of Interpretive Programs for the Center for the World Center for Birds of Prey in Boise, ID. He manages bird of prey release programs for the Peregrine Fund throughout the Western United States. Studying raptors in ten countries, he examined the avian influenza in raptors in Mongolia and the possible links to bar-headed geese.

The measures include the number of articles per research category, the number of countries participating per research category, and the number of citations per category.

In addition to describing the nature and extent of the literature, it is important to maintain a sense of perspective about the larger context in which events occur. From the point of view of a researcher looking at the potential for wild birds to transport a virus to over sixty countries, it is easy enough to see these events as significant in themselves. However, systematic mapping helps to understand these events within a larger context.

Methods and Limitations

The search terms for the Qinghai case study systematic map include Qinghai, H5N1, wild birds, waterfowl, virus, railway, avian influenza, ecohealth, climate change, ecology, and environment. I compare aggregate results of WoS database searches for the major themes and search terms. The study inclusion criteria include only those articles or other documents that are relevant to the Qinghai case study. This section of the chapter visualizes and analyzes the results.[704]

The Web of Science (WoS) tags publishes literature with the research categories at the journal level with over 250 different categories in the sciences, social sciences, and arts and humanities. WoS reviews each category yearly for changes and additions. The total number of citations for a particular paper or an aggregate research category is a metric that many researchers use to evaluate the impact of the research. One bias is that WoS categorizes certain journals under “multidisciplinary sciences," so all the articles covered in that journal, no matter the subject, are tagged "multidisciplinary sciences." This applies to

[704] Data from the searches are in Appendix 2.

the journals *Science*, *Nature*, and *PLOS One*. It is, however, possible to obtain a more fine-grained breakdown of research categories within the larger "multidisciplinary" category.

For most analyses, the vertical axis is the number of articles for each research category, the horizontal axis is the number of countries for each research category, and the size of the circle represents the relative number of aggregate citations for each research category. In this way, the circle size is a proxy for scientific impact and interest.

Qinghai-Tibet Plateau: Science and Technology

The first query relates to the science and technology research at the Qinghai-Tibet Plateau. The purpose is to obtain a broad view of how avian flu research compares with other research at the plateau.

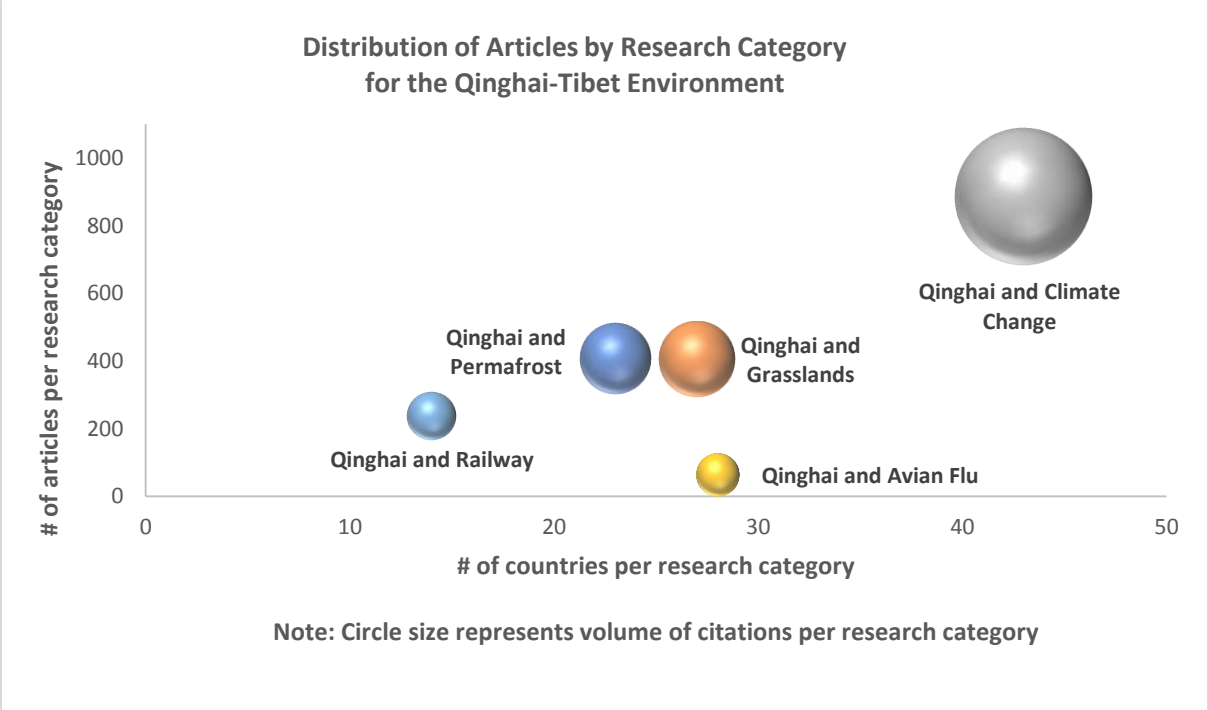

Figure 19. Qinghai-Tibet Plateau research categories, B. Canavan 2015.

Figure 19 reflects the distribution of 2,398 articles comparing seven searches related to science and technology studies on the Qinghai-Tibet Plateau. Topics with the most publications are climate change, permafrost, and grasslands. As illustrated, the publications for avian influenza at the plateau are rather small in number compared to these other environmental problems. Climate change on the plateau is drawing the most attention and, judging from the size of the circle, has the greatest number of article citations. The Qinghai-Tibet permafrost and grasslands draw similar research interest to each other, but far less than climate change. Comparing these environmental and technical issues to avian flu, they all have more publications and citations than the search on "Qinghai" and "Avian Flu." Scientific investigation relative to H5N1 in wild birds at Qinghai dates back to 2005. However, issues such as climate change and the QTR are also quite contemporary. The railway was opened for operation in 2006.

H5N1 avian influenza: the scientific engagement

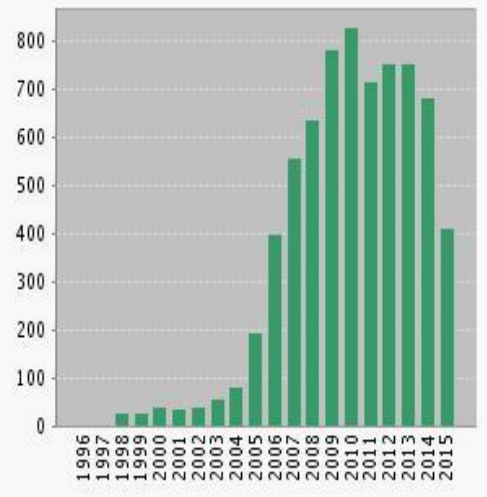

Figure 20. Distribution of H5N1 literature by year. B. Canavan.

The next query searched for publications with the topic "H5N1" without limits on place, date, or other subtopics. The purpose was to capture the volume of the H5N1 publications and characterize the nature of these publications. As illustrated in **Figure 20**, the search yielded 7,038 articles published from 1997 to 2015. After events at Qinghai in 2005, and the possibility that wild birds carried the virus to countries remote from the source, it is clear that interest in H5N1 surged.

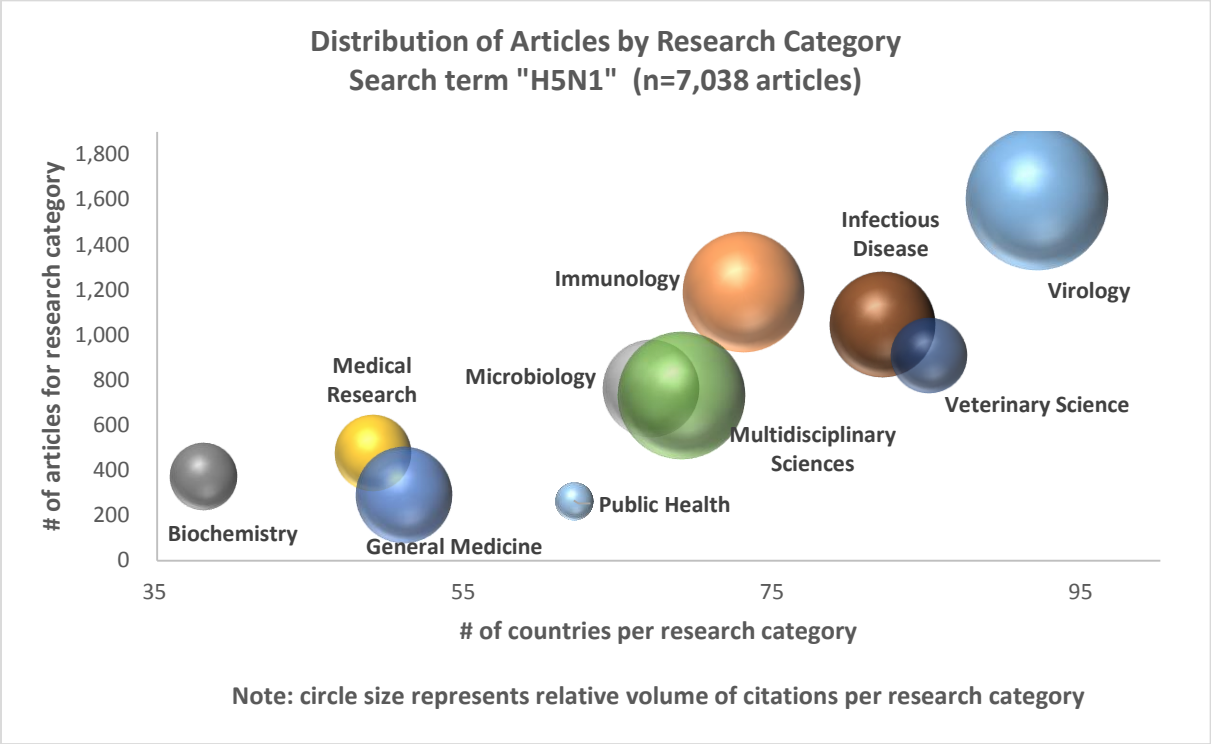

Figure 20. H5N1 by Research Category. B. Canavan, 2015

I then examined the distribution of this universe of 7,038 articles by research category. **Figure 20** illustrates the top twelve research categories for H5N1 publications: virology, immunology, infectious disease, veterinary science, microbiology, biochemistry, multidisciplinary sciences, experimental research, biotechnology, pharmacology, public health, and general medicine. Multidisciplinary categories further subdivide into veterinary sciences, virology, infectious disease, ecology, immunology, biodiversity, and environmental sciences. It is interesting to see that public health did not produce as many research publications as infectious disease or veterinary science. Most of the H5N1 research falls into the virology category.

The organizations participating in much of this H5N1 research represented in these seven thousand articles include the CDC, University of Hong Kong, St. Jude's Research

Hospital, Chinese Academy of Sciences, USDA, Erasmus University, NIH, University of Wisconsin, University of Tokyo, and the University of California System among others.

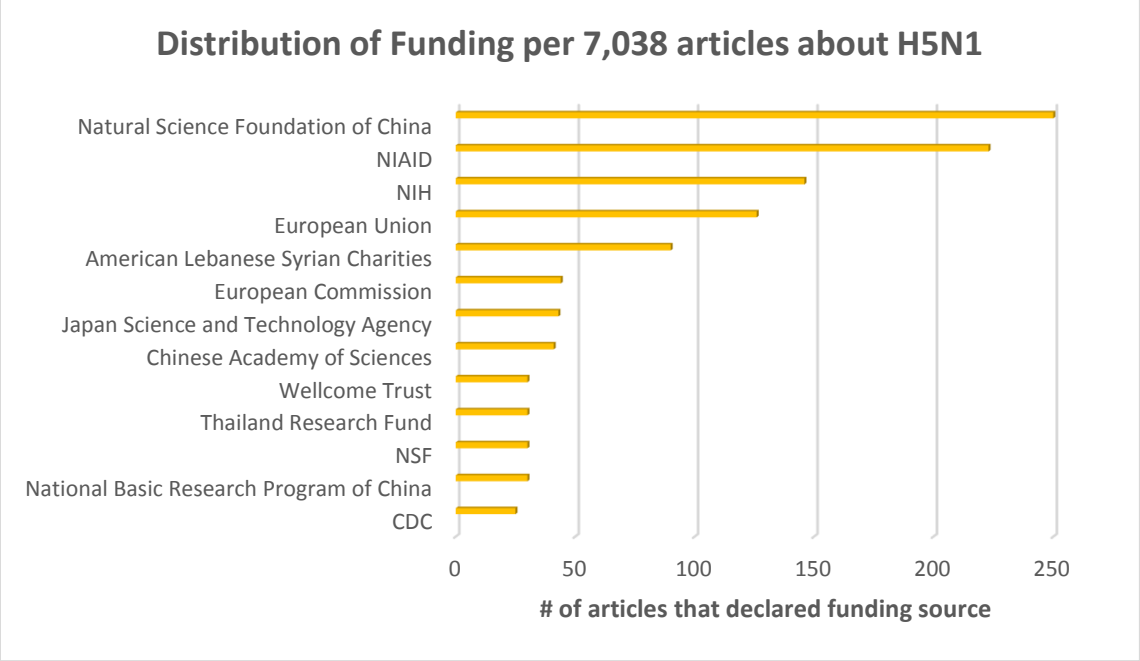

Figure 22. Funding for H5N1 Research. B. Canavan, 2015.

Figure 22 illustrates the funding for H5N1 research, when this information is available, limited to the top tier of funders. Many research projects have multiple funding agencies. The funders for much of the published H5N1 research are The National Science Foundation of China and the National Institute of Allergy and Infectious Diseases (NIAID) of the United States.

Avian Influenza and Qinghai: the Heart of the Matter

The next search focuses on themes and issues that are most specific to the case study. Completing a searching "H5N1" and "Qinghai" yields 111 publications.[705]

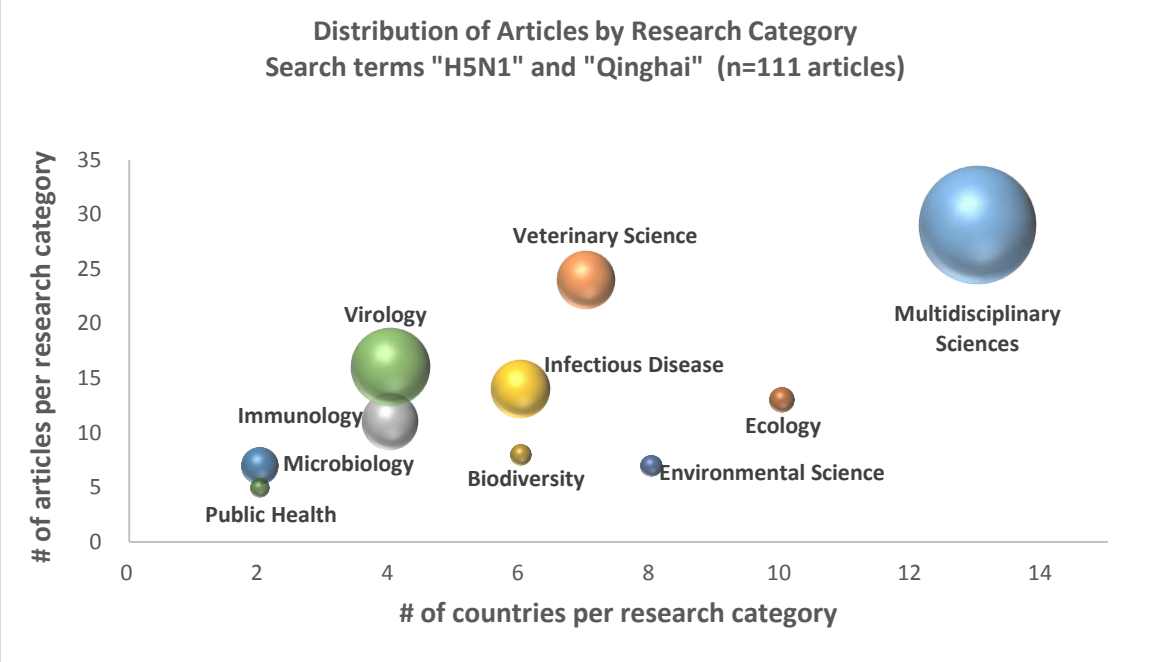

Figure 23. H5N1 and Qinghai by Research Category. B.Canavan, 2015.

Figure 23 illustrates the distribution of these articles across research categories. The category tags for these publications show many multidisciplinary categories, a reflection of both the journals and the science itself. About 75% of these publications were journal articles, 10% were proceedings review, and 7% were review articles. The journals publishing most of these articles were *Avian Diseases, PLOS One, Emerging Infectious Diseases, Ecohealth, PNAS, Science, Nature*, the *Journal of Wildlife Diseases*, as well as several virology publications.

[705] A list of these publications with citations is included in Appendix I. Sources are also part of the dissertation bibliography.

A related query examined the funding organizations for research studies in the core collection of 111 publications. **Figure 24 illustrates** that the FAO, USGS, and the Chinese Academy of Sciences funded many of the studies regarding Qinghai and H5N1. USGS participation was a minimal part of the 7,038 sources for H5N1 research, not limited to a particular place. However, their participation for Qinghai-H5N1 is substantial. FAO and USGS have unique skills and expertise for projects that involve wildlife, virology, and spatiotemporal mapping. Technology, and the experts who use it, opened up new ways to visualize and track avian influenza in the field.

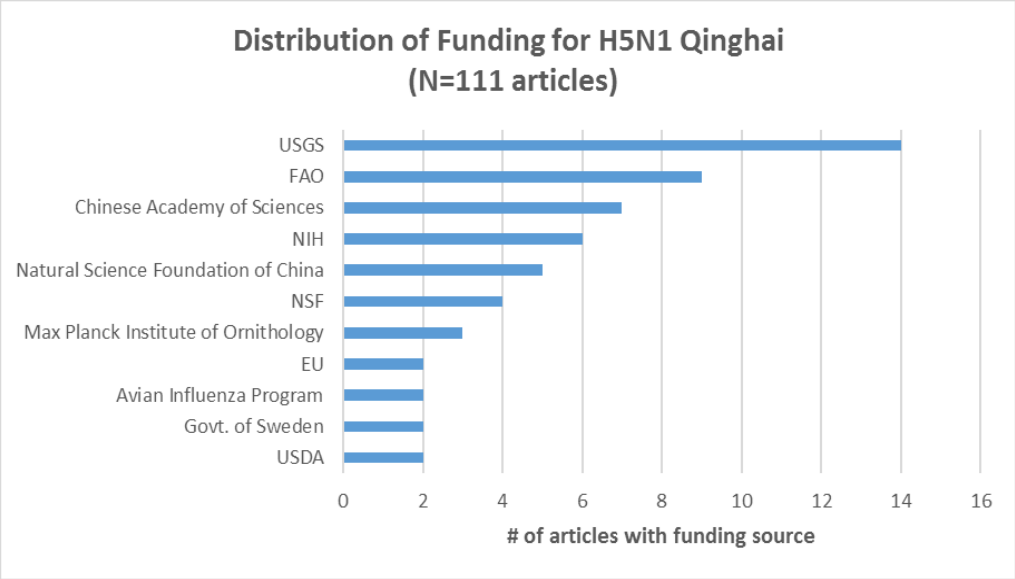

Figure 24. Funding for Qinghai-H5N1. B. Canavan, 2015

Figure 25 illustrates the volume of Qinghai-H5N1 research sources by country with at least two Qinghai-H5N1 research articles. Again, individual publications can have several countries participating and this is particularly true for Qinghai research.

