The pandemic is prompting widespread use–and misuse–of real-world data

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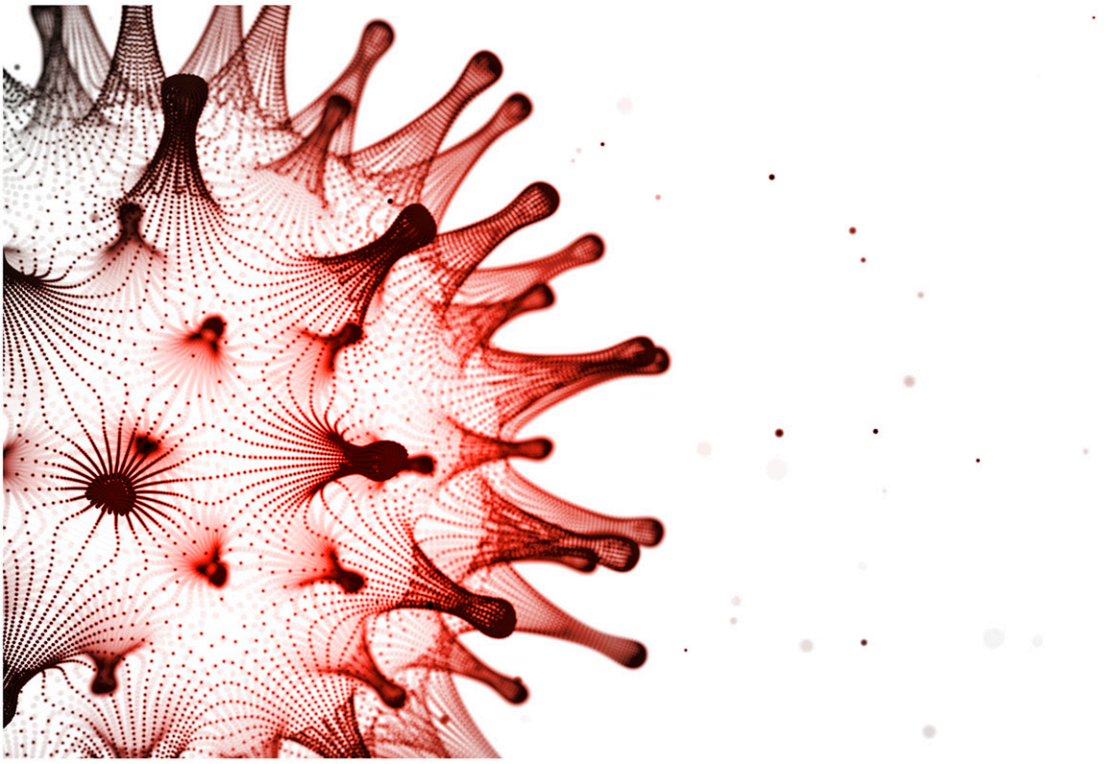
COVID-19 has swept across the world, overwhelming healthcare systems and raising countless questions about how best to diagnose patients, treat infections, save lives, and contain the pandemic. In short order, researchers have launched randomized trials to uncover pharmacologic interventions that hold the promise of preventing or lessening the severity of the disease. But getting results takes time. And time was a luxury that doctors on the frontlines of the coronavirus fight could ill afford in the early months of the pandemic.

Desperate for medical insights without delay—and hoping to address other questions not answerable in a specialized research environment—researchers, pharmaceutical companies, and government agencies immediately turned to health information captured through insurance claims, electronic medical records, patient registries, and other so-called "real-world" data sources.

By analyzing trends in COVID-19 datasets, the research community rapidly helped fill in knowledge gaps around disease symptoms, risk factors, racial disparities, and more. Such observational methods also hinted at which treatments seemed to be making an impact—and which were not—all in near real time.

But harnessing this type of real-world data is a tricky business. It requires high-quality data collection and proper methodological considerations. There are established guidelines on how best to plan, execute, and report observational studies in a way that ensures



The dangers of COVID-19 present an unprecedented opportunity to leverage diverse, real-world data sources to inform medical and regulatory responses. But researchers and clinicians must be careful not to sacrifice methodological rigor. Image credit: Shutterstock/keyframelab.

