Benchmarking the COVID-19 Pandemic: How Historical Analogs May Guide Our Understanding and Approach

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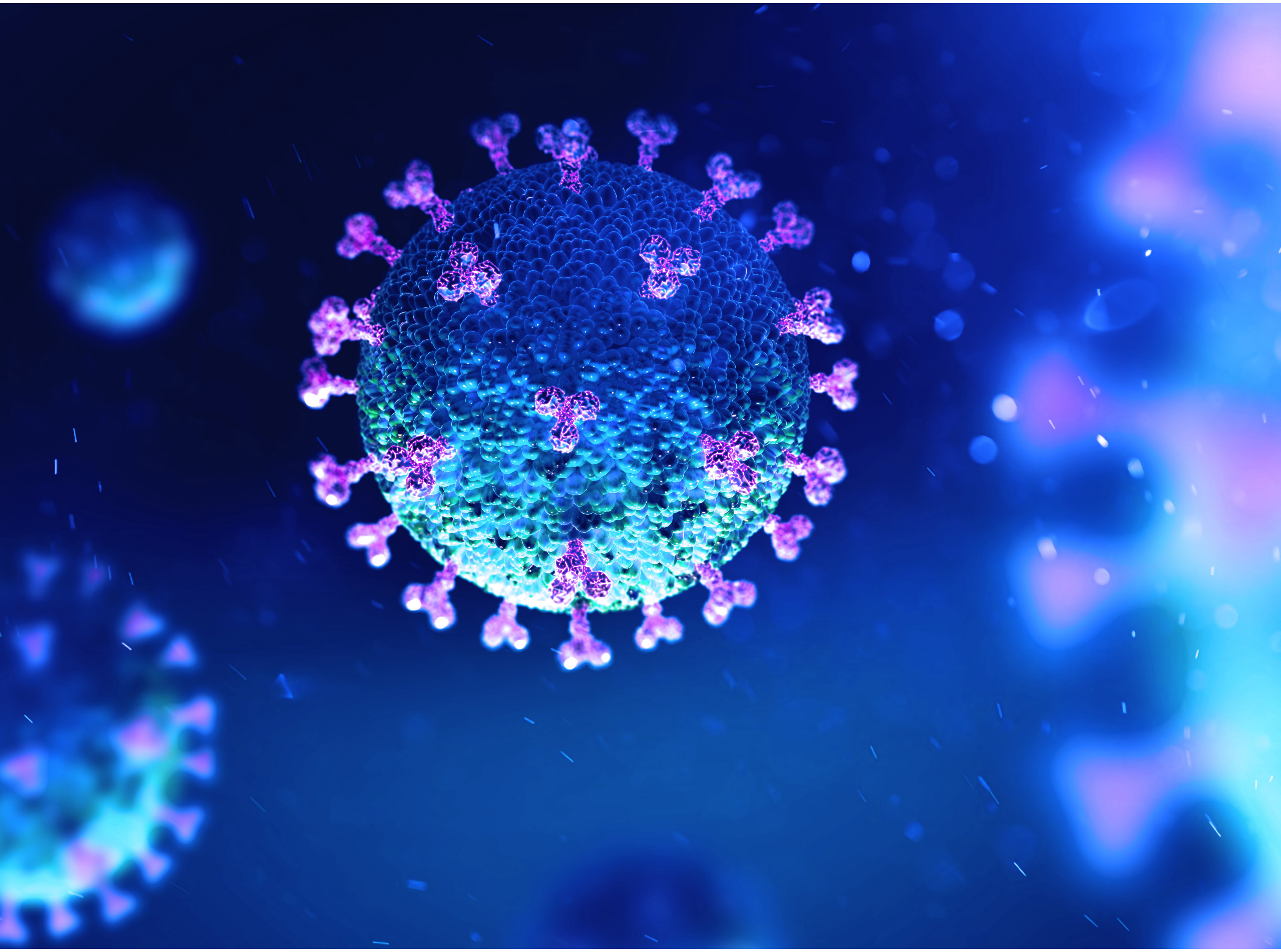

INTRODUCTION

The unprecedented nature of the novel coronavirus (SARS-CoV-2), which causes COVID-19, is undisputed among experts, political leaders, and civilians globally. With approximately 23.9 million cases and 820,000 deaths worldwide, there are very few singular events that have produced such a devastating impact. [1] This is especially the case in the United States (U.S.) – the current global epicenter of the pandemic – which issued a Level 3 pandemic notice in March 2020, suggesting that U.S. citizens avoid nonessential travel. [2]

Further signaling the lack of precedent for this global crisis, the CDC has never issued a travel advisory of this magnitude for an infectious condition, as international travel advisories are generally left to the State Department. To date, there have been almost 5.8 million reported cases and over 160,000 deaths in the U.S. since the outbreak of the novel coronavirus. This death toll exceeds that of any other pandemic in modern history, with the exception of the Spanish flu, which claimed approximately 675,000 U.S. lives over two years. The devastation of the COVID-19 pandemic is so grave that the most comparable impact on human lives may come from U.S. military conflicts. In only four months' time, the pandemic has produced more than double the U.S. death toll of the Vietnam War, surpassed that of the first World War, and continues to approach the magnitude of deaths incurred from other multi-year conflicts, including World War II and the Civil War. (See Figure 1 for U.S. death tolls associated with historical events). [3]

BENCHMARKING EXPLAINED

As strategic consultants and market researchers, we've asked ourselves how we can characterize the impact of something with no true analog, as no other clinical condition has taken as many lives or wreaked havoc on the U.S. healthcare system in as short a period of time as has the

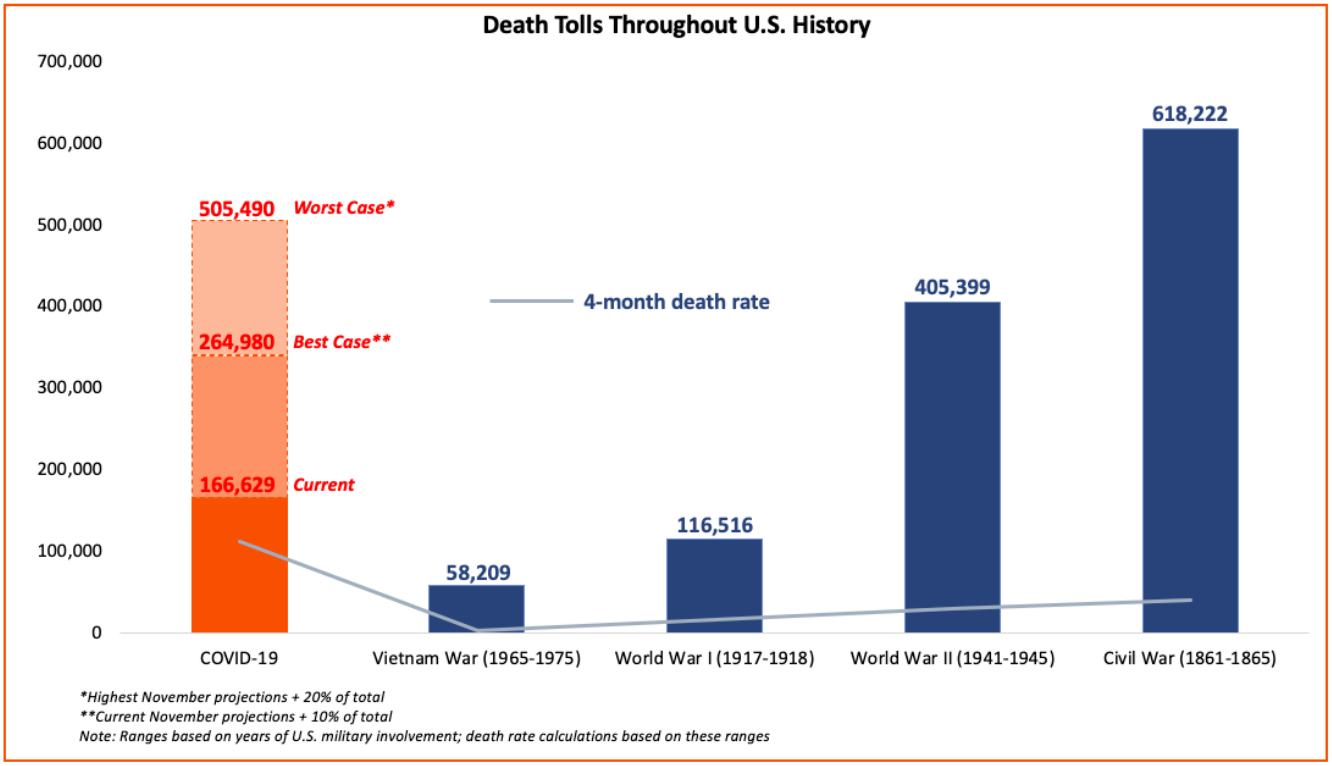

Figure 1. Death Tolls Associated with U.S. Historical Events

OUR BENCHMARKING DEFINITION
1) The practice of comparing select metrics of the COVID-19 pandemic with similar reference points to better understand how to design and improve current approaches ***OR*** 2) The practice of comparing the efficacy existing approaches or responses to pandemics to emerging approaches to better understand how to optimize overall strategy

spread of SARS-CoV-2. We have discovered the best approach for discussing something with no clear comparator is to place it within constructs we understand through benchmarking. This methodology allows us to more accurately gauge the novelty of this pandemic from multiple angles and, thus, understand how our responses, resources, and progress in this situation may compare to those we have faced in the past and those we may be forced to face in the future.

Additionally, situations in which benchmarking is difficult or infeasible often give rise to significant opportunities for innovation, paving the way for existing public and private institutions to step up and practice responsible stewardship of our public health infrastructure. Highlighting opportunities for greater data surveillance generates an important call to action for establishing best practices through exemplary approaches.

METHODOLOGY

We investigated seven discrete categories, which we believe are actionable and can advance our approach to the COVID-19 pandemic. By

Category	Ability to Benchmark	Discussion Topics
Transmissibility	**High** ✓ Metrics are well-defined ✓ Data is sufficient ✓ Precedent from other IDs	• Ability to benchmark SARS-CoV-2 transmissibility • Similarities to vaccinated conditions • Key differences between COVID-19 and historical pandemics
Testing and Infection Rates	**Moderate** ✓ Metrics are well-defined × Data is sufficient × Precedent from other IDs	• Ability to broadly test and capture infection rate data • Limitations in benchmarking our detection strategy • Comparators for diagnostic leadership from other fields
Direct Mortality and Morbidity	**Moderate** ✓ Metrics are well-defined ✓ Data is sufficient × Precedent from other IDs	• Ability to reliably benchmark mortality and morbidity • How COVID-19 compares to other leading causes of death • Expected shifts in population health
Immunity and Vaccination	**Moderate** ✓ Metrics are well-defined × Data is sufficient ✓ Precedent from other IDs	• How SARS-CoV-2 attributes compare to vaccinated viruses • Outlook for discovering a vaccine according to experts • Role of the human antibody in establishing immunity
Treatment	**Moderate** ✓ Metrics are well-defined × Data is sufficient × Precedent from other IDs	• Current approaches to COVID-19 treatment • Implications and novelty of immune activation in COVID-19 • Need for collaboration / a standard treatment algorithm
Hospital Capacity and Logistics	**Low** × Metrics are well-defined × Data is sufficient × Precedent from other IDs	• Ability to benchmark capacity / resource requirements • Historical COVID-19 resource use comparators • Need for resource centralization for public health crises
Indirect Mortality and Morbidity	**Low** × Metrics are well-defined × Data is sufficient × Precedent from other IDs	• Ability to quantify COVID-19 impact on healthcare delivery • Limitations quantifying impact on care quality / public health • Need for vertical collaboration across healthcare stakeholders

ID= infectious disease

analyzing these characteristics separately, we can more clearly contextualize the condition and understand how our responses to unconventional analogs throughout history may inform our approach to COVID-19. These categories include the following: transmissibility, testing and infection rates, direct mortality and morbidity, immunity and vaccination, treatment, hospital capacity and logistics, and indirect mortality and morbidity.

SECTION 1: TRANSMISSBILITY

Key Findings

• Metrics for characterizing disease transmissibility are well-founded, allowing us to quickly place COVID-19 in the context of other viral conditions to inform proper response tactics

• Though SARS-CoV-2 is highly transmissible, it is not more easily spread than some other well-known infectious conditions; this precedent should reassure us that our social policies and PPE will be relatively effective at mitigating spread

• As a society, we would benefit from additional data on the exact degree to which policies impact disease transmissibility across various public settings (e.g., when traveling via airplane, in restaurants, while commuting)

Understanding How the Spread of COVID-19 Compares to Other Conditions

Two of the most concerning elements of SARS-CoV-2 are its transmissibility and detectability – the former much higher than experts originally suspected and the latter much lower. One expert from a major academic center in Boston explained how perceptions of the virus have evolved.

“Early on, we were worried about those with symptoms, as we believed they were the ones who would spread the virus, and it was easy to identify who was sick; what we didn’t appreciate is how much transmission occurs before individuals actually show signs of illness. This is the nature of a highly transmissible, airborne illness, because the droplets remain suspended in the air even

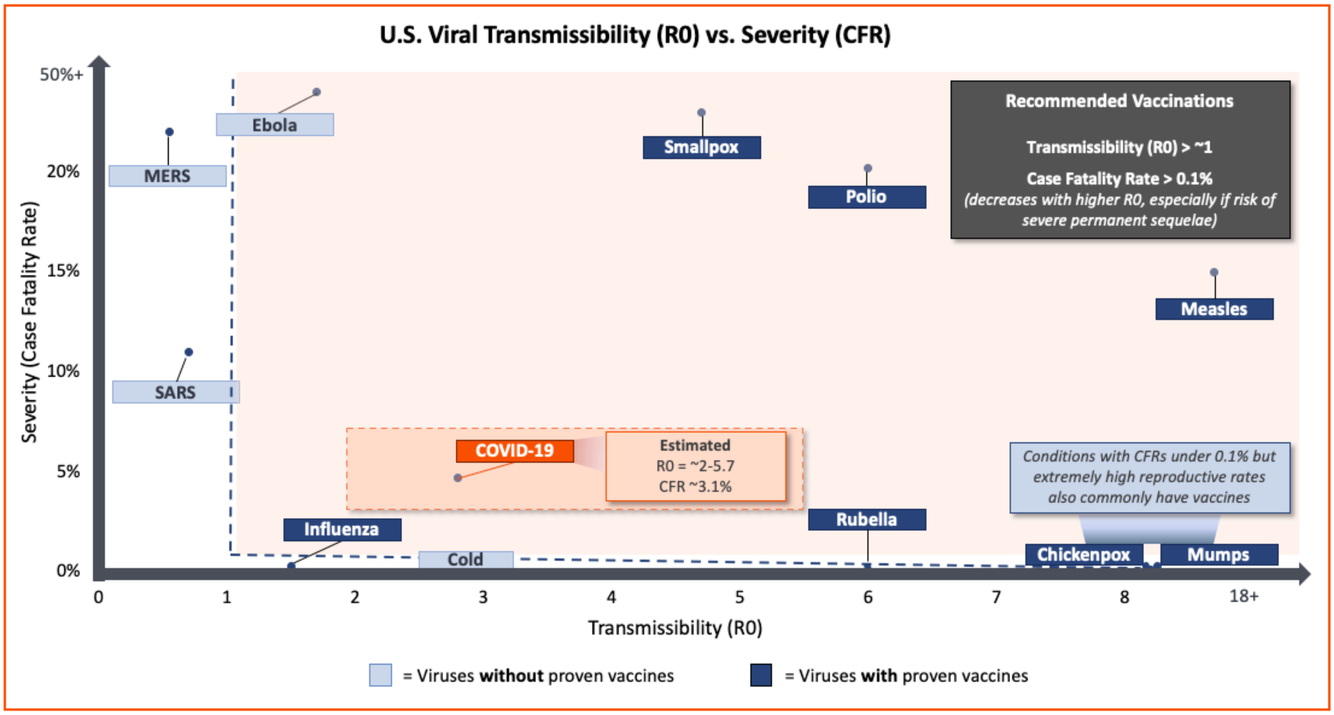

Figure 2. Viral Reproduction Rate (R0) and Case Fatality Rates of Common Infectious Conditions

when the individual isn't coughing." (Chief, Division of Infectious Diseases, Boston, MA)

Although there is currently still speculation around the primary transmission mechanism of COVID-19 – respiratory droplet versus aerosol transmission – its transmissibility has been relatively well-characterized. Compared to other seasonal conditions, COVID-19 has a very high reproductive rate (R0). R0 is defined as the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection. Fortunately, we have well-founded guidelines for characterizing disease transmissibility, which allows us to benchmark against similar infectious conditions throughout history and respond accordingly with the proper social guidelines.

To place COVID-19 into context, it is important to recognize that current estimates predict it is likely more contagious than the common cold and over 2 times more contagious than influenza. In contrast, MERS and SARS, though more deadly, were less transmissible, which made it less urgent to quickly uncover effective preventive measures. Most conditions for which vaccinations are regularly recommended have a case fatality rate (CFR) over approximately 0.1% and an R0 value over 1. Ebola is an exception to this rule – though it was transmissible and deadly enough to warrant a vaccine, the virus was spread through fluid transmission and was confined to a small enough area that it subsided on its own. (See Figure 2 for the transmissibility and fatality rates of several infectious conditions). R0 and CFR estimates may be subject to change as more data is generated, but most studies predict the COVID-19 reproductive number value falls between 2 and 5.7 and its CFR value is at 3.4% in the U.S. [1] The current approach of rapid exploration into therapeutic interventions and vaccinations is validated as COVID-19 falls similarly within the transmissibility and severity thresholds of other common viruses with proven vaccines.

Another metric experts use to characterize infectious conditions is the dispersion factor (k) – which measures the extent to which a disease clusters. The lower the k-value, the greater the proportion of transmissions coming from a small number of people – in these cases, superspreading events and venues are more significant. For example, the dispersion factor for the Spanish flu was about k=1, meaning each infected individual was approximately equally likely to transmit the virus to another induvial. In contrast, the SARS dispersion factor was around k=0.16, which is why superspreading was such a matter of concern. [2]

Estimates for the SARS-CoV-2 dispersion factor vary widely, though researchers out of the London School of Hygiene & Tropical Medicine estimate the k-value sits around 0.1, with approximately 10% of cases attributing to 80% of the spread. Experts find this promising, as this implies that there is wide variability in contagion among infected individuals and a small proportion successfully spreading the virus to others – with chance of transmission estimated almost 20 times higher in indoor settings versus outdoors. Theoretically, this means that many chains of infection may die out on their own if we follow responsible public health practices. [2] Looking at SARS for comparison, given its relatively similar dispersion factor, responses to contain the spread can be affirmatory and enlightening for more recent and forward-looking approaches for the novel coronavirus. Within the first four months of the first cases of SARS at the tail end of 2002, WHO and CDC issued health alerts and guidelines for state and local health departments on the virus. Guidelines specifically directed on precautions of aerosol-generating procedures and management of healthcare and institutional exposures. The CDC was also quick to instate travel advisories as well as take immediate actions to identify and isolate cases. Using similar tactics to today's approaches in controlling the spread of SARS-CoV-2, WHO was able to declare the SARS outbreak contained by mid-2003. [3]

Despite the unprecedented nature of SARS-CoV-2, the ability to recognize analogous transmissibility concerns of this condition to those in the past sparked both a regulatory response and a wave of vaccination efforts. This connection and corresponding response and action are promising. Moving forward, it will also be important to capture metrics that help us understand how exactly our social guidelines and policies affect the transmissibility of the condition. Currently, we do not have reliable data from past infectious conditions to understand the true effects of regulatory action (PPE, social distancing, etc.), so we must conduct this analysis continuously throughout the COVID-19 pandemic. Reliable surveillance data will allow us to critique and adapt our approaches accordingly as we continue to manage the current pandemic and any similar issues that may arise down the line.

SECTION 2: TESTING AND INFECTION RATES

Key Findings

- Given current data, it is unclear what proportion of individuals have been infected with SARS-CoV-2 in the U.S., though preliminary seroprevalence data suggest estimates are significantly higher than the proportion diagnosed

- Benchmarks for establishing an effective seroprevalence strategy are limited, as no other infectious conditions in recent U.S. history have infected so many individuals so quickly with such lethality

- Diagnostic leaders in other medical fields, such as oncology, may provide a relevant framework for how commercial entities could establish diagnostic and surveillance leadership in the SARS-CoV-2 space; the role of Foundation Medicine in cancer diagnostics offers a relevant comparator

The Need for Standardization in Population-wide Testing

Although experts have the metrics to characterize SARS-CoV-2, detecting the virus has proven more difficult. As of August 2020, it is unclear approximately what proportion of the U.S. population has been infected with the virus (e.g., have detectable antibodies), as studies have been decentralized across the country and there is no clear tracking mechanism in place. Scattered seroprevalence studies suggest that under 10% of the population has been infected thus far, with only data collected during major outbreaks (such as in New York City) suggesting proportions exceeding this threshold. (See Figure 3 for early seroprevalence data collected by the CDC). However, infection rate estimates are much greater than the proportion of the population that has been formally diagnosed, suggesting that many cases are going undetected. [1,2]

“These studies are getting better, but they have not been extremely consistent or reliable. Some preliminary studies show more people have antibodies than you would have expected based on the numbers sick, but then we have healthcare workers who definitely think they were exposed, but their tests are coming back negative – it’s really hard to tell.” (Infectious Disease Specialist, New York City, NY)

To address this discrepancy, at the end of June 2020, the CDC launched the COVID-19 Serology Surveillance Strategy, announcing that they plan to work with various private and public stakeholders to better understand the infection rate and how long antibodies can be detected post-infection. [3] Conversely, a public message from the Trump administration in mid-July 2020 requesting that hospitals no longer report COVID-19 data to the CDC, but rather directly to the Department of Health and Human Services, complicates the picture, leaving many with a lack of clarity as to how exactly this data is being utilized. [4]

How data is ultimately collected will be extremely important for establishing how the U.S. oversees similar processes in the future in the face of public health emergencies, as there are no clear historical analogs upon which to base this national strategy. This is because no infectious conditions in recent history were able to infect so many U.S. citizens so quickly and with such lethality, which made real-time tracking less necessary in the past than it is in this case. We have robust retrospective analyses of national seroprevalence data, but efficient tracking is now far more pressing.

Seroprevalence Data Collected by the CDC
April 20, 2020 – June 27, 2020

Region	Seroprevalence	Dates of Collection
NYC Metro	19.5%	6/15-6/21
Connecticut	6.3%	6/15-6/17
Philadelphia Metro	3.8%	6/14-6/20
South Florida	2.9%	4/20-4/24
Missouri	0.8%	6/15-6/20
Minnesota	4.3%	6/15-6/27
Western Washington	1.7%	6/15-6/20
Utah	1.5%	6/15-6/24

Figure 3. Early Seroprevalence Data from the CDC

Given this lack of precedent, we believe it is important to look to other fields, such as oncology, to understand how healthcare providers have established methods of receiving quick and reliable diagnostic results in given disease areas. Generally, in these cases, a single, proven standardized technology from one or several commercial leaders is used to process and report results. Note that testing is also not patient-driven in these fields – results come from a coordinated effort between healthcare providers, commercial partners, and even federal stakeholders.

Malignant conditions are the second leading cause of death in the U.S. on an annual basis (see Section 3 for details, sources, and how this compares to the COVID-19 death toll). COVID-19, which is expected to be the third leading cause of death in the U.S in 2020, presents a health crisis similar to that posed by cancer – although not chronic, it is a condition which requires a vast quantity of healthcare resources, strains the healthcare system, poses a relatively high risk of mortality in the general population, and, most saliently, will require a systematic and timely diagnostic approach if we are to collect the data necessary to properly manage the condition on a large scale.

One quality benchmark to consider for the kind of standardized SARS-CoV-2 testing we would hope to see in the future is the role Foundation Medicine plays in cancer diagnostics. Foundation Medicine was founded in 2007 and launched its first commercial diagnostic assay – FoundationOne – in 2012. [5] The company quickly began partnering with multiple pharmaceutical companies to test patient samples, accumulating over 30 partnerships by 2018. [6] This company was successful in 1) establishing leadership in oncology diagnostics because they centralized data from multiple scattered initiatives and 2) creating an assay with predictive value because of their robust and unbiased data set. Manufacturers have found great utility in leveraging FoundationOne as a companion diagnostic test due to its ability to predict response to FDA-approved targeted therapies. Foundation Medicine also serves as a quality benchmark for commercial diagnostic leadership because they are continuously refining their data in more mature markets (e.g., Non-Small Cell Lung Cancer) and continuously enhancing their diagnostic data set and algorithms in those markets for which their assays currently have less predictive value. This type of continuous data collection effort would be necessary to build a robust and accurate testing platform for SARS-CoV-2 as well as demonstrate the long-term value of testing on a large scale.

There is currently no clear commercial authority in SARS-CoV-2 diagnostics or surveillance – and for good reason. As Zach Cooper, associate professor at the Yale School of Public Health and in Yale's Department of Economics, writes, "Huge numbers of tests are needed urgently. In all likelihood, presuming a vaccine is developed, the demand for testing will erode in 18 months. That means asking firms to bear huge costs to scale up production and figure out how to deliver tests without the usual runway to recoup startup expenses. Reaching the necessary volume of testing will cost more than we ever would have considered paying pre-pandemic." The atypical demand curve for COVID-19 tests provides a disincentive for companies to develop and distribute a product – there is no long-term stability in this model. [7]

Given that the commercial incentive to provide testing at scale is lacking, a company would presumably need to seek additional funding from the federal government or secure a large number of commercial partners to produce their product at scale. Before funding and additional resources are secured, the company must prove the efficacy and efficiency of its platform – if a company were to prove the potential of its technology, Congress and the federal government would be far more likely to devote additional resources to COVID-19 testing. There is clear opportunity for leadership in this regard. Establishing leadership would require that a company partner with multiple private and public entities and collect the data required to prove the value of their approach and the reliability of their central tracking capabilities. A leading company would also ideally remove the patient-driven component of testing, using more objective methods to test the overall population.

SECTION 3: DIRECT MORTALITY AND MORBIDITY

Key Findings

• Current projections based on the case fatality rate (CFR) place COVID-19 as the third leading cause of death in the U.S. in 2020, behind only heart disease and cancer

• By current estimates, an individual's odds of dying from COVID-19 exceed their odds of dying from any other preventable cause in 2020, validating current safety precautions to prevent the spread of disease

• COVID-19 is likely to drive major population health movements, in terms of how individuals prevent spread of disease, but also in creating the infrastructure to assist patients in managing their acute and chronic conditions more autonomously; this is expected to have a long-lasting effect on healthcare administration in the U.S.

Contextualizing the COVID-19 Death Rate

There are various ways to frame the death toll caused by the COVID-19 pandemic in ways we can contextualize – namely by looking at the leading causes of death in the U.S., the annual U.S. death rate, COVID-19 death rates in relation to influenza, and individual odds of dying from top causes within the next year. The best available metric to analyze deaths caused by COVID-19 is the case fatality rate (CFR), which is the proportion of deaths recorded out of the total diagnosed population. Certain research organizations, such as Johns Hopkins, also have the tools to predict the net annual mortality (NAM) rate with some degree of accuracy, though projections have been continuously updated as society changes practices and unanticipated spikes arise. On the other hand, the infection fatality rate (IFR) – proportion of deaths out of all infected individuals – is not well understood and may not be for some time due to limits to the feasibility of widespread testing. More data will be required to understand how many COVID-19 cases are subclinical or asymptomatic, and how this affects current estimates of the mortality rate.

As of August 2020, projections based on the case fatality rate (CFR) predict that COVID-19 will become the third overall cause of death in in the U.S. in 2020, behind only heart disease and cancer. (See Figure 4 for top annual causes of death in the U.S.). [1] It is notable that the death

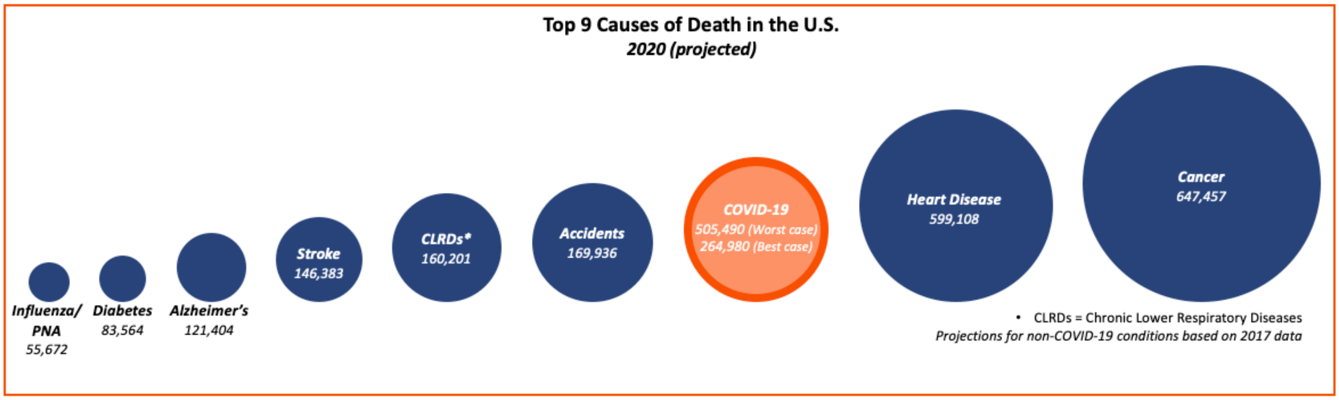

Figure 4. Top Causes of Death in the U.S. – *2020 (projected)*

toll associated with COVID-19 sits at somewhere approximately 10 times that of influenza. [2]

“I think precedents create boundaries - influenza is a good one. We know millions will get it a year, hundreds of thousands will be hospitalized, and tens of thousands will die. COVID is different because it is more transmissible and more lethal. The other extreme is something like Ebola which is less transmissible than COVID but far more lethal in some ways.” (Chief, Division of Infectious Diseases, Boston, MA)

With these mortality rates in mind, the annual death rate in the U.S. could increase anywhere from 9% to 14% year-over-year from 2019 to 2020, a drastic increase from the consistent 1.2% year-over-year increase from 2014 to 2019. [3, 4, 5] Beyond the overall death toll in the U.S., it is important to assess how this pandemic may impact individual citizens. When compared to other preventable causes of death (not including chronic conditions), the average individual’s odds of dying from COVID-19 in 2020 exceeds that of any other unanticipated cause of death.

The average U.S. citizen is over 10 times more likely to die from COVID-19 than in a motor-vehicle crash in 2020, and approximately 36 times more likely to die from COVID-19 than from gun assault (See Figure 5 for individual odds of dying from preventable events in the U.S.). [6] These sobering statistics only emphasize how important it is that we properly resource hospitals, ensure timely delivery of PPE, and work toward effective medical interventions.

Controlling the death rate will require advancement in our understanding of treatment and social cooperation. There is both a viral and an inflammatory component to the condition, and many experts believe that each component must be addressed separately to successfully treat severe cases of COVID-19 in the absence of a vaccine (See Section 5 for more details on treatment). This will require a multidisciplinary effort in running trials, drafting treatment guidelines, and mass communication of effective treatment strategies.

Individual behaviors will also play a large role in controlling the death rate. Unlike other deadly conditions – such as heart disease and cancer – individuals can control their exposure to the condition. Coordinated population health initiatives will be crucial moving forward, both to address how individuals behave in reaction to the pandemic and to enhance how many U.S. patients manage their other acute and chronic conditions remotely. This shift could ultimately provide existing patients more effective tools for disease management – a byproduct of the pandemic that will hopefully persist and eventually create a healthier future for U.S. citizens.

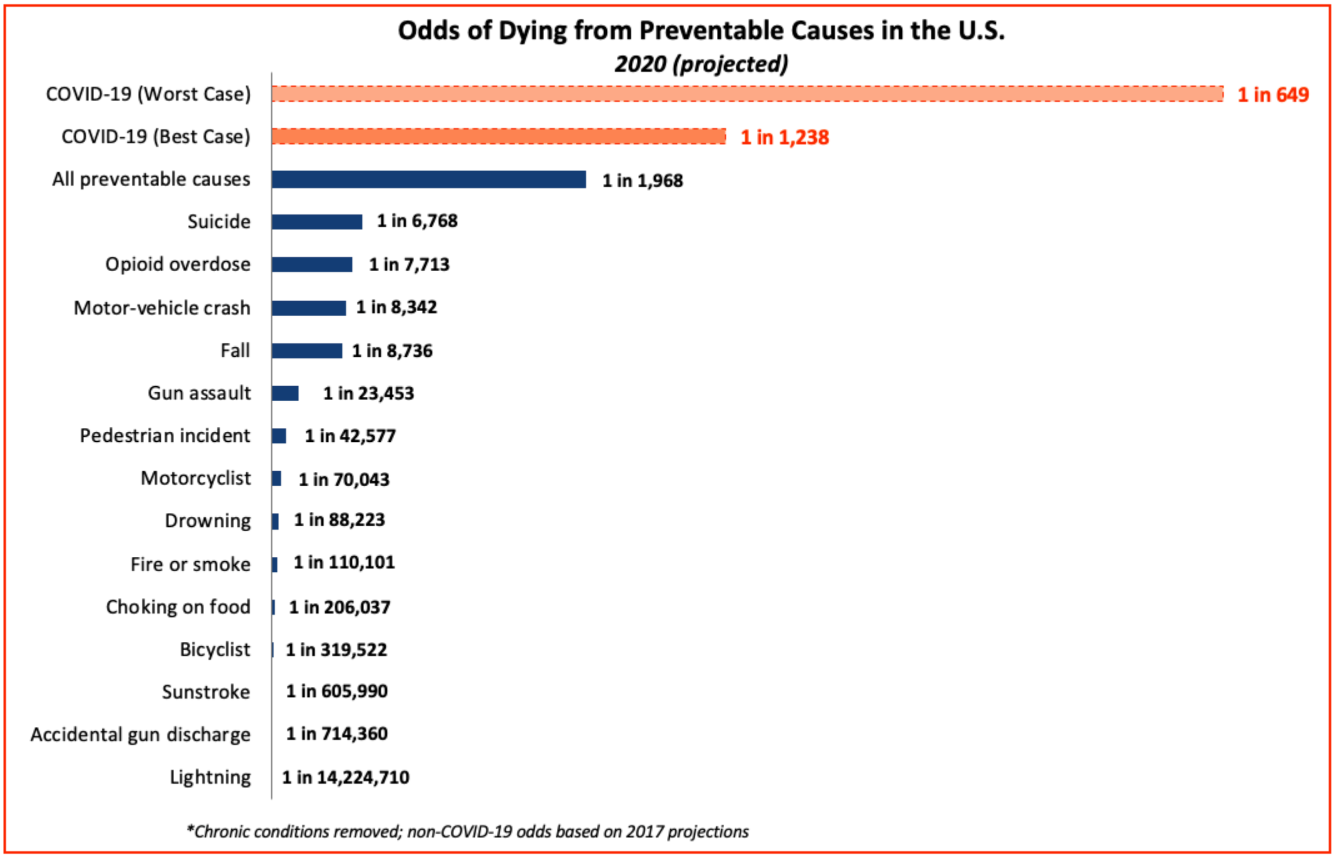

Figure 5. Individual Odds of Dying from Preventable Causes in the U.S. – *2020 (projected)*

SECTION 4: IMMUNITY AND VACCINATION

Key Findings

• In general, the SARS-CoV-2 genome is not considered vastly more complex than those of other viruses for which we have discovered vaccines, which reassures experts developing a vaccine is a feasible task

• Experts currently understand very little about the role human antibodies play in establishing immunity to the virus, clouding the ability to predict whether herd immunity could ultimately protect vulnerable populations

• Various unknowns about human immunity and immune response as a secondary factor of disease pathology highlight a need for collaboration between infectious disease and immunology experts, and signal an opportunity for leadership in the space

Vaccination Efforts and Understanding Immunity

The ability to create an effective vaccine for an infectious condition, fortunately, is generally not associated with its transmissibility, severity, or lethality. For this reason, experts believe developing a vaccine against SARS-CoV-2 is possible—perhaps before the end of 2020. Recall from Section 1 that most viruses for which we have developed vaccines fall within a certain range of transmissibility (R0 > ~1) and lethality (CFR > ~0.1%) – a range within which COVID-19 lies – and that in the absence of a vaccine, we can only impact the former through health-conscious policies and behaviors. This highlights the importance of coordinated public efforts to decrease the transmissibility of the virus. We regularly vaccinate against conditions which are far less fatal and less transmissible (in the case of influenza) than SARS-CoV-2, so precedent would suggest that there is high enough incentive to invest in alternative social, political, and economic measures to decrease its spread until a vaccine is developed.

According to experts, technically, vaccinating against the SARS-CoV-2 virus should not be any more difficult than vaccinating against measles, mumps, or rubella – all of which are caused by similar single-stranded RNA viruses. [1] Experts express cautious optimism that this virus does not possess the same elements that make vaccinating against conditions like HIV and influenza so difficult.

“This is a much less complex virus than HIV or even influenza as far as the genetic variation – there are tiny differences throughout the world and no evidence that it is mutating rapidly enough to escape vaccine regulation.” (Chief, Division of Infectious Diseases, Boston, MA)

In contrast to SARS-CoV-2, the influenza genome contains eight separate segments, which allow for wide genetic variability, making it much easier for this virus to “escape” from a vaccine. Similarly, the two components of HIV that make it so difficult to vaccinate against – the fact that it attacks and takes advantage of the immune system and its retrovirus machinery – are fortunately not relevant to the SARS-CoV-2 virus. Unlike HIV, which mutates too rapidly for antibodies to clear the infection, SARS-CoV-2 appears to have a much lower mutation rate, allowing a potential vaccine to activate the adaptive immune system to produce antibodies like most other vaccines. Also dissimilar to HIV, introducing an attenuated SARS-CoV-2 virus may not produce high risks of full infection, due to the lack of retroviral functionality in SARS-CoV-2.

It is still unclear how immune activation may affect our ability to vaccinate against the virus. Experts predict some potential early hurdles in developing a vaccine, due to the possibility of SARS-CoV-2 overstimulating the human immune system (see Section 5 for greater detail). Some adverse reactions, especially in live vaccine trials, are expected, though they will not likely impact ultimate vaccine efficacy. (See Figure 6 for attributes of various viral entities which affect our

Attributes of Viral Entities With Vaccines Either Developed or In Development

	SARS-CoV-2 Virus: Vaccine TBD	Smallpox: Live Vaccine	Influenza: Inactive Vaccine	HIV: Not Vaccinated
Mutation Rate	Low*	Very Low	High	Very High
Risk of Vaccine Overstimulating Immune System	Yes	No	No	No
Risk of Vaccine Undermining Immune System	No	No	No	Yes

Green = Positive for vaccine development; Orange = Negative for vaccine development

**Still under investigation*

Figure 6. Attributes of Viral Entities with Vaccines Developed / In Development

ability to vaccinate against them).

If a vaccine is developed, the need to re-vaccinate against the virus on an ongoing basis will largely depend on the viral mutation rate, data which is not yet available, though will be critical to understand as developments unfold.

Regardless, experts are encouraged by the number of major innovative groups deeply engaged in vaccine development. The federal government has spent upwards of $9 billion in support across seven key players as of August 2020, with Sanofi Pasteur and GlaxoSmithKline having received the largest allocation thus far. [3] These well-funded groups are expected to have the resources to quickly scale and manufacture an efficacious product.

Both healthy and ill citizens can contribute to this effort by engaging with large-scale clinical trials and data collection efforts. It is still unclear whether herd immunity may ultimately protect individuals and communities from the virus, but until then, collaboration between infectious disease specialists and immunology experts will be crucial for understanding who has immunity, if immunity may be sustained over time, and how medical interventions must be developed and modified accordingly.

SECTION 5: TREATMENT

Key Findings

• Researchers are currently testing treatments which address 1) the SARS-CoV-2 virus itself (anti-viral medications) and 2) the human autoinflammatory response to the virus (anti-inflammatory medications)

• Historical analogs reveal that anti-viral medications have not generally had a significant clinical effect on infected populations, with very limited data on how they affect viral load or transmission rates

• The human immune response to the SARS-CoV-2 virus is not well understood, but data shows a clear association between immune activation/inflammation and severe symptoms of COVID-19; historically, anti-inflammatory medications have worked well across autoimmune and hematological conditions, which is encouraging to experts

Analyzing the Components of a Potential COVID-19 Treatment Algorithm

Though many researchers are optimistic that we will eventually discover a SARS-CoV-2 vaccine, in the meantime, healthcare providers and patients are curious about the effectiveness of existing treatment options, such as most recently— convalescent plasma. To understand how well treatments work, it is first important to understand what aspects of COVID-19 researchers and industry personnel seek to treat. In terms of benchmarking, we are particularly interested in the treatment of two specific components of the disease: 1) the virus itself, and 2) the autoinflammatory processes triggered in response to viral presence, with the latter process only occurring in more severe cases of COVID-19. Given both of these manifestations, researchers suspect that there may