



Collaboration Across the Pond: Influenza Virus Research

Interwar United States and Britain

December 31, 2014

Barbara C. Canavan
PhD Candidate, Oregon State University
canavanb@onid.oregonstate.edu



© 2014 by Barbara C. Canavan

Note: This research report is presented here with the author's permission, but should not be cited or quoted without the author's consent. Rockefeller Archive Center Research Reports Online is an ongoing publication of the Rockefeller Archive Center (RAC) under the general direction of James Allen Smith, Vice President of the RAC and Director of Research and Education. Research Reports Online is intended to foster the network of scholarship in the history of philanthropy and to highlight the diverse range of materials and subjects covered in the collections at the RAC. These reports are drawn from essays submitted by researchers who have visited the Archive Center, most of whom have received grants-in-aid from the Archive Center to support their research. The ideas and opinions expressed in this report are those of the author and not of the Rockefeller Archive Center.

Introduction

The 1918-19 influenza pandemic was truly a nightmare disease, a great natural event in the early days of the twentieth century. Historians report that it was the most devastating infectious disease outbreak since the plague swept Europe and Asia in the fourteenth century.¹ The official mortality estimates of the 1918 flu continue to rise as investigators find new data.² Based on recent historical epidemiology, the global deaths from the pandemic were between 50 and 100 million.³

Following the pandemic, the United States, Britain, Australia, and Russia escalated their influenza research. This report focuses on interwar research at the Rockefeller Institute for Medical Research (RIMR), the Rockefeller International Health Division (IHD), and their collaboration with Britain's Medical Research Council (MRC). My purpose is first to highlight how joint efforts between RIMR and MRC challenged the longstanding dogma of influenza as a strictly human disease. Secondly, I examine correspondence among virus researchers at IHD and MRC during World War II vaccine trials. These letters are not only revelatory about scientific understanding of the influenza virus itself but also highlight concerns about vaccine production.⁴ Every flu virus was suspect of taking on the characteristics of the catastrophic pandemic of 1918.

Whatever the cause, the war on influenza as a disease commenced in full following the pandemic.⁵

Primary sources include documents from the Rockefeller Archive Center from the International Health Board and the Richard E. Shope Papers. In addition, this research draws from many scientific reports and secondary sources.

Challenge to Dogma: Post Pandemic Understanding of the Influenza Virus

By the time the 1918-19 pandemic ended, it would be decades before any scientist could see an influenza virus under an electron microscope and begin to visualize its complexities. Through the 1920s and early 1930s, the influenza virus could not be stained or cultivated. Researchers studied influenza by observing responses of experimental animals. Some researchers claimed that influenza was caused by a filter-passing agent (not retained by standard bacteriological filters) called a virus. Historian of science Angela Creager describes how these filterable agents had been identified in humans (influenza), animals (fowl plague), and plants (tobacco mosaic virus), making virus research important for many disciplines.⁶

Both the British and American scientists showed great interest in filterable viruses in the 1920s. Filter-passing organisms offered new opportunities for medical science and fresh justifications for virus research at both RIMR and MRC.⁷ Simon Flexner, the director of RIMR for its first three decades, wrote of the interrelations of humans, other higher animals, bacteria, protozoa, and “those minute still unclassified, invisible filter-passing viruses of disease.”⁸ Although no one was quite certain about etiology of influenza, in 1920 MRC 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.”⁹ By 1927, Thomas Rivers, head of infectious disease at RIMR, had published a compendium of all the filterable viruses discovered to date.¹⁰ Yet, the nature of the virus remained an open question through the early 1930s.¹¹

There was one aspect about influenza that seemed certain: it was strictly a human disease. However, during the pandemic, J.S. Koen, a veterinarian and inspector for the U.S. Bureau of Animal Industry in Iowa believed he discovered a porcine version of influenza.¹² In fact, Koen was convinced that what he called “swine flu” was the very same “Spanish flu” that infected humans.¹³ Of course, local pig farmers rejected this claim. Richard E. Shope, a researcher at the RIMR Dept. of Animal Pathology Lab near Princeton, grew up near pig farms in Iowa and was intrigued by the stories circulated by Koen and others. Flexner wrote, “It is interesting to note that in 1918 a widely prevalent disease appeared in Iowa which bore certain clinical resemblances to human influenza and inflicted severe economic losses.”¹⁴

With a study of a swine influenza epidemic in 1928-29 in Iowa, the start of a new story about flu began to emerge. Shope isolated the influenza virus from pigs in 1930 and demonstrated that it was causative organism of a swine disease.¹⁵ Soon thereafter, RIMR influenza researcher Thomas Francis confirmed Shope’s results with samples from human cases in Puerto Rico and Philadelphia.¹⁶ Shope was quite adamant that hogs caught the flu from humans and that the virus has survived in that species of animal since 1918.¹⁷ Decades later, virus expert 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 some unlucky swine received.”¹⁸ It was quite an accepted concept in science and society that animals got influenza from humans. During episodes of the “fowl plague”, scientists believed that chickens got the flu virus from their human handlers.¹⁹

