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Commentary

Impact of Technological Developments on Infectious Disease Epidemiology: Lessons From the First 100 Years of the *American Journal of Epidemiology*

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Technological developments in laboratory and epidemiologic methods, combined with increasing computing power, have synergistically increased our understanding of the epidemiology of infectious disease. Using historical examples from the first 100 years of the *American Journal of Epidemiology*, we illustrate how these developments provided the foundation for the rapid detection of the agent causing coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), from its transmission efficiency and modalities, risk factors, and natural history to the evaluation of new vaccines and treatments to control its spread and impact. Comparisons with timelines for elucidation of the epidemiology, natural history, and control of other infectious diseases, including viral hepatitis, humbly remind us of how much past discoveries have paved the way for more rapid discovery of and response to new pathogens. We close with some comments on a potential future role of the *Journal* in infectious disease epidemiology.

history of epidemiology; history of medicine; infectious diseases; molecular epidemiology

Abbreviations: AJE, *American Journal of Epidemiology*; AJH, *American Journal of Hygiene*; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Editor's note: *The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the* American Journal of Epidemiology.

The journal we now know as the *American Journal of Epidemiology* (AJE) began its life in 1921 as the *American Journal of Hygiene* (AJH). The AJH was dedicated to the "publication of original research in the broad fields of hygiene, preventive medicine and public health" (1, p. 1) and was the home for papers of all types relating to what Dr. Milton Terris called "the first epidemiologic revolution" (2, p. 15): the application of epidemiologic methods primarily to the prevention of infectious diseases. These public health efforts resulted in tremendous scientific advances in our understanding of the transmission and control of infectious diseases, from basic science work related to the agents themselves to epidemiologic methods. This flowering of public health also stimulated a proliferation of new specialty journals focused on laboratory methods in microbiology, immunology, statistics, infectious and noninfectious disease, social and preventive medicine, and applied public health practice—but none specifically focused on epidemiology.

To fill this gap, in 1965 the AJH was renamed the AJE. As the Editors noted in the first issue of the AJE,

> It appears that workers in microbiology and related fields are amply served by journals at the present time. The field of epidemiology is less well represented. Since World War II the epidemiologic approach to disease, and particularly chronic disease, has acquired greatly increased importance, but so far as we are aware there is no journal in the English language which has the word epidemiology in its title (1, p. 1).

The new name signaled that the *Journal* would increase the number of published papers on epidemiologic methods and noninfectious diseases. This intent was successful: In 1965, 85% of the research papers were on infectious diseases

(47% on virology and 27% on laboratory studies). By 1989, there were no laboratory papers, and 19% of papers were on infectious diseases (3, 4). Since then, the proportion of infectious disease papers in the *Journal* has hovered around 20%. In 2000, the *Journal* published 307 research articles, and a search with the term "infection" found 72 papers on infectious disease (23% of the total); for 2010, the numbers were 72/314 (23%), and for 2020, 84/297 (28%). The unintended consequences of this policy have been to encourage infectious disease epidemiologists to submit their manuscripts elsewhere. This not to say that important infectious disease papers do not appear in the AJE; for example, a 1970 paper that has been cited 88 times is one of the only papers published before the advent of severe acute respiratory syndrome that describes the seroepidemiology of coronavirus infection in adults and children (5).

It is therefore ironic that at this 100th anniversary of the AJE, we are in the midst of a coronavirus pandemic. Epidemiology has played and continues to play an essential role in monitoring the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identifying the emergence of new strains, describing the transmission system, and planning and evaluating methods of control, treatment, and prevention—including vaccines. Despite the politicization of vaccination and other prevention measures, the speed with which SARS-CoV-2 was identified and sequenced, the application of genomic sequencing to monitor virus evolution, the development of publicly available surveillance dashboards at local, state, and national levels, the initiation of cohort studies, the description of the virus's natural history, and the development and evaluation of diagnostic agents, therapeutic agents, and many highly effective vaccines has been phenomenal—especially when compared with responses to previous public health crises over the past 100 years.

