

COVID-19 Through Time

Have gains in medical knowledge about COVID during the pandemic's first year led to gains in the moral application of that knowledge?

The only solid piece of scientific truth about which I feel totally confident is that we are profoundly ignorant about nature.

– Lewis Thomas

In the spring 2020 pandemic surge in New York, as patients in respiratory distress began to overwhelm intensive care units, the state came very close to having to implement an ethically draconian protocol for patient care: triage decisions for the allocation of ventilators. New York was seemingly well prepared for this contingency because the New York State Task Force on Life and the Law, of which I am a member, published ventilator allocation guidelines in 2015 following an earlier pandemic flu scare. While certainly not perfect, the guidelines were probably the most widely discussed document regarding ventilator allocation as the nation entered the pandemic at the start of 2020.

The schema applied the Sequential Organ Failure Assessment (SOFA) tool—a protocol for using clinical evidence to assess critically ill patients—to allocate scarce resources during future influenza pandemics. It used a physiologically neutral (and aspirationally nondiscriminatory) measure of multisystem organ failure to assess likelihood of survival from acute respiratory failure. Once the proper public health authorities declared an emergency warranting the use of crisis standards of care, patients would be classified into four color-coded categories for triage: not likely to survive the acute infection despite maximal efforts (blue); sick but not in need of ventilatory support (green); critically ill with isolated respiratory failure, but most likely to survive if ventilated (red); survival prospects uncertain even with a ventilator (yellow). Yellow patients would receive a ventilator after all red patients got one.

Central to the triage process of SOFA was the periodic reassessment of patients after they were assigned a color to determine if their condition warranted continued ventilator access. The guidelines made clear that during a pandemic, nothing is guaranteed forever, especially a ventilator. They stipulated that “official clinical assessments at 48 and 120 hours after ventilator therapy has begun are conducted to determine whether a patient continues with this treatment.... After the 120 hour assessment, patients are evaluated every 48 hours.” In the context of crisis standards of care, this seemed like a reasonable approach to allocation.

Except it wasn't. Growing clinical experience, hard won in the few weeks COVID-19 had ravaged New York, revealed that patients took too long to recover to use these standards. If we evaluated patients at 48, 120, and then every 48 hours and there wasn't sufficient recovery, the timetable laid out in the SOFA framework would lead to tragic choices. COVID-19 patients who might recover if kept on a ventilator would be prematurely removed from one.

The guidelines were never implemented for many reasons, among them the political toxicity associated with questions of triage. But here I focus on another reason, one that is rarely considered in discussions of medical science and its application to the mission of saving lives and alleviating suffering: the dual nature of time. The interplay of time, knowledge, judgment, and action is an essential determinant of how science works in the real world. The ethical application of what we know to what we do depends on understanding this interplay.

In retrospect, the source of our error in seeking to apply the triage guidelines to COVID-19 was obvious, but the implications of the misunderstanding are obscure. The assessment schedule in the ventilator

allocation guidelines was designed for pandemic flu, not the coronavirus. It was a classic case of analogic reasoning gone astray. Pandemic flu had a much quicker course than COVID-19, and the time frame for periodic reassessment for the former was ill-suited to the latter. COVID-19 patients needed much more time on the ventilator to declare themselves as beyond cure. For some patients who were sedated while intubated, there came an atypically long period of reversible unconsciousness. It wasn't a matter of hours but weeks or even a month before extubation was possible. Their pace of recovery was more akin to the trajectories of patients with severe structural brain injury and disorders of consciousness than an infectious disease.

Learning in time

The uncertain state of medical knowledge is a reality that all doctors must come to accommodate as they strive to develop sound clinical judgment. During medical school and residency, surety and doubt learn to coexist, in an uneasy tension that allows for clinical work to proceed over the course of a doctor's career.

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This alliance, between surety and doubt, has been disrupted by the pandemic. Faced with critically ill patients with a heretofore unknown (and deadly) pathogen and obliged to provide care, experienced clinicians will question what they know and the state of available knowledge, reverting back to the epistemic ambivalence they experienced during their professional training. The clinician's developmental regression is made all the more frightening by fears of contagion, their own mortality, and the safety of their family.