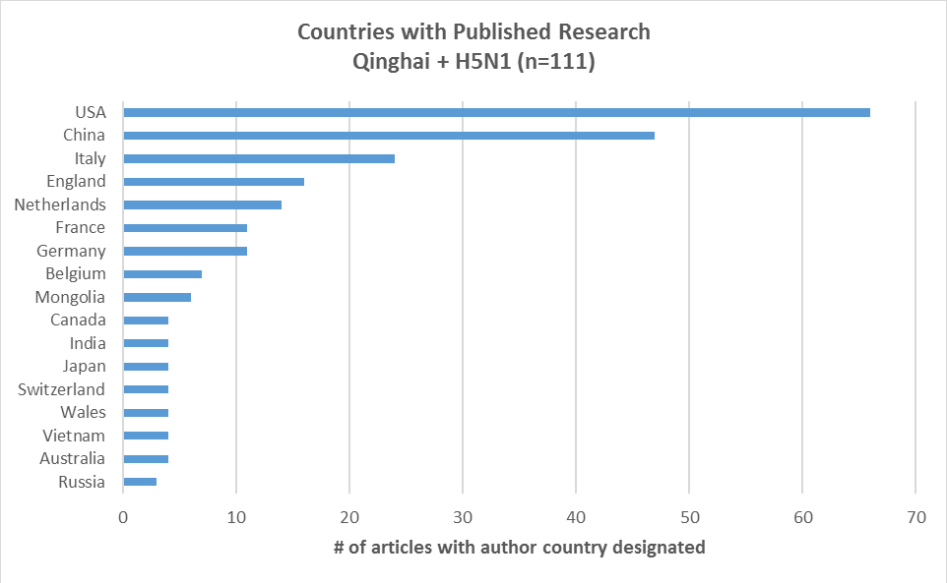

Figure 25. Counties with published research for Qinghai-H5N1. B. Canavan, 2015

In summary, based on the systematic mapping, climate change on the Qinghai-Tibet Plateau is drawing much more attention than avian influenza at the same location. Most of the highly cited publications for avian flu at Qinghai were from headline-grabbing events such as the first human death from bird flu in 1997 as well as the articles highlighting migrating birds as the vectors of disease. [706] One highly cited article from 2006 offered prediction forecasts for a H5N1 pandemic. About twenty articles referenced various interdisciplinary studies of bird flu at Qinghai. Researchers from the United States had the lion's share of research publications about Qinghai-H5N1, although China's contribution is quite substantial.

[706] See Appendix 2 for a complete list of articles, research categories, and citation counts.

Based on an analysis of the case study details as well as the systematic review of the literature, research for avian influenza at Qinghai reveals remarkable trans-disciplinary science. These interdisciplinary studies at Qinghai represent new ways of gaining knowledge about avian influenza based on field science. In particular, the collaboration among USGS and FAO researchers with their colleagues in China highlights a promising approach for investigating the avian influenza from an ecological perspective, one that crosses disciplinary boundaries. The USGS and the FAO have jointly led and even funded much of the research relevant to the emergence of H5N1 at Qinghai.[707] The authors cited most frequently were the lead researchers from FAO and USGS. These organizations have unique skills and expertise for projects that involve wildlife, virology, and spatiotemporal mapping. Not everyone would agree that spatiotemporal investigations get us any closer to halting the spread of avian flu disease. However, these research methods do shed light on "viral traffic," the ecological pathway for inter-species transmission of the avian flu virus.

It is notable that studies of H5N1 emerging at Qinghai are quite limited and specialized compared to research of avian influenza on a global scale. There were 7,048 articles about H5N1compared to only 111 about H5N1 and Qinghai. Climate change and Qinghai produced 887 results. Yet, this dissertation argues that there are connections between emergence of bird flu at Qinghai and environmental degradation, including climate change, on the plateau. A search for H5N1 and Qinghai and Climate produced no results in WoS but Google Scholar picked up about 20 articles. Thus, research directed at the dilemma of climate change in conjunction with avian flu appears to be small compared to the amount of research dedicated to other environmental issues on the plateau. The reason may be that

[707] Per personal communication with Scott Newman, most of the money for the eco-virological studies comes from USAID, the Emerging Pandemic Threats program. It is possible that these funds were then directed to FAO, USGS, and other agencies.

the bird flu events at Qinghai are recent. Alternatively, it is possible that the interdisciplinary paradigm remains rather limited for avian flu science.[708]

In addition, while scientists are aware of the geopolitical aspects of the Qinghai-Tibet Railway, there have been few, if any, prior studies linking the railway, the goose farms, and the avian flu outbreaks. The interdisciplinary science conducted at Qinghai and highlighted in this dissertation serves as a model for future investigations of the human-animal-environment interface.

[708] Mike Osborne, personal communication, Dec 2015.

Chapter Six: High Politics and Pandemic Predictions

This chapter traces how researchers learned to develop vaccines in order to prevent or at least mitigate the effects of human influenza and how they encountered the capricious nature of the flu virus. Vaccines, hailed as a twentieth century success story, have led to dramatic decline in the number of infectious disease cases in many countries. However, the path is challenging for scientists who want to get ahead of the ever-changing influenza virus. This history is of early vaccine production during World War II, efforts to understand and even predict influenza cycles, and current controversies about avian flu research. Although the world has not yet seen an avian influenza with sustained transmission among humans, bird flu is the quintessential virus to which humans have little or no prior immunity.

The first section (Early Influenza Research and Vaccine Trials) examines collaboration during the 1930s and 1940s among leaders in influenza research at the Rockefeller International Health Division (IHD) in New York and at the Medical Research Council (MRC) in Britain. From 1935-1960, influenza was the most extensively studied virus in the U.S. affecting humans [709] The driving forces for this "war on influenza" were fear of another pandemic and optimism for the prospects of disease prevention through vaccines.[710] This history of influenza collaboration draws from archival sources at the Rockefeller Archive Center (RAC) among other sources.

The second section (History of Predictive Theories for Pandemic Flu) examines how scientists came to perceive cyclical patterns in the characteristics and timing of influenza

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[709] John M. Eyler, "De Kruif's Boast: Vaccine Trials and the Construction of a Virus," *Bulletin of the History of Medicine* 80, no. 3 (2006), 413.

[710] Cooter, "Of War and Epidemics." According to Cooter, the coupling of wars and epidemics in the western world was a late-Victorian phenomenon driven by military medical interests that includes the metaphor of war on disease.

pandemics. Then, I examine how scientists applied these predictive theories of influenza to the swine flu of 1976. Scientific and public uncertainty about influenza clashed within the context of American politics (Swine Flu 1976: Applying Predictive Theories). My interpretations draw from material at the Ford Presidential Library, the U.S. National Archives, Congressional testimony, as well as from interviews with individuals who were present during this critical juncture in American public health and politics.

The final section (Avian Flu: Research Controversies) explores the unsettled landscape of avian influenza experiments as well as the scientific and public understanding of a virus at the human-animal-environment interface.

6.1 Early Influenza Research and Vaccine Trials

Pandemic of 1918: The Demon of Origins

The 1918-19 influenza pandemic was truly a nightmare disease and one of the most dramatic events in medical history. Historian of medicine D.K. Patterson argued that it was the most devastating infectious disease outbreak since the plague swept through Europe and Asia in the fourteenth century.[711] Based on historical epidemiology, global deaths from the 1918 pandemic were between 50 and 100 million.[712] Understandably, every flu virus since that time has been suspect for its potential to cause the next catastrophic influenza pandemic.[713] Following the 1918 pandemic, the United States, Britain, Australia, and Russia

[711] Patterson, *Pandemic Influenza 1700-1900.*
[712] Niall P. A. S. Johnson and Juergen Mueller, "Updating the Accounts: Global Mortality of the 1918-1920 'Spanish' Influenza Pandemic," *Bulletin of the History of Medicine* 76, no. 1 (2002): 105–15; Jeffery K. Taubenberger and David M. Morens, "1918 Influenza: The Mother of All Pandemics," *Emerging Infectious Disease* 12, no. 1 (January 2006).; Stephen Morse, personal communication, 2011-2012.
[713] Taubenberger and Morens, "1918 Influenza: The Mother of All Pandemics."

greatly escalated their influenza research. The focus here is on the American (IHD) and British (MRC) influenza research collaboration during the 1930s and 1940s.

After the 1918 pandemic, it would be decades before any scientist could see an influenza virus under an electron microscope and begin to visualize its complexities. Although no one was quite certain about the cause of influenza, in 1920 British influenza researcher C.H. Andrewes wrote, "Evidence for a filter-passing virus as the primary cause for the disease is suggestive, but at present a final verdict cannot be given."[714] According to historian Michael Bresalier, the challenges of pandemics created new opportunities for both MRC and IHD and both organizations embraced these prospects for new research fields of investigation.[715] Yet, the nature of the influenza virus remained an open question well into the 1920s. There were unanswered questions about influenza origins and cycles and how to reduce the terrible human toll of the disease. Researchers at IHD noted it would require extensive investigation to control influenza.[716] It was clear that control over influenza was what they wanted to achieve.

With the study of a swine influenza epidemic in 1928-29 in Iowa, a new narrative about flu emerged. Richard Shope, a Rockefeller Institute researcher in animal pathology, isolated an influenza virus from pigs in 1930 and demonstrated that this filterable virus was the cause of the swine disease.[717] Regardless of what scientists would ultimately discover about animals and influenza viruses, Shope had shattered the traditional dogma that influenza was strictly a human disease.[718] He was the first to propose that swine influenza was the

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[714] Andrewes, "The Bacteriology of Influenza," 125.
[715] Michael Bresalier, "Fighting Flu: Military Pathology, Vaccines, and the Conflicted Identity of the 1918–19 Pandemic in Britain," *Journal of the History of Medicine and Allied Sciences* 68, no. 1 (January 1, 2013): 87–128.
[716] "The Study of Influenza", December, 1937, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC
[717] Shope, "Swine Influenza."
[718] Crosby, *America's Forgotten Pandemic*, 2003, 303.

surviving prototype of the 1918 pandemic virus based on his experimental results.[719] Throughout the 1930s, curiosity and questions about the possible link between swine and human flu persisted. Scientists at IHD regularly received inquiries from public health officials about the correlation between the presence of swine flu and human flu.[720] At that time, IHD influenza research Thomas Francis suggested that scientists really did not know if the flu virus was of human origin passed to animals or of animal origin.[721]

Shope's discovery encouraged the work of virus researchers at MRC who, in turn, isolated an influenza virus from humans in 1933.[722] Smith, Andrewes, and Laidlaw conducted immunological tests on Britain's survivors of the 1918 pandemic and determined that the disease had been due to the swine influenza virus.[723] In 1934, Francis obtained influenza viral specimens from a flu epidemic in Puerto Rico.[724] He was the first American scientist to isolate a human influenza virus.

The Puerto Rico flu strain reproduced well in eggs, allowing for the growth of huge quantities of virus.[725] Earnest Goodpasture's technique of using chick embryos as a medium for growing viruses was much less expensive for the culture of viruses compared to the use of animals. Using this egg-based method, Max Theiler at IHD developed an effective vaccine for yellow fever that was available in 1935.

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[719] Shope, "The Incidence of Neutralizing Antibodies for Swine Influenza Virus in the Sera of Human Beings of Different Ages."; Taubenberger and Morens, "Influenza Revisited."
[720] Sippy to Francis, April 21, 1936, Folder 6, Box 50, Series 4, RG 5, IHD Records, FA115, RF, RAC
[721] Francis to Sippy, May 29, 1936, Folder 6, Box 50, Series 4, RG 5, IHD Records, FA115, RF, RAC
[722] Wilson Smith, C.H. Andrewes, and P.P. Laidlaw, "A Virus Obtained from Influenza Patients," *The Lancet* 222, no. 5732 (July 1933): 66–68.
[723] Peyton Rous, 1957, "Presentation of the Kober Medal to Richard Shope," p. 31, Folder 2, Biographical General 1935-1965, Box 1, FA199, Richard E. Shope Papers, RU, RAC
[724] Francis, "Transmission of Influenza by a Filterable Virus."
[725] Claude Hannoun, "The Evolving History of Influenza Viruses and Influenza Vaccines," *Expert Rev Vaccines.* 12, no. 9 (2013): 1085–94.

Vaccine development typically lagged many years, sometimes decades, after initial pathogen isolation. In the case of influenza, the interval from virus isolation in 1933 to trial vaccine was only about three years. Beginning in 1936, an influenza vaccine was ready to test. This is the focus of the next section.[726]

In summary, since the 1933 isolation of a human influenza virus, scientists have invested considerable resources in a steady flow of influenza viral strains across institutions.[727] Historian John Eyler argued that from 1935 to1960 influenza was the "most extensively studied virus in the U.S. affecting humans. Polio was a close second."[728]

Vaccine: Trials and Tribulations

Influenza investigators at IHD and MRC had reasons to be optimistic in the mid-1930s regarding the prospects for developing a flu vaccine. Researchers had isolated the human flu virus and developed animal models for vaccine experimentation.[729] Although IHD and MRC independently developed vaccine development, American scientists had more resources, first through IHD and, by 1940, through the U.S. Army Commission.[730]

IHD and MRC had two interrelated strategies – to identify the causative agent for flu and to produce vaccines rapidly. I turn to the particulars of how IHD and MRC researchers conducted their studies and how they negotiated the uncertain landscape of vaccine development. Correspondence between Frank Horsfall (IHD) and C.H. Andrewes (MRC), both leaders in influenza research in their respective institutions, reflects the central role for

[726] Bonanni and Santos, "Vaccine Evolution." Paolo Bonanni and José Ignacio Santos, "Vaccine Evolution," *Perspectives in Vaccinology* 1, no. 1 (August 2011): 1–24.
[727] Caduff, "Anticipations of Biosecurity."
[728] Eyler, "De Kruif's Boast", 413.
[729] Kilbourne, "A Race with Evolution: A History of Influenza Vaccines."
[730] Hannoun, "The Evolving History of Influenza Viruses and Influenza Vaccines."

IHD and MRC in global flu research and vaccine production prior to the creation of the World Health Organization in the late 1940s.

Replacing Thomas Francis as the leader of influenza research at IHD, Frank Horsfall led an elaborate study of influenza from the mid-1930s that included the study of immune reactions of animals and humans to influenza viruses.[731] He had a large technical staff, ample laboratory space, financial support, and a staff that was equipped to investigate epidemic problems on an international scale.[732] For these purposes, experimental animals were central to virus research.

During the 1930s, ferrets were the preferred animal for flu transmission studies because ferrets and humans share similar lung physiology and mimic the conditions under which a flu virus could transmit among mammals.[733] Researchers passed ferret throat washings through a filter, inoculated into the ferrets and then used to inoculate other ferrets. One investigator at IHD wrote that there was a great shortage of ferrets, making flu experiments more difficult.[734] Sometimes, they had to resort to using different animals, such as mongooses. Horsfall noted that to inject a mongoose intracerebrally takes at least three persons and "enough ether to kill ten ferrets." It was, he added, "difficult to kill them at all."[735] By 1934, both IHD and MRC were able to transmit flu viruses among ferrets and then pass the viruses to mice through intranasal inoculations. Thereafter, researchers maintained flu viruses by continuous animal passage in mice.[736]

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[731] Thomas Francis had an appointment at New York University for several years before his permanent career move to the University of Michigan.
[732] George K. Hirst, "Frank Lappin Horsfall, Jr., A Biographical Memoir," Memoir (Washington D.C.: National Academy of Sciences, 1979), 238.
[733] The ferret model is well suited for studying both the pathogenicity and transmissibility of human and avian influenza viruses.
[734] Bauer to Boyd, March 10, 1936, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC
[735] Horsfall to Shope, June 28, 1939, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC
[736] Eyler, "De Kruif's Boast."

IHD and the U.S.D.A. funded the first influenza vaccine experiments with humans in 1935-36, trials led by Joseph Stokes from the University of Pennsylvania. This vaccine trial included 800 people at the New Jersey Home for the Feeble-minded. Testing live flu vaccines, Stokes measured the antibody response of 248 people and 11,000 mice. Researchers used mouse lungs to grow the vaccine containing rodent protein that, in turn, caused reactions in some vaccinated patients.[737]

In 1936-37, there was a much larger trial involving 5,000 people from five institutions, again funded through IHD. By this time, Stokes was able to use chick embryo tissue to culture the vaccine.[738] Comparing vaccinated individuals from control groups, the reduction of febrile illness in the vaccinated group was 35%-65%. This vaccine experience was more convincing to researchers.[739] Thus, by 1936 investigators had evidence that human immunity would occur following a subcutaneous injection of that agent that included the influenza virus.[740]

Optimism among flu researchers soon spilled over to communications with the public. An article by microbe expert and author Paul de Kruif, a former Rockefeller researcher, appeared in *Reader's Digest* in 1936, in which he boasted that medical science was "about to conquer influenza."[741] Frederick Russell, a founder of IHD, expressed confidence that answers to most of the influenza questions were at hand. During a U.S. flu epidemic in 1937, Russell did not want to let the "opportunity be lost" to make vaccine.[742]

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[737] Stokes et al., "Results of immunization by means of active virus of human influenza"; Eyler, "De Kruif's Boast."
[738] "The Study of Influenza", December, 1937, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC
[739] Davenport, "The Search for the Ideal Influenza Vaccine."
[740] Eyler, "De Kruif's Boast," 410.
[741] Paul de Kruif, "The Flu-Trappers," *Reader's Digest*, February 1936.
[742] Russell to Bauer, February 15, 1937, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

Funded by the Metropolitan Life Insurance Company, a five-year study commenced in 1936 at Letchworth Village near New York City, a state mental institution with 3,500 residents.[743] The intent of the latter trial was to study the relationship between antibody response and the incidence of disease. While vaccines tested on animals in the lab were satisfactory, the human trials were inconclusive and highly variable in both design and method. The results of the Letchworth Village Trial revealed that some persons with high antibody titers got sick with influenza and, according to Eyler, there seemed to be no identified titer that guaranteed protection.[744] Yet, through these trials, vaccine was produced, showed some promise of success in humans, and became available in large quantities for researchers.

