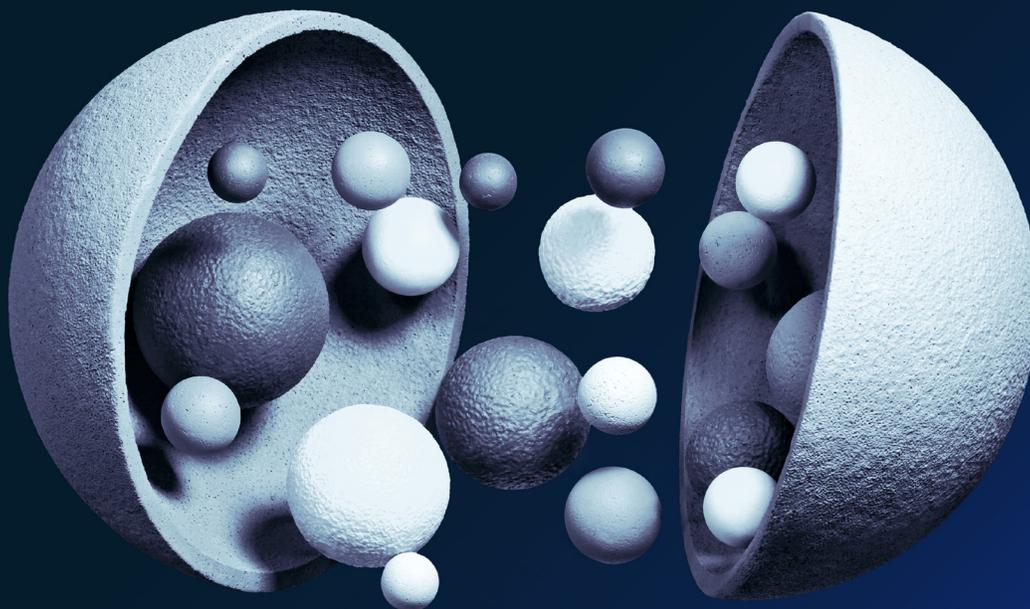


Risk Practice

# COVID-19 briefing note: May 13, 2020

Our latest perspectives on the coronavirus outbreak, the twin threats to lives and livelihoods, and how organizations can prepare for the next normal.

*by Matt Craven, Mihir Mysore, and Matthew Wilson*



**As the reopening of** economies continues across much of Europe and North America, it's worth taking stock of the epidemiological situation and trends that will define the months ahead. At the time of this writing, the official counts of cases and deaths from COVID-19 have passed four million and 280,000, respectively. Recent studies have made increasingly clear that each of these figures is a significant underestimate. Population antibody surveys suggest that official counts are underestimating the true number of cases by a factor of five or more (although in several cases the methodology has been called into question) (Exhibit 1).

Comparisons of 2020 and 2019 mortality rates show that substantially more people are dying this year, although we don't know how much of this is due to missed deaths from COVID-19 rather than excess mortality from other causes (Exhibit 2).

## The pandemic and public health—five trends to watch

With lives at stake, a thoughtful approach is paramount. Here are the five emerging trends that private-sector leaders need to monitor.

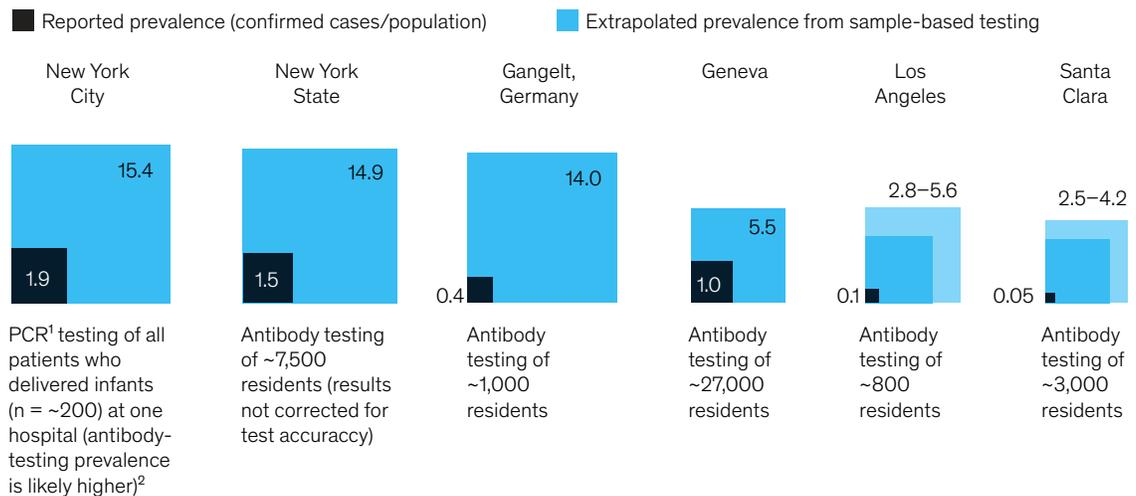
### There are still many places where the epidemic is getting worse