Consider the "Clinical Practice" feature in the *New England Journal of Medicine* reviewing the treatment of severe COVID-19, first published online in May 2020. Written by colleagues from Weill Cornell Medical College following their experience during the spring surge in New York City, the piece was a first draft of medical history. But what distinguished the article was its uncharacteristic editorial tone. While it made recommendations about care, the authors were tentative, indeed uncertain, about their observations and conclusions in all manner of care from ventilator management to the use of emerging therapeutics.

By way of example, the "Areas of Uncertainty" section, a regular feature of this series, began with the stark admission that "Little is known about the pathogenesis and treatment of this new disease." One does not generally see such candor in a review article. And juxtaposed with this acknowledgement was an attempt to share what was known. To that end, the authors did their best to synthesize available data and stand in the breach given the urgent need for expert counsel. Their recommendations are hedged with cautionary ellipses about "conflicting advice" and "pending results of randomized trials" for candidate therapies for which "the risks and benefits ... are also unknown." The article concludes with an admonition to clinicians to "discuss available clinical trials with patients" and the "value of autopsies with families of patients who do not survive."

The starkness of these final recommendations speak to the uncertain state of current medical knowledge, the need to collect systematic data, and ultimately to confirm with autopsy the diagnoses made at the bedside. One reads the essay impressed by the humility of these greatly experienced authors, unable to reconcile confidence in their scholarship with the contingency of an unfamiliar disease.

With the passage of time the paper was in final form and in print in early December 2020 with an update to reflect the advance of medical knowledge. Risk factors for the disease were further delineated, with age identified as the most important predictor of critical illness and death. Absent in the initial paper, the "strong influence" of race, ethnicity, and social determinants was now highlighted. The revealed truths from the autopsy table turned clinical concerns about diffuse alveolar damage into demonstrable fact. This fact substantiated the view that the lung pathology seen in severe COVID-19 was consistent with acute respiratory distress syndrome. This data further informed an approach to ventilator management geared to spare lung injury. This strategy was based on informed, but less than validated, speculation in the original manuscript.

The first draft of medical history had been rewritten. Most tellingly, in a congratulatory statement made by omission, the confession that "little is known about the pathogenesis and treatment" of COVID-19 was struck from the paper.

Time helped to transform a diagnosis into a prognosis, which is essentially a forward projection of a diagnosis over time. One notable example of this evolution was the strategy of early intubation of patients who appeared to be in imminent risk of respiratory collapse. Patients with falling oxygen levels and respiratory muscle fatigue have been traditionally

Illustration by Shonagh Rae



candidates for immediate intubation and mechanical ventilation because these signs indicated impending respiratory failure, a life-threatening emergency. But curiously, many COVID-19 patients tolerated these stressors and were able to avoid intubation, especially if aided by noninvasive positive airway pressure devices used to treat sleep apnea, and by proning (having patients lie on their stomach). Indeed, growing clinical experience showed that patients who were quickly put on mechanical ventilators fared less well than those for whom such treatment was either avoided or delayed. Aggressive care, which had been life-saving for other, seemingly analogous conditions in the past, turned out to be potentially counterproductive. So, over time, we had learned two very different things about COVID and about time that challenged our former understanding: first, that delaying ventilation was often desirable; second, that if ventilation became necessary, it might be

needed for much longer periods than for other diseases.

Medical progress depended upon the passage of time, with inquiry occurring through structured research and, more often, clinical practice—what the American philosopher and pragmatist John Dewey described as experiential learning by doing. Time became a balm for the uncertainty bred of ignorance, or at least for some of it. It provided an opportunity to make sense of one's clinical observations and experiential learning and transform a disorganized set of novel findings into more coherent insights that would improve patient outcomes.

Medicine without time

We doctors take time for granted, yet it is embedded in everything we do. We speak of incubation periods, duration of treatment, and prognostication and life expectancy. We have specialties such as pediatrics and geriatrics that track the life cycle. And our hospitals are

governed by shifts and even visiting hours.