Yet, there were critical gaps in understanding influenza viruses. IHD and MRC investigators assumed that there were a limited number of potential flu strains, and that strains were identical or very closely related. By the late 1930s, it became clear that flu strains from the same epidemic were very similar, regardless of location, when compared to strains from the same place in different years.[745] This suggested for the first time that influenza viruses were shifting and mutable. By 1937, both Burnet and Andrewes confirmed that there was antigenic variation among human flu strains.[746]

Despite collaborative investigations and public optimism, influenza in the 1930s remained vaguely defined. It was easy to confuse its clinical picture with closely related respiratory illnesses. Investigators did not fully understand the extent and duration of

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[743] Siegel and Muuckenfuss, "A study in active immunization against epidemic influenza and pneumococcus pneumonia at Letchworth Village."
[744] Eyler, "De Kruif's Boast," 422.
[745] Magill and Francis, "Antigenic Differences in Strains of Epidemic Influenza Virus."; Eyler, "De Kruif's Boast," 429
[746] F. M. Davenport, "The Search for the Ideal Influenza Vaccine," *Postgraduate Medical Journal* 55, no. 640 (February 1979): 78–86.

immunity produced either by influenza viruses or by vaccines.[747] There was confusion about the transmission of influenza across species. For example, when Horsfall discovered a flu subtype in a mouse, Andrewes saw no reason why there should not be a mouse flu related to human flu given the correlation of swine and human flus. Andrewes, however, noted that a "mouse flu" designation would make "life a lot more difficult."[748] Horsfall concurred that a "mouse flu" would only further complicate the influenza picture.[749] They determined to define and adopt influenza nomenclature that was more precise, one that would eliminate the confusion of having human and animal influenza lumped together.

By the late 1930s, Francis identified that flu exists in multiple types (A, B, C), thus allowing for easier identification of a flu strain.[750] In 1940, officials at IHD and MRC agreed upon a standard nomenclature and invited others in the field of influenza research to follow suit. Their joint report defined clinical influenza as an "etiologically indefinite symptom complex resembling influenza," leaving the door open to rather flexible interpretations in the future.[751] This report referenced the definitive sources for influenza research and experiments, namely publications by Horsfall, Andrewes and other IHD and MRC researchers.[752] The authors also recommended that IHD and MRC certify any new flu viruses prior to any official "christening" in future scientific reports. This nomenclature report included an important caveat: "Influenza-like diseases attacking primarily animals other than

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[747] "The Study of Influenza", December, 1937, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC
[748] Andrewes to Horsfall, March 25, 1939, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC
[749] Horsfall to Andrewes, April 4, 1939, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC
[750] Dehner, *Influenza*, 64.
[751] "The Nomenclature of Influenza", 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC
[752] Stuart-Harris, Smith, and Andrewes, "The Influenza Epidemic of January-March, 1939"; Herbert. Stuart-Harris, Andrewes, and Smith, *A Study of Epidemic Influenza, with Special Reference to the 1936-7 Epidemic*; Francis et al., "Studies with Human Influenza Virus during the Influenza Epidemic of 1936-37."; Francis, "Epidemic Influenza: Studies in Clinical Epidemiology," 915; Horsfall, Hahn, and Rickard, "Four Recent Influenza Epidemics: An Experimental Study."

man (e.g. swine flu) should be excluded from the [influenza] A, B, C terminology."[753] Thus, OHD and MRC omitted animals from the first official nomenclature standards for influenza.

As the war escalated during 1940, Andrewes remarked to Horsfall, "The war is so loathsome that we try not to think about it and just work like the devil."[754] A few weeks later, Andrewes confidentially asked Horsfall if it were possible to get influenza vaccine made in the U.S. on a large-scale and sent to England for a massive immunization effort. American corporations had asked MRC what they could do to help with medical projects during the war. Andrewes did not want to respond until he cleared the potential vaccine production with IHD. Andrewes asked Horsfall about the stability of the vaccine and whether it would lose its potency; the toxicity of the vaccine and the likelihood of "unpleasant reactions"; and, finally, whether the large-scale manufacturing would be feasible.[755]

Horsfall replied that the efficacy of the vaccine was fundamentally unknown.[756] Horsfall feared that such an experiment would not approximate conditions of naturally occurring influenza disease. Mass production, if it were even feasible, would require a large plant staffed with doctors, trained technicians, and special equipment for the freezing and drying of large quantities of vaccine. Clearly, in 1940, the US vaccine development was not ready for a wartime mass vaccination effort.

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[753] Horsfall et al., "The Nomenclature of Influenza."
[754] Andrewes to Horsfall, June 24, 1940, Folder 8, C. H. Andrewes 1937-1948, Box 1, Series 4, Rockefeller Institute Virus Labs, RG 5, FA115, RF, RAC.
[755] Andrewes to Horsfall (confidential), July 2, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC
[756] Horsfall to Andrewes, July 16, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

Despite these cautions and lack of understanding from both sides, Horsfall offered an encouraging prospect to Andrewes.

> Should you wish to gamble on the possibility that the new vaccine will be effective…I think an official request for it would be considered favorably here.[757]

Perhaps Horsfall was aware that the U.S. Army would soon establish an Armed Forces Epidemiology Board (AFEB) for the control of influenza and other epidemic diseases, even before the U.S. entered the war. In any case, with the spread of a widespread epidemic for 1940-41, there was little time to test vaccines.[758]

Horsfall's laboratory at IHD developed a vaccine to use in the third human vaccine trial during the 1940-41 flu epidemic. This "complex vaccine" contained several influenza antigens rather than just one. It was the first trial to use IHD-produced vaccine. The trial was at fifteen state mental institutions in Florida and Alabama with about sixteen thousand patients and included an unvaccinated control group.[759] Horsfall mentioned to Andrewes how fortunate the United States was to have access to a number of penal institutions and asylums.[760] Horsfall provided an optimistic interview to *Colliers* and *Atlantic Monthly* about the potential of his new vaccine.[761] Horsfall's lab produced one million doses for military use in Britain.[762] He assured Andrewes that up to 250,000 doses of vaccine per month were forthcoming.[763]

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[757] Ibid.
[758] Hirst, "Frank Lappin Horsfall, Jr., A Biographical Memoir," 241.
[759] Horsfall, et al., "Studies on the Efficacy of a Complex Vaccine against Influenza A."
[760] Horsfall to Andrewes, May 9, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC
[761] Eyler, "De Kruif's Boast," 424.
[762] Horsfall to Andrewes, September 14, 1940, Folder 536, Box 54, Series 100, RG 1, RF, RAC
[763] Andrewes to Horsfall, September 26, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

A bit more cautious, Andrewes wrote to Horsfall,

> You probably feel that we are in altogether too much in a hurry to use large quantities of vaccine before knowing if it is any good…normally we should not, as scientific men, want to hurry like this, but if we get an epidemic or pandemic this winter we simply have to act now or never even if we are gambling.[764]

Andrewes' communication was an early indication of a concept that would endure in public health - it was better to gamble with vaccine than gamble with lives by being unprepared for a pandemic.

Within a few months, the situation did not look so promising. British authorities balked at permitting use of American vaccine containing "living virus matter."[765] Andrewes wrote to Horsfall, "When one gets to hundreds of thousands, the chance of some improbable event…ceases to be negligible."[766] In other words, the risk-benefit of the vaccines became a consideration in the gamble with vaccine versus the potential of illness or death from a pandemic. None of the million doses of vaccine IHD sent to MRC made it into the arms of British soldiers.

Horsfall's 1940-41 vaccine trials were inconclusive. An IHD director reported that the results were unsatisfactory to those at the Rockefeller Foundation.[767] While there were no observed adverse reactions to the vaccinations, George Hirst of IHD, Horsfall's boss, was

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[764] Andrewes to Horsfall, August 7, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC
[765] Andrewes to Horsfall (Western Union Cable), December 3, 1940, Folder 8, Box 1, Series 4, RG5, IHD Records, FA115, RF, RAC. Live-attenuated vaccines are more complicated to use than other types of vaccines and a number of problems were identified: instability of the attenuation, risk of recombination with wild strains, pre-existing immunity preventing infection by the vaccine strain and instability of the live preparations. However, inactivated vaccine required larger quantities of the antigen in order to induce immunity.
[766] Andrewes to Horsfall, December 10, 1940, Folder 9, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC
[767] Bauer to Francis, October 24, 1941, Folder 123, Box 12, Series 4, RG 5, IHD Records, FA115, RF, RAC

convinced that attempting to test vaccines in mental institutions was "not a good thing." He cautioned there was insufficient staff to follow-up on patients. Thereafter, IHD switched to testing vaccines in penal institutions only, as there were a greater number of individuals for follow-up with a population that was well under their control.[768] Behind the scenes, Horsfall found his immunological studies rather discouraging at times. The multiplicity of viral strains with differing characteristics that turned up in his laboratory seemed to diminish the hope of controlling influenza by vaccines.[769]

To control influenza during the war in the United States, in 1941 the Army Epidemiology Board created a "Commission on Influenza," headed by Thomas Francis who was then at the University of Michigan. Francis took the lead to develop vaccine for the Army. His team grew flu virus in fertilized chicken embryos, killing the virus, and concentrating the material.[770]

In 1943-44, a year with an active flu season, Francis mounted a large-scale test with Army soldiers. This field trial in the United States successfully demonstrated a reduction in influenza among those vaccinated.[771] Assessing results of vaccinations from both vaccinated and unvaccinated individuals before and after the flu epidemic showed a reduction of about fifty percent of influenza incidence among vaccinated persons.[772] Although evidence

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[768] Hirst to Francis, November 13, 1942, Folder 123, Box 12, Series 4, RG 5, IHD Records, FA115, RF, RAC
[769] George W. Corner, *History of the Rockefeller Institute 1901-1953 Origins and Grown* (New York: Rockefeller Institute Press, 1953), 467.
[770] Dehner, *Influenza*, 68.
[771] Francis, "The Development of the 1943 Vaccination Study of the Commission on Influenza."
[772] Hirst to Francis, April 3, 1944, "Activities during the past year in connection with the Influenza Commission", Folder 166, Box 15, Series 4, RG 5, IHD Records, FA115, RF, RAC

indicated that flu vaccine offered good protection, the duration of immunity remained unclear.[773]

Production of the Commission's vaccine went into high gear, and in 1945, the U.S. military vaccinated all personnel. This was a successful effort in that soldiers who received the vaccine got the flu at much lower rates than the unvaccinated soldiers did.[774] There was a sense of relief, an overall satisfaction that the researchers had found a way to protect their nations' soldiers. Soon, the vaccine would be available to the general population. Francis quietly considered shifting the focus of his research to cancer, as he felt that all the influenza problems were now resolved.[775]

In summary, in the 1930s and 1940s, influenza researchers came to understand how the mutable flu virus would challenge their vaccine efforts. If the 1930s initiated vaccine development, the 1940s were a period during which it became clear that no easy victory was in sight. Researchers at IHD and MRC took on the challenge and certainly advanced the knowledge of influenza. The essential dilemma was to project what the virus might become without knowing its precise path.

Post War and the WHO: To Catch a Virus

An epidemic of influenza appeared in the US in1947, striking both the vaccinated and unvaccinated.[776] Despite success in producing good results in field trials in 1943 and the Army vaccine trial of 1945, the same vaccine failed to give protection against influenza in

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[773] Hirst to Appleget, December 20, 1944, Folder 361, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC; "Vaccination Study of Prison Groups during Epidemic of Influenza A 1943-1944", March 5, 1945, Folder 122, Box 12, Series 4, RG 5, IHD Records, FA115, RF, RAC

[774] Hirst to Appleget, December 20, 1944, Folder 361, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

[775] Francis to Bauer, March 7, 1944, Folder 122, Box 12, Series 4, RG 5, IHD Records, FA155, RF, RAC; Eyler, "De Kruif's Boast," 424.

[776] Francis, "Vaccination against Influenza"; Dehner, *Influenza*, 69.

1947.[777] IHD reported, "Last year's vaccinations against influenza seemed to give little or no results due to the occurrence of an antigenically different strain of virus."[778] It appeared that the virus had changed and the same vaccine that worked so well in 1945 did not protect citizens in 1947.

Thus, by the late 1940s, new experience with vaccine trials had shattered the model of the flu virus as a rather static agent. British and Australian researchers, including Andrewes and M.F. Burnet, agreed.[779] Burnet argued that flu survives on antigenic novelty and the prospects for a vaccine seemed dim. Richard Taylor, Director of the Rockefeller's New York Laboratories, suggested that antigen change in the flu virus is "continued, unlimited, and unpredictable."[780] Controversies ensued about the reasons for the 1947 vaccine failure. According to Eyler, American investigators disagreed with their British colleagues.[781] The nature of the disagreement was whether researchers could produce a vaccine that would be protective against multiple strains of influenza with one annual immunization. The question revolved around the mutability of the influenza virus.

Francis, then at the University of Michigan, and his successor, Fred Davenport, were uneasy with the hopeless outlook for creating vaccine to protect against a flu virus. Francis was convinced that all flu viruses had the same antigenic components and that a vaccine could include all of those components.[782]

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[777] T van Helvoort, "A Bacteriological Paradigm in Influenza Research in the First Half of the Twentieth Century," *History and Philosophy of the Life Sciences* 15, no. 1 (1993): 3–21.
[778] Taylor to all Personnel, December 10, 1947, Folder 351, Box 32, Series 4, RG 5, IHD Records, FA115, RF, RAC
[779] Burnet, "Some Biological Implications of Studies on Influenza Viruses."
[780] Taylor, "Studies on Survival of Influenza Virus Between Epidemics and Antigenic Variants of the Virus."
[781] Eyler, "De Kruif's Boast," 431.
[782] Francis, "The Current Status of the Control of Influenza."

Viewpoints about the nature of the influenza virus diverged further during the late 1940s post-war consolidation of influenza research through the World Health Organization (WHO).[783] The WHO created the World Influenza Centre in London in 1947, with nearly 100 bases around the world, with an allocation of three thousand dollars and Andrewes as its Director.[784] Andrewes was not overly optimistic about either the prospects for controlling influenza or vaccine production. He cautioned that influenza was likely to produce mutant strains against which existing vaccines would not be effective. To avert another 1918 pandemic, Andrewes urged a greater understanding of the epidemiology of influenza, its mutations, and their spread.[785]

There was much work to accomplish. Investigators had not yet compared flu virus strains from year to year, nor had they compared co-occurring strains from different countries in the same year. Andrewes wanted to collect strains from epidemics occurring at different times and places, in hopes of completing a picture of the epidemiological behavior of influenza.[786] Andrewes called for international collaboration to avoid economic loss from influenza and he made three suggestions for achieving this: collect and distribute information, coordinate lab work, and train lab workers from a number of regional laboratories. Through diligent observation and experiments, Andrewes suggested it might eventually be possible to produce vaccine in time to protect countries not yet exposed to the viruses.[787]

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[783] WHO/Influenza/16, "Expert Committee on Influenza."
[784] The 2015 value is about $37,000. This is a puny amount for such a major undertaking.
[785] Gautier (WHO) to Taylor, September 15, 1947, Folder 9, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC.
[786] Ibid., p. 2-3
[787] Andrewes, World Health Organization – Interim Committee, August 13, 1947, "International Collaboration in the Influenza Field", Folder 9, Box 1, Series 4, RG 5, IHD Records FA115, RF, RAC

The World Health Organization took over the global influenza research from IHD and MRC in 1948, mostly funded during its first decade by the United States. The WHO continued to worry about the recurrence of a 1918-like flu pandemic and the need to detect changes in a circulating flu virus at the earliest possible moment. The goal was to identify a new viral strain as soon as it appeared anywhere in the world in order to develop a protective vaccine. In this way, identification of a potential pandemic flu virus was coordinated with the vaccine manufacturing cycle.[788]

In 1952, the WHO formed an "Expert Committee on Influenza." The expert committee had a specific charge to watch for shifts in circulating flu viruses in order to make accurate forecasts of the times and places of epidemics.[789] Committee participants, including Andrewes, attempted to isolate and catalog all the influenza viruses in circulation, a daunting task that helped to uncover influenza strains in a wide range of species. Concern for the origins of human pandemic influenza led the WHO to encourage and coordinate work on animal influenza virus ecology in the 1950s.[790] This group soon found many influenza subtypes in a variety of wild species including birds, swine, and a new equine subtype in horses.[791]

The manufacturing of vaccines in the United States remained slow.[792] The flu virus was injected into fertilized chicken eggs, harvested, and inactivated by means of a chemical additive, purified, diluted to dose strength, shipped, and delivered to many public health institutions. All this had to happen while maintaining vaccine sterility and few facilities had

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[788] Dehner, *Influenza*, 72.
[789] WHO/Influenza/16, "Expert Committee on Influenza."
[790] Kaplan, "The Role of the World Health Organization in the Study of Influenza."
[791] Heller, Espmark, and Viridén, "Immunological Relationship between Infectious Cough in Horses and Human Influenza A"; Sovinova et al., "Isolation of a Virus Causing Respiratory Disease in Horses."
[792] Payne, "The Influenza Program of WHO."

the infrastructure for mass production.[793] In 1955, the Cutter incident, one of the worst pharmaceutical disasters in U.S. history, exposed several thousand children to live poliovirus because of a flaw in the manufacturing process of the Salk polio vaccine.[794] Many children died. This was a setback for all vaccines. Now many perceived the vaccination itself as gambling with lives, and this perception challenged notions of the risks and benefits of vaccines.

The 1957 Asian flu pandemic presented the first real opportunity for the WHO to track a flu strain as it emerged in order to secure development of a vaccine. The early detection plan failed. Neither the WHO surveillance nor U.S. Military's monitoring detected the rapidly spreading flu virus of 1957 in time. Dehner attributed the vaccination failure to a combination of factors: reluctance to challenge the prevailing system of profit-driven manufacturers and, as the evidence suggested, a rather mild flu strain.[795] The pandemic spread too quickly to rely on 1950s technology for manufacturing vaccine in bulk. After the 1957 pandemic, British influenza expert Stuart-Harris remarked that influenza vaccines were experimental with no known public health value.[796]

Although the response to the 1968 Hong Kong Flu pandemic was quicker than that in 1957, the pandemic peaked before release of the vaccine. Only the Soviet Union claimed limited success in protecting its citizens.[797] Unproductive vaccination campaigns in 1957 and 1968 reinforced the idea that early detection of a virus and rapid decision-making were crucial. Eyler referred to vaccine production as a continuous "crash program" to produce

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[793] Dehner, *Influenza*, 81.
[794] Paul A. Offit, *The Cutter Incident: How America's First Polio Vaccine Led to the Growing Vaccine Crisis*, (Yale University Press, 2005).
[795] Dehner, *Influenza*, 79, 75.
[796] Stuart-Harris, "The Present Status of Prophylactic Immunization Against Influenza."
[797] Ždanov and Antonova, "The Hong Kong Influenza Virus Epidemic in the USSR."

vaccine just in time, an apt description.[798] Yet, a small cadre of influenza experts, on whom the WHO depended, maintained faith in technical solutions for early virus detection. From this faith in technology, theories to predict influenza pandemics emerged.

6.2 Historical Perspectives: Predictive Theories of Pandemic Flu

Since the first isolation of the influenza virus in the 1930s, experts have attempted to predict pandemics based on virus characteristics, natural cycles, or both. Early flu detection and faster vaccine production were crucial to blunt disease spread. Theories to predict influenza included three aspects – virus recycling, periodicity, and antigenic shifts. Virus recycling hypothesized that distinct influenza strains "recycled" with one virus replacing the last in the order they originally appeared.[799] Periodicity is the time between pandemic outbreaks. Antigenic shift refers to an abrupt, major change that produces a novel influenza virus to which humans have no prior immunity.