To put this amazingly rapid technological response into perspective, in this commentary we discuss some historical papers that highlight the foundations on which the public health response to SARS-CoV-2 was built. In our review of past issues of the *Journal*, we were overwhelmed by the number of choices, so the selections naturally reflect our own personal perspectives and interests. We hope this brief review encourages the reader to examine the history of the epidemiology of their favorite disease/condition by perusing previous issues of the *Journal*. Herein, we first highlight how the combination of technological developments in laboratory and epidemiologic methods with increasing computing power has synergistically increased our understanding of infectious diseases. To provide perspective on the trajectory from discovery of new pathogens to eventual development of preventive/treatment strategies, we trace the history of viral hepatitis through the pages of the AJE. We close with some comments on a potential future role of the AJE in infectious disease epidemiology.

TECHNOLOGICAL DEVELOPMENTS AND INFECTIOUS DISEASE EPIDEMIOLOGY

The integration of modern molecular techniques with epidemiologic methods was essential for the identification of SARS-CoV-2 and remains essential for outbreak investigation and surveillance. Epidemiologists in the early 20th century also embraced new methods for identifying, growing, and testing infectious agents as a means of enhancing investigations of outbreaks and monitoring illnesses. For example, a 1925 investigation of a scarlet fever outbreak in Flint, Michigan, associated with eating ice cream (6) included the use of a skin test for scarlet fever published just 1 year prior to help confirm the epidemic's source as the person who prepared the ice cream. This paper was also notable for the completeness of the investigation, which included active case-finding, culturing of the noses and throats of household contacts of symptomatic cases, and a comparison of food consumption among cases and controls. The latter fact led Dr. Alfredo Morabia to suggest in a 2013 AJE publication that Flint was one of the birthplaces of the case-control study (7).

Descriptive epidemiology and surveillance of viral infections is greatly enhanced by seroepidemiology, which enables identification of infection history, recent infection, and asymptomatic infection. Seroepidemiology used in ongoing surveillance in households has greatly increased our understanding of the transmission and pathogenesis of many viral infections: adenovirus (8), coxsackievirus and echovirus (9), and rhinovirus, influenzavirus, and SARS-CoV-2 (10–12). Results of a landmark household study of viruses, the Viral Watch program, were reported in the AJE: The *Journal* published 9 Viral Watch articles in all between 1966 and 1971 (8, 9, 13–19). Viral Watch conducted ongoing surveillance of households in metropolitan New York. Results provided important information on respiratory and fecal excretion of virus, humoral immunity, intrafamilial spread, and illness for coxsackievirus and echovirus infections (9), rhinovirus (15), and adenovirus (16). The amount of work required in the laboratory and for data analysis was heroic in comparison with what it takes to conduct similar analyses today, as now multiple viruses can be detected using a single molecular diagnostic panel and the associated antibodies using a multipathogen serological assay. Virus was grown in primary monkey kidney and HEp-2 cell cultures, and virus was identified using hemagglutinin-inhibition, complement-fixation, or conventional serum neutralization tests. To detect antibodies, serum dilutions were mixed with virus and inoculated into HEp-2 cell cultures and read for cytopathic effect after 9–12 days. In addition, results of each laboratory test were manually punched on a separate punch card. For the study of adenovirus (16), more than 102,000 cards were sorted chronologically by family and person using a system that sorted the cards and printed out a table of the sorted results. All analysis was completed by manual extraction from this display. Compare this with rapid detection of SARS-CoV-2 using polymerase chain reaction or antigen tests, followed by rapid data analysis, which enable posting of surveillance results daily on local-, state-, and national-level dashboards. The adenovirus study alone (16) had been cited 222 times as of April 15, 2022, according to Web of Science (Clarivate plc, London, United Kingdom), with 4 citations in 2021.

