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COMMENTARY

COVID-19 and the future of clinical epidemiology

Katrina Armstrong^{a,b,*}, Ralph Horwitz^c

^aDepartment of Medicine, Massachusetts General Hospital, D740 GRB, 55 Fruit Street, Boston, MA 02114, USA

^bHarvard Medical School, Boston, MA, USA

^cTemple University School of Medicine, Philadelphia, PA, USA

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Abstract

Clinical epidemiology, the “basic science for clinical medicine”[1], has changed substantially over the last 50 years, moving its focus from clinician driven research and clinical settings to large cohorts and trials, NIH funding, and practice guidelines. The COVID-19 pandemic created major challenges for clinicians who needed to make urgent decisions about the management a new disease and for researchers who needed to understand the clinical syndrome and the questions of greatest importance to the pandemic response. Addressing these challenges reunited clinicians and researchers in collaborative efforts to inform decisions about disease risk, prevention, prognosis and treatment, at least in part because of the shared sense of the need to ration scarce resources, the rapid evolution of understanding of the clinical syndrome, the recognition of widespread uncertainty, and the emphasis on the common good over individual credit. Only time will tell whether the experience during COVID-19 will revive the original practice of clinical epidemiology as “the application by a physician who provides direct patient care, of epidemiologic and biometric methods to the study of diagnostic and therapeutic process in order to effect an improvement in health”[2]. © 2021 Elsevier Inc. All rights reserved.

What is new

- Impact of COVID-19 on the field of clinical epidemiology is just beginning to be understood.
- Much has been written about the challenges of epidemiologic research during the pandemic.
- This commentary is the first to highlight how the experience of linking clinicians and epidemiologic researchers during the pandemic revived the original mission of clinical epidemiology.
- Examples from the pandemic can inform future efforts to strengthen the linkage between the clinical and investigational worlds that was central to the creation of the field of clinical epidemiology.

The field of clinical epidemiology was first described in a 1938 presidential address to the American Society of Clinical Investigation. At a time when clinical investigation was largely focused on laboratory based experiments

and public health on the prevention of communicable disease, the address articulated the need to bring together the two disciplines into a new field that would be concerned with the “circumstances ... under which human disease is prone to develop”[1]. Over the subsequent decades, this new field brought together clinicians and epidemiologists to improve clinical research and clinical care [2]. By understanding epidemiology, clinicians learned to apply epidemiologic principles and probabilistic thinking to clinical decision making and to make inferences from comparisons across groups rather than individual patients. By connecting to clinical care, epidemiology expanded beyond its traditional focus on transmissible infections to the full range of acute and chronic diseases. Since the seminal publications articulating the value of the field in the *Annals of Internal Medicine* in the 1970s, clinical epidemiology has led to major advances in the understanding of disease risk, prognosis and treatment and contributed to substantial reductions in disease mortality [3–5].

Over the last decades, the connection between the clinician and the epidemiologist that drove the creation of this new field has frayed. The original conceptualization of clinicians directly applying research findings to clinical decisions for individual patients has changed over time [6]. Increasingly research findings have been translated into

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* Corresponding author. Tel.: 617-726-8447.

E-mail address: karmstrong6@mg.harvard.edu (K. Armstrong).

guidelines, guidelines into insurance coverage determinations and hospital policies, and insurance and hospital policies into standardized clinical decisions [7]. As the volume of research has grown, clinicians have grown to rely upon predigested evidence summaries like Up to Date and “Dr. Google” instead of original research publications. The initial enthusiasm for imbuing probabilistic reasoning and epidemiologic principles throughout medical school curricula has faded, in part because of challenges in creating effective preclinical epidemiology courses and the continued dominance of basic science departments at many leading medical schools.