While much of the media narrative is about reopening, many countries, including several of the largest emerging economies, are still on the “upslope” of the epidemic, with daily case counts increasing (Exhibit 3). While an increasing number of countries and regions have proven that they can use lockdowns to drive a reduction in cases, to date, we have few examples of success outside higher-income countries. The next few weeks will be critical tests of our ability to “bend the curve” in more countries with varying contexts and healthcare capacity. In some

Exhibit 1

## Official case counts may be capturing a fraction of the true totals.

Reported and extrapolated prevalence of COVID-19, % (as of April 29, 2020)



<sup>1</sup>Polymerase chain reaction.

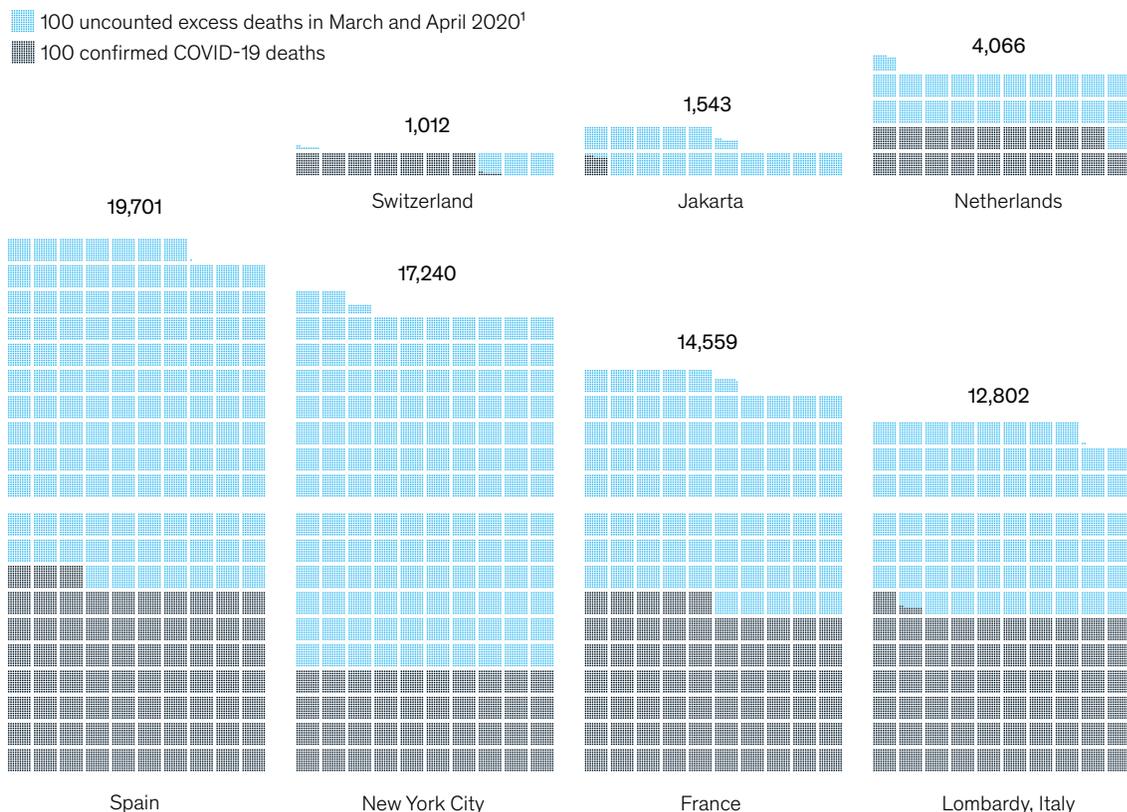
<sup>2</sup>Results not corrected for test accuracy.