Whether masks should be mandated and whether masks prevent SARS-CoV-2 transmission has been a "hot button"

issue throughout the coronavirus disease 2019 (COVID-19) pandemic. Over the course of the last 100 years, multiple studies have clearly demonstrated that many diseases—malaria, syphilis, and typhus, for example—are not spread through airborne transmission. Therefore, it is not surprising that following these discoveries some physicians questioned whether masks were indeed necessary during surgery or delivery to prevent staphylococcal or streptococcal infections. Even today, staphylococcal and streptococcal infections remain the most common causes of surgical-site infections. In a 1939 paper, MacDonald noted that despite "present knowledge of bacteriology and its application in scrupulous operating and delivery room technic, infections due to hemolytic staphylococci and streptococci continue" (20, p. 75). The author used a novel air centrifuge (the Wells air centrifuge) to quantify the amounts of staphylococci and hemolytic streptococci in the air in various locations in a hospital over the course of the day. He then quantified the associations between the amount of bacteria present and the numbers of individuals present at the sampling points (20). The Wells air centrifuge separates bacteria in the air and deposits it on agar at a volume of approximately 2 cubic feet (61 cm^3) per minute (21). MacDonald concluded that there was a possibility of wound infection from droplet nuclei (20). Studies such as these provided the basis for requiring masks during surgery and the use of masks or biosafety cabinets when handling infectious agents.

Readers may recall that there was initially some speculation that SARS-CoV-2 may have come from a laboratory leak (22, 23). What they may not know is that principles of biosafety were not codified in the United States until 1984, although the US Army Biological Research Laboratories at Fort Detrick had begun evaluating the risks of handling infectious microorganisms and developing safe practices in the 1940s (24). Laboratory-associated infections, such as a laboratory outbreak of Q fever (now designated a Biosafety Level 3 pathogen) reported in the AJH in 1946 (25), were the stimulus for developing a biosafety code. In the Q fever outbreak, researchers were growing *Rickettsia* in eggs. Six of the 8 individuals working with the eggs developed Q fever. The 2 workers who did not become ill wore 2 masks over the mouth and nose at all times when working in the egg room (25). Since the development of the biosafety code, movies such as *Outbreak* (26) have familiarized the general public with at least a Hollywood version of Biosafety Level 4 laboratory setups, including positive pressure suits and biosafety cabinets. However, there is always a chance for human error, and we should not take it for granted that researchers appropriately practice biosafety when handling hazardous pathogens and that facilities are appropriately built and maintained to minimize risk of a laboratory leak.

Throughout the first year or so of the COVID-19 pandemic, there was much controversy over whether SARS-CoV-2 was transmitted primarily via droplets or aerosols and whether fomite transmission was possible. Establishing person-to-person direct transmission (e.g., via sexual activity) and the corresponding transmission probabilities might be expected to be simpler than transmission via droplets or aerosols, but in practice creative study designs are required. Several papers published in the *Journal* during the 1970s and 1980s demonstrate this creativity. While sexual transmission of gonorrhea has long been assumed, estimating the probability of transmission between individuals is more complicated. In 1978, Hooper et al. (27) estimated the risk of gonorrhea acquisition by following a cohort of volunteer crew members of a large naval vessel over a 4-day liberty period in the western Pacific. The authors determined the prevalence of gonorrhea among women to whom the sailors were exposed and estimated the transmission probability by the sailors' numbers of sex partners and the frequency of sexual intercourse with a single partner (27). The transmission of cytomegalovirus among adults was creatively addressed in a 1975 seroepidemiologic study by Davis et al. (28). They compared the prevalence of cytomegalovirus antibody among nuns working as nurses or schoolteachers with that among women admitted to a private hospital, women admitted to a county hospital, and women visiting a sexually transmitted infection (then called venereal disease) clinic. Cytomegalovirus antibody levels abruptly rose during young adulthood in all groups except the nuns, suggesting that sexual or intimate salivary contact may be a significant mode of cytomegalovirus transmission among adults.