Now imagine medical practice devoid of a sense of time. That was the early days of COVID-19, when all these temporal biomarkers were taken from us, and perhaps most tragically visiting hours were taken from our patients, who often had to suffer in horrid isolation and die alone without the comfort of family.

In her brilliant book *Longitude*, Dava Sobel describes the eighteenth-century invention of the first ship chronometer accurate enough to allow for confident navigation. By knowing the time in one's home port and on board, captains could determine longitude, changing seafaring forever. Ship navigation was made immeasurably safer and more reliable.

Going to sea without a chronometer became unthinkable. But medicine found itself in a similar state during the early days of the pandemic. Consider how achronological our knowledge of COVID-19 was. At the beginning of the pandemic, we did not know the period of incubation and thus did not know how long people suspected of carrying the virus should be quarantined—a word taken from *quarantino*, a derivative of the Italian number *quaranta*, which speaks to the 40 days of isolation during medieval plague days. Even though the roots of quarantine speak to a fixed duration, during the pandemic, quarantine has been in temporal flux. On December 2, 2020, the Centers for Disease Control and Prevention revised its recommendations, shortening quarantine from 14 to 10 days for asymptomatic individuals.

Our clinical sense of time, our expectations about how patients would present, were distorted. During the spring surge in New York we were surprised to see patients presenting to emergency wards seemingly in mild distress, yet their oxygen levels were frighteningly low and indicative of far more advanced disease than their signs or symptoms might have suggested. The patients did not look as sick as they were. This gave clinicians the false security, bred of earlier experiences with other conditions, that they had time to act—that is, until the clock quickly ran out and patients needed emergency intubation to save their lives. This temporal pattern of presentation was new to the novel virus.

COVID-19 also defied temporal expectations about duration. When my hospital was deluged by patients during the spring surge that struck Manhattan, we viewed COVID-19 as an acute disease with a rapid and unpredictable onset. But over time we learned that for those who survive, the duration of illness can be prolonged with the potential for permanent disability, creating a new descriptor: COVID long-haulers, those with ongoing fatigue, respiratory limitations, and other enduring symptoms. Ali Gholamrezaezhad, a clinical radiologist at the University of Southern California Keck School of

Medicine, has tracked patients into their chronic phase with follow-up lung CT scans. When asked about how we will learn more about the disease's late trajectory, he quipped, "The problem is to assess long-term consequences, the only thing you need is time."

On the research front, time became a primary outcome by which to assess remdesivir, a drug originally developed to treat Ebola. Clinical trials were designed to demonstrate whether this repurposed agent could shorten time to recovery for hospitalized patients, a pace of recovery we still don't understand. Consider the speculations about COVID-19's typical trajectory: following a rebound from early symptoms, the disease comes back with a vengeance during the second week because of a cytokine storm or immune response. Such fears were expressed when President Trump was released precipitously from Walter Reed National Medical Center and returned to the White House. In hindsight, it's probable his rather uneventful second week was a consequence of the immunity conferred by the Regeneron monoclonal antibodies, the anti-inflammatory actions of the steroid drug dexamethasone, and the antiviral effects of remdesivir—beneficial interventions that only added further uncertainty about the time course of the disease.

Chronos and kairos

All these questions about the interplay of time and medicine are the heartbeat of our uncertainty. But they reflect only one aspect of time, questions of duration, intervals of observation, treatment or natural history, the time needed to learn by doing. This is chronological time, what the Greeks called *chronos*.

But the Greeks had a second, more nuanced notion of time they termed *kairos*. It is in *kairos* that we will encounter the value choices that undergird uncertainty during the pandemic. In contrast to *chronos*, which measures travel time or how long something might take, *kairos* is more qualitative. As I have written elsewhere, *kairos* "measures nothing but takes the measure of an occasion." If *chronos* clocks the time it takes to travel to a destination, *kairos* asks whether we should undertake the journey—is this the right time? When we think about uncertainty, time, and the pandemic, we need to think of both conceptions to take the full measure of these historic times.

Indeed, it could be argued that to consider *chronos* alone leads to a deeper sense of uncertainty because broader value questions have neither been adequately recognized nor properly interrogated. *Chronos*, which speaks to quantitative or biological considerations, falls short with respect to the qualitative dimensions of an individual's illness captured by *kairos*.