Regardless of what scientists would ultimately discover about animals that host the influenza virus, Shope had shattered the traditional dogma that influenza was strictly a human disease.²⁰ He was the first to propose that swine influenza was the surviving prototype of the 1918 pandemic virus based on his experimental results.²¹ Shope's discovery stimulated the work of virus researchers at MRC who, in turn, isolated an influenza virus from humans in 1933.²² Smith, Andrewes, and Laidlaw conducted immunological tests on survivors of the 1918 pandemic and determined that the disease had been due to the swine influenza virus.²³ MRC readily acknowledged the stimulus Shope's discovery had given them.²⁴ Thereafter, Shope and Andrewes developed a close friendship in their joint work and indirectly paved the way for extensive influenza research collaboration across the pond.²⁵

Since the 1933 isolation of human influenza virus, bioscientists have invested considerable resources in a steady flow of influenza viral strains across species and institutions.²⁶ This was especially true of the collaboration between IHD and MRC. Wilbur Sawyer, the head of IHD, inquired of Shope if there was any possibility that the swine influenza virus could survive a trip by air travel.²⁷ Sawyer estimated it would take about a week by air and, if the package was small enough, the cost might not be prohibitive. Thus, 1935 marks the start of the flow of influenza strains for what was one of the world's most comprehensive experiments with influenza viruses and their evolution.

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 across the United States regarding the possible correlation between the presence of swine flu and human flu.²⁸ At that time, Francis suggested that scientists really did not know if the flu virus

was of human origin passed to animals or of animal origin.²⁹ Researchers at IHD noted it would require further extensive investigation to control influenza.³⁰

Frank L. Horsfall at IHD led an elaborate study of influenza in its various aspects from the mid-1930s, including the epidemiology of the disease and the immune reactions of animals and human beings to the influenza viruses. The Rockefeller Foundation offered Horsfall a large technical staff, abundant laboratory space, generous financial support, and a staff that was equipped for large-scale fieldwork to investigate epidemic problems on an international scale. There were some feverishly performed experiments in laboratory animals and humans.³¹ One investigator wrote that there was a great shortage of ferrets, making flu experiments more difficult.³² Sometimes, investigators had to resort to using different animals. 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.”³³

Although researchers assumed that human flu was distinct from swine flu, they believed that human strains were identical or very closely related. Challenges to this understanding would emerge during the U.S. vaccine trials. By the late 1930s, it became clear to both RF and MRC that strains from the same epidemic were very similar, regardless of location when compared to strains from the same place in different years.³⁴ Ideas about a shifting and mutable influenza virus started to take hold.

Vaccine Trials: Efforts to Tame the Influenza Virus

Historian of medicine, John M. Eyler provides rich historical material regarding vaccine trials in the United States in the 1930s and 1940s. He argues that from 1935-1960 influenza was the “most extensively studied virus in the U.S. affecting humans.”³⁵ U.S. researchers attempted

to construct a “master strain of the influenza virus”, one that would yield an effective vaccine.³⁶ To complement Eyler’s findings about the construction of influenza knowledge, this section of the report examines selected correspondence among lead scientists of IHD and MRC during the vaccine trials of the late 1930s and early 1940s. Most interesting are the letters exchanged between Horsfall and Andrewes, both leaders in influenza research in their respective institutions. This correspondence occurred just prior to the creation of the Army Epidemiology Board for influenza research in the U.S. and prior to the creation of the World Health Organization.

Fears of another 1918 pandemic continued to drive and stimulate scientific research. During a flu epidemic in the US in 1937, Frederick Russell, one of the creators of Rockefeller Foundation’s IHD, wrote that the flu in circulation during that year was “more like a pandemic than anything we have had since 1918.”³⁷ However, Russell expressed optimism that answers to most of the influenza questions were at hand. He urged that given a likely pandemic, he did not want to let the “opportunity be lost” to make vaccine.³⁸

Russell was not alone in his optimism. In the mid-1930s, microbe expert Paul de Kruif wrote an article in which he predicted that medical science was “about to conquer influenza.”³⁹ Yet, influenza remained vaguely defined and its epidemiological and clinical picture confused by the existence of closely related respiratory illnesses. Specifically, the extent and duration of immunity produced by influenza viruses were not well understood.⁴⁰

There continued to be confusion about the transmission of influenza across species. 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 noted that a “mouse flu” designation would make “life a lot more difficult”.⁴¹ Horsfall concurred

that a “mouse flu” would only further complicate the influenza picture.⁴² They sought to define and adopt influenza nomenclature that was more precise.