Mathematical models have been used throughout the current pandemic to model viral transmission dynamics, to understand and predict SARS-CoV-2 evolution, and to plan and evaluate prevention efforts. However, the sophisticated methods used today to understand and forecast SARS-CoV-2 are relatively new and reflect the technical revolution in laboratory methods (e.g., polymerase chain reaction, "-omics"), increased computing power, and development of dynamic mathematical modeling approaches over the past 50 years. Yet the benefit of a synthesis of laboratory methods with increased computing power and development of mathematical modeling tools for understanding transmission dynamics was illustrated 40 years ago. In a 1982 paper, Longini et al. (29) informed a mathematical model with influenza serological and viral isolation data to compare the ease of household spread and intensity in community spread of influenza A(H1N1), influenza A(H3N2) and influenza B. More recently, Magiorkinis et al. (30) proposed an approach for evaluating the community effect of human immunodeficiency virus (HIV) interventions that takes advantage of the molecular evolutionary dynamics of pathogens to evaluate the number and length of new transmission chains.

Finally, the COVID-19 pandemic brought social and racial disparities to the forefront of the conversation—disparities in risk of infection, ability to adopt nonpharmaceutical and pharmaceutical preventive interventions, disease outcomes, and mortality. Yet, these health disparities have long been observed for infectious diseases. In a 1940 cohort study, Brailey (31) documented significantly higher rates of tuberculosis mortality among children of Color than among White children seen at the Johns Hopkins Hospital. In a 1957 household study, Gelfand et al. (32) documented a higher incidence of poliomyelitis infection (detected via viral isolation or new antibody or both) among children of Color than among White children of low socioeconomic status; White children of high socioeconomic status had the lowest risk. And in 1993, disparities in HIV seroprevalence by racial/ethnic group were noted (33).

As these examples illustrate, there have been significant developments in laboratory and epidemiologic methods over the last 100 years that laid the foundations for a rapid response to the COVID-19 pandemic. It has been less our technological and methodological capability than failures in implementation and secular changes in the public perception (and in some cases trust) of science and public health that have undermined public health mitigation approaches (34, 35) and challenged rapid containment of SARS-CoV-2.

HEPATITIS VIRUSES: DISCOVERY TO PREVENTION

For the general public, the pace at which we learned about SARS-CoV-2, from its basic virology and routes of transmission to its pathogenesis and clinical features, may have felt slow; but it was actually remarkably fast! And the speed was in large part due to advances in the types of laboratory and statistical techniques described above. Perusing the history of epidemiology and public health in the pages of the *AJE* humbly reminds us of how many years were required to develop our current understanding of past scourges. As an example, we trace here the evolution of our understanding of hepatitis viruses, a task that, once it began in earnest in the early 20th century, did not result in a vaccine (1981 for hepatitis B, 1995 for hepatitis A) or a cure (2011 for hepatitis C) for decades. (Hepatitis A, B, C, D, and E are different viral species but share a common name because of their association with clinical hepatitis.)

The first descriptions of hepatitis or jaundice—including initial descriptions of transmission—are found on clay tablets from the third millennium BC. Outbreaks were reported in the 17th, 18th, and 19th centuries, usually associated with military campaigns (36). However, it was not until the 20th century that reports describing the disease's epidemiology and transmission led to the recognition that there were 2 forms of hepatitis—serum and infectious. Moreover, while outbreaks were reported in the 20th century, not until 1965 was the "Australia antigen" (hepatitis B) identified, and the virology of any hepatitis virus was not defined until the 1970s.