We have seen glimmers of *chronos* and *kairos* in the

chronicling of the pandemic. An April 2020 editorial in *The Lancet* about palliative care invoked both of these ancient conceptions of time. The editors wrote, “Time is short when patients deteriorate quickly, health professionals are overworked, isolation is mandated, and families are advised not to touch and even be in the same room as loved ones.” To be aware of the pace of decline—*chronos*—is only part of caregivers’ concern. *Kairos* asks us to appreciate the moral significance of the timing of our decisions. The rapid course of deterioration of patients from respiratory failure (*chronos*) brings the timeliness and appropriateness of end-of-life decisions (*kairos*) into focus in a way made all the more poignant when family ties are severed by isolation. A derivative notion of “the measure of an occasion” in modern medical ethics is the doctrine of proportionality, the balancing of burdens and benefits that inform all clinical decisions. Whether stated or not, proportionality is invoked from the most routine of clinical interventions to decisions about major surgery.

Weighing risks and benefits has been especially challenging during the pandemic because of the

We simply cannot know whether a switch to triage would have saved more lives than the default approach of first come, first served. Our poor understanding of both the disease’s duration and the right time for putting a patient on a ventilator resulted in a species of normative uncertainty that, in turn, reflected the temporal dislocation of *chronos* and *kairos*. The times favored neither conception of time, and this gave us pause. Insight came to me only in writing this essay, when I was better prepared by my special temporal position to appreciate last spring’s disjunction of *kairos* from *chronos*. In the heat of the pandemic I was too in the moment to understand the relationship between time and moral judgment. Without experience to draw upon, and faced with novel ethical challenges, I was forced to contemplate *kairos* before having the benefit of being informed by the evidence provided by *chronos*. It was a heart-wrenching position to be in, one experienced by all clinicians confronting the coronavirus. But through this act of expository reflection comes some modicum of insight, perhaps even wisdom about the limitations of moral judgment under such contingent circumstances. As the philosopher Søren Kierkegaard famously reminds us,

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uncertainty imposed by a novel disease we have yet to understand. *Chronos* is a necessary precondition to *kairos*, when deeper proportionate choices must be made. But these value choices do not disappear when we have insufficient clinical information. What remains is the burden of *kairos* uninformed by *chronos*. Uncertainty, and worse, results when the usual temporal milestones about disease trajectory are unavailable to pave the way for tough value choices.

This is the condition we faced in spring 2020 as we considered adopting a triage protocol for assigning ventilators. As we came to appreciate that COVID-19 patients took longer to recover (than those with pandemic influenza), we still didn’t know (then or now) exactly how long. The guidelines could have been revised to accommodate a longer course of ventilatory support before reevaluation occurred. But even this could not be done with confidence. With these questions of *chronos* unanswered, it remained premature to tangle with *kairos*. We were just not ready to change established norms and move from a first come, first served approach into utilitarian allocation. It was not the *right time* to accept the exigencies of triage.

“life must be understood backwards,” adding that “life can never really be understood in time simply because at no particular moment can I find the necessary resting-place from which to understand it—backwards.” And so it was for our uncertainty about whether to adopt crisis standards of care for ventilator allocation in New York.

In our times

As I write in mid-March, rates of infection are falling dramatically across the country and vaccination is proceeding at rates exceeding President Biden’s optimistic projections voiced at the start of his administration. Upward of 75% of 75-year-olds, the most vulnerable group, have been immunized, and the increased supply of vaccines has led to the president’s call for all Americans to be considered eligible for vaccination as of May 1. This hard-won success represents what is possible as data are generated that allow *chronos* to inform *kairos*: moral judgments, as well as clinical judgments, can evolve and improve.