Recycling: The doctrine of "original antigenic sin"

In 1957, a Dutch researcher, J. Mulder, found that a large percentage of the elderly population produced antibodies to the new flu strain that year. A common method for studying influenza was to measure antibody production to a new strain among people of different ages and at different locations.[800] Humans mount strong antibody reactions to a prior virus infection. Thus, Mulder reasoned, this older population must have encountered

[798] Eyler, "De Kruif's Boast," 438.
[799] Dowdle, "Influenza Pandemic Periodicity, Virus Recycling, and the Art of Risk Assessment," 34.
[800] Dehner, *Influenza*, 97.

the 1957 virus at some point early in their lives. Mulder hypothesized that the 1957 Asian flu was a return of the Russian flu virus of 1889.[801]

Dehner described how Mulder rushed his lab results to the WHO that, in turn, requested further experiments from their network of researchers. Within several months, influenza labs in Australia and the United States reported a similar antibody pattern among the elderly.[802] Fred Davenport, who succeeded Francis as the head of the U.S. military commission on influenza from 1955-1971, took notice of this development.[803]

Influenza virus recycling assumed that the flu virus has a limited number of possible forms and that they repeated, depending on the immunity levels of individuals within a population. In other words, the flu virus recycled after sufficient time for a new crop of susceptible people to accumulate. It appeared that a "newer" flu virus must have some evolutionary advantage to occupy the ecological niche of an older strain. Davenport argued that virus recycling resulted in different age segments of the population with varying amounts of exposure to each virus.[804] There was some evidence to support recycling and little else for researchers to explain perceived patterns in the appearance of influenza pandemics. Although complex and difficult to prove, the virus recycling theory gained some credibility within the scientific community.[805] Thus, the seeds of the influenza virus recycling theory were planted by the late 1950s.

In 1960, Thomas Francis proposed a more formal foundation for the recycling theory known as the doctrine of "original antigenic sin." This doctrine proposed that the first flu

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[801] Mulder and Masurel, "Pre-Epidemic Antibody against 1957 Strain of Asiatic Influenza in Serum of Older People Living in the Netherlands"; Mulder, "Asiatic influenza in The Netherlands."
[802] Dehner, *Influenza*, 96.
[803] Francis took a professorship at the University of Michigan.
[804] Davenport and Hennessy, "Predetermination by Infection and by Vaccination of Antibody Response to Influenza Virus Vaccines."
[805] Dowdle, "Influenza A Virus Recycling Revisited."

exposure, typically during childhood, leads to a powerful lifelong antibody response. Subsequent infections to different flu viruses also produced antibodies but these antibody responses were not as pronounced as the original flu infection.[806] High antibodies to a particular strain suggested that the new strain was the same, or very similar, to the person's first influenza infection. With the benefit of vaccines, Francis reasoned, the "original sin" of infection could be replaced with a "blessing" of induced immunity to influenza.[807]

Francis considered that about ten years were required for a virus to circulate and confer some immunity within a population.[808] The 1968 pandemic appeared eleven years after the 1957 Asian pandemic in a pattern of periodicity that looked to mimic the viruses of 1947 and 1957. Furthermore, persons older than 85 years had existing antibodies to the 1968 virus, suggesting that this virus had appeared previously in the human population.[809]

Relying on this doctrine of "original antigenic sin" to gauge the human immune reaction to a flu virus, influenza researchers hypothesized that over time a population develops a resistance to a family of flu viruses. Theoretically, a virus then retreats because it cannot sustain a chain of infection in the human population. A new flu virus comes along, infecting an increasing proportion of the population born before that family of viruses last circulated.

During 1968, the WHO revised influenza naming conventions that further reinforced the recycling theory. This new system grouped flu viruses by their surface components, H and N.[810] The H3N2 Hong Kong strain was part of the H3 family of flu virus; the 1957 virus was an H2N2, part of the H2 family; and the 1918 pandemic was an H1N1 that belonged to

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[806] Dehner, *Influenza*, 97.
[807] Francis, "On the Doctrine of Original Antigenic Sin," 578.
[808] Ibid.
[809] Masurel, "Serological Characteristics of a 'New' Serotype of Influenza A Virus."
[810] H for hemagglutinin and N for neuraminidase.

the H1 family.[811] In this way, the new naming convention supported the idea that the number of influenza antigens is finite.

By the early 1970s, interpretations based on sera provided evidence that the swine virus (H1 family) had last appeared in 1918, the Hong Kong virus (H3 family) in 1900, and the Asian (H2) virus in 1890. Not ten years apart, but the viruses did emerge in the same sequence. Researchers argued that the H3 Hong Kong flu of 1968 spread because those previously exposed to H3 (presumably from an epidemic of 1900) constituted a small fraction of the population.[812] To some supporters of the recycling theory, the next pandemic virus in the sequence was the swine virus of 1918.[813] This evoked some measure of fear among the scientists.

However, it is noteworthy that 1900 was a year without a recorded pandemic or even a recognizable epidemic. Dehner described how researchers dug through old records to find what appeared to be a slightly elevated number of influenza cases during 1900.[814] Perhaps, there was a flu epidemic of 1900 but records were lost. Alternatively, perhaps researchers were choosing facts to align with a theory.[815] Ultimately, virologist Dowdle concluded that the H3 responsible for the Hong Kong flu had a legacy not from 1900, but from the pandemic of 1889-90.[816]

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[811] Davenport et al., "Interpretations of Influenza Antibody Patterns of Man"; Masurel, "Serological Characteristics of a 'New' Serotype of Influenza A Virus."
[812] Dowdle, "Influenza Pandemic Periodicity, Virus Recycling, and the Art of Risk Assessment."
[813] Masurel and Heijtink, "Recycling of H1N1 Influenza A Virus in Man"; Davenport et al., "Interpretations of Influenza Antibody Patterns of Man."
[814] Dehner, *Influenza*, 98.
[815] Chamberlin, "Studies for Students: The Method of Multiple Working Hypotheses."
[816] Dowdle, "Influenza Pandemic Periodicity, Virus Recycling, and the Art of Risk Assessment." The author supported the claim for virus recycling only for the H3 subtype of influenza that appeared in 1889 and again in 1968. No other flu virus recycling claims substantial evidence.

Kilbourne's Theory: Antigenic Shift and Recycling

During the 1970s, another influenza theory entered the arsenal of the researcher. Virologist Edwin Kilbourne combined the theory of influenza periodicity (the ten or eleven-year cycle) with the theory of antigenic shift.[817] Melding these theories, Kilbourne argued that major antigenic shifts occurred in roughly 11-year cycles that included 1947, 1957, and 1968. He reasoned that an 11-year cycle represented a plateau following dissemination of virus in the population.[818]

Antigenic shift is an abrupt, major change in the influenza virus to which most people have little or no protection. Since 1952, the WHO had charged its Expert Committee on Influenza to watch for antigenic shifts in order to make accurate forecasts of when and where a flu pandemic would appear.[819]

In early 1971, the U.S. National Institutes of Allergy and Infectious Diseases (NIAID) established a "Subcommittee on Influenza" to study the unique and unsolved problems presented by influenza. There was acknowledgement of failure of the two previous national immunization programs (in 1957 and 1968) and of influenza's economic and health burdens. The eight NIAID workshops on influenza between 1971 and 1975 would prove to be very important for collaboration within the scientific community of influenza researchers.[820] The proceedings from these meetings provide a rich source of background information about theories of virus recycling, antigenic shift, and periodicity.[821]

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[817] Kilbourne was an internationally recognized research scientist who developed a new vaccine each year by intermingling genes of different viral strains. As described in chapter three, antigenic shift is the process by which strains of two or more different flu viruses combine to form a new viral subtype having a mixture of the surface antigens of the original strains.
[818] Kilbourne, "Epidemiology of Influenza."
[819] WHO/Influenza/16, "Expert Committee on Influenza," 3.
[820] Kilbourne, Butler, and Rossen, "Specific Immunity in Influenza"; Kilbourne et al., "Influenza Vaccines"; Seal, Sencer, and Jr., "A Status Report on National Immunization against Influenza."
[821] Selby, *Influenza: Birus Vaccines and Strategy*.

The participants argued that a genetic recombination between dissimilar human strains or between human and animal strains of influenza virus would result in a radically new virus. The proceedings emphasized that the introduction of an antigenically new viral variant that confronts an "immunologically inexperienced" population results in pandemic disease.[822]

The 1973 NIAID Workshop proceedings included a conceptual diagram from Kilbourne et al. that illustrated a hypothetical correlation between population antibodies (due to exposure to a virus) and the incidence of influenza in that population in a cycle of about 10 years (**Figure 26**). The predictive theory of antigenic shift was powerful and convincing to many scientists. Some scientists claimed that the virus recycling theory pointed to swine flu as the next epidemic flu virus to re-emerge.[823] In addition, during the 1974 workshop, participants predicted that the next pandemic would appear by the end of the decade.[824] Kilbourne, a participant and leader at the NIAID

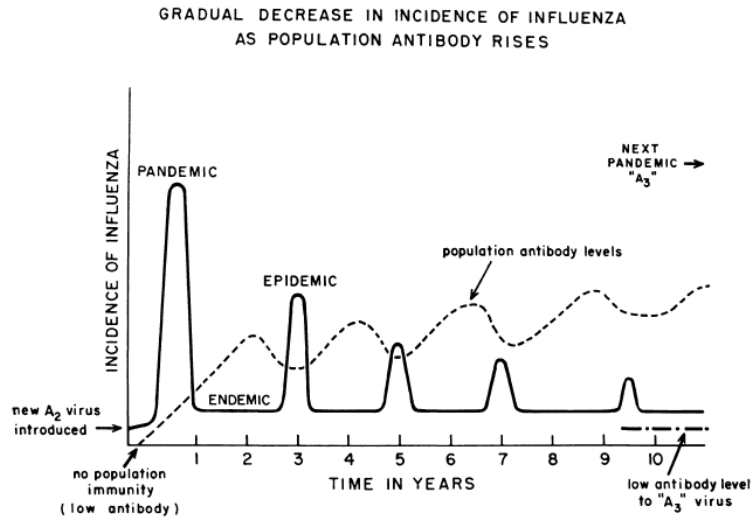

Figure 1. Inverse correlation between levels of antibody in a population and the magnitude of influenza epidemics (reprinted from *Sandoz Panorama* 6:7, 1968 with permission of Sandoz Pharmaceuticals, East Hanover, N.J.).

Figure 26. Influenza Recycling Theory. In Kilbourne, E. D., W. T. Butler, and R. D. Rossen. "Specific Immunity in Influenza: Summary of Influenza Workshop III." February 1, 1973: 221.

[822] Kilbourne, Butler, and Rossen, "Specific Immunity in Influenza."
[823] Masurel and Marine, "Recycling of Asian and Hong Kong Influenza A Virus Hemagglutinins in Man."
[824] Kilbourne, Butler, and Rossen, "Specific Immunity in Influenza."; Kilbourne et al., "Influenza Vaccines," 771.

workshops, addressed the 11-year pandemic cycle and antigenic shift in his own 1975 textbook. However, it is noteworthy that Kilbourne added an important caution in his book:

> Predictions concerning the next pandemic rest on the flimsy structure of a series of two instances of decennial prevalence (1946-1957 and 1957-1968).[825]

Furthermore, Kilbourne argued that one can easily "misread the past" and that "these meager data should not be over interpreted."[826] He explained that a virus of low virulence may produce severe disease in a highly susceptible host, and a virulent virus may produce asymptomatic infection in a host that is resistant.[827] He argued for virulence and transmissibility as the most important markers for influenza. However, researchers did not know very much about these characteristics in the 1970s.

Despite cautions and diverse scientific opinions, there is evidence that predictive theories of influenza became entrenched in dialog among scientists and from them to the public. For example, in a rather unusual request, in 1974 a pharmaceutical firm asked the CDC for the precise timing of the next flu pandemic, including its severity and geographical location.[828] Although CDC did not possess this information, the request illustrates how widespread was the idea of prediction for the "next" pandemic. In another instance, the NIAID incorporated predictive theories into their 1975 Congressional testimony for funding appropriations, emphasizing that the agency must move quickly after a viral mutation in order to create a vaccine in time and that such a viral shift occurs about every ten years.[829] Soon thereafter, the Bureau of Biologics (folded into the U.S. Food and Drug Administration

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[825] Kilbourne, "Epidemiology of Influenza," 495. Kilbourne argued that the influenza cycle was speeding up due to the seeding of a virus through jet travel.
[826] Ibid.
[827] Ibid., 505.
[828] Brady to Sencer, letter, October 14, 1974, "Flu", RG 442, Box 34, NARA-SE Region.
[829] Schreiber to Jacobs, re: Influenza Virus Vaccine, October 28, 1975, NIH Files, RG 433, Box 150, NARA-College Park.

in 1988) argued that given the predictability of virus mutation, "…worse years can be expected before the end of the decade."[830] Thus, predictive theories of influenza had made their way from the scientific realm into the political realm.

In summary, many virologists and public health experts perceived that flu epidemics appeared in predictable cycles based on historical and serological evidence. Some researchers believed that influenza theories not only explained events retrospectively but could also apply predictively. However, in order for any predictive theory to be worthwhile, it had to be practical and provide advance warning of a pandemic. The next section examines how well predictive theories played out within a political context during the Swine Flu crisis of 1976 when investigators attempted to outrun the influenza virus to predict the next big pandemic.

6.3 Swine Flu 1976: Applying Predictive Theories

The year 1976 was a political and social transition in the post-Watergate, post-Vietnam era in the United States. Ford was struggling in the election campaigns, a time of increasing discomfort and distrust in American politics.[831] Challengers from both the Republican and Democratic parties considered Ford a weak, indecisive leader.[832]

In late 1975, Donald Rumsfeld (Secretary of Defense) and Dick Cheney (White House Chief of Staff) signed a joint letter to Ford threatening to resign (with identical resignations attached) unless they got more control over the operation of the White House. The letter to President Ford stated "... there are growing questions about your leadership,

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[830] Meyer to Gallasso, Nov 28, 1975, 1, NIH Files, RG 443, Box 150, NARA-College Park.
[831] Laurie Garrett, *The Coming Plague: Newly Emerging Diseases in a World Out of Balance*, (Penguin, 1995).
[832] Arthur M. Silverstein, *Pure Politics and Impure Science: The Swine Flu Affair* (Baltimore: Johns Hopkins University Press, 1981).

capabilities and competence."[833] Rumsfeld and Cheney urged the President to demonstrate leadership. They advised Ford to cancel skiing trips (nor should he go to Paris or China) and that he should organize his time within the "stereotype" of a President. They advised Ford that true leaders often hear screams of opposition. There was, they said, no need for Ford to compromise.[834]

Cheney and Rumsfeld remained in office for the balance of the Ford administration, suggesting that change did come to the White House. Instead, perhaps Ford ignored them. Immunologist Arthur Silverstein, an aide in 1976 to Senator Edward Kennedy on health matters, remarked, "Dick Cheney was a huge politician, and his job as the Chief of Staff was to man the political fences." Silverstein suggested that Cheney had considerable input in decisions of public health in general and swine flu in particular in 1976.[835]

During January of 1976, leading influenza scientists converged at Rougemont, Switzerland to develop a global strategy for dealing with the next flu pandemic. It was the theory of antigenic shift that took center stage as a tool to predict the next influenza pandemic. Some participants argued that an antigenic shift in the influenza virus always signaled an impending pandemic based on past pandemics.[836] Dehner referred to this as, "…an almost audible ticking sound to preparations for the next pandemic."[837] There were, however, voices of dissent. Dowdle, chief virologist at CDC, argued that there was no

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[833] Cheney and Rumsfeld, "To Gerald Ford Re Re-Election and Rumsfeld and Cheney Resignations. Action Memorandum for the President" Rumsfeld Archives.
[834] Ibid.
[835] Silverstein, 2011 recorded interview by Caitlin Hawke and Barbara Canavan, Research Associates for the Hertog Global Strategy Initiative, Columbia University.
[836] Tyrell, "Conclusions, Proceedings of a Working Group on Pandemic Influenza, Rougemont, 26-28 January 1976."; Dowdle and Gregg, "Morbidity and Mortality Surveillance - USA," 89.
[837] Dehner, *Influenza*, 110.

evidence that the flu virus followed a cyclical pattern and there was "…no justification to assume that its virulence would be the same."[838]

Thus, by 1976, speculation was widespread that a new pandemic strain was due. But few agreed on its character or dimensions. Silverstein remarked that Kilbourne's book, considered the definitive text for influenza, promulgated recycling and antigenic shift theories. Kilbourne was the absolute expert, knew the science of influenza, and knew the disease. Silverstein said, "He was a very important voice. His suggestion of the 11-year cycle was taken very seriously, and it looked true."[839]

Silverstein summed up the state of knowledge and contradictory information about influenza in 1976:[840]

- The longer-term experience was that the flu occurred at unpredictable intervals.
- Recent experience suggested an 11-year cycle and a new pandemic might not be far off.
- Science had no way to predict in advance the severity of a pandemic.
- The 1918 pandemic was caused by a swine flu.
- Vaccines were available that may protect against influenza.
- Pandemics spread more quickly in the age of jet travel.

It is within this political and scientific context that the swine flu events of 1976 unfolded.

In February 1976, an outbreak of swine flu struck the Fort Dix Army base in New Jersey, killing a 19-year-old private and infecting hundreds of soldiers.[841] Officials gathered at CDC in Atlanta and decided that the consequences of not vaccinating the public should a pandemic break out, were far worse than the consequences of an epidemic that would never

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[838] Dowdle, "Influenza: Epidemic Patterns and Antigenic Variation," 341.
[839] Silverstein, 2011 recorded interview.
[840] Silverstein, *Pure Politics and Impure Science*, 22–23
[841] Gaydos et al., "Swine Influenza A at Fort Dix, New Jersey (January-February 1976). II. Transmission and Morbidity in Units with Cases."

appear. Participants reported a crisis atmosphere and anxiety that the next pandemic had arrived.[842]

Coincident to the flu outbreak at Fort Dix, the *New York Times* published an op-ed by Kilbourne in which he emphatically stated that pandemics occur in every decade – 1946, 1957, and 1968 – and that "those concerned with public health had best plan without further delay for an imminent natural disaster."[843] Kilbourne emphasized that a major mutation in the virus would result in a pandemic. Within a week, the *New York Times* reported, "The possibility was raised today that the virus that caused the greatest world epidemic of influenza in modern history ...the pandemic of 1918-19 may be returned."[844]

Shortly before the swine flu outbreak at Fort Dix, historian Alfred Crosby had published in *Epidemic and Peace*(1976).[845] This book graphically described the social and economic costs of the 1918 pandemic and it was a popular, if shocking, read. In the midst of the potential epidemic, the CDC sent copies of the book to all immunization directors.[846] In addition, the Department of Health, Education, and Welfare (HEW) provided copies to colleagues, White House officials, and directly to President Ford.[847] Thus, *Epidemic and Peace* served as a reference book for swine flu decision-makers and the media.[848] According to Silverstein, the swine flu gave Ford an "…opportunity to lead in an important area that the American people would understand."[849] It was a way to show himself as strong and decisive.