Source: Bloomberg; *Economist*; Land NRW (Germany); medRxiv; *New England Journal of Medicine*; *New York Times*; ny.gov Swissinfo; University of Southern California

Exhibit 2

## Official death counts may be capturing a fraction of the true totals.

Potential COVID-19 death totals (as of April 29, 2020)



<sup>1</sup> Compared with 2015–19 average death counts, varying dates in March/April.

Source: Bloomberg; *Economist*; Land NRW (Germany); medRxiv; *New England Journal of Medicine*; *New York Times*; ny.gov Swissinfo; University of Southern California

of these countries, the absolute number of deaths is relatively low; interventions against COVID-19 will need to be viewed through the lens of both lives and livelihoods.

### Reopening is a massive natural experiment—make sure you learn from it

We have never before attempted to shut down the

modern global economy, much less reopen it in the setting of an ongoing pandemic. We have a few examples of strategies that seem to work better, or worse, but none of us know with any certainty the best actions. Even places with strong initial responses like Hong Kong and Singapore have faced challenges as they reopen.<sup>1</sup> China has also seen an increase in cases in the past few days.<sup>2</sup>

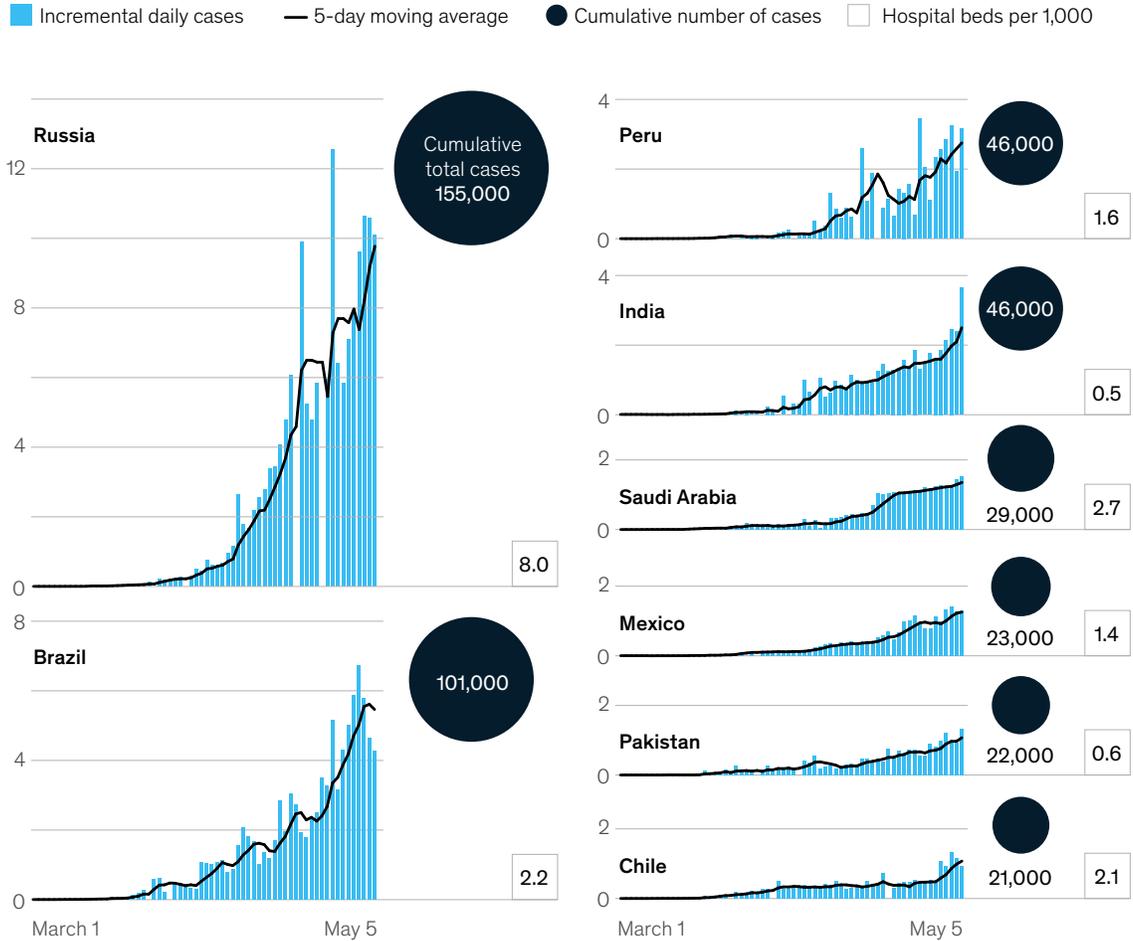
<sup>1</sup> Jill Terrier Ramos, "Fact-check: Did countries that reopened see a spike in coronavirus?," *Austin American-Statesman*, April 20, 2020, statesman.com; Suzanne Sataline, "Covid-19's resurgence in Hong Kong holds a lesson: Defeating it demands persistence," *Statnews*, March 26, 2020, statnews.com; Scott Neuman, "Emergency declared in Japanese prefecture hit by 2nd wave of coronavirus infections," NPR, April 13, 2020, npr.org; "Japan's Abe extends state of emergency to May 31," Al Jazeera, May 4, 2020, Aljazeera.com; Abigail Leonard, "This Japanese island lifted its coronavirus lockdown too soon and became a warning to the world," *Time*, April 24, 2020, time.com; "AP photos: Beijing slowly reopens amid falling virus cases," Associated Press, March 25, 2020, ap.com; Philip Oltermann, "Germans urged to stay at home amid fears Covid-19 infection rate is rising again," *Guardian*, April 28, 2020; theguardian.com; Adam Rogers, "The Asian countries that beat Covid-19 have to do it again," *Wired*, April 6, 2020; wired.com.

<sup>2</sup> "China reports rise in Covid-19 cases, Beijing calls for vigilance," *France 24*, May 11, 2020, france24.com.

Exhibit 3

**Many major emerging markets are still seeing rapid case growth.**

Daily reported cases of COVID-19 for countries with more than 10,000 cumulative cases, thousands



Source: Eurostat; Johns Hopkins University; *New York Times*; Organisation for Economic Co-operation and Development; Our World in Data; World Bank; World Health Organization

In the United States, there is only a loose correlation between disease prevalence and plans for reopening. States with more cases generally plan to reopen later, but there are exceptions.

A similar point can be made about businesses' plans to reopen. Companies are planning different approaches, even based on the same underlying fact base. This implies that leaders across the public and private sectors should build learning and adaptation into their reopening plans from

the start. Relevant lessons might come from other geographies, other sectors, or from peers and competitors. Leaders should be prepared to incorporate new information and alter their approaches, either incrementally or radically, as new information becomes available.

Resurgence seems to be not a question of if but when, where, and how bad. Many experts are focused on a potential second wave of COVID-19 in the northern hemisphere this autumn.<sup>3</sup> This

<sup>3</sup> Lena H. Sun, "CDC director warns second wave of coronavirus is likely to be even more devastating," *Washington Post*, April 21, 2020, washingtonpost.com.

# Leaders should build learning and adaptation into their reopening plans from the start.

is certainly possible. But focusing on the risks of autumn and winter causes us to look past the summer, which is risky because it is sooner and because it is when many jurisdictions will be reopening and testing.

## **R is important, but so is the absolute number of new cases**

Over the past few months, many have become more familiar with epidemiological concepts like the reproduction number (R) of a virus. R defines the transmissibility of a pathogen, as measured by the average number of people to whom each infected person transmits. R is a measure of change; it tells us how fast the epidemic will expand or shrink. Values greater than one define a growing epidemic, while those less than one define a shrinking one.

R has been getting a lot of attention, for example, in defining the packages of interventions that can yield  $R < 1$  in a given setting. But the absolute number of cases is also important. Imagine two cities, each with an R of 0.9, implying a slightly declining epidemic. But one of the cities has 1,000 new cases per day and the other has ten. The former faces a far higher risk in reopening than the latter.

In practice, we are seeing countries and regions take divergent approaches to this question (Exhibit 4). Hubei Province in China waited until reported cases were near zero to reopen, whereas Italy and Spain took the first steps to reopening with daily case counts at more than 1,000. Every location needs to balance public-health and economic imperatives; we can't say which approach is better, but we are likely to learn more about what works in the weeks and months ahead.

## **It's (still) all about testing, tracing, and targeted quarantine**

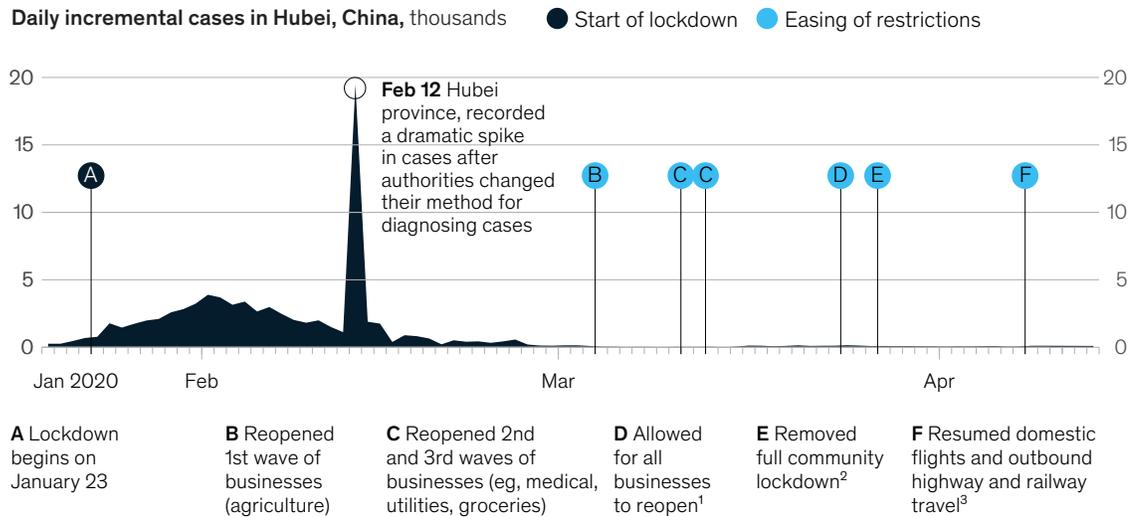
Significant resources are required to run a program of testing, contact tracing, isolation, and quarantine at the required scale, but relative to the economics of lockdowns or global recession, these costs are trivial. Many countries are still far short of where they need to be on testing, and contact-tracing programs remain a patchwork. Our recent article provides more details on contact tracing. Strengthening these programs remains an urgent priority for many geographies. This point is no less important for having been made frequently.

In any country, here are the four metrics to watch in assessing the strength of test, trace, and quarantine efforts:

- **Test positivity rate**, which measures (imperfectly) the extent to which testing systems are capturing all cases. The World Health Organization recommends a target of less than 10 percent positivity.
- **Tests per million population**, a measure of the depth of testing.
- **Average number of contacts identified per case**, which measures how effective contact-tracing systems are at identifying and isolating the likely next generation of cases. The figure will tend to be lower in lockdown settings than when people are moving and interacting freely.
- **Fraction of cases arising from contact lists**, a measure of the portion of cases arising from known sources versus undetected community transmission.

## Countries have chosen to reopen with varying numbers of recent cases.

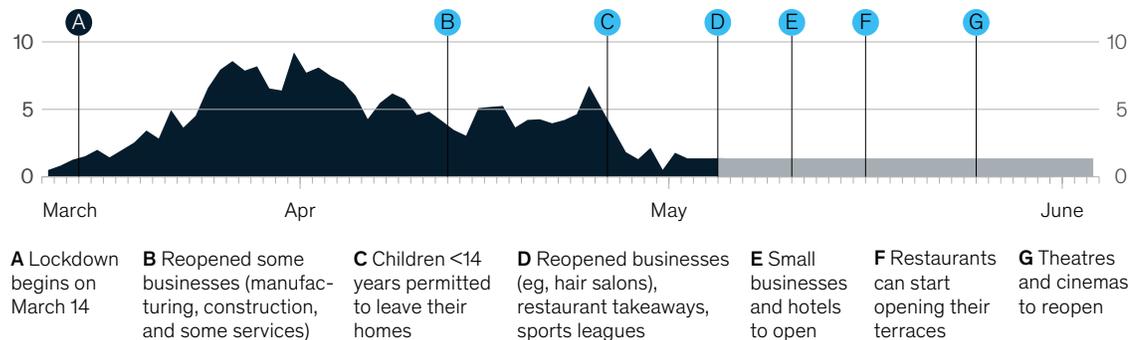
### Entering lockdown and lockdown easing, by country



### Daily incremental cases in Italy, thousands



### Daily incremental cases in Spain, thousands



<sup>1</sup>Upon individual assessment, as of April 7, 2020.

<sup>2</sup>People encouraged to stay home as much as possible, and schools remain closed.

<sup>3</sup>Domestic flights resumed, excluding Beijing; outbound highway and railway travel resumed after rollout of mobile app that indicates road- and rail-travel contagion risks.

Source: BBC.com; *National Business Daily* (China); The Local (thelocal.it); Wuhan Municipal Health Commission

An element of transmission dynamics now beginning to receive more attention is transmission *within* households.<sup>4</sup> We may need to rethink the current model of home isolation and develop modified strategies for mild and asymptomatic cases given that isolation can prove difficult for many. Any new model should of course ensure a comfortable experience for those who test positive, so that they're strongly inclined to follow the recommended approach.

### **Innovation—and clinical evidence—leads to hope**

The speed and scale of the R&D response to the COVID-19 outbreak is unprecedented in human history, with billions of dollars being spent and committed in pursuit of drugs, vaccines, and diagnostics for the virus. Today, there are more than 150 vaccines in the pipeline, and 200 drug candidates. On diagnostics, beyond the RT-PCR<sup>5</sup> and classic lateral-flow immunoassays already in use for many viral and antibody tests, new technologies such as CRISPR<sup>6</sup> have already been granted emergency-use authorization by the US Food and Drug Administration.<sup>7</sup>

The past few months have seen the launch of numerous trials in an effort to find therapies and vaccines—with some challenges from studies that are too small in size, or not randomized or controlled. As of early May, more than 1,700 trials are in progress targeting COVID-19 and related complications. More of these are randomized and controlled clinical studies—and some are starting read out results, providing evidence to support new approaches to prevent and manage COVID-19 infection and associated complications. The expert consensus is that enhanced treatments for COVID-19 will likely be available by the end of 2020; and only 12 to 18 months will likely be needed<sup>8</sup> to bring a vaccine to market at sufficient scale for widespread immunization, compared with the typical five or more years. Some developers have

even indicated a vaccine may be available sooner for limited use, with an emergency-use authorization for health workers issued as early as this fall.<sup>9</sup>

Here are five areas to watch:

- ***The great vaccine-platform race.*** At the time of writing, 13 vaccines are already in clinical trials, and the full pipeline spans a massive range of platforms, including RNA, DNA, inactivated viruses, protein subunits, and virus-like particles (VLPs). The virus and viral-vector approaches are traditional; others are nascent. Each platform will start to produce data in the months ahead, starting with evidence of vaccine safety and then potentially demonstrations of immunogenicity (and even efficacy) toward the end of the year, though we still need to better understand the link between immunogenicity and correlates of protection. While having multiple platforms in development increases the likelihood of a successful vaccine, each platform has different competitors, ranging from smaller biotech companies to multinationals, as well as distinct manufacturing requirements, with implications for the scale-up of capacity.
- ***A more nuanced understanding of the uses of different therapeutics.*** The initial discussion on drugs has focused almost exclusively on repurposed antivirals and antimalarials for treatment. The 200-plus candidates currently in development cover a broad range of use cases—from postexposure to prophylaxis, and from mild and moderate to severe cases. The more than 1,700 active trials are expanding the focus from drugs that directly attack the virus to those that confer immunity and to those that target complications of COVID-19 such as cytokine-release syndrome (CRS) and, more recently, acute respiratory distress syndrome (ARDS). Labs are deploying a wide

<sup>4</sup> Hao-Yuan Cheng, Shu-Wan Jian, and Ding-Ping Liu, "Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset," JAMA Network, May 1, 2020, jamanetwork.com.

<sup>5</sup> Reverse transcriptase polymerase chain reaction.

<sup>6</sup> Clustered regularly interspaced short palindromic repeats.

<sup>7</sup> For the full list, see "Emergency use authorization," fda.gov.

<sup>8</sup> Nicoletta Lanese, "When will a COVID-19 vaccine be ready?," Live Science, April 2020, livescience.com.

<sup>9</sup> Steve Usdin, "End of the beginning for COVID-19 vaccines," *Biocentury*, May 2, 2020, biocentury.com.

array of platforms, from repurposed antivirals (as mentioned above) to monoclonal and polyclonal antibodies to neutralize the virus to immune modulators for ARDS/cytokine storms, and even cell-therapy approaches for late-stage disease. The emergency-use authorization for remdesivir is an important milestone for COVID-19 drug development as well. In the coming months, we anticipate that a more nuanced understanding of the different use cases and the types of approaches being tested will help reduce the mortality rate of COVID-19 and also change the standard of care.

- ***A new normal and unrealized opportunity for data sharing.*** Unlike the experience with prior epidemics (including Ebola), COVID-19 has been characterized by unprecedented sharing of prepublication data, analyses, and results via medRxiv, a collaborative platform. This proliferation of information can support innovation and has been rapidly integrated into both the media and policy discussions—sometimes, however, to unfortunate effect. Looking forward, as the scientific community seeks to make meaningful interpretations of the thousands of running studies, we need to bring together the patient-level data from the hundreds of small, undersize, not-well-controlled, compassionate-use, and observational studies, in a responsible way. Meta-analyses of such studies will help us know if therapies actually work, at what dosing and clinical regimen. There are efforts underway in the ecosystem to address this—and hopefully a collaborative model emerges that could remain with us postpandemic.
- ***The impact of novel R&D models.*** Competitors are collaborating in ways never expected.<sup>10</sup> Companies are banding together in multilateral collaborations, some formal and some informal, to advance innovation. For example, leading plasma manufacturers are partnering in novel ways to produce a single unbranded immunoglobulin product; more than 15 pharma companies are collaborating in a COVID-19 R&D forum to advance, individually and collectively, the most promising drugs and vaccines; and decades-long competitors Sanofi and GSK are partnering on COVID-19 vaccine development. Novel master protocols, often with inspired names (such as Solidarity, Recovery, and ACTT), are being used to simultaneously test multiple drugs.<sup>11</sup> Innovators are deploying novel development plans and trial designs as well; for example, Pfizer and BioNTech are simultaneously testing four vaccines in their combined Phase I/II study. These approaches are not without risk given the parallel work in traditionally sequential stage-gated processes.
- ***The challenge of separating the signal from the noise.*** With Ebola, a substantial R&D mobilization ran into difficulties recruiting patients to test all of the approaches being considered. Some of these same challenges are happening with COVID-19. Ensuring that studies are well controlled and appropriately powered will be critical to understanding what actually works. Further, data sharing will hold the key to advance our understanding and interrogation of the benefit/risk trade-off. Multiple prioritization efforts are attempting to do this but are still in the early stages. In some ways, the scale of the mobilization may be the biggest challenge.

<sup>10</sup> David Beier and Max G. Bronstein, “Partnership offers hope for COVID drug development,” *Biocentury*, May 8, 2020, biocentury.com.

<sup>11</sup> Lauren Martz, “Master protocols emerge as a critical clinical tool against COVID-19,” *Biocentury*, April 11, 2020, biocentury.com.

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