As is often the case, the epidemiology of infectious hepatitis/hepatitis A was well understood before the actual causative agent was isolated and identified. The earliest reports of "infectious hepatitis" with jaundice outbreaks appear in the pages of the AJH beginning in 1946. These reports identified outbreaks among military personnel (37, 38), in schools (39), and in households and communities (40). Detailed assessments, particularly among military personnel, helped investigators work out aspects of the transmission and natural history of the disease. Articles identified the typical symptoms and clinical course and suggested that the most likely route of transmission was fecal-oral (then called intestinal-oral) because most outbreaks pointed to polluted water supplies, large numbers of flies carrying human excrement, and poor environmental sanitation. Additional investigations identified common-source outbreaks with contaminated water supplies (41) and transmission chains likely taking place in schools and homes (39). What is most striking about these early reports is the amount of detail that is provided on the cases and the approach (analogous to a laboratory notebook), the in-depth discussion of biases in the data, and the use of methodology that is still being employed today (e.g., calculation of epidemic curves and age- and time-specific attack rates).

One of the first reports of serum or parenterally transmitted hepatitis (subsequently identified as hepatitis B) was published in the AJH in 1954. In that paper, Masi et al. (42) described an outbreak of parenterally transmitted hepatitis via injections of manufactured medications free of human serum in a nonmilitary population. Subsequent reports further characterized the epidemiologic and clinical features of hepatitis B using methodology not dissimilar to approaches used today. For example, in a 1962 report in the *Journal*, Prince et al. (43) commented on a "mass" serum enzyme survey conducted at an army recruit training center in South Korea to characterize the burden of what was then called anicteric hepatitis. The authors identified clinical and laboratory features which revealed less well understood signs of chronic active hepatitis. Subsequently, large serosurveys appeared more frequently in the AJE, including reports from Thailand demonstrating an incredibly high population prevalence of hepatitis B surface antigen positivity and initial signals suggesting the now well established significantly higher viral persistence among children (44). Seminal studies in Alaska Natives showed that hepatitis B could be transmitted among household members (45). Further studies demonstrated that hepatitis B could also be transmitted via sexual activity (46), from mother to child (47), and nosocomially (48). In additional studies, investigators worked out the difference and meaning of various serological markers for hepatitis B, including the surface antigen (49), surface antibody (50), and core antibody (50).

In the years that followed, AJE articles documented the evolution of our understanding of hepatitis viruses. In 1982, a seroprevalence study in the US military (51) demonstrated that the prevalence of what was then classified as non-A, non-B hepatitis (now called hepatitis C) varied from 27% in Germany to 3% in South Korea. A description of the epidemiology of the hepatitis B delta variant in Italy was published in the AJE in 1983 (52). (The hepatitis B delta variant, otherwise known as hepatitis D, can only propagate in the presence of hepatitis B.) This report demonstrated that hepatitis D was endemic in southern Italy and episodic and was associated with transmission among people who inject drugs in northern Italy. Hepatitis E was first discovered in 1978 as part of an outbreak (53), but a description of its epidemiology did not find its way into the AJE until 2010 (54) via a report describing the epidemiology of hepatitis E in Bangladesh. Other AJE papers evaluated various interventions, including use of human serum immunoglobulin to prevent hepatitis A (55), pre- and postexposure prophylaxis for hepatitis B (56), and finally vaccination for hepatitis B (57).

INFECTIOUS DISEASE EPIDEMIOLOGY AND THE FUTURE OF THE AJE

In our review of infectious disease papers from the first 100 years of the AJE, we observed the development of fundamental methods of modern infectious disease epidemiology.

As we have seen, many methods developed in the last century are still being applied today. The methods of outbreak investigation used in the 1925 study of streptococcal infection and ice cream (6) were the same as those used today. The author verified the existence of the outbreak, established a case definition, implemented case-finding by testing contacts, conducted descriptive epidemiology to generate hypotheses, and tested the hypothesis with an analytical study. Descriptive epidemiologic studies combined with new laboratory methods identified new infectious agents and how they were transmitted and allowed researchers to estimate transmission probabilities. Essentially, many of the approaches that were used to elucidate the features of viral hepatitis are the same as those used for SARS-CoV-2.