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[842] Rensberger, "Flu Vaccine Drive Meets Snags That Could Limit It."
[843] Kilbourne, "Flu to the Starboard! Man the Harpoons! Fill'em With Vaccine! Get the Captain! Hurry!"
[844] Schmeck, "U.S. Calls Flu Alert On Possible Return Of Epidemic's Virus."
[845] Crosby, *Epidemic and Peace*. Decades later, Crosby re-published this book as *America's Forgotten Pandemic: The Influenza of 1918.*
[846] Millar, "Letter to Immunization Project Directors, Subject: Epidemic & Peace, 1918 (CDC, June 1976), NIIP Reading File, RG 442, Box 1, NARA SE Region."
[847] Neustadt and Fineberg, *The Swine Flu Affair*, 19.
[848] Tolsma handwritten notes, April 27, 1976, "Influenza staff meeting notes," RG 442, Box 38, NARA-SE Region.
[849] Silverstein, 2011 recorded interview.

On March 18, an action memo from the Department of Health, Education, and Welfare (HEW) stated that severe epidemics, or pandemics, of influenza occur at approximately 10-year intervals and reinforced the link between swine flu with the pandemic of 1918.[850] Just prior to Ford's announcement of the Nationwide Influenza Immunization Program on March 24, the White House staff gathered for a top level meeting that included Cheney, officials from HEW, and the director of the Office of Budget and Management (OMB). In a document entitled "Scientific Evidence on Likelihood and Success of Immunization" the OMB director asked, "What is the contrary virology argument against the massive immunizations?"[851] There is no documentary record of a response to this question.

Concerned that the U.S. was on the verge of a devastating epidemic, Ford ordered a Nationwide Influenza Immunization Program (NIIP). Congress quickly appropriated $135 million and the drive to vaccinate 150 million Americans began. Ford called on Jonas Salk and Albert Sabin to help brand and build confidence for the NIIP. Some observers argued that the blue ribbon panel of advisors at the White House press conference served as "window-dressing" for a decision that had already been made by the White House.[852] Journalist Laurie Garrett argued that when Ford went on national television, flanked by Sabin and Salk, this was the turning point that ended healthy skepticism and "put politics in the Swine Flu driver's seat." Knowing the Republican president would not veto a bill to fund the NIIP, the Democratic House attached $1.8 billion dollars in environmental spending to the bill.[853]

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[850] Neustadt and Fineberg, *The Swine Flu Affair*.
[851] Lynn, "Uncertainties Surrounding a Federal Mass Swine Influenza Immunization Program. James M. Cannon Files, President: 3/22/76 (Swine Flu), Box 52, Ford Presidential Library."
[852] Boffey, "Anatomy of a Decision," 638.
[853] Garrett, "The American Bicentennial: Swine Flu and Legionnaires' Disease," 1995, 58.

A significant issue was that the language used to gain political attention is not the same language needed to communicate with the public. Once politicized, the swine flu language shifted from possible, to probable, to certainty that this was the flu strain of 1918. Director of the CDC David Sencer used the term "strong possibility" to describe the likelihood of a flu pandemic during 1976. Mathews, head of HEW, changed the possible into a "will be."[854] Mathews estimated that five hundred thousand deaths in 1918 would translate to one million deaths in 1976 based on the proportional increase in population.[855] Sencer described the virus as "related" to the 1918 virus. Mathews described it as a "return of the 1918 flu virus."[856] When President Ford signed the NIIP bill, he remarked to the press, incorrectly, that the Fort Dix swine flu was identical to the deadly 1918 variety.[857]

For the first time, the production of 200 million doses of vaccine was feasible due to improvements in manufacturing.[858] There had never been a mass vaccination campaign of this scale. Due to the lead-time required, the CDC had to make quick decisions for vaccine production. The scientists and public health officials decided that it would be "far better to gamble with money than to do nothing and thereby to gamble with lives".[859] Everyone agreed to proceed with vaccine production but not everyone agreed to administer the vaccine in the absence of pandemic spread.[860]

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[854] Neustadt and Fineberg, *The Swine Flu Affair*, 12.; Garrett, "The American Bicentennial: Swine Flu and Legionnaires' Disease," 17.
[855] Silverstein, *Pure Politics and Impure Science*.
[856] David Mathews, "Remarks by David Mathews, HEW Secretary" (HEW, April 2, 1976), RG 442, "Information 1976, 3. Newspaper Clippings, Press Release." Box 10, NARA-SE Region.
[857] Garrett, "The American Bicentennial: Swine Flu and Legionnaires' Disease," 1994; Silverstein, *Pure Politics and Impure Science*, 1981.
[858] Begley, "The Failure of the 1976 Swine Influenza Immunization Program," 43.
[859] Seal, "Summary of Decision-Making Regarding Swine Flu Influenza, NIH Files, RG 433, Box 150, NARA-College Park," 341–42.
[860] Schmeck, Jr., "Experts Agree on Flu Vaccine Policy."

Russell Alexander of the University of Washington was a member of the influential Advisory Committee on Influenza Practices (ACIP) and wrote that unless there was another outbreak of swine flu, there should be no actual plan to administer the vaccine.[861] Kilbourne's counter-argument was that stockpiling the vaccine was unrealistic and ignored how quickly flu can spread, adding to massive vaccine distribution problems.[862] A taskforce led by Dowdle studied the pros and cons of stockpiling the vaccine. The consensus from all meetings was that stockpiling the vaccine was not an acceptable alternative to a "fully committed vaccination program."[863] Some observers argued that it was difficult to sell a program that involved buying vaccine but delayed the decision to administer it.[864] Perhaps the $130 million appropriation was too much money to request from Congress with such an open-ended contingency.

In April, at the first congressional hearings to create the NIIP, it was once again clear that predictive theories had entered the political realm. As chairperson of the Subcommittee on Health, Senator Edward Kennedy opened the hearing by stating that history has shown that there had been a major outbreak of flu every ten years. He also said the virus in question was "akin" to the one that caused the 1918 pandemic.[865] Senator Beall testified, "This flu strain caused an epidemic approximately 50 years ago, killing over 548,000 Americans and 20 million worldwide."[866]

Kennedy announced that the purpose of the hearing was to discuss the basis for the decision to create the largest immunization campaign the nation had ever initiated. However,

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[861] Alexander to Sencer, (April 7, 1976) "Stockpiling Issues," RG 442, Box 11, NARA-SE Region.
[862] "Swine Flu"; Boffey, "Anatomy of a Decision."
[863] Dowdle et al. to Millar, re: stockpiling, June 7, 1976, "H-3 20 Freedom of Information Act related to the Guillain-Barre Syndrome," RG 442, Box 45, NARA-SE Region.
[864] Boffey, "Anatomy of a Decision."
[865] Kennedy testimony on April 1, 1976, *Congressional Hearing before the Subcommittee on Health*, 1.
[866] Beall testimony on April 1, 1976, *Congressional Hearing before the Subcommittee on Health*, 54.

most of the testimony was about expediting the program. There is no evidence that Congress examined the basis for the decision during the early months of the NIIP.[867] Scientists, politicians, and industry representatives lined up to praise the efforts of a prevention strategy in public health. Robert Hingson, a professor of public health at Vancerbilt University, testified that the NIIP reflected the great dream of mass immunizing an entire population challenged by a preventable epidemic.[868] It was a Congressional love fest, and there was something for everyone.

As the congressional testimony for the NIIP continued, Kilbourne reiterated his concern that pandemics always occurred following an antigenic shift in flu viruses. There were also concerns that a flu virus could disappear after its first wave, only to reappear the following season. In an unpublished section of a *New York Times* op-ed, Kilbourne pointed to the perpetual indifference to influenza, the lack of unsubsidized vaccine, and the fifty million people vulnerable to the disease.[869] This unpublished portion reveals some of the public health motivations and concerns of Kilbourne and his colleagues.

Yet, a month later, Kilbourne wrote, "It is unfair and probably unwise to keep using this [the 1918 virus link] as a justification for the vaccination program. To trade in fears is something that will come back to haunt us."[870] At the same time, the dean of the University of the Texas School of Public Health remarked that the 1918 link was the very reason the government was building a mass immunization program and experts should continue to stress the connections to 1918.[871] Others countered that it was misleading to compare the swine flu

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[867] Kennedy testimony on April 1, 1976, *Congressional Hearing before the Subcommittee on Health*, 2.
[868] Begley, "The Failure of the 1976 Swine Influenza Immunization Program," 44.
[869] Kilbourne, Edwin Kilbourne, "Letter to Editorial Page Editor of the New York Times - original form as written by Kilbourne," April 6, 1976, NIH Files, RG 433, Box 150, NARA-SE Region.
[870] Charles Taylor, "UPI Wire," May 7, 1976, "CDC Liability Proposal", RG 442, Box 8, NARA-SE Region.
[871] Ibid.

to the 1918 pandemic and that the press had overplayed this aspect.[872] An editorial in the *New York Times* suggested that assumptions about a 1918-like pandemic created an artificial analogy.[873] White House officials suggested that Jonas Salk write editorial responses in response to criticism.[874]

Behind the scenes, a core group of virologists and public health officials assessed the risk of a potential swine flu epidemic during 1976.[875] Fifteen participating scientists (five from a virology group and ten from a public health group) concluded that if the swine influenza virus were to circulate in the United States, the epidemic would more likely resemble those of 1957 and 1968 rather than of 1918. Steve Schoenbaum, the facilitator and author of the findings from the panel, said it was difficult to escape the reality that the experts simply did not know the probability of a flu pandemic and that participants did not converge in their responses.[876] The virologist group estimated the probability of further swine flu outbreaks at about ten percent, a factor used in the cost-benefit model to determine at what level the NIIP would be worth the cost. The cost-benefit analysis indicated that if the NIIP were able to vaccinate at least 59 per cent of the U.S. adult population, the program would be economically justifiable.[877]

Journalist Philip Boffey followed the swine flu story from the beginning and interviewed many of the principals in and out of government. He reported that most

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[872] Rensberger, "Flu Vaccine Drive Meets Snags That Could Limit It."
[873] New York Times, "Flu Vaccine - Editorial."
[874] Cannon to Cavanaugh, Cannon to Cavanaugh, re: Conversation with David Mathews this Morning on the NY Times Editorial on Flu Vaccine (White House, April 6, 1976), James M. Cannon Files, folder entitled, "Swine Flu, April 1-12, 1976," Box 34, Ford Presidential Library.
[875] The researchers used The Delphi technique developed by the RAND Corporation in the late 1960's as a forecasting methodology. Delphi is particularly appropriate when decision-making is required in a political environment, or when the decisions affect strong factions with opposing preferences.
[876] Schoenbaum, M.D., personal communication. Schoenbaum, McNeil, and Kavet, "The Swine-Influenza Decision"; Dowdle, "Influenza Pandemic Periodicity, Virus Recycling, and the Art of Risk Assessment."
[877] Schoenbaum, McNeil, and Kavet, "The Swine-Influenza Decision."

participants guessed the probabilities of flu were much smaller than was apparent from the rhetoric and that scientists did not believe that it would be as severe as the 1918 flu. Based on results from Boffey's anonymous polling of virologists and public health experts, he arrived at a median estimate of 29% chance of a pandemic in 1976. According to Boffey, the participants determined that the consequences of failure in the event of a pandemic were greater than the consequences of acting too quickly.[878] This was a consistent theme.

Harvard statistician F. Mosteller read Boffey's article in *Science* and wrote a response to address the question of whether the estimates for the probability of a pandemic were lower than the rhetoric would suggest. Specifically, he regarded the phrase "very real possibility" (as expressed by President Ford) as the official rhetoric needing quantification. In Mosteller's view, the world "possibility" in probability simulation had a value of 20 percent. For the population studied, Mosteller argued that the official rhetoric was in line with the reported probability estimates.[879]

As months went by without any sign of additional flu outbreaks, the NIIP became increasingly controversial. CDC officials consistently reported the probability of a pandemic as "unknown."[880] Flu predictions became a huge public relations problem. Undaunted, the ACIP proclaimed in an official bulletin that when a major antigen change occurs in the influenza virus, the new virus will rapidly spread worldwide.[881]

Ronald Hattis, a former CDC official, wrote that he was embarrassed and disappointed by the lack of candor and the political tactics used to rush this program through. He argued "…the liability for side effects and accidents for vaccinating the low-risk

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[878] Boffey, "Anatomy of a Decision," 638.
[879] Mosteller, "Swine Flu."
[880] Neustadt and Fineberg, *The Swine Flu Affair*, 16, 23, 25, 50, 73, 74.
[881] CDC Liability Proposal, "Recommendation of the Public Health Service Advisory Committee on Immunization Practices/Influenza Vaccine Preliminary Statement," RG 442, Box 8, NARA-SE Region.

populations is worrying physicians and public agencies." Hattis argued there might be massive backlash to the next public health program due to loss of credibility.[882] True today as it was then - experts walk a fine line as both scientists and as advocates for the public's wellbeing.

With no further swine flu outbreaks through the summer, the insurance companies, fearing liability over adverse vaccine reactions, refused to indemnify vaccine manufacturers. Congress refused to pass a law making the government liable for such events from swine flu vaccine.[883] There was a growing sense that the government had over-reacted with the NIIP. Critics speculated the vaccine itself might be worse than the disease.[884] Sidney Wolfe, a co-founder of the Health Research Group with Ralph Nader, argued that "on the prevention side, you don't even get to the issue of does the benefit of preventing disease outweigh the risks of the immunization because there isn't any disease." [885] In fact, Wolfe referred to the 1976 flu as the "Swine Flu Vaccine Disease" in congressional testimony.[886]

By the summer of 1976, British scientists published results of experiments that argued that the swine flu virus in the U.S. appeared to be very mild and was not likely to establish itself in humans.[887] Soon thereafter, CDC published an article claiming that even if the virus did not appear, public health actions would be valuable to demonstrate "…our capacity and our will to marshal resources quickly to protect our population against a new disease."[888] With the President as the chief sponsor and no more outbreaks of the swine flu,

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[882] Hattis to Sencer, re: National Influenza Immunization Program: Critique and Alternatives", June 13, 1976, RG 442, Box 21, NARA-SE Region.
[883] Rensberger, "Flu Vaccine Drive Meets Snags That Could Limit It."
[884] Boffey, "Soft Evidence and Hard Sell."
[885] Wolfe, 2011 recorded interview.
[886] Wolfe, *Congressional Hearing on Swine Flu Immunization Program - June 28, 1976*, 137.
[887] Beare and Craig. "Virulence for Man of a Human Influenza-A Virus Antigenically Similar to 'Classical' Swine Viruses."
[888] Sencer, "Swine Influenza Vaccination Campaign," first page.

perhaps CDC considered that arguing for the collateral benefits of NIIP was the best approach. But in the longer term, CDC had the most to lose from this strategy.

Despite these obstacles and criticisms, the White House attempted to shut out all doubters and skeptics. There would be an occasional scolding from Cheney to White House staff about the importance of NIIP -- it was "vitally important that this one not slip through the cracks."[889] Occasionally, there would be a finger wagging directly from Ford to staff following delays in the NIIP, "…this program damn well better run right."[890] Editorials suggested that Ford would reap political dividends from the swine flu program in an election year.[891]

As the NIIP program was scuttled over insurance liability issues, vaccine production delays, and the lack of any further disease outbreaks, Ford's reputation was on the line. He sent a letter to Congressional leaders stating that the threat of pandemic was genuine, data were scientific, and that the vaccine was safe and effective.[892] Ford blamed Congress for failing "…to act to protect 215 million American from the threat of swine flu."[893] Observing that Ford was the chief supporter of the NIIP, journalists asked Ford's press secretary why the National Academy of Sciences did not offer an opinion of the NIIP. The press response was that Ford had many advisors from diverse organizations as well as from Sabin and Salk.[894]

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[889] Cheney to Lynn and Cannon (White House, June 7, 1976), James M. Cannon Files, folder entitled, "Swine Flu, June 1-July 18, 1976," Box 34, Ford Presidential Library.
[890] "Swine Flu Vaccine" (White House, September 2, 1976),"Swine Flu", Ron Nessen Papers 1974-77, Box 120, Ford Presidential Library.
[891] Editor, "Flu Vaccine."
[892] Ford letter to the Speaker of the House and President of the Senate (White House, August 4, 1976), Ron Nessen Papers, "Swine Flu," Box 29, Ford Presidential Library.
[893] "Press Release" (White House, August 6, 1976), Robert Orben Files, 1974-77; "8/6/76 Swine Flu Statement," Box 67, Ford Presidential Library.
[894] "White House Press Conference" (White House, August 4, 1976), Ron Nessen Papers, Box 21," Ford Presidential Library.

During the summer of 1976, there was an outbreak of Legionnaire's Disease (a bacterial lung disease unrelated to the flu but with similar symptoms) in Philadelphia with cases of illness and death.[895] Although this illness was unrelated to the swine flu, it scared Congress into thinking it could be the long-promised influenza. Ford used Legionnaire's disease as a lever to compel Congress to pass legislation that indemnified vaccine manufacturers so the NIIP could proceed on course.[896] Consensus among observers was that Congress would have dropped the legislative efforts had it not been for the outbreak of Legionnaires' disease.[897]

Arthur Silverstein recalled his time as Senator Kennedy's aide and coordinator for many of the swine flu congressional hearings, "If Jerry Ford hadn't come out with his press conference and run down the Congress, for not having acted as it should have he said, I think that was it. You know, Kennedy never would have done anything! He [Ford] embarrassed Congress, he embarrassed Kennedy, and actually he embarrassed Paul Rogers [chair of the House Subcommittee on Health and the Environment]."[898]

Once the mass flu vaccinations started up in the fall, Guillain-Barré Syndrome (GBS) emerged, an adverse reaction associated with the swine flu vaccine.[899] GBS is a disorder in which the body's immune system attacks part of the peripheral nervous system. Muscle weakness or paralysis affects both sides of the body. GBS was diagnosed at a rate significantly higher than expected among swine flu shot recipients in the Fall of 1976.[900] The

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[895] Fraser, et al. "Legionnaires' Disease: Description of an Epidemic of Pneumonia."
[896] Lyons, "House Panel Approves Flu Insurance Bill."
[897] Garrett, "The American Bicentennial: Swine Flu and Legionnaires' Disease," 1994; Hilleman, "Cooperation Between Government and Industry in Combating a Perceived Emerging Pandemic"; Schwartz, "Swine Flu Fiasco."
[898] Silverstein, 2011 recorded interview.
[899] Stephen Morse, personal communication, 2011. According to Morse, it is likely that swine flu vaccine was the cause of GBS.
[900] Schonberger, et al. "Guillain-Barre Syndrome: Its Epidemiology and Associations with Influenza Vaccination."