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the validity and relevance of the evidence gathered (1). Yet researchers and clinicians can sometimes neglect those guidelines, especially during a health crisis in which the rush to publish has spawned some suspect research practices, according to some observers.

The pandemic thus presents an unprecedented opportunity to leverage diverse, real-world data sources to inform medical and regulatory responses to the public health emergency. Yet, at the same time, says Almut Winterstein, a pharmacoepidemiologist from the University of Florida in Gainesville, the need for speed should not come at the expense of methodological rigor and detail.

"That's [the] balance that needs to be maintained," says Winterstein, who served as president of the International Society for Pharmacoepidemiology until this past August. "On the one hand, you need real-world data in order to have complete evidence for decision making. But at the same token, you have to follow proper epidemiological methods and consider and address the biases in the data before making any causal inferences."

Getting Real

Randomized clinical trials have long been the gold standard for gathering robust evidence that a treatment may "work." However, the internal validity of this approach often comes at the expense of generalizability, because not all patients are necessarily reflected in any given study population. And so, physicians and drug developers have long relied on real-world data analyses to extend the relevance of clinical trial results. Patient reports from real-world settings have also helped regulators ensure the long-term safety of medical products on the market. Such data sources are increasingly helping to support label expansions of approved therapies as well.

Yet, at the same time that there is an explosion in real-world data applications, the science surrounding this strategy remains in its infancy. Agencies such as the US Food and Drug Administration (FDA) are trying to determine best practices from a regulatory perspective. Meanwhile, journal editors and reviewers are struggling under the weight of real-world study submissions—with mixed results.

"Overall, in my reading of observational papers, there has certainly been very large variation in the quality of papers published," says Anton Pottegård, a pharmacoepidemiologist at the University of Southern Denmark in Odense. In May, Pottegård, together with colleagues from across Europe, published a checklist detailing eight methodological "considerations" for real-world drug studies related to COVID-19 (2). Five months on, however, many researchers seem not to have taken notice, as evidenced by a "substantial number" of reports with "clearly flawed methodologies," he says.

In particular, Pottegård says he is concerned with the large number of observational papers addressing efficacy of interventions in COVID-19 patients, "something that is inherently difficult to get right and as such is better left to randomized, controlled trials."

Cynthia Girman, a longtime pharmaceutical executive at Merck in Kenilworth, NJ, who now consults on observational data methods, chalks the problem up to inexperience with the analytical approach among many researchers. "A lot of people who are not familiar with real-world data sources have sort of jumped in," she says.

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For better or worse, Girman adds, when it comes to the use of real-world data, "the pandemic has brought out a lot of good, bad, and ugly."

The Hydroxychloroquine Affair

The good, bad, and ugly of real-world data can be seen in stark relief when considering the story of hydroxychloroquine, an antimalarial drug once touted by US President Donald Trump for its supposed antiviral effects. [Randomized trials later showed that hydroxychloroquine offers little if any benefit to coronavirus patients and could possibly be harmful (3).]

The good: After initial reports of hydroxychloroquine's promise, researchers working within both public and private health systems dug into their hospital records and found that the drug failed to reduce the risk of ventilation or death.

The bad: Unfortunately, this relatively quick "correction" within the scientific community was not quick enough. Infectious disease specialists had already started widely prescribing the drug. The FDA also issued an emergency use authorization (EUA)—and all because of little more than a preliminary observational study involving just 36 patients (4). The agency later revoked the emergency waiver and doctors stopped administering hydroxychloroquine, but not before the government had stockpiled more than 60 million doses and tens of thousands of patients needlessly received the useless medicine. Unfounded assertions from politicians about the drug's effectiveness didn't help matters.

The ugly: A little-known data analytics firm called Surgisphere Corporation in Palatina, IL, reported a chilling mortality risk among patients with COVID-19 who took hydroxychloroquine (5, 6)—a finding that almost derailed randomized testing of the drug. Articles were quickly retracted and trials restarted after critics challenged the study's methods and the legitimacy of the company's dataset, purportedly amassed from medical records of nearly 100,000 infected patients treated in 671 hospitals worldwide. It is still unclear whether, as some suspect, any authors engaged in deliberate fraud—a deception that experts say would be easier with hospital record collections than with prospective trial data amassed under the oversight of monitoring committees and review boards. Either way,

experts say the incident damaged public trust and delayed scientific progress.