Soon thereafter, officials at IHD and MRC agreed to use standard nomenclature and invited others in the field of influenza research to follow suit. Their joint report described that the clinical picture historically recognized as influenza “is not a single etiological entity”, leaving the door open to rather flexible interpretations in the future.⁴³ The report references publications from the late 1937-1940 by Horsfall, Andrewes and other IHD and MRC researchers who had described clinical influenza based on their own experiments, considered to be the definitive sources.⁴⁴ The authors recommended that new viruses be cleared through IHD and MRC prior to any official “christening” in future scientific reports.⁴⁵ It is noteworthy that the report, ultimately published in the *Lancet*, includes an important caveat: “Influenza-like diseases attacking primarily animals other than man (e.g. swine flu) should be excluded from the [influenza] A, B, C terminology.”⁴⁶ Thus, animals were omitted in the first official nomenclature standards for influenza.

As the war escalated during 1940, 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. He feared a disastrous epidemic. American corporations had been asking MRC if there was anything they could do to help with medical projects during the war.⁴⁷ Andrewes did not want to respond to these organization until he had cleared the potential vaccine production with IHD. Andrewes asked Horsfall about the stability of the vaccine and whether it would lose its potency after two months; the toxicity of the vaccine and the likelihood of “unpleasant reactions”; and, finally, whether the large-scale manufacturing would be feasible.⁴⁸

Horsfall responded to Andrewes that IHD had not tried or made any plans to test the efficacy of the vaccine (producing active immunity in humans) by the experimental infection of vaccinated human volunteers. He emphasized that it was uncertain that such an experiment would approximate conditions of naturally occurring disease. Horsfall cautioned that the vaccine was of “entirely unknown efficacy as regards prophylaxis against epidemic influenza.” Mass production, if it were feasible, would require a large plant staffed with doctors, trained technicians, and special equipment for the freezing and drying of large quantities of vaccine. No plant for this purpose existed. Despite these cautions, Horsfall wrote, “Should you wish to gamble on the possibility that the complex vaccine will be effective...I think an official request for it would be considered favorably here.”⁴⁹

Later that summer, Andrewes noted to Horsfall that, “you probably feel that we are in altogether too much 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.”⁵⁰ This is an early example of how researchers attempt to outrun the influenza virus to predict the next big pandemic in order to secure the production of vaccine.

Large amounts of vaccine were prepared by IHD and shipped to Britain during the war. In one instance, Andrewes thanked Horsfall for his cable reporting that IHD can make 250,000 doses of vaccine a month, as this would be most helpful for Andrewes upcoming consultations.⁵¹ However, within a few months the situation did not look so promising. Andrewes sent a cable to Horsfall that British authorities balked at permitting use of vaccine containing “living virus matter.”⁵² Andrewes wrote that British authorities have been more doubtful about the advisability of using living vaccine, at least compared to the United States. He added, “When one

gets to hundreds of thousands, the chance of some improbable event... ceases to be negligible". He hoped that all the efforts of IHD would prove worthwhile for Britain in their plans to protect citizens against influenza.⁵³

A vaccine trial was conducted in 1940-41 with a new "complex vaccine" developed by Horsfall and administered by him in fifteen state prisons in Florida and Alabama. Both trials included unvaccinated controls.⁵⁴ Horsfall had mentioned to Andrewes that they were fortunate to have access to a number of penal institutions and asylums.⁵⁵ Eyler reports that Horsfall would provide an optimistic interview to *Colliers* and *Atlantic Monthly* about the potential of his "complex vaccine".⁵⁶ However, these vaccine trials were inconclusive. Bauer wrote to Francis that these results were unsatisfactory to those at the Rockefeller Foundation.⁵⁷ The authors of an IHD report cautioned that vaccine was unlikely to offer protection against influenza for an entire year or more.⁵⁸

Based on historian George Corner's interviews and research, Horsfall found his immunological studies rather discouraging, because the multiplicity of viral strains with differing immunological characteristics that turned up in his laboratory seemed to diminish the hope of controlling influenza by vaccines.⁵⁹ Researchers who work with infectious agents walk a fine line between advocacy for their science and public dissemination and understanding of their work.

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. The board recommended that the Commission conduct a study of vaccination in the Army.⁶⁰ The army made extensive plans to vaccinate the troops in 1945.⁶¹ From his own experience in Britain, Andrewes argued that vaccination could reduce influenza

incidence by 35% to 50%. Although not as dramatic a reduction in disease as they would like, Andrewes wanted to recommend to that they use vaccine the following winter. However, Andrewes had become “less hopeful” that the vaccine would do any good.⁶²

Reporting on the 1941 vaccine trial, George Hirst of ISD described to Francis that 3,000 persons were vaccinated, of whom over 2,000 were in mental institutions. While there were no observed adverse reactions to the vaccinations, Hirst was convinced that attempting to test vaccines in mental institutions was “not a good thing”.⁶³ He cautioned there was insufficient staff to follow-up on reactions. Hirst noted that Rockefeller was switching to testing vaccines in penal institutions only, as there were a greater number of trusted individuals to conduct routine follow-up.