White House suspended the NIIP once the GBS emerged. NIIP had been a catalyst to expand and improve the national disease surveillance system. It is ironic that this surveillance caught the GBS that, in turn, crashed the NIIP program.

The congressional hearings in the aftermath of the "swine flu fiasco" were brutal. According to historian Charles Thorpe, congressional hearings serve as a "ceremonial of truth" in which the government asserts its social and political norms.[901] In the case of swine flu, there was both praise and accountability through congressional hearings.[902] A CDC official testified,

> In 1957 and in 1968 the country moved cautiously but the influenza virus did not. In 1976, the country moved quickly but the influenza virus did not…the virus is ahead three touchdowns to none.[903]

Yet, the NIIP retained valuable supporters. Senator Jacob Javits complimented CDC on its surveillance program. Javits called the "NIIP program a courageous decision on the part of public health officials. Such a massive public health program has never been attempted."[904] With 40 million people getting flu vaccines, Javits did not consider the program a failure.

In their 1977 *The Swine Flu Affair*, historians Neustadt and Fineberg argued that the underlying assumptions about the flu virus went unchallenged in 1976 and NIIP put the reputation of public health on the line. The authors presented 1976 as a "fiasco" of public health policy. This book solidified the collective memory of swine flu events as a perfect storm of over-zealous scientists and inept public officials. The authors placed responsibility

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[901] Thorpe, "Disciplining Experts."
[902] U.S. Government Accountability Office, "The Swine Flu Program."
[903] Millar, *Congressional Hearing on Review and Evaluation of the Swine Flu Program*, 40–41.
[904] Javits, *Congressional Hearing on Suspension of the Swine Flu Immunization Program, December 17, 1976*.

for this on the CDC and not on White House actions.[905] It is interesting to note that in its first 1977 printing, *The Swine Flu Affair* was an HEW publication.

Decades later, in a testament to the enduring legacy of the 1976 swine flu, during the 2009 swine flu pandemic President Obama announced that *The Swine Flu Affair* would serve as a reference book to guide actions. Decision-makers in 2009 wanted to avoid what they perceived as the strategic and tactical mistakes of 1976. Many of the principals involved in the 1976 swine flu, including one of the authors of *The Swine Flu Affair* (Harvey Fineberg, then President of the U.S. Institutes of Medicine), accompanied Obama on the podium during his press conference about the 2009 pandemic.[906] In a strange echo of 1976, an expert accompanies the President onto the podium to make pronouncements about influenza. The history is thus circular, drawing on reports of itself, a narrative that entangled the storytellers.

In a 2011 interview, Silverstein provided an insider's view of the events of 1976 from the political side. He argued that *The Swine Flu Affair* misinterpreted much of what occurred in 1976. The book was not faulty in describing what had happened but did not capture *why* events unfolded as they did. Silverstein believed that when Ford assumed responsibility for the program, he essentially shut out dissent from within the government.[907] Although the suggestions to build NIIP came from the scientists and public health advisers, those with political responsibility accepted the circumstances as sufficient justification to sponsor the program without further question. Once they made a commitment at the political level, there was no turning back. Ford fashioned his public stand from the choices he made.[908]

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[905] Neustadt and Fineberg, *the Swine Flu Affair*, 81.
[906] Barack Obama, "Statement by the President on Today's Meeting to Discuss the 1976 Flu Outbreak | The White House," June 30, 2009.
[907] Silverstein, 2011 recorded interview.
[908] Silverstein, *Pure Politics and Impure Science*, 133.

Historian Charles Rosenberg argued that predictive theories about influenza became assumptions upon which to build political decisions. Anomalies in a flu virus became facts. Perceptions and fears of the 1918 influenza morphed into public assumptions about the potential experience of a new pandemic.[909] Garrett also argued that in 1976, there was no clear separation of the scientific theories, contingent and uncertain, from the process of politics.[910] As Taleb argued, information can be toxic when it inflates the confidence of an "expert" prediction. [911]

Since 1976, scientific understanding of the influenza virus and its natural history has expanded. A lesson from 1976 is that major antigenic shifts in flu viruses do not necessarily lead to pandemics. Nathan Wolfe argues that "risk literacy" is an important part of pandemic preparedness - an informed public can better understand and interpret information on pandemics.[912] There is evidence to suspect, however, that the public remains somewhat skeptical about flu shots.

Prior to the 1976 Swine Flu, the CDC conducted a consumer study based on their concern over public acceptance of vaccination - only 27% of elderly adults sought flu shots during inter-pandemic periods. These results indicated that 40% of those polled did not think that the flu shot was necessary or did not know about it.[913] In 2010, the Harvard School of Public Health reviewed 20 national opinion polls taken at various points during the 2009 H1N1 pandemic. They concluded that at least 50% of the American population was not convinced that influenza was a serious health threat or they were concerned about the vaccine's safety, or both. Thus, in 1976, 40% of the population did not believe

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[909] Rosenberg, *Explaining Epidemics*.
[910] Garrett, "The American Bicentennial: Swine Flu and Legionnaires' Disease," 1994.
[911] Taleb, *The Black Swan*, xxi–xxii.
[912] Wolfe, *The Viral Storm*.
[913] CDC, "Vaccine Associated Disability -- A Problem for Public Health."

in "flu shots"; while in 2009, 50% of the population survey was not concerned with the threat of flu.[914] It appears that Americans were even less convinced by predictions of the "next" pandemic in 2009 than they were thirty-five years before. Inaccurate predictions of either the timing or severity of a flu pandemic robs public health of its credibility.

At the same time, there have been many improvements in influenza vaccines and, in most years, the flu shot has been reasonably effective with limited adverse reactions. In 2012, virologists conducted a meta-analysis on the 5,707 studies since 1967 to discern how well influenza vaccine protects against infection. The researchers found that influenza vaccines provide moderate protection against confirmed influenza, but such protection is absent in some seasons. Evidence for protection in adults aged 65 years or older is lacking. While this was not a ringing endorsement for flu vaccination, researchers assert that even moderate protection reduces the risks associated with influenza for the population at large.[915] Efforts are under way for a universal influenza vaccine that would protect against the inevitable mutations of flu viruses.

According to historian of medicine Howard Markel, these windows into the history of disease and its political context are revelatory about a society's administrative and political "strengths and shortcomings" in response to epidemics.[916] Fascination with the sudden microbe that kills few in spectacular fashion too often distracts from the impact of infectious scourges that kill millions every year. Human influenza is such a virus, revealing itself in a

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[914] SteelFisher et al., "The Public's Response to the 2009 H1N1 Influenza Pandemic."
[915] Vincent Racaniello, "How Good Is the Influenza Vaccine?," *Virology Blog*, November 3, 2011; Michael T Osterholm et al., "Efficacy and Effectiveness of Influenza Vaccines: A Systematic Review and Meta-Analysis," *The Lancet Infectious Diseases* 12, no. 1 (January 2012): 36–44.
[916] Howard Markel, "Contemplating Pandemics: The Role of Historical Inquiry in Developing Pandemic-Mitigation Strategies for the Twenty-First Century," in *Ethical and Legal Considerations in Mitigating Pandemic Disease*, ed. Stanley M Lemon et al., Forum on Microbial Threats (Washington D.C.: The National Academies Press, 2007), 44.

new form each year. Estimates show that while pandemic influenza can be deadly, the cumulative effects of inter-pandemic outbreaks are generally of greater consequence.[917]

6.4 Avian Flu: Research Controversies

Since 1997, when avian flu jumped the species barrier to infect humans, researchers and public health officials have worried about the potential of H5N1 to spark a pandemic. Today, avian flu experiments are at the center of controversies about influenza research. "Dual-use research of concern" (DURC) is life sciences research that is intended for benefit, but which might easily be misapplied to do harm.[918] These concerns emerged in the mid-twentieth century in the context of wartime research and advances in biological knowledge.[919] After 9/11 and the anthrax attacks, spending on biodefense in the United States soared.

Recent studies on influenza viruses have led to renewed attention on DURC, as there is an ongoing debate over whether the benefits of gain-of-function (GOF) experiments outweigh concerns over biosecurity and biosafety. "Gain of function" is not a precise term, as sometimes there is loss of function in experiments and the terminology is too ambiguous.[920] GOF experiments produce viral mutations that confer new or enhanced activity (or loss) on a protein. At issue is the fact that GOF experiments can increase the transmission or pathogenicity, or both, of a virus in the course of an experiment.

The center of the GOF controversy with H5N1 involved separate experiments conducted in 2011 by Yoshihiro Kawaoka at the University of Wisconsin and Ron Fouchier of the Erasmus Medical Center in The Netherlands. Their GOF research resulted in a genetic

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[917] Kavet, "A Perspective on the Significance of Pandemic Influenza," 1063.
[918] Office of Science Policy, "Dual Use Research of Concern."
[919] Institute of Medicine, *Perspectives on Research with H5N1 Avian Influenza: Scientific Inquiry, Communication, Controversy*.
[920] Vincent Racaniello, et al., "aTRIP and a Pause," *This Week in Virology #321* (January 25, 2015).

manipulation to produce a virus capable of transmission among ferrets to model how this transmission might occur in humans.[921] Kawaoka took an H5N1 avian virus and combined it with an H1N1 human virus that had circulated in 2009. He then tested this hybrid virus on ferrets and found that the virus spread through airborne droplets. However, the hybrid virus lost virulence and no ferrets died. Fouchier conducted a similar experiment with ferrets. Fouchier's experiments did not kill the ferrets that caught the flu virus through airborne transmission, but it did kill ferrets after introducing a high dose of the hybrid virus directly into the animal's trachea. Articles describing how the scientists engineered the H5N1virus immediately raised concerns that the publications themselves would provide a blueprint for bioterrorism.

The National Science Advisory Board for Biosecurity (NSABB) declared a temporary moratorium on both the research and the publication of research results in *Nature* and *Science*. When the WHO met to review the science in question, they recommended publishing the research results.[922] The result of the GOF controversy is a vigorous debate about the appropriateness of the researchers' work, the risks associated with the work, as well as censorship of scientific publications.[923]

Proponents of GOF emphasize that discovery in science leads to unanticipated advances. The broader benefit of GOF experiments has been more difficult to evaluate, given that the uses of scientific findings are often not immediately apparent. Opponents of

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[921] Ferrets show similar clinical signs of disease, such as fever, coughing, and sneezing, and flu viruses that spread among humans usually spread in ferrets as well.

[922] Herfst et al., "Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets"; Imai et al., "Experimental Adaptation of an Influenza H5 HA Confers Respiratory Droplet Transmission to a Reassortant H5 HA/H1N1 Virus in Ferrets." This research was published after a moratorium of several months.

[923] Institute of Medicine, *Perspectives on Research with H5N1 Avian Influenza: Scientific Inquiry, Communication, Controversy: Summary of a Workshop*.

GOF cite a list of mishaps including recent laboratory accidents.[924] The risk of a GOF experiment unleashing a devastating epidemic plays on a well-founded human fear, while the potential benefits of the research are considerably harder to articulate.

One reason that conflicts arise, according to Laurie Garrett, is that there is little consensus about the role of government and what is appropriate within a biosecurity context compared to a public health context.[925] In addition, GOF experiments simultaneously touch on two very important features in human life: health and security. Historian/philosopher Foucault wrote that both health and security lack internal principles of limitation – one could never have too much survival or security - leading to inflationary demands for both.[926]

In October 2014, the White House announced that the U.S. Government was implementing a "pause" of new funding for research involving GOF experiments that enhance pathogenicity or transmission of flu, SARS or MERS.[927] MERS and corona virus research received waivers from the moratorium, but some avian influenza research is on hold for at least a year. The moratorium stands while federal officials, NSABB, and the National Research Council (NRC) conduct a review scheduled for release in 2016.

This 2014 research "pause" was a surprise to many in the scientific community. During a public forum at the New York Academy of Medicine, virologists expressed concern that the misunderstandings about avian flu GOF experiments could have a chilling effect on all scientists who work with dangerous agents. The number of scientists working on GOF research is already rather small.[928] Others see benefits to a pause. For example, in an

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[924] McNeil Jr., "C.D.C. Closes Anthrax and Flu Labs After Accidents."
[925] NY Academy of Medicine, *Influenza Virus and Beyond*.
[926] Michel Foucault, "The Risks of Security," in *Power: Essential Works of Foucault, 1954-1984*, ed. Paul Rabinow, vol. 3 (New York: New Press, 2000), 373.
[927] The White House Office of Science and Technology Policy, "Doing Diligence to Assess the Risks and Benefits of Life Sciences Gain-of-Function Research."
[928] NY Academy of Medicine, *Influenza Virus and Beyond*.

Ecohealth editorial, researchers suggested that the "pause" in avian influenza research is an opportunity to examine the environmental determinants of avian flu spread, the human-animal-environment interface.[929]

Also at issue is communication from scientists to the public. Following his H5N1 experiments, virologist Fouchier remarked that this was, "…probably one of the most dangerous viruses you can make."[930] Both the popular and scientific press called the experimental mutation of the H5N1 virus one that "could change world history if it were ever set free."[931] With a headline screaming, "An Engineered Doomsday," the *New York Times* editorial board declared that scientists should not have done these experiments at all.[932] This generated fear and misunderstanding among the public, the press, and even some scientists.[933] At times, we are in a feedback loop with the media that often touts a worst-case scenario without adding clarity to the complexities of emerging viruses.

Avian influenza is an example of a spectacular but rare variety of epidemic disease with a tendency toward public and media over-reaction (Ebola is another example). Legal scholar Sunstein argued that inaccurate assessment of risk stems from "probability neglect," a persistent inability of humans to respond in rational fashion to dire risks with very low probability. Individuals overweigh risks associated with phenomena that are considered "unknown."[934] By cutting off avian flu research, we may be entering a time in which the "unknowns" dominate scientific discourse, resulting in even more skewed risk-benefit

[929] Jeggo et al., "EcoHealth and the Influenza A/H5N1 Dual Use Issue."
[930] Enserink, "Scientists Brace for Media Storm Around Controversial Flu Studies."
[931] Ibid.
[932] "An Engineered Doomsday."
[933] Racaniello, "Origin of the H5N1 Storm."
[934] Price-Smith, *Contagion and Chaos : Disease, Ecology, and National Security in the Era of Globalization*.

analyses. However, with the continual evolution of influenza viruses and the potential for zoonotic events leading to pandemics, it remains important to maintain vigilance.

Chapter Seven: Conclusions and Broader Impacts

As an animal disease that crosses species barriers, avian influenza has had considerable global impact on the poultry industry, wild bird populations, and human health. From 1997 to 2015, avian flu epizootics emerged dozens of times with many outbreaks involving millions of birds with the spillover of disease to people. Currently, avian influenza (subtype H5N1) is the most widespread animal disease ever recorded.[935] This dissertation set out to examine the role of avian flu viruses in human influenza ecology and to determine what factors contributed to the sharp escalation of bird flu events in the last few decades.

The mutable nature of the influenza virus itself has shaped scientific assumptions and knowledge about influenza for decades and continues to do so. Knowledge about flu viruses is partial, always changing. From the accumulated historical and scientific evidence presented in this dissertation, it is clear that influenza transmission in animals and humans is part of a tightly connected viral web. Evidence suggests that viral transmission in domestic poultry, spillover to wild birds and humans, and the potential for subsequent pandemic spread, are all increasing.

Since the first isolation of the influenza virus in the 1930s, experts have attempted to predict epidemics based on virus characteristics, natural cycles, or both. Since that time, scientists have come to understand the capricious nature of the influenza virus. Historical analysis reveals that influenza pandemics are unpredictable in terms of both subtype and severity. When an avian flu virus sickened and killed humans during 1997 in Hong Kong, speculative predictions about avian flu reinforced narratives of fear. The influenza virus continues to surprise, to reveal itself in new forms.

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[935] McMichael, Neira, and Heymann, "World Health Assembly 2008: Climate Change and Health."

The natural experiment in avian influenza at Qinghai mobilized a small community of virus hunters who assessed influenza both in its milieu as well as under the microscope. Researchers investigated the movement of avian viruses along the Central Asian Flyway, a scale relevant to the wild bird hosts.[936] By taking advantage of U.S. Geological Survey (USGS) expertise in satellite telemetry, geospatial mapping, and waterfowl monitoring, researchers discovered how the wild birds at Qinghai likely encountered the H5N1 virus at their wintering grounds. Technological expertise, outside of the virologists' traditional methods, was essential in producing new knowledge about avian influenza at Qinghai. Spatiotemporal analyses and eco-virological studies were part of an approach to examine ecological relationships at the center of "viral traffic," the place where viruses transfer to new hosts. This is an innovative model for integrating environmental and disease factors and encouraged collaboration across what had previously been deep organizational and professional silos. Avian flu science at Qinghai represents science beyond laboratory.

While these scientific studies at Qinghai did not stop the spread of avian influenza, they revealed a specific ecological pathway for the transfer of avian viruses among chickens, ducks, captive-bred geese, and wild geese. In terms of the controversy about the role of migrating birds in the long distance transmission of avian flu, I conclude from the evidence that the spread of avian flu from Qinghai to Europe since 2005 occurred via migratory pathways. At a more localized level, poultry movement also spreads avian viruses among domestic and wild birds as well as people. At Qinghai, farmed or captive wild birds have become a bridge between the wild and the domestic.[937]

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[936] Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau," 2011.
[937] Lyle Fearnley, "Wild Goose Chase: The Displacement of Influenza Research in the Fields of Poyang Lake, China," *Cultural Anthropology* 30, no. 1 (February 17, 2015): 12–35; Fearnley, "The Birds of Poyang Lake: Sentinels at the Interface of Wild and Domestic"; Takekawa et al., "Victims and Vectors."

Wild birds have become vectors of a disease that had previously been pathogenic only for chickens. This has major implications and suggests that it will be very difficult, if not impossible, to halt the escalation of bird flu epizootics. A consequence is that avian viruses remain available for reassortment with other, possibly more dangerous, viruses.

The avian flu story offers insights into some wider dilemmas surrounding animal health and food production. Factory agribusiness generates artificial ecologies that would not persist in nature because of the disease costs they would incur. The role of factory farms is that the intensive confinement of poultry facilitates the frequency and scale of avian flu outbreaks. Agricultural practices have become a dominant factor determining the conditions in which zoonotic pathogens evolve, spread, and eventually enter the human population.[938] The escalation of avian flu outbreaks may be an inadvertent "biological fallout" of industrial food production.[939]

There is no historical analog to the current increase in environmental change, factory food production, and their impacts on the microbial world. Viruses adapt to changing environments and are quick to exploit man made or natural imbalances. Experts claim that changing environmental conditions around the world have fostered the spread of new viruses - HIV, Lassa, Ebola, avian influenza, and others.[940]

Based on evidence reinforced through case study examples, this dissertation concludes that multiple factors operated synergistically to escalate global bird flu outbreaks at Qinghai that threaten the health of many species. These factors include the increased density of people, poultry, and waterfowl; environmental destruction and fragmented

[938] Slingenbergh et al., "Ecological Sources of Zoonotic Diseases."
[939] Wallace, "Breeding Influenza."
[940] Garrett, *The Coming Plague*.

ecosystems; climate change; and industrial livestock production. Avian influenza outbreaks are not merely chance mutations in a virus but are a result of these antecedent conditions.