Uncertain Times

A more recent controversy centers on the therapeutic value of blood plasma donated by COVID-19 survivors. According to an August analysis (7) of more than

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>
> —Miguel Hernán

35,000 critically ill patients who received infusions of this antibody-rich brew under a government-backed "expanded access" program (also called "compassionate use") led by the Mayo Clinic in Rochester, NY, the treatment appears safe and has the potential to ward off death.

Those results prompted the FDA to issue an EUA for the treatment, known as convalescent plasma. But the study's lack of a placebo group makes it impossible to say for certain just how effective plasma therapy might be—and many experts blame the choice of study design for that ambiguity. Political maneuvering further inflated the therapy's potential impact.

To gain definitive answers about the approach's clinical benefit, some hospitals are now refusing to provide convalescent plasma except through a controlled trial. Yet recruitment has been slow, in part because many patients, fearing they might get a placebo through a randomized study, have opted to go to medical centers that are guaranteeing the real thing.

It didn't have to be this way. More than 105,000 patients enrolled to receive plasma therapy under the Mayo-led program. "If instead of having done that observational study," says Rory Collins, an epidemiologist at the University of Oxford in the United Kingdom, "they'd actually randomized just a fraction of those patients, we'd know the answer now" about whether the treatment is truly life saving.

Between the political push to make convalescent plasma widely available and the initial study design, clinical leaders and FDA officials "actually made it harder to get the answer and they've wasted precious time," Collins says. "How many people will die as a result?"

For his part, Michael Joyner, an exercise physiologist and anesthesiologist who led the Mayo study, defends the protocol, citing the many uncertainties and logistical challenges around administering plasma therapy. But after a few months, once his team had sorted out procedural issues and generated some hypotheses worth testing, he acknowledges (speaking at a September virtual meeting of the American Society of Gene and Cell Therapy) that a "hybrid model" might have been preferable, with large medical centers offering the therapy in randomized trials and rural clinics continuing to make the treatment available on a compassionate use basis.

The episode underscores the need for well-designed clinical trials, even in the throes of a global pandemic, says former FDA commissioner Robert Califf, who now leads health strategy and policy at Google Health and Verily Life Sciences in South San Francisco, CA. "It's an ongoing dilemma that if you lower the standards too much you end up with a situation in which people really come to believe in the treatment even though we never develop the evidence of whether it's any good or not," he says.

It's not that observational studies and real-world data analytics don't have their place in the pandemic response. When it comes to drug treatments, these methods can, for example, help researchers better understand how risk factors such as age, sex, underlying health conditions, and medication use drive outcomes to coronavirus infection. And even if limited in their capacity to definitively establish the efficacy of therapeutic interventions, they can evaluate safety or help confirm the results of randomized trials regarding toxicity and clinical benefit in daily medical practice or in different patient populations.

With the antiviral drug remdesivir, for instance, real-world experience suggests that children and pregnant women stand to benefit from the COVID-19 treatment, even though those vulnerable groups were excluded from controlled trials. After-the-fact data collection has also pointed the way toward therapies worth testing in randomized trials—many of which turned out to be disappointments, as happened with hydroxychloroquine. "It's not either/or," Califf says. "You need both [methodologies] for different purposes."

Countless Caveats

The challenge is making sure that real-world data studies are applied to the appropriate sorts of questions. Oftentimes, patients who receive a medical treatment also are at an increased or decreased risk for various health outcomes. Or they're more or less likely to have certain underlying conditions. And unless statisticians adjust for known differences among patient groups or choose the wrong comparator populations, they can be led to draw spurious conclusions. Indeed, there are many opportunities for confounding factors, selection bias, and other sources of error to creep into observational analyses—and surveys of the biomedical literature suggest that those problems are pervasive.