In 1943-44, a year with an active flu season, a field trial in the United States successfully demonstrated a reduction in influenza among those vaccinated.⁶⁴ Assessing the results of vaccinations was based on serological analysis of certain flu strains from both vaccinated and unvaccinated individuals before and after a flu epidemic.⁶⁵ The results showed a reduction of about fifty percent of influenza incidence among vaccinated persons. Although evidence indicated that flu vaccine offered good protection, the duration of immunity remained unclear.⁶⁶

Despite success in producing good results in field trials in 1943 and 1945, the same vaccine did fail to provide protection in 1947.⁶⁷ 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.”⁶⁸ This challenged the existing model of the virus as a rather static unchanging agent. Based on a retrospective analysis, it appears a novel virus, one that had not been observed in prior experiments, had caused the outbreak.⁶⁹

Controversies ensued about the reasons for the vaccine failure in 1947. R.M. Taylor of IHD suggested that antigen change in the virus is “continued, unlimited, and unpredictable”.⁷⁰ British and Australian researchers, including Andrewes and Burnet, agreed.⁷¹ British expert Stuart-Harris considered influenza vaccines experimental with no known public health value.⁷² Based on Eyer’s research, American investigators, including Francis on the Influenza Committee, disagreed.⁷³ Francis and his successor, Davenport, were uneasy with the hopeless outlook for creating vaccine to protect against a flu virus with an endless capacity for change.

Ultimately, the viewpoints about the very nature of the influenza virus diverged in the late 1940s post-war consolidation of influenza research through the World Health Organization (WHO).⁷⁴ In 1948, the WHO created the World Influenza Centre in London with an allocation of 3000 dollars and Andrewes as its director.⁷⁵ The Centre had nearly 100 bases around the world and became the center for influenza research. Andrewes cautioned that influenza was likely to produce mutant strains. He argued that existing vaccines would be unlikely to be effective. To avert another 1918, Andrewes urged a greater understanding of the epidemiology of influenza, its “mutants”, and their spread. He admitted that authorities did not know much about the prevalence of influence in different countries, and from year to year. He did not know, for example, whether the rise and fall of epidemics in a particular country was due to endemic strains or importation of flu strains from other regions. Apparently, virus strains had not been compared in one country from year to year, nor compared to co-occurring strains from different countries in the same year. However, through diligent observation and experiments, Andrewes suggested it might eventually be possible for production of vaccine in time to protect countries not yet exposed to the viruses.⁷⁶

Andrewes called for international collaboration to avoid economic loss from influenza and he made three suggestions for achieving it: collect and distribute information, coordinate lab work, and train lab workers from a number of regional laboratories. Andrewes wrote, “It is important to collect now a number of strains from epidemics occurring at different times and places, in hopes of completing more quickly a picture of the epidemiological behavior of influenza.”⁷⁷

WHO established a surveillance system to catch novel stains of influenza so that manufacturers could make vaccines in advance of a pandemic. They worried about the recurrence of a 1918-like pandemic and the need to detect changes in a circulating flu virus at the earliest possible moment. In 1952, the *Expert Committee on Influenza* had its first meeting. The most significant finding was that antigenic shifts in a circulating virus signaled that a pandemic was about to emerge. The committee was charged to watch for shifts in circulating flu viruses in order to make accurate forecasts of the times and places of epidemics. They 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.⁷⁸ However, the manufacturing of vaccines remained slow.⁷⁹

Conclusions

It has been nearly 100 years since the 1918 pandemic. Many scientists believe that we are in a unique pandemic era since 1918 because all the influenza viruses, subtype A, in circulation since that time are direct descendants of the 1918 virus.⁸⁰ Virologists have long attempted to predict pandemics based on virus characteristics and/or natural cycles. Predictions are notoriously unreliable. Yet, by their very nature, viruses are impossible to predict. The most enduring lesson from early influenza research is the daunting challenge to detect pandemics and

determine their severity and spread. In some respects, viruses are the classic epistemic objects whose force lies in what they might become without knowing the precise path.⁸¹

Public health is forced to make decisions before the details about the virus are known. Vaccine production based on growth of virus in eggs is slow and not always consistent. Perhaps historians in the next century will look back with some pity at our dependence on egg-based vaccine technologies.⁸² Eyler accurately refers to vaccine production as a continuous crash programs to produce vaccine just in time.⁸³ Yet, estimates show that while pandemic influenza can be deadly, the cumulative effects of inter-pandemic outbreaks may be of greater consequence.

By examining influenza virus research in the interwar period, it is possible to cast light not only on important science in the first half of the twentieth century, but also on fundamental questions about the relationship between viruses, humans, and other species. Since the 1950s, researchers have discovered that various influenza viruses circulate in humans, horses, marine mammals, pigs, and especially birds. From what they now understand, the primordial source of all influenza viruses is wild aquatic birds. Combining historical sources with molecular biology, researchers argue that the 1918 flu virus was likely avian in origin and that it developed a few key mutations to infect the human population.⁸⁴ It remains unclear if, during the pandemic of 1918, humans passed the influenza virus to pigs or vice versa. What is more convincing is that humans are part of an intricate viral web with other species, a network that science is just beginning to unravel.

End Notes

¹ David K. Patterson, *Pandemic Influenza 1700-1900* (Rowman & Littlefield Publishers, 1986), xv.