This dissertation argues that a comprehensive understanding of influenza as a virus at the human-animal-environment interface is the optimal means to uncover the "upstream" causes of bird flu, most of which reside in human activities.

The Qinghai-Tibet Railway (QTR), the world's highest altitude train, served as a proxy to capture the environment, technology, and geopolitics of the Qinghai region in the case study. I envisioned the railway as a contemporary metaphor for a post-industrial world where nature, culture, and technology interact in increasingly complex ways. As portrayed in Leo Marx's *Machine in the Garden*, a locomotive bursts onto the scene almost from nowhere, forever spoiling a pastoral ideal.[941] However, in the case of the QTR, the "spoiling" is far more profound. The permafrost is melting and shifting in response to a warming climate, thus undermining the foundations beneath the tracks.[942]

The Qinghai-Tibet Plateau is at the leading edge of global climate change. It is likely that the magnitude of climate change in the coming decades will exceed climatic changes in the recent past. The microclimate of Qinghai Lake is warming even faster. As a place at the center of an avian influenza outbreak among wild birds that spread to over sixty countries, this may be significant.

This dissertation concludes that Qinghai is at the center of complex evolutionary changes in viruses that coincide with human exploitation and climate-induced shifts in the environment. Although effects of climate change are not easy to quantify, humankind may be underestimating the biological response to warming. Events and science at Qinghai serve

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[941] Marx, *The Machine in the Garden.*
[942] Peng et al., "Building a 'Green' Railway in China."

as powerful real-world examples to understand avian influenza and to gain insights into the radical changes under way in our natural environment. The Qinghai-Tibet Plateau is a critical place to detect the geophysical, social and health impacts of climate and environmental change in early twenty-first century.

Finally, Qinghai serves as a metaphor for how phenomena can overtake humans far in advance of understanding the causes for such phenomena. The role of the contingent and unseen is powerful. The challenge is to understand the linkages among complex phenomena that operate at multiple spatial and temporal scales. As a place at the crossroads of interconnected global phenomena such as avian influenza and climate change, Qinghai provides a lens to envision the unintended consequences of natural and human forces over the coming decades.

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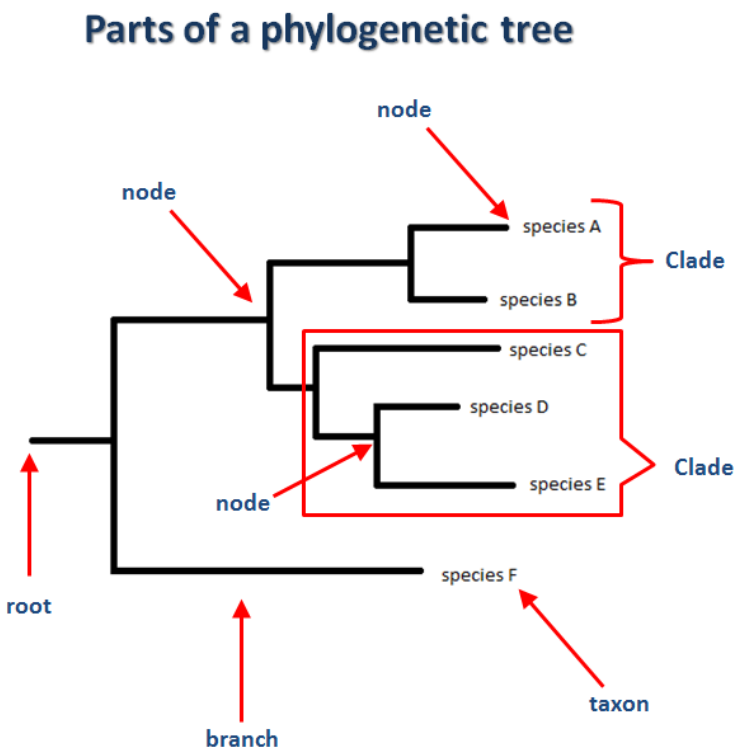
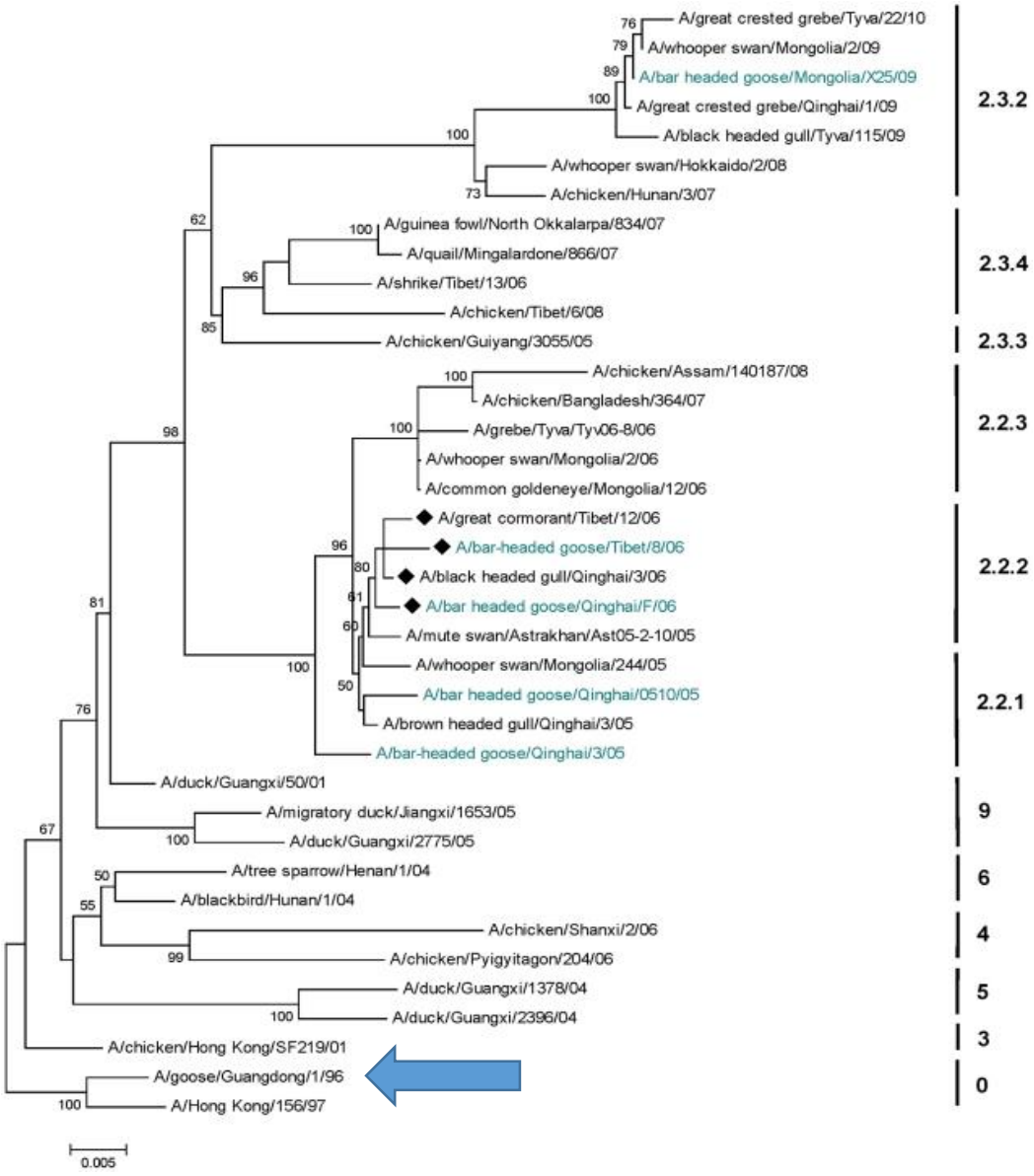
Appendix 1: Overview of a Phylogenetic Tree



Phylogenetics trees contain information about the inferred evolutionary relationships among a set of viruses. A clade is a group of organisms that includes an ancestor and *all* descendants of that ancestor.

The horizontal dimension gives the amount of genetic change. The horizontal lines are branches and represent evolutionary lineages changing over time. The longer the branch in the horizontal dimension, the larger the amount of change.

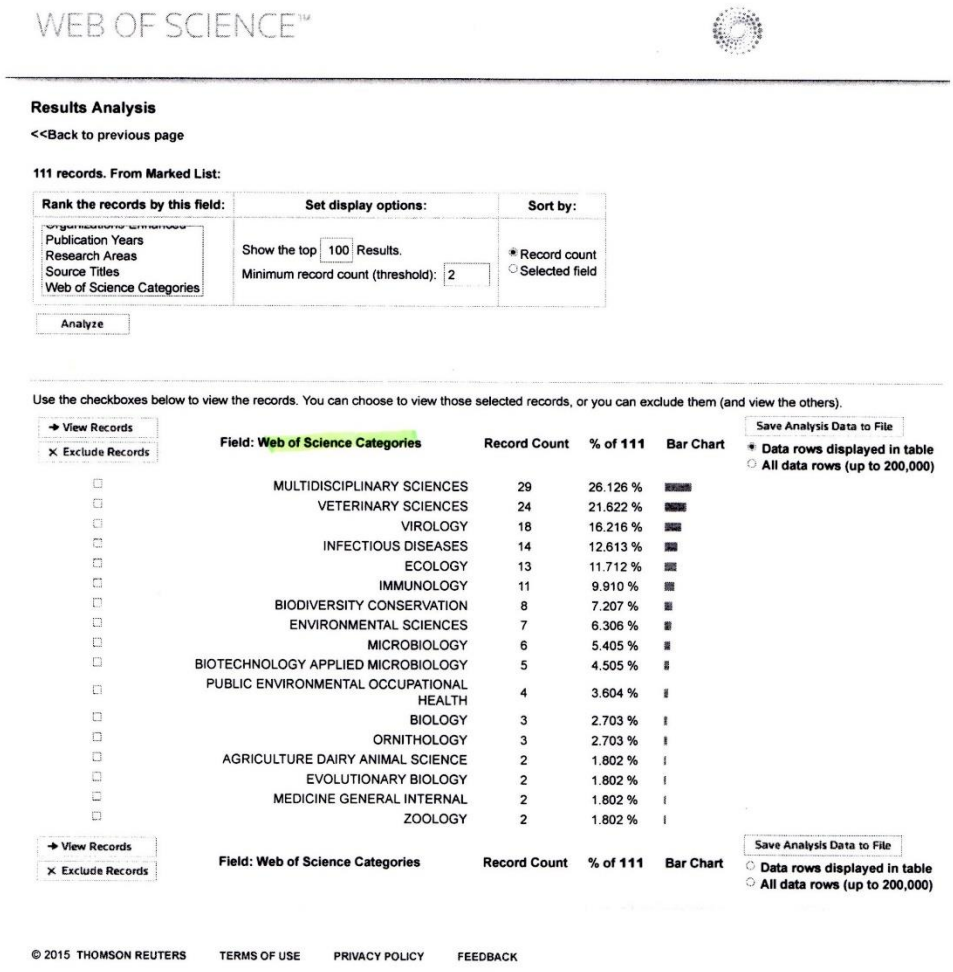
Appendix 1: Phylogenetic Tree of H5N1 Virus for Bar-Headed Goose, 2005-2009



Phylogenetic relationships of H5N1inferred by neighbor-joining analysis based on fragment of the HA gene. The large arrow points to the ancestor virus, A/goose/Guangdong/1/96. Viruses isolated from the bar-headed goose are highlighted and the grouping of isolates from Tibet and Qinghai are indicated by a symbol (♦).[943] A high value (i.e., 100) next to each node means that there is strong evidence that the sequences to the right of the node cluster together. This is a statistical measure.

[943] Diann J Prosser et al., "Wild Bird Migration across the Qinghai-Tibetan Plateau: A Transmission Route for Highly Pathogenic H5N1," *PloS One* 6, no. 3 (2011): e17622.

Appendix 2: Results of Systematic Mapping for "Qinghai-H5N1" Research Categories



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111 records. From Marked List:

Rank the records by this field:	Set display options:	Sort by:
Publication Years Research Areas Source Titles Web of Science Categories	Show the top 100 Results. Minimum record count (threshold): 2	◉ Record count ○ Selected field

Analyze

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others).

→ View Records
× Exclude Records

Save Analysis Data to File
◉ Data rows displayed in table
○ All data rows (up to 200,000)

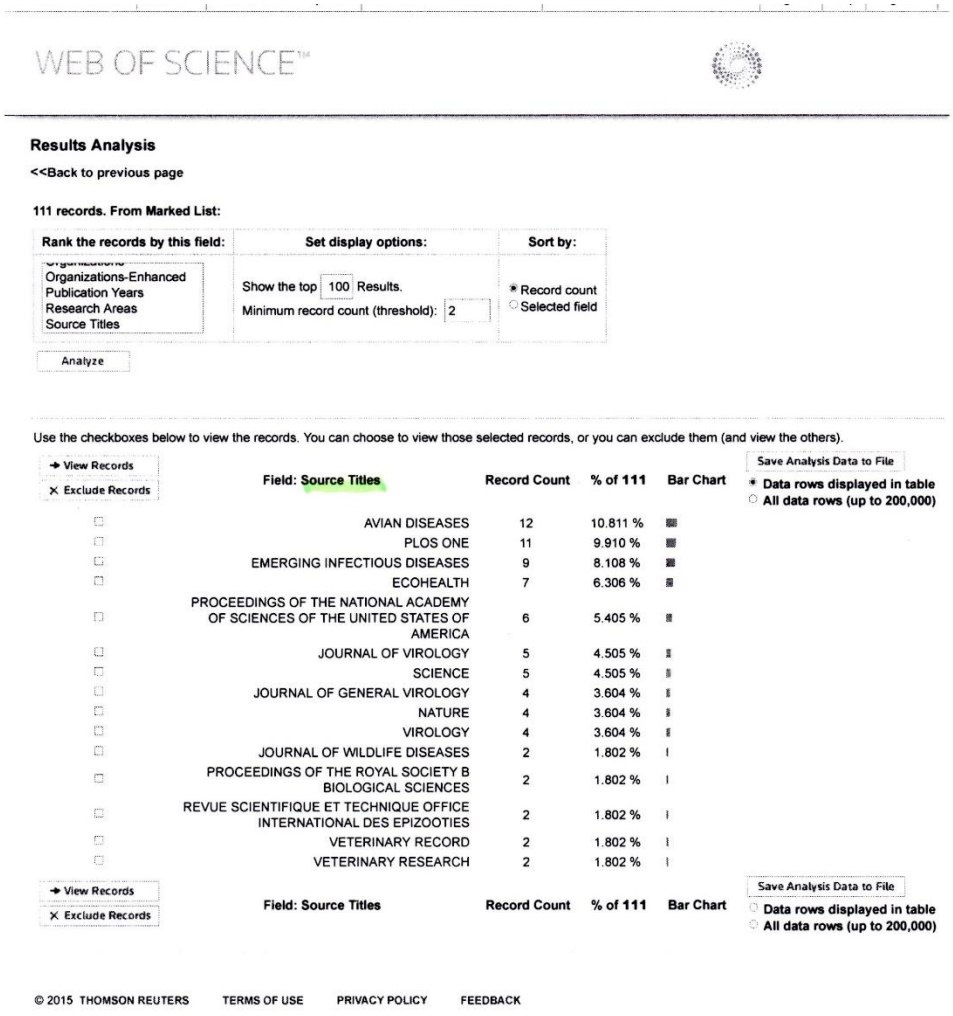
Field: Web of Science Categories	Record Count	% of 111	Bar Chart
MULTIDISCIPLINARY SCIENCES	29	26.126 %	
VETERINARY SCIENCES	24	21.622 %	
VIROLOGY	18	16.216 %	
INFECTIOUS DISEASES	14	12.613 %	
ECOLOGY	13	11.712 %	
IMMUNOLOGY	11	9.910 %	
BIODIVERSITY CONSERVATION	8	7.207 %	
ENVIRONMENTAL SCIENCES	7	6.306 %	
MICROBIOLOGY	6	5.405 %	
BIOTECHNOLOGY APPLIED MICROBIOLOGY	5	4.505 %	
PUBLIC ENVIRONMENTAL OCCUPATIONAL HEALTH	4	3.604 %	
BIOLOGY	3	2.703 %	
ORNITHOLOGY	3	2.703 %	
AGRICULTURE DAIRY ANIMAL SCIENCE	2	1.802 %	
EVOLUTIONARY BIOLOGY	2	1.802 %	
MEDICINE GENERAL INTERNAL	2	1.802 %	
ZOOLOGY	2	1.802 %	

→ View Records
× Exclude Records

Save Analysis Data to File
○ Data rows displayed in table
○ All data rows (up to 200,000)

Field: Web of Science Categories | Record Count | % of 111 | Bar Chart

Appendix 2: Results of Systematic Mapping "Qinghai-H5N1" Publication Titles



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111 records. From Marked List:

Rank the records by this field:	Set display options:	Sort by:
Organizations-Enhanced Publication Years Research Areas Source Titles	Show the top 100 Results. Minimum record count (threshold): 2	◉ Record count ○ Selected field

Analyze

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others).

→ View Records
× Exclude Records

Save Analysis Data to File
◉ Data rows displayed in table
○ All data rows (up to 200,000)

Field: Source Titles	Record Count	% of 111	Bar Chart
AVIAN DISEASES	12	10.811 %	
PLOS ONE	11	9.910 %	
EMERGING INFECTIOUS DISEASES	9	8.108 %	
ECOHEALTH	7	6.306 %	
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	6	5.405 %	
JOURNAL OF VIROLOGY	5	4.505 %	
SCIENCE	5	4.505 %	
JOURNAL OF GENERAL VIROLOGY	4	3.604 %	
NATURE	4	3.604 %	
VIROLOGY	4	3.604 %	
JOURNAL OF WILDLIFE DISEASES	2	1.802 %	
PROCEEDINGS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES	2	1.802 %	
REVUE SCIENTIFIQUE ET TECHNIQUE OFFICE INTERNATIONAL DES EPIZOOTIES	2	1.802 %	
VETERINARY RECORD	2	1.802 %	
VETERINARY RESEARCH	2	1.802 %	

→ View Records
× Exclude Records

Save Analysis Data to File
○ Data rows displayed in table
○ All data rows (up to 200,000)

Appendix 2: Results of Systematic Mapping "Qinghai-H5N1" Research Organizations

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111 records. From Marked List:

Rank the records by this field:	Set display options:	Sort by:
Group Authors Languages Organizations Organizations-Enhanced	Show the top 100 Results. Minimum record count (threshold): 2	◉ Record count ○ Selected field

Analyze

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others).