What has changed? Within-host and population mathematical models are increasingly being used to enhance different epidemiologic endeavors—from designing studies to generating refined hypotheses to evaluating interventions (58). High-throughput laboratory techniques have made population studies of human pathogens, the microbiome, human genetics, and immunology possible, and epidemiologic studies integrating molecular methods have mined biorepositories to identify the contributions of infectious agents to cancer, type 1 diabetes, arthritis, and heart disease. Hepatitis viruses B and C, *Helicobacter pylori*, human papillomavirus, and human herpesvirus 8 are now known to cause cancer; there is also increasing evidence of the direct and indirect effects of the microbiome on cancer risk (59). Further, new technologies are exploring synergies between pathogens. For example, it has long been observed that there is an increased risk of bacterial pneumonia following influenza infection (60); recent discoveries demonstrate that *Streptococcus pneumoniae* and influenzavirus literally bind together to their mutual benefit (61). We have just begun to describe the role of the microbial communities in and on the human body (the microbiome) in positively and negatively mediating our physical and mental health, and the marks that exposures of all kinds—physical, microbial, and mental—make on our epigenomes.

What also has changed is our previous misplaced optimism that technological advances alone will be sufficient to prevent, treat, control, and ultimately eradicate infectious diseases. Infectious diseases are and will likely remain of clinical and public health importance. In addition to underscoring that point, the COVID-19 pandemic has highlighted that effective ongoing scientific communication and public trust are essential in order to implement public health interventions—especially in the face of scientific uncertainty. This requires building and maintaining a trained public health workforce capable of both applying the latest technological advances *and* navigating the political minefield that is certain to emerge along with a pandemic. This workforce needs the foundational skills in surveillance that are essential for identifying outbreaks. These workers also must be capable of conducting descriptive epidemiologic studies not just to identify susceptible populations but also to describe transmission dynamics and the genomic epidemiology of the causal agent and to provide accurate empirical data to inform transmission modeling. These can be followed by analytical epidemiologic studies addressing host-pathogen, pathogen-pathogen, and host-microbiome-pathogen interactions that will provide the foundational knowledge required to develop diagnostics, prognostics, treatments, and preventatives. Finally, implementation studies are necessary to ensure that effective diagnostic, therapeutic, and preventive tools are available and accessed equitably across populations and geographies.

Conducting these necessary descriptive, analytical, and implementation studies poses new epidemiologic challenges. The laboratory methods may be available, but making sense of the resulting high-dimensional data and associations between multiple sets of high-dimensional data—for example, immunological response to polymicrobial communities—is complex. Moreover, proper interpretation of laboratory measurements requires understanding of the effects of environmental, genetic, behavioral, and socioeconomic factors on the measures. Similarly, as our non-laboratory data sources continue to expand to include more complex data from a wide variety of sources (i.e., electronic health data, medical claims, mobile phones, social media), "big data" analytics will be needed to manage data at the appropriate temporal and spatial scales. Finally, implementation studies will require novel designs to evaluate impact while simultaneously assessing barriers to and facilitators of scale-up. A major challenge for epidemiologists of the future will be to develop ways to integrate information from the population level to the molecular level and from the mind and body and to use that integration to identify ways to maintain health and prevent disease.

The proliferation of journals addressing multiple aspects of infectious disease has only accelerated since 1965. However, papers describing novel ways to integrate population and laboratory methods to describe the occurrence and identify causes of disease, and their application in epidemiologic practice, remain hard to place. This is also true for large descriptive and hypothesis-generating studies, as well as papers introducing novel designs for assessing the impact of interventions for controlling transmission and mitigating adverse outcomes. We hope that over the next 100 years the AJE will be the home for foundational papers that advance our understanding of the effects of host-pathogen, pathogen-pathogen, and host-microbiome-pathogen interactions on the public's health and the modifying effects of human actions on those interactions.

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