

The 1918–1919 Influenza Pandemic as Covered in *The Journal of Immunology* from 1919 to 1921

The deadly 1918–1919 influenza pandemic generated an impressive body of immunological research into the cause and prevention of the disease, and that urgency is reflected in the many articles on influenza published in *The Journal of Immunology* from 1919 to 1921. Because bacteria had been shown to be causative of other infectious diseases, including typhoid fever and diphtheria, and viruses were not yet understood as more than filter-passing agents, most scientists of the time believed the cause of influenza to be bacterial. German physician Richard Pfeiffer had isolated bacteria from influenza patients during the previous pandemic of 1892 and believed that these bacteria were the cause of influenza; the bacteria had come to be known as Pfeiffer's bacillus or *Bacillus influenzae* or *B. influenzae* (now *Haemophilus influenzae*). By the time of the 1918 pandemic, many scientists had embraced Pfeiffer's hypothesis, and researchers were attempting to establish the etiological significance of *B. influenzae* to the disease by examining cases from the unfolding influenza pandemic.

Immunologists cultured and isolated bacteria from patient samples, including throat swabs, sputum samples, pleural effusions, and lung exudates, with mixed results. In 1919, C. Roos from the Mulford Biological Laboratories in Glenolden, Pa., reported that a collective review of all influenza samples analyzed by the laboratory beginning with the epidemic of 1915–1916 identified *B. influenzae* in “50 to 90 per cent of the cases.”¹ In September and October of 1918, Roos specifically examined 33 specimens from cases of clinical influenza characterized by a sharp onset and isolated *B. influenzae* from 27 (82 percent), although streptococci and pneumococci were also commonly present, being found in 25 (76 percent) and 20 (61 percent) of the specimens, respectively. Although *B. influenzae* could not be reproducibly isolated from all cases of influenza examined, Roos and others placed little significance on the



Demonstration at the Red Cross Emergency Ambulance Station in Washington, D.C., during the influenza pandemic of 1918, c. 1918, Library of Congress, Prints & Photographs Division

negative findings, ascribing them to improper specimen collection or culture technique.² Nevertheless, the inconsistent presence of *B. influenzae* in patient samples, its presence in healthy individuals, and the isolation of other types of bacteria from influenza patients cast doubt on the theory that Pfeiffer's bacillus was the cause of influenza.

William H. Park (AAI 1916, president 1918), laboratory director, New York City Board of Health, Division of Pathology, Bacteriology,

and Disinfection, contended that, to establish etiological significance, it was not sufficient merely to establish the presence of Pfeiffer's bacillus in all (or nearly all) cases of the influenza but that it was also necessary to show that the same strain or type was present in all cases. Under the direction of Park, Eugenia Valentine (AAI 1920) and Georgia M. Cooper (AAI 1920) injected rabbits with cultures of *B. influenzae* and tested each antiserum against the same (homologous) culture and against other cultures of *B. influenzae* isolated from the lung, larynx, or trachea of influenza patients.³ They were surprised to find a multiplicity of strains and could conclude only that “*B. influenzae* is not the primary etiological agent in epidemic influenza.” The lack of a “hypothetical pandemic strain” was later confirmed by similar methods by other investigators, including Arthur F. Coca (AAI 1916, secretary-treasurer 1918–1945, editor-in-chief 1920–1948) and Margaret F. Kelley of New York Hospital and Cornell University.⁴ Other papers, however, presented contradictory findings. In one such paper, F. M. Huntoon (AAI 1918) and S. Hannum demonstrated that antiserum protected mice from heterologous strains of *B. influenzae*.⁵ So it was that, long after the pandemic subsided, uncertainty remained about whether this microorganism was the primary cause of influenza or whether it was a secondary opportunistic invader.

Despite the uncertainty surrounding the cause of influenza, the lethality of the 1918 outbreak lent particular urgency to the question of prevention, and a number of investigators worked to develop a vaccine against the disease. During the height of an influenza epidemic occurring in New Orleans in the fall of 1918, Charles W. Duval and William H. Harris of Tulane University vaccinated approximately five thousand individuals with a chloroform-killed *B. influenzae* preparation.⁶ They reported that only 3.3 percent of those vaccinated developed influenza, compared with 41 percent of the unvaccinated control group. Duval and Harris concluded that, although the number of vaccinated persons was few, the results were “interesting and significant from the standpoint of prophylaxis.” In New York City, Park, in collaboration with other members of an influenza commission and the workers of the New York City Department of Health, undertook a comprehensive study of acute respiratory infections—



Street car conductor in Seattle not allowing passengers aboard without a mask, c. 1918, National Archives at College Park, College Park, MD

work that was funded through a grant from the Metropolitan Life Insurance Company. The first issue of *The Journal of Immunology* from 1921 (vol. 6, no. 1) was dedicated exclusively to this topic and the resulting series of papers.⁷ As part of this series, Park and his colleagues tested combined vaccines made from *B. influenzae* and strains of streptococcus, pneumococcus, and staphylococcus on 1,536 employees of the Metropolitan Life Insurance Company.⁸ Their results were somewhat less striking than the findings of Duval and Harris, as they found no difference in respiratory disease overall (including influenza) between the inoculated and control groups. However, it was noted that the vaccinated group showed the “beneficial influence” of a lower incidence of pneumonia.