→ View Records
× Exclude Records

Save Analysis Data to File
◉ Data rows displayed in table
○ All data rows (up to 200,000)

Field: Organizations-Enhanced	Record Count	% of 111	Bar Chart
CHINESE ACADEMY OF SCIENCES	24	21.622 %	
UNITED STATES GEOLOGICAL SURVEY	20	18.018 %	
UNIVERSITY OF HONG KONG	13	11.712 %	
ST JUDE CHILDREN S RESEARCH HOSPITAL	12	10.811 %	
FOOD AGR ORG UNITED NATIONS	9	8.108 %	
UNITED STATES DEPARTMENT OF AGRICULTURE USDA	8	7.207 %	
UNIVERSITY OF OKLAHOMA	7	6.306 %	
CIRAD	6	5.405 %	
ERASMUS UNIVERSITY ROTTERDAM	6	5.405 %	
MONGOLIAN ACAD SCI	6	5.405 %	
UNIVERSITE LIBRE DE BRUXELLES	6	5.405 %	
UNIVERSITY OF CALIFORNIA SYSTEM	6	5.405 %	
WETLANDS INT	6	5.405 %	
BEIJING NORMAL UNIVERSITY	5	4.505 %	
CHINESE ACADEMY OF AGRICULTURAL SCIENCES	5	4.505 %	
FONDS DE LA RECHERCHE SCIENTIFIQUE FNRS	5	4.505 %	
MAX PLANCK SOCIETY	5	4.505 %	
QINGHAI LAKE NATL NAT RESERVE	5	4.505 %	
TSINGHUA UNIVERSITY	5	4.505 %	
UNIVERSITY OF GEORGIA	5	4.505 %	
UNIVERSITY OF MARYLAND COLLEGE PARK	5	4.505 %	
UNIVERSITY OF UTAH	5	4.505 %	
UNIVERSITY SYSTEM OF GEORGIA	5	4.505 %	
UNIVERSITY SYSTEM OF MARYLAND	5	4.505 %	
UTAH SYSTEM OF HIGHER EDUCATION	5	4.505 %	
BANGOR UNIVERSITY	4	3.604 %	
BOMBAY NAT HIST SOC	4	3.604 %	
CHINA AGRICULTURAL UNIVERSITY	4	3.604 %	
NATIONAL INSTITUTES OF HEALTH NIH USA	4	3.604 %	
NIH FOGARTY INTERNATIONAL CENTER FIC	4	3.604 %	
UNIVERSITY OF BIRMINGHAM	4	3.604 %	
UNIVERSITY OF WISCONSIN MADISON	4	3.604 %	

Appendix 2: Results of Systematic Mapping "Qinghai-H5N1" Funding Agencies

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111 records. From Marked List:

Rank the records by this field:	Set display options:	Sort by:
Countries/Territories Document Types Editors Funding Agencies	Show the top 100 Results. Minimum record count (threshold): 2	◉ Record count ○ Selected field

Analyze

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others).

→ View Records
× Exclude Records

Save Analysis Data to File
◉ Data rows displayed in table
○ All data rows (up to 200,000)

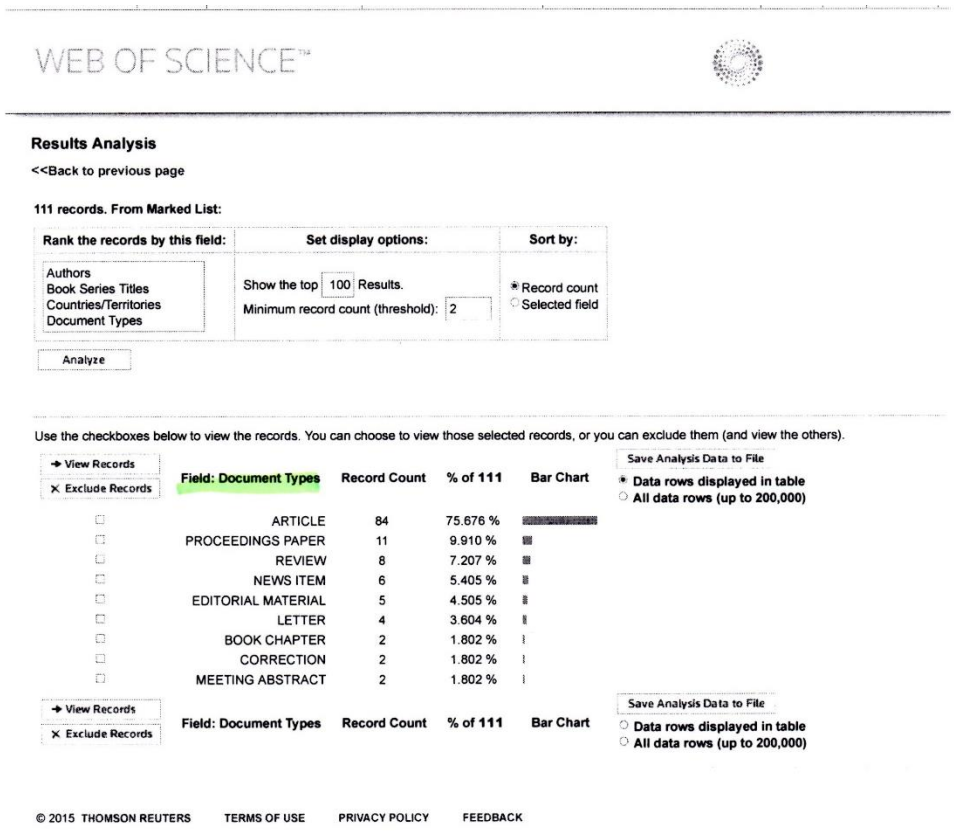
Field: Funding Agencies	Record Count	% of 111	Bar Chart
CHINESE ACADEMY OF SCIENCES	5	4.505 %	
NATIONAL NATURAL SCIENCE FOUNDATION OF CHINA	5	4.505 %	
FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS	4	3.604 %	
NATIONAL INSTITUTES OF HEALTH	4	3.604 %	
NATIONAL SCIENCE FOUNDATION	4	3.604 %	
MAX PLANCK INSTITUTE FOR ORNITHOLOGY	3	2.703 %	
U S GEOLOGICAL SURVEY	3	2.703 %	
UNITED NATIONS FOOD AND AGRICULTURE ORGANIZATION	3	2.703 %	
WESTERN ECOLOGICAL RESEARCH CENTER	3	2.703 %	
ALASKA SCIENCE CENTER	2	1.802 %	
AVIAN INFLUENZA PROGRAM	2	1.802 %	
CAS	2	1.802 %	
EU	2	1.802 %	
FAO	2	1.802 %	
GOVERNMENT OF SWEDEN	2	1.802 %	
NIH	2	1.802 %	
PATUXENT WILDLIFE RESEARCH CENTER	2	1.802 %	
UNITED STATES GEOLOGICAL SURVEY PATUXENT WILDLIFE RESEARCH CENTER	2	1.802 %	
USDA	2	1.802 %	
USGS	2	1.802 %	

→ View Records
× Exclude Records

Save Analysis Data to File
○ Data rows displayed in table
○ All data rows (up to 200,000)

(73 records(65.766%) do not contain data in the field being analyzed.)

Appendix 2: Results of Systematic Mapping "Qinghai-H5N1" Document Types



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111 records. From Marked List:

Rank the records by this field:	Set display options:	Sort by:
Authors Book Series Titles Countries/Territories Document Types	Show the top 100 Results. Minimum record count (threshold): 2	Record count Selected field

Analyze

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others).

→ View Records
× Exclude Records

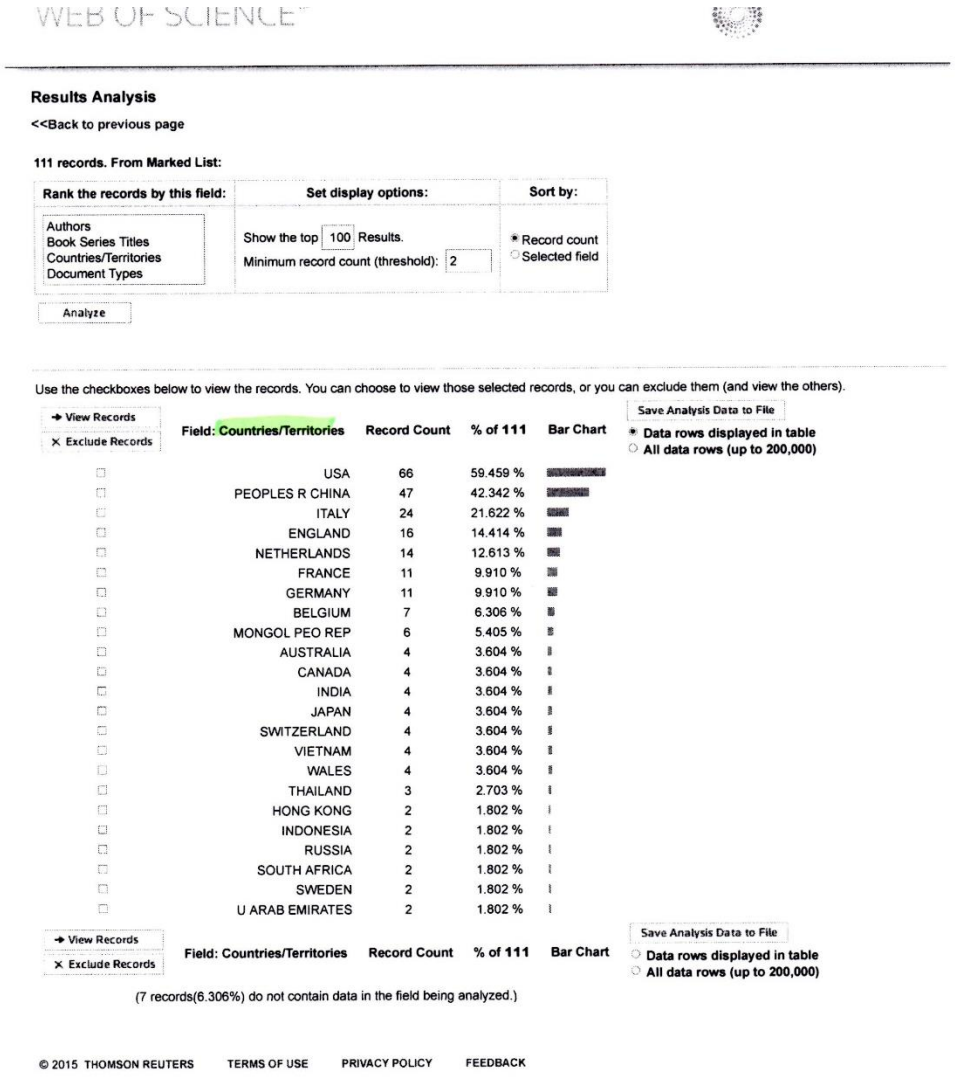
Save Analysis Data to File
Data rows displayed in table
All data rows (up to 200,000)

Field: Document Types	Record Count	% of 111	Bar Chart
ARTICLE	84	75.676 %	
PROCEEDINGS PAPER	11	9.910 %	
REVIEW	8	7.207 %	
NEWS ITEM	6	5.405 %	
EDITORIAL MATERIAL	5	4.505 %	
LETTER	4	3.604 %	
BOOK CHAPTER	2	1.802 %	
CORRECTION	2	1.802 %	
MEETING ABSTRACT	2	1.802 %	

→ View Records
× Exclude Records

Save Analysis Data to File
Data rows displayed in table
All data rows (up to 200,000)

Appendix 2: Results of Systematic Mapping "Qinghai-H5N1" Research Countries



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111 records. From Marked List:

Rank the records by this field:	Set display options:	Sort by:
Authors Book Series Titles Countries/Territories Document Types	Show the top 100 Results. Minimum record count (threshold): 2	Record count Selected field

Analyze

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others).

→ View Records
× Exclude Records

Save Analysis Data to File
Data rows displayed in table
All data rows (up to 200,000)

Field: Countries/Territories	Record Count	% of 111	Bar Chart
USA	66	59.459 %	
PEOPLES R CHINA	47	42.342 %	
ITALY	24	21.622 %	
ENGLAND	16	14.414 %	
NETHERLANDS	14	12.613 %	
FRANCE	11	9.910 %	
GERMANY	11	9.910 %	
BELGIUM	7	6.306 %	
MONGOL PEO REP	6	5.405 %	
AUSTRALIA	4	3.604 %	
CANADA	4	3.604 %	
INDIA	4	3.604 %	
JAPAN	4	3.604 %	
SWITZERLAND	4	3.604 %	
VIETNAM	4	3.604 %	
WALES	4	3.604 %	
THAILAND	3	2.703 %	
HONG KONG	2	1.802 %	
INDONESIA	2	1.802 %	
RUSSIA	2	1.802 %	
SOUTH AFRICA	2	1.802 %	
SWEDEN	2	1.802 %	
U ARAB EMIRATES	2	1.802 %	

→ View Records
× Exclude Records

Field: Countries/Territories | Record Count | % of 111 | Bar Chart

Save Analysis Data to File
Data rows displayed in table
All data rows (up to 200,000)

(7 records(6.306%) do not contain data in the field being analyzed.)

Appendix 2: Results of Systematic Mapping "Qinghai-H5N1" Research Authors

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111 records. From Marked List:

Rank the records by this field:	Set display options:	Sort by:
Authors Book Series Titles Countries/Territories Document Types	Show the top 100 Results. Minimum record count (threshold): 2	◉ Record count ○ Selected field

Analyze

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others).

→ View Records
× Exclude Records

Save Analysis Data to File
◉ Data rows displayed in table
○ All data rows (up to 200,000)

Field: Authors	Record Count	% of 111	Bar Chart
NEWMAN SH	20	18.018 %	
TAKEKAWA JY	17	15.315 %	
PROSSER DJ	16	14.414 %	
LEI FM	13	11.712 %	
WEBSTER RG	12	10.811 %	
YAN BP	12	10.811 %	
GILBERT M	10	9.009 %	
GUAN Y	10	9.009 %	
LI TX	10	9.009 %	
XIAO XM	10	9.009 %	
DOUGLAS DC	9	8.108 %	
PEIRIS JSM	7	6.306 %	
BATBAYAR N	6	5.405 %	
HOU YS	6	5.405 %	
LI YD	6	5.405 %	
CAPPELLE J	5	4.505 %	
CHEN H	5	4.505 %	
CUI P	5	4.505 %	
GAIDET N	5	4.505 %	
GUO S	5	4.505 %	
HE YB	5	4.505 %	
MUNDKUR T	5	4.505 %	
PERRY WM	5	4.505 %	
SHORTRIDGE KF	5	4.505 %	
SLINGENBERGH J	5	4.505 %	
XING Z	5	4.505 %	
XU B	5	4.505 %	
YIN ZH	5	4.505 %	
BALACHANDRAN S	4	3.604 %	
BISHOP CM	4	3.604 %	
BUTLER PJ	4	3.604 %	
CHEN HL	4	3.604 %	
FEARE CJ	4	3.604 %	
KAWAOKA Y	4	3.604 %	
KRAUSS S	4	3.604 %	
LI KS	4	3.604 %	
NATSAGDORJ T	4	3.604 %	
OSTERHAUS ADME	4	3.604 %	
PEIRIS M	4	3.604 %	

Appendix 2: Publications Qinghai-H5N1[944]		
Publication	**Research Categories**	**# Citations**
Alexander, Dennis J. "Summary of Avian Influenza Activity in Europe, Asia, Africa, and Australasia, 2002-2006." *Avian Diseases* 51, no. 1 Suppl (March 2007): 161–66. doi:10.1637/7602-041306R.1.	Veterinary Science	133
Artois, M, et al. "Outbreaks of Highly Pathogenic Avian Influenza in Europe: The Risks Associated with Wild Birds." *Revue Scientifique et Technique (International Office of Epizootics)* 28, no. 1 (April 2009): 69–92.	Veterinary Science	24
Bi, Yuhai, et al. "Highly Pathogenic Avian Influenza A(H5N1) Virus Struck Migratory Birds in China in 2015." *Scientific Reports* 5 (August 11, 2015): 12986. doi:10.1038/srep12986.	Multidisciplinary	0
Bourouiba, L, et al. "Spatial Dynamics of Bar-Headed Geese Migration in the Context of H5N1." *Journal of the Royal Society, Interface / the Royal Society* 7, no. 52 (November 6, 2010): 1627–39. doi:10.1098/rsif.2010.0126.	Multidisciplinary	14
Boyce, Walter M., et al. "Avian Influenza Viruses in Wild Birds: A Moving Target." *Comparative Immunology, Microbiology and Infectious Diseases* 32, no. 4 (July 2009): 275–86. doi:10.1016/j.cimid.2008.01.002.	Immunology Microbiology Veterinary Science	26
Breban, Romulus, et al. "The Role of Environmental Transmission in Recurrent Avian Influenza Epidemics." *PLoS Computational Biology* 5, no. 4 (April 2009): e1000346. doi:10.1371/journal.pcbi.1000346.	Biochemical methods Computational Bio	83
Brown, Justin D, et al. "Experimental Infection of Swans and Geese with Highly Pathogenic Avian Influenza Virus (H5N1) of Asian Lineage." *Emerging Infectious Diseases* 14, no. 1 (January 2008): 136–42. doi:10.3201/eid1401.070740.	Immunology Infectious Disease	106
Brown, Justin D., et al. "Persistence of H5 and H7 Avian Influenza Viruses in Water." *Avian Diseases* 51, no. s1 (March 1, 2007): 285–89. doi:10.1637/7636-042806R.1.	Veterinary Science	151
Brown, Justin, et al. "Survivability of Eurasian H5N1 Highly Pathogenic Avian Influenza Viruses in Water Varies between Strains." *Avian Diseases* 58, no. 3 (September 2014): 453–57. doi:10.1637/10741-120513-ResNote.1.	Veterinary Science	0

[944] Research categories and citation counts are from Web of Science as of 10/09/2015.

Publication	Research Categories	Citations
Butler, Declan. "Blogger Reveals China's Migratory Goose Farms near Site of Flu Outbreak." *Nature* 441, no. 7091 (May 18, 2006): 263. doi:10.1038/441263a.	Multidisiplinary	15
Butler, Declan. "Doubts Hang over Source of Bird Flu Spread." *Nature* 439, no. 7078 (February 16, 2006): 772. doi:10.1038/439772a.	Multidisiplinary	4
Cappelle, Julien, et al. "Risks of Avian Influenza Transmission in Areas of Intensive Free-Ranging Duck Production with Wild Waterfowl." *EcoHealth* 11, no. 1 (March 2014): 109–19. doi:10.1007/s10393-014-0914-2.	Biodiversity Ecology Environmental Sci	2
Capua, Ilaria, and Dennis J. Alexander. "Animal and Human Health Implications of Avian Influenza Infections." *Bioscience Reports* 27, no. 6 (November 20, 2007): 359–72. doi:10.1007/s10540-007-9057-9.	Cell Biology	33
Causey, Douglas, and Scott V. Edwards. "Ecology of Avian Influenza Virus in Birds." *The Journal of Infectious Diseases* 197, no. s1 (February 15, 2008): S29–33. doi:10.1086/524991.	Immunology Infectious Disease Microbiology	17
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