These are bright spots worthy of celebration, and predictably, some state officials are taking a victory lap, easing up on social distancing and mask mandates. Yet if

this pandemic has taught us anything, it is to be humble when anticipating what will come next. While there is much to celebrate in bringing several excellent vaccines forward within a year, much about the vaccines remains unknown given the ultrafast rollout and the Food and Drug Administration's Emergency Use Authorization, most notably their duration of immunity. This remains a question that will hopefully be answered by studies that follow up on the initial clinical trials to look at the vaccines' effects on much larger populations. Beyond efficacy is the related question of toxicity. While there have been rare episodes of anaphylaxis, the reported diagnosis of acute idiopathic thrombocytopenic purpura (a blood disorder characterized by an abnormal decrease in the number of platelets) that resulted in a fatal brain hemorrhage in a previously healthy 56-year-old obstetrician/gynecologist is particularly noteworthy. Whether the vaccine triggered an autoimmune response against this individual's platelets is unknown. Capturing the partial explication offered by temporal association, the vaccine expert Paul Offit observed, "Right now we're guessing. It's an association in time, but not necessarily a causal association."

The future effects of the vaccination are not yet fully understood, either individually or on a population basis. The most pressing question is whether herd immunity will be achieved fast enough to dampen the reproductive opportunism of more malignant viral variants—variants that may have the capacity to elude the protective immunity of current vaccines. In this race against *chronos*, decisions to ease up on social distancing policies—*kairos*—will run up against the rate of vaccination and the evolutionary pace of variant development, perhaps the most unpredictable of timelines. As Francis Collins, the director of the National Institutes of Health, recently put it, "We are reading evolution's lab notebook.... Every time one of these pops up, it's telling us exactly how evolution benefits at the expense of the fitness of humankind."

We must still see how this plays out, amid remaining areas of uncertainty both scientific and sociological. For all the science and technology that predated COVID-19, we were woefully unprepared for the onset of the pandemic. As we transition into this next chapter of the pandemic where variants and evolutionary forces are exerting themselves, it is important to maintain a sense of humility and appreciate that certainty and uncertainty, and *chronos* and *kairos*, are never fully reconciled. They are always evolving in their balance and interrelationship, and good medicine and medical science are about continually negotiating that balance.

So as we consider our moment and what the future holds, there is a third dimension of time that we must embrace, and that is the study of the past. Whether it

is a study of the Plague of Athens or the Spanish flu pandemic of 1918, it is only through history that we can understand our own times. In the moment of crisis, whether it is a pandemic, a war, or an insurrection, we are consumed by the pace of events. It is all about *chronos*. *Kairos* comes later and provides the deeper, indeed historical, perspective that we lack as the story is unfolding. Thinking ahead, I hope I will have the chance to read the history that others will write about our times when they chronicle the COVID-19 pandemic, years hence. I hope that our efforts to achieve some imperfect, early measure of *kairos* in the present will be deemed prudent by those future historians. Time will tell....

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RECOMMENDED READING

- David A. Berlin, Roy M. Gulick, and Fernando J. Martinez, "Severe Covid-19," *New England Journal of Medicine* 383, no. 19 (2020): 2451–2460.
- Joseph J. Fins, "Sunshine Is the Best Disinfectant, Especially During a Pandemic," *Health Law Journal of the New York State Bar Association* 25, no. 2 (2020): 141–146.
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- Barrie J. Huberman, Debjani Mukherjee, Ezra Gabbay, Samantha F. Knowlton, Douglas S. T. Green, Nekee Pandya, Nicole Meredyth, Joan M. Walker, Zachary E. Shapiro, Jennifer E. Hersh, Mary F. Chisholm, Seth A. Waldman, C. Ronald MacKenzie, Inmaculada de Melo-Martín, and Joseph J. Fins, "Phases of a Pandemic Surge: The Experience of an Ethics Service in New York City during COVID-19," *Journal of Clinical Ethics* 31, no. 3 (2020): 219–227.
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- Reza Shahpori, H. Tom Stelfox, Christopher J. Doig, Paul J. E. Boiteau, and David A. Zygun, "Sequential Organ Failure Assessment in H1N1 Pandemic Planning," *Critical Care Medicine* 39, no. 4 (2011): 827–832.
- John E. Smith, "Time, Times, and the 'Right Time': *Chronos* and *Kairos*," *The Monist* 53, no. 1 (1969): 1–13.