At the same time as these forces have been pulling clinicians away from epidemiology, epidemiologic research has been moving further and further from the clinical setting. Over time clinical epidemiology has naturally progressed from clinic-based studies designed to find relatively large effects to large cohort studies and randomized controlled trials designed to identify much smaller effects. The need for scale has driven study protocols and operations away from clinical environments to separate study-based infrastructures for enrolling and following participants. Funding from the National Institutes of Health has become paramount for success in academic medicine with grant reviews often prioritizing scale, study design and statistical analysis over integration with clinical perspectives and expertise. The increase in research productivity and funding enabled by these large collaborative studies has meant that academic promotion increasingly depends on access to large cohorts instead of creation of new clinically focused studies. Given the separation of these efforts from the clinical setting, many clinicians engaged in clinical epidemiology moved further and further away from the bedside until they often had relatively little of the clinical activity that would inform their research and inspire students and residents.

While this natural evolution of clinical epidemiology has brought many benefits in the scope, rigor and generalizability of clinical epidemiologic research, it has led the field increasingly far from the original mission of the field—to improve clinical care and epidemiologic research by linking the two worlds – even as there is growing concern about the importance of that mission. More and more evidence suggests that clinicians remain uncomfortable with probabilistic reasoning and that this discomfort contributes to medical errors, particularly in diagnosis and appreciating disease severity, and to insufficient engagement of patients in their clinical decisions [8,9]. This discomfort also hampers important efforts to improve the value of care as such efforts require clinicians to consider probabilistic benefits and harms at a population level. Without clinicians comfortable in bringing population level evidence to clinical decision making, it is proving extremely challenging to leverage clinical “big data” from the clinical world to improve patient care and outcomes. The time it takes for a research finding to impact clinical practice continues to be

measured in decades in part because current funding models make it difficult to move quickly to answer important clinical questions and to ensure that studies are relevant to current clinical practice [10]. Failure to connect clinical observation to clinical research hampers the ability of research to focus on the most clinically important questions and to be informed by careful observations across groups of patients. Limited connection to the clinical frontlines contributes to insufficient understanding of diagnostic complexity, leading to measurement error and lost opportunities for novel scientific insights. Classification issues that have long been recognized in areas like mental health are growing as access to novel clinical and biological data drives clinicians to revise current approaches to diagnostic taxonomies. Integration of the clinical perspective may be particularly important for disparities research as clinician experience with the realities faced by vulnerable populations can inform study methods, measures and implementation.

As with many fields in biomedical research, the COVID-19 pandemic has been a major disruption to clinical epidemiology. Much has been written about the challenges created by this disruption including the quantity and quality of information that is being produced [11]. Concerns about waste of resources and validity of publications are widespread, often focusing on the growth in preprints and the pressure on journals for rapid publication amidst a deluge of submissions [12–14]. At the same time, this disruption has reunited clinicians and researchers in collaborative efforts to inform decisions about disease risk, prevention, prognosis, and treatment (Fig. 1) at a time of immense clinical and public health need, creating an important opportunity to revisit the original mission of clinical epidemiology, the “basic science for clinical medicine” [15]. Understanding the factors that drove these efforts in a large U.S. academic hospital may provide insight into future opportunities for clinical epidemiology to deliver upon its promise to improve clinical care and epidemiologic research.

Assessment of disease risk and prognosis was the first priority as the pandemic developed. While risk assessment initially focused on travel exposure in early 2020, community spread rapidly overwhelmed those efforts in many places. By mid-March, clinicians were seeing rapidly increasing numbers of admissions with presumed COVID-19 and turned to basic clinical observations and tabulations of patient characteristics and patient outcomes to make observations about risk and prognosis. These tabulations identified a number of potential risk factors, including older age, male sex, obesity, and diabetes, which echoed prior reports from China and Italy [16]. However, these tabulations also identified an unexpected predominance of certain neighborhoods among the admissions, particularly a predominantly Hispanic, low-income neighborhood. These observations, made independently by multiple clinicians caring for COVID-19 patients on different floors, were enabled by the early addition of a list of COVID-19 patients in