Take, for example, a recent study from biostatistician Jessica Franklin and her colleagues at Brigham and Women's Hospital in Boston, MA. They assessed the design choices that went into 155 published observational studies, each of which used insurance claims, medical records, or some other real-world data source to determine whether taking diabetes medications increases a person's risk of developing cancer (8). Most of the studies, they found, were filled with methodological missteps and avoidable biases—for instance, nearly two-thirds of the studies suffered from a distorting effect known as immortal time bias, which stems from delays in participant classifications and can lead researchers to spuriously conclude that drugs are

safer or riskier than they truly are. "It's really scary," says Franklin, when you see how prevalent such missteps are.

Her team has since looked at another 75 observational studies—some published as recently as last year—that examined the safety or efficacy of drugs for diabetes, heart disease, or osteoporosis. "The results are not any better," says Franklin, whose group presented the findings at International Society for Pharmacoeconomics and Outcomes Research annual meeting in May 2020. "There are still a ton of problems."

Faced with a barrage of bad science, some researchers have insisted that only randomized trials can produce reliable findings and ensure patient safety. But others say the methods, not the approach, are the issue. "There is a lot we can learn from observational studies if we do them right," says Miguel Hernán, an epidemiologist at the Harvard T.H. Chan School of Public Health in Boston, MA.

Pushing on the Accelerator

Recognizing the need for more rigorous types of analyses—and for community standards more broadly—two nonprofits, the Reagan-Udall Foundation for the FDA and Friends of Cancer Research, both based in Washington, DC, joined forces in April and launched a new forum for stakeholders to share ideas, strategies, solutions, and concerns around how best to leverage real-world data during the pandemic.

Through weekly virtual meetings, "people now have a place where they can bring questions, or they can bring results, and they get this peer review on steroids within the discussion," says Susan Winckler, chief executive of the Reagan-Udall Foundation, a congressionally mandated organization charged with helping modernize regulatory science. And although the initiative, dubbed the "COVID-19 Evidence Accelerator," is focused on the current crisis, "it's clearly learnings and understandings that are going to extend far beyond the pandemic," she says.

The FDA has also entered into separate research collaborations with individual health technology companies, including Aetion, in New York, NY, and Syapse, in Radnor, PA (both participants in the Evidence Accelerator as well), to identify which types of data are best suited to characterizing COVID-19 patient populations and their medication use. This has proven particularly challenging with the pandemic because of inconsistencies in hospital coding and reporting, along with differences in how doctors define presumed positive cases.

Despite many imperfections in the data, the vast amounts of patient information, when analyzed correctly, have begun to offer important insights. In July, for example, the FDA's Oncology Center of Excellence and Syapse presented data on health records from more than 212,000 people living with cancer, which highlighted the significantly elevated risks of hospitalization, invasive ventilation, and death for cancer patients who developed COVID-19 compared with those without a coronavirus infection.

Jeremy Rassen, CSO and president of Aetion, says his company's analytics platform includes a broad array of data resources, all linked in a way that provides "a singular view of a patient in all different care settings"—including before, during, and after any coronavirus-related hospitalization. That patient-level data allowed researchers at Aetion, working with another healthcare data company called HealthVerity in Philadelphia, PA, and a pair of academic researchers, to test whether certain blood pressure medications might be having an impact on the severity of the COVID-19.

Because the novel coronavirus enters human cells through a receptor also involved in modulating blood pressure, early on in the pandemic some doctors had suggested that patients should stop taking two popular varieties of hypertension drugs—ACE inhibitors and angiotensin receptor blockers—because they might make infections worse.

Yet when Rassen and his colleagues dove into the files from thousands of individuals, they found that people newly diagnosed with COVID-19 were no more likely to land in a hospital if they were taking one of these fretted-over medications or another type of blood pressure drug that works through an entirely different mechanism (9). If anything, the ACE inhibitors and angiotensin receptor blockers seemed to be protective. The real-world data ran counter to the perceived wisdom.

It's just one example, but it underscores the importance of a real-world data approach that's both innovative and careful. "We need to be bringing data into all of these conversations in ways that we haven't done in the past," says FDA principal deputy commissioner Amy Abernethy, emphasizing the importance of thwarting a false dichotomy between observation methods and randomized trials. She says that the intense scrutiny of COVID-19 studies, data, and treatments could help researchers and clinicians "accelerate how to find the complementarity" of the two approaches.

"This as an urgency at a time when our data sources have changed markedly," she adds, "and we haven't fully explored what that makes possible."

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