The cause of influenza would not be definitively resolved until the 1930s, with the isolation of swine influenza virus by Shope⁹ and the subsequent isolation of human influenza virus by Smith, Andrewes, and Laidlaw.¹⁰ Whereas Pfeiffer’s hypothesis regarding the bacterial cause of influenza was ultimately proven incorrect, it was generally agreed then, as now, that most of the deaths from the 1918–1919 influenza pandemic were due to secondary bacterial infections¹¹—and that some of the early vaccines could have, in fact, prevented the rate of bacterial pneumonia and death from the disease.¹²

Modern influenza research continues to be presented in *The Journal of Immunology* nearly one century after these early papers appeared in the wake of the 1918 pandemic. Topics of research include the role of innate immune defenses in protection, the specificity of the T cell memory response, and mechanisms for improving vaccination, among others. Contemporary papers examine the immune response to recent strains, including swine-origin H1N1 influenza virus, the cause of the 2009 pandemic, and highly pathogenic avian H5N1 influenza viruses, speculated to be the possible source of a new pandemic. Much research remains to be done to fully staunch infection and death from seasonal outbreaks and future pandemics of the disease, but, if recent research is a fair indicator of future initiatives, immunology as a field will yield key findings for understanding influenza and limiting the menace it poses to public health.

¹ C. Roos, “Notes on the Bacteriology, and on the Selective Action of *B. influenzae* Pfeiffer,” *The Journal of Immunology* vol 4 (1919): 189–201.

² For instance, Roos pointed out that *B. influenzae* is “seldom found in the specimens of nasal secretions.” He further noted that he, as a frequent sufferer of common colds, “has been able to demonstrate this fact repeatedly on himself.”

³ Eugenia Valentine and Georgia M. Cooper, “On the Existence of a Multiplicity of Races of *B. influenzae* As Determined by Agglutination and Agglutinin Absorption,” *The Journal of Immunology* vol 4 (1919): 359–379.

⁴ A.F. Coca and M.F. Kelley, “A Serological Study of the Bacillus of Pfeiffer,” *The Journal of Immunology* vol 6 (1921): 87–101.

⁵ E.M. Huntoon and S. Hannum, “The Role of *Bacillus influenzae* in Clinical Influenza,” *The Journal of Immunology* vol 4 (1919): 167–187.

⁶ C.W. Duval and W.H. Harris, “The Antigenic Property of the Pfeiffer Bacillus As Related to Its Value in the Prophylaxis of Epidemic Influenza,” *The Journal of Immunology* vol 4 (1919): 317–330.

⁷ W.H. Park, A.W. Williams, and C. Krumwiede, “Microbial Studies on Acute Respiratory Infection with Especial Consideration of Immunological Types,” *The Journal of Immunology* vol 6 (1921): 1–4. For more on Anna W. Williams, see “Anna Wessels Williams, M.D.: Infectious Disease Pioneer and Public Health Advocate,” *AAI Newsletter*, March/April 2012, pp. 50–51.

⁸ A.I. Von Sholly and W.H. Park, “VII. Report on the Prophylactic Vaccination of 1536 Persons Against Acute Respiratory Diseases, 1919–1920,” *The Journal of Immunology* vol 6 (1921): 103–115.

⁹ R. Shope, “Swine Influenza. III. Filtration Experiments and Etiology,” *The Journal of Experimental Medicine* vol 54 (1931): 373–385.

¹⁰ W. Smith, C. Andrewes, and P. Laidlaw, “A Virus Obtained from Influenza Patients,” *Lancet* vol 2 (1933): 66–68.

¹¹ D.M. Morens, J.K. Taubenberger, and A.S. Fauci, “Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness,” *The Journal of Infectious Diseases* vol 198 (2008): 962–970.

¹² Y. Chien, K.P. Klugman, and D.M. Morens, “Efficacy of Whole-Cell Killed Bacterial Vaccines in Preventing Pneumonia and Death during the 1918 Influenza Pandemic,” *The Journal of Infectious Diseases* vol 202 (2010): 1639–1648.