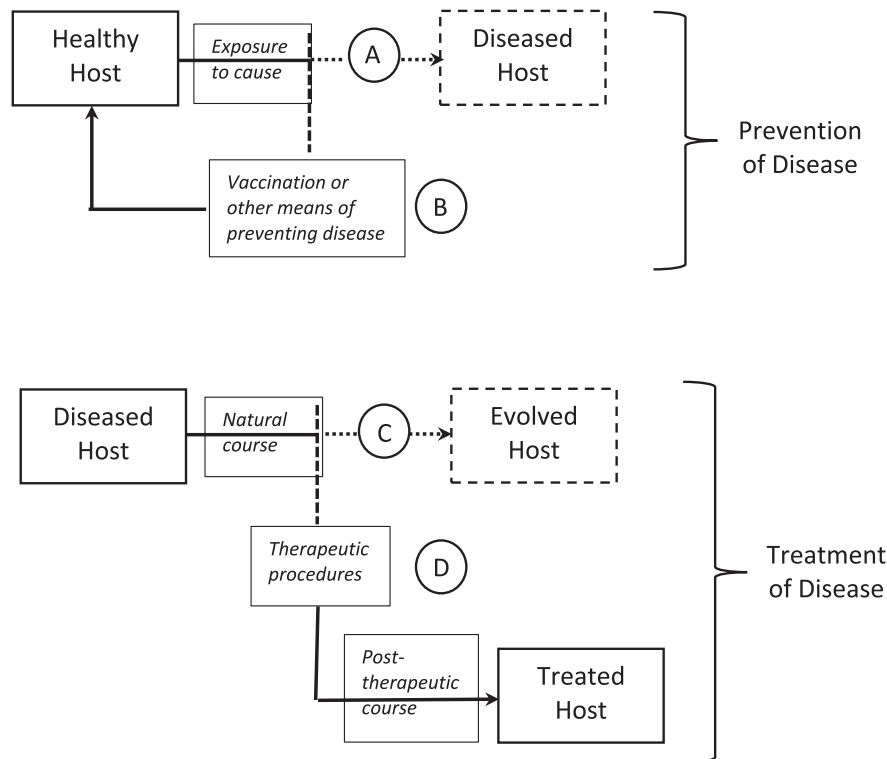


Fig. 1. Questions of Risk (A), Prevention (B), Prognosis (C), and Treatment (D) in COVID-19. Adapted from Feinstein AR. Clinical epidemiology. I. The populational experiments of nature and of man in human illness. *Ann Intern Med.* 1968;69(4):807-820.

the hospital to the electronic medical record. Recognizing that these tabulations were largely hypothesis generating, the teams moved quickly to reproduce the observation using public health data on infection numbers by neighborhood and, from there, to develop and implement interventions designed to reduce transmission in these low-income neighborhoods.

As concerns grew about the number of patients overwhelming existing hospital capacity, clinical focus turned to questions of disease severity and prognosis to inform decisions about who should be admitted, who should be transferred to critical care, and who should be discharged. Based upon reports from other countries, protocols were developed for measuring potential predictors of progression including oxygenation. In the inpatient services, clinical observations of rapid and unanticipated declines in oxygenation led to measurement of inflammatory biomarkers as potential prognostic indicators. Clinicians following patients over time in the hospital observed that increases in these markers were associated with disease progression and delayed discharge in patients who appeared to be on a problematic trajectory. In the ambulatory setting, procedures were established to check on patients with phone calls, largely assessing symptoms such as dyspnea, and to refer in patients for evaluation if their symptoms progressed. These efforts were central to triaging limited inpatient bed capacity in the initial surge, likely contributing to the system's ability to provide care for all patients in

need in the appropriate location despite the dramatic surge in case numbers.

At the same time that progress was being made in understanding risk and prognosis, it quickly became apparent that COVID-19 diagnosis was going to be complicated [17]. Initial diagnostic tests detected viral RNA in the nasopharynx using polymerase chain reaction (PCR) methods; however, test validation was limited by lack of samples from patients with known disease, creating uncertainty about test characteristics. Once the PCR test became clinically available, clinicians observed that some patients with presumed COVID-19 had negative tests, raising new questions about test sensitivity [18]. While repeat PCR testing became accepted as the gold standard for diagnosis, test availability was limited creating major bottlenecks for patient flow through the hospital. Initially, clinical teams initiated a process of review by an infectious disease expert of all patients with negative tests to determine which patients required repeat testing. This process led to the identification of clinical features that were correlated with a positive repeat test and the creation of a decision rule, known as COVID risk calculator or CORAL, to enable the clinician to risk stratify patients with an initial negative test. Implementation of CORAL resulted in a reduction in the time that patients were in diagnostic limbo and in the more efficient use of the limited COVID-19 test capacity [19].

The third area of priority for clinicians was the evaluation of potential interventions for treating COVID-19

given the relatively high mortality rates in untreated hospitalized patients in Italy and China. Within the first few weeks after COVID-19 cases were detected in the United States, hundreds of potential treatments were proposed encompassing a wide range of approaches to antiviral and immunomodulatory activity as well as a number of more esoteric approaches such as light therapy and herbal supplements. Given the number of potential treatments and the predicted surge of patients, it became apparent that prioritization and coordination of randomized controlled trials would be needed. Even as plans were being developed for potential platform trials, the predicted flow of patients and scarcity of personal protective equipment (PPE) meant that any approach that involved investigators obtaining institutional review board (IRB) approval and then deploying their research teams to floors to enroll eligible patients was going to be highly problematic from both an institutional and enrollment perspective. A novel, clinician led effort was developed to prioritize trials prior to IRB submission, deploy institutional resources to support the top priority trials, and screen and allocate eligible patients to the open trials [20]. This effort enabled the hospital to initiate and complete several key investigator-initiated trials, contribute significant numbers to major national trials, and minimize the burden to patients, clinical teams, and PPE supplies.

Even as these efforts were ongoing, clinicians were asking for consensus guidance about management decisions, particularly around potential treatments. Two parallel and synergistic efforts were initiated to rapidly incorporate new evidence into clinical decision making: Fast Literature Assessment and Review (FLARE) and COVID Here and Now Treatment Guidance (CHANT). Led by critical care clinicians initially focusing on the management of acute respiratory distress syndrome, FLARE brought together knowledge from related diseases, insights from human biology and pathophysiology, and growing COVID related evidence to create in-depth reviews of topics suggested by clinicians [21]. The CHANT process was led by infectious diseases (ID) physicians and used a modified Delphi approach to generate dynamic treatment guidance documents that encompassed the range of management questions facing the front-line clinicians. The CHANT team grew to include nearly 100 experts with many ID clinicians but also subgroups focusing on cardiology, immunology, nephrology, hematology, neurology, and pregnancy. They held daily virtual meetings to discuss cases and new information arising from careful clinical observation of different management strategies. Early in the surge, this approach identified the effect of prone positioning patients on hypoxemia, the prothrombotic state and need for careful anticoagulation to enable interventions like renal replacement therapy, and the benefit of supportive care in managing cardiac involvement. Across hospitals, clinicians noted the striking inflammatory response and attempted to modulate that response, with the critical importance of disease severity and timing of immunomodulation becoming increasingly clear as

clinical experience increased. Through CHANT, clinicians making careful clinical observations joined with clinical investigators to improve the care of COVID patients even as large-scale clinical trials were being developed.

In summary, the COVID-19 pandemic created a major challenge for clinicians who needed to make urgent decisions about prevention, diagnosis and treatment of a new disease and for researchers who needed to understand the clinical syndrome and the questions of greatest importance to the pandemic response. Clinical epidemiology was central to addressing these challenges for several reasons. The scarcity of resources (including tests, inpatient beds, and trial participants) forced clinicians to use careful clinical observation across groups of patients and both probabilistic and population-based approaches to decision making [2,15]. The dynamic uncertainty about the clinical syndrome and disease definition required researchers to depend upon real time clinical insights for study design and implementation. In clinical areas that often claim certainty when it does not exist, acknowledging uncertainty became the norm [22,23]. Finally, the urgency of the need to save lives led to an emphasis on the collective good over individual credit across the research community and a new clarity about the importance of clinical epidemiology for advancing clinical care among many clinical leaders. While the impact of COVID-19 on clinical epidemiology was unparalleled, these factors are far from unique to COVID-19. The opportunity now is for academic medicine to build upon this experience to maximize the impact of clinical epidemiology on our ability to understand, prevent, and treat disease.

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