² Stephen S Morse, “Emerging Infections: Condemned to Repeat?,” 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); K D Patterson and G F Pyle, “The Geography and Mortality of the 1918 Influenza Pandemic,” *Bulletin of the History of Medicine* 65, no. 1 (1991): 4–21; F. M Burnet and Ellen Clark, *Influenza; a Survey of the Last 50 Years in the Light of Modern Work on the Virus of Epidemic Influenza* (Melbourne: Macmillan, 1942).

³ 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).

⁴ Russell to Bauer, February 15, 1937, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁵ Roger Cooter, “Of War and Epidemics: Unnatural Couplings, Problematic Conceptions,” *Social History of Medicine: The Journal of the Society for the Social History of Medicine / SSHM* 16, no. 2 (August 2003): 283–302. According to Cooter, the coupling of wars and epidemics in the western world was a late-Victorian phenomenon driven by military medical interests. He argues that out of this came the metaphor of war on disease.

⁶ Angela N. H Creager, “Mobilizing Biomedicine: Virus Research,” in *Biomedicine in the Twentieth Century: Practices, Policies, and Politics*, ed. C. Hannaway (Amsterdam, Netherlands: IOS Press, 2008), 172.

⁷ 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): 419.

⁸ Simon Flexner, October 31, 1930, Folder 18, “Sketch of the First Twenty-Five Years of RIMR”, p. 360.

⁹ C.H. Andrewes, “The Bacteriology of Influenza,” in *Ministry of Health Report*, 12, 1920, 125.

¹⁰ T. Rivers, “Filterable Viruses a Critical Review,” *J. Bacteriology* 14, no. 4 (1927): 217–258.

¹¹ Angela N. H Creager, *The Life of a Virus: Tobacco Mosaic Virus as an Experimental Model, 1930-1965* (Chicago: University of Chicago Press, 2002).

¹² JS Koen, *A Practical Method for Field Diagnosis of Swine Diseases*, vol. 14 (Veterinary Publishing Company, 1919).

¹³ Gina Kolata, *Flu : The Story Of The Great Influenza Pandemic*, (Touchstone, 2001).

¹⁴ Simon Flexner, October 31, 1930, Folder 18, "Sketch of the First Twenty-Five Years of RIMR", Box 10, Vol. 18, Scientific Reports of the Laboratories to the Corporation and to the Board of Scientific Directors of RIMR 1929-1930, p. 447, FA145, RU, RAC

¹⁵ Richard E. Shope, "Swine Influenza," *The Journal of Experimental Medicine* 54, no. 3 (July 31, 1931): 349–359.

¹⁶ T. Francis, "Transmission of Influenza by a Filterable Virus," *Science (New York, N.Y.)* 80, no. 2081 (November 16, 1934): 457–59.

¹⁷ Francis to Sippy, May 29, 1936, Folder 6, Box 50, Series 4, RG 5, IHD Records, FA115, RF, RAC; Richard E. Shope, "Swine Influenza".

¹⁸ 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

¹⁹ 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): 590–596.

²⁰ Alfred W. Crosby, *America's Forgotten Pandemic: The Influenza of 1918*, (Cambridge ; New York: Cambridge University Press, 2003), 303.

²¹ 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.

²² Wilson Smith, C.H. Andrewes, and P.P. Laidlaw, "A Virus Obtained from Influenza Patients," *The Lancet* 222, no. 5732 (July 1933): 66–68.

²³ 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

²⁴ George W. Corner, *History of the Rockefeller Institute 1901-1953 Origins and Growth* (New York: Rockefeller Institute Press, 1953), 299–300.

²⁵ C.H. Andrewes, 1971, "Biographical Memoir. Richard Edwin Shope (1901-1966)", p. 180-183, Folder 3, Box 1, FA199, Richard E. Shope Papers, RU, RAC; Peyton Rous, 1957, "Presentation of the Kober Medal to Richard Shope," p. 35, Folder 2, Biographical General 1935-1965, Box 1, FA199, Richard E. Shope Papers, RU, RAC.

²⁶ C. Caduff, "Anticipations of Biosecurity.," in *Biosecurity Interventions: Global Health and Security in Question* (New York: Columbia University Press, 2008), 257–77.

²⁷ Sawyer to Shope, April 6, 1935, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

²⁸ Sippy to Francis, April 21, 1936, Folder 6, Box 50, Series 4, RG 5, IHD Records, FA115, RF, RAC

²⁹ Francis to Sippy, May 29, 1936, Folder 6, Box 50, Series 4, RG 5, IHD Records, FA115, RF, RAC

³⁰ “The Study of Influenza”, December, 1937, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

³¹ George K. Hirst, *Frank Lappin Horsfall, Jr., A Biographical Memoir*, Memoir (Washington D.C.: National Academy of Sciences, 1979), 238.

³² Bauer to Boyd, March 10, 1936, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

³³ Horsfall to Shope, June 28, 1939, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

³⁴ T. P. Magill and Thomas Francis, “Antigenic Differences in Strains of Epidemic Influenza Virus: I. Cross Neutralization Tests in Mice,” *British Journal of Experimental Pathology* 19, no. 5 (October 1938): 273–84.

³⁵ 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.

³⁶ *Ibid.*, 437.

³⁷ Russell to Bauer, February 15, 1937, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

³⁸ *Ibid.*

³⁹ Paul de Kruif, “The Flu-Trappers,” *Reader’s Digest*, February 1936.

⁴⁰ “The Study of Influenza”, December, 1937, Folder 359, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁴¹ Andrewes to Horsfall, March 25, 1939, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁴² Horsfall to Andrewes, April 4, 1939, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁴³ “The Nomenclature of Influenza”, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁴⁴ Stuart-Harris, Smith, and Andrewes, “The Influenza Epidemic of January-March, 1939”; Charles Herbert. Stuart-Harris, C.H. Andrewes, and W. Smith, *A Study of Epidemic Influenza, with Special Reference to the 1936-7 Epidemic.*, Special Report Series, Medical Research Council 228 (London, 1938); Thomas Francis et al., “Studies with Human Influenza Virus during the Influenza Epidemic of 1936-37,” *JAMA* 109 (1937): 566–69; Thomas Francis, “Epidemic Influenza: Studies in Clinical Epidemiology,” *Annals of Internal Medicine* 13, no. 6 (December 1, 1939): 915; F. L. Horsfall, R. G. Hahn, and E. R. Rickard, “Four Recent Influenza Epidemics: An Experimental Study,” *The Journal of Clinical Investigation* 19, no. 2 (March 1940): 379–92.

⁴⁵ “The Nomenclature of Influenza”, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁴⁶ F.L. Horsfall et al., “The Nomenclature of Influenza,” *The Lancet* 236, no. 6110 (October 1940): 413–14.

⁴⁷ Andrewes to Horsfall (confidential), July 2, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁴⁸ Ibid.

⁴⁹ Horsfall to Andrewes, July 16, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁵⁰ Andrewes to Horsfall, August 7, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁵¹ Andrewes to Horsfall, September 26, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁵² Andrewes to Horsfall (Western Union Cable), December 3, 1940, Folder 8, Box 1, Series 4, RG5, IHD Records, FA115, RF, RAC

⁵³ Andrewes to Horsfall, December 10, 1940, Folder 9, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁵⁴ F. L. Horsfall, et al., "Studies on the Efficacy of a Complex Vaccine against Influenza A," *Public Health Reports (1896-1970)* 56, no. 38 (1941): 1863.

⁵⁵ Horsfall to Andrewes, May 9, 1940, Folder 8, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁵⁶ Eyler, "De Kruif's Boast," 424.

⁵⁷ Bauer to Francis, October 24, 1941, Folder 123, Box 12, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁵⁸ "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

⁵⁹ Corner, *History of the Rockefeller Institute 1901-1953 Origins and Growth*, 467.

⁶⁰ Francis to Hirst, May 20, 1942, Folder 123, Box 12, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁶¹ Hirst to Appleget, December 20, 1944, Folder 361, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁶² Andrewes to Horsfall, May 23, 1941, Folder 9, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁶³ Hirst to Francis, November 13, 1942, Folder 123, Box 12, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁶⁴ Thomas Francis, "The Development of the 1943 Vaccination Study of the Commission on Influenza," *Am. J. Epidemiol.* 42, no. 1 (1945): 1-11.

⁶⁵ 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

⁶⁶ Hirst to Appleget, December 20, 1944, Folder 361, Box 33, Series 4, RG 5, IHD Records, FA115, RF, RAC.

⁶⁷ 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.

⁶⁸ Taylor to all Personnel, December 10, 1947, Folder 351, Box 32, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁶⁹ E. D. Kilbourne et al., “The Total Influenza Vaccine Failure of 1947 Revisited: Major Intrasubtypic Antigenic Change Can Explain Failure of Vaccine in a Post-World War II Epidemic,” *Proceedings of the National Academy of Sciences* 99, no. 16 (August 6, 2002): 10748–52, doi:10.1073/pnas.162366899.

⁷⁰ R. M. Taylor, “Studies on Survival of Influenza Virus Between Epidemics and Antigenic Variants of the Virus,” *American Journal of Public Health and the Nations Health* 39, no. 2 (Feb 1949): 171–78.

⁷¹ F. M. Burnet, “Some Biological Implications of Studies on Influenza Viruses,” *Bulletin of the Johns Hopkins Hospital* 88, no. 2 (February 1951): 119–80.

⁷² C. H. Stuart-Harris, “The Present Status of Prophylactic Immunization Against Influenza,” *British Medical Journal* 2, no. 5048 (October 5, 1957): 777–79.

⁷³ Eyler, “De Kruif’s Boast,” 431.

⁷⁴ World Health Organization, “Expert Committee on Influenza” (Geneva, Switzerland, September 9, 1952), WHO/Influenza/16, Archives of World Health Organization.

⁷⁵ Gautier (WHO) to Taylor, September 15, 1947, Folder 9, Box 1, Series 4, RG 5, IHD Records, FA115, RF, RAC

⁷⁶ 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

⁷⁷ *Ibid.*, p. 2-3

⁷⁸ World Health Organization, “Expert Committee on Influenza,” 3.

⁷⁹ A.M. Payne, “The Influenza Program of WHO,” *Bulletin of the World Health Organization* 8, no. 5–6 (1953): 755–92.

⁸⁰ Taubenberger and Morens, “1918 Influenza: The Mother of All Pandemics.”

⁸¹ Hans-Jorg Rheinberger, “Cytoplasmic Particles,” in *Biographies of Scientific Objects*, ed. Lorraine Daston (Chicago: University of Chicago Press, 2000), 272.

⁸² Stephen C. Redd et al., “1918 and 2009: A Tale of Two Pandemics,” *Public Health Reports* 125, no. Suppl 3 (2010): 5.

⁸³ Eyler, “De Kruif’s Boast,” 438.

⁸⁴ Martin Enserink, “From Two Mutations, an Important Clue about the Spanish Flu,” *Science* 315, no. 5812 (February 2, 2007): 582–582.

Works Cited

Primary Sources

Rockefeller Archive Center (RAC):
International Health Board/Division Records (IHD)
Richard E. Shope Papers

Archives of the World Health Organization
WHO/Influenza/16

Scientific Reports and Secondary Sources

- Andrewes, C.H. “The Bacteriology of Influenza.” In *Ministry of Health Report*, 110–25. 12, 1920.
- Barry, John M. *The Great Influenza: The Story of the Deadliest Pandemic in History*. Penguin Books, 2005.
- Bresalier, M. “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): 400–424.
doi:10.1093/shm/hkr162.
- Burnet, F. M. “Some Biological Implications of Studies on Influenza Viruses.” *Bulletin of the Johns Hopkins Hospital* 88, no. 2 (February 1951): 119–80.
- Burnet, F. M., and Ellen Clark. *Influenza; a Survey of the Last 50 Years in the Light of Modern Work on the Virus of Epidemic Influenza*. Melbourne: Macmillan, 1942.
- Caduff, C. “Anticipations of Biosecurity.” In *Biosecurity Interventions: Global Health and Security in Question*, 257–77. New York: Columbia University Press, 2008.
- Cooter, Roger. “Of War and Epidemics: Unnatural Couplings, Problematic Conceptions.” *Social History of Medicine: The Journal of the Society for the Social History of Medicine / SSHM* 16, no. 2 (August 2003): 283–302.
- Corner, George W. *History of the Rockefeller Institute 1901-1953 Origins and Growth*. New York: Rockefeller Institute Press, 1953.
- Creager, Angela N. H. “Mobilizing Biomedicine: Virus Research.” In *Biomedicine in the Twentieth Century: Practices, Policies, and Politics*, edited by C. Hannaway. Amsterdam, The Netherlands: IOS Press, 2008.

-
- . *The Life of a Virus: Tobacco Mosaic Virus as an Experimental Model, 1930-1965*. Chicago: University of Chicago Press, 2002.
- Crosby, Alfred W. *America's Forgotten Pandemic: The Influenza of 1918*. 2 edition. Cambridge ; New York: Cambridge University Press, 2003.
- De Kruif, Paul. "The Flu-Trappers." *Reader's Digest*, February 1936.
- Enserink, Martin. "From Two Mutations, an Important Clue About the Spanish Flu." *Science* 315, no. 5812 (February 2, 2007): 582–582. doi:10.1126/science.315.5812.582.
- Eyler, John M. "De Kruif's Boast: Vaccine Trials and the Construction of a Virus." *Bulletin of the History of Medicine* 80, no. 3 (2006): 409–38. doi:10.1353/bhm.2006.0092.
- Francis, T. "Transmission of Influenza by a Filterable Virus." *Science (New York, N.Y.)* 80, no. 2081 (November 16, 1934): 457–59. doi:10.1126/science.80.2081.457-a.
- Francis, Thomas. "Epidemic Influenza: Studies in Clinical Epidemiology." *Annals of Internal Medicine* 13, no. 6 (December 1, 1939): 915. doi:10.7326/0003-4819-13-6-915.
- . "The Development of the 1943 Vaccination Study of the Commission on Influenza." *Am. J. Epidemiol.* 42, no. 1 (1945): 1–11.
- Francis, Thomas, TP Magill, M Beck, and ER Rickard. "Studies with Human Influenza Virus during the Influenza Epidemic of 1936-37." *JAMA* 109 (1937): 566–69.
- Hirst, George K. *Frank Lappin Horsfall, Jr., A Biographical Memoir*. Memoir. Washington D.C.: National Academy of Sciences, 1979.
- Horsfall, F. L., R. G. Hahn, and E. R. Rickard. "Four Recent Influenza Epidemics: An Experimental Study." *The Journal of Clinical Investigation* 19, no. 2 (March 1940): 379–92. doi:10.1172/JCI101140.
- Horsfall, F.L., E.H. Lennette, E.R. Rickard, C.H. Andrewes, Wilson Smith, and C.H. Stuart-Harris. "The Nomenclature of Influenza." *The Lancet* 236, no. 6110 (October 1940): 413–14. doi:10.1016/S0140-6736(00)98518-0.
- Horsfall, F. L., E. H. Lennette, E. R. Rickard, and G. K. Hirst. "Studies on the Efficacy of a Complex Vaccine against Influenza A." *Public Health Reports (1896-1970)* 56, no. 38 (1941): 1863. doi:10.2307/4583865.
- Johnson, Niall P. A. S., 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. doi:10.1353/bhm.2002.0022.
- Kavet, J. "A Perspective on the Significance of Pandemic Influenza." *American Journal of Public Health* 67, no. 11 (November 1977): 1063–70.
- Kilbourne, E. D., C. Smith, I. Brett, B. A. Pokorny, B. Johansson, and N. Cox. "The Total Influenza Vaccine Failure of 1947 Revisited: Major Intrasubtypic Antigenic Change Can Explain Failure of Vaccine in a Post-World War II Epidemic." *Proceedings of the National Academy of Sciences* 99, no. 16 (August 6, 2002): 10748–52. doi:10.1073/pnas.162366899.
- Koen, JS. *A Practical Method for Field Diagnosis of Swine Diseases*. Vol. 14. Veterinary Publishing Company, 1919.
- Kolata, Gina. *Flu: The Story Of The Great Influenza Pandemic*. Touchstone, 2001.
- Laver, William Graeme. "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. doi:10.1353/pbm.2004.0066.
- Magill, T. P., and Thomas Francis. "Antigenic Differences in Strains of Epidemic Influenza Virus: I. Cross Neutralization Tests in Mice." *British Journal of Experimental Pathology* 19, no. 5 (October 1938): 273–84.
- Morse, Stephen S. "Emerging Infections: Condemned to Repeat?" In *Microbial Evolution and Co-Adaptation: A Tribute to the Life and Scientific Legacies of Joshua Lederberg*, edited by David A Relman, Margaret Hamburg, Eileen R. Choffnes, and Allison Mack. Forum on Microbial Threats. Washington D.C.: The National Academies Press, 2009.

-
- Patterson, David K. *Pandemic Influenza 1700-1900*. Rowman & Littlefield Publishers, 1986.
- Patterson, K D, and G F Pyle. "The Geography and Mortality of the 1918 Influenza Pandemic." *Bulletin of the History of Medicine* 65, no. 1 (1991): 4–21.
- Payne, A.M. "The Influenza Program of WHO." *Bulletin of the World Health Organization* 8, no. 5–6 (1953): 755–92.
- Redd, Stephen C., Thomas R. Frieden, Anne Schuchat, and Peter A. Briss. "1918 and 2009: A Tale of Two Pandemics." *Public Health Reports* 125, no. Suppl 3 (2010): 3–5.
- Rheinberger, Hans-Jorg. "Cytoplasmic Particles." In *Biographies of Scientific Objects*, edited by Lorraine Daston. Chicago: University of Chicago Press, 2000.
- Rivers, T. "Filterable viruses a critical review." *J. Bacteriology* 14, no. 4 (1927): 217–58.
- Shope, Richard E. "Swine Influenza." *The Journal of Experimental Medicine* 54, no. 3 (July 31, 1931): 349–59.
- . "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): 669–84.
- Smith, Wilson, C.H. Andrewes, and P.P. Laidlaw. "A Virus Obtained from Influenza Patients." *The Lancet* 222, no. 5732 (July 1933): 66–68. doi:10.1016/S0140-6736(00)78541-2.
- Stuart-Harris, C. H. "The Present Status of Prophylactic Immunization Against Influenza." *British Medical Journal* 2, no. 5048 (October 5, 1957): 777–79.
- Stuart-Harris, Charles Herbert., C.H. Andrewes, and W. Smith. *A Study of Epidemic Influenza, with Special Reference to the 1936-7 Epidemic*. Special Report Series, Medical Research Council 228. London, 1938.
- Stuart-Harris, CH, Wilson Smith, and C.H. Andrewes. "The Influenza Epidemic of January-March, 1939." *The Lancet* 235, no. 6075 (February 3, 1940): 205–11.
- Taubenberger, Jeffery K., and David M. Morens. "1918 Influenza: The Mother of All Pandemics." *Emerging Infectious Disease* 12, no. 1 (January 2006).
- . "Influenza Revisited." *Emerging Infectious Diseases* 12, no. 1 (January 2006): 1–2. doi:10.3201/eid1201.051442.
- Taylor, R. M. "Studies on Survival of Influenza Virus Between Epidemics and Antigenic Variants of the Virus." *American Journal of Public Health and the Nations Health* 39, no. 2 (February 1949): 171–78.
- Van Helvoort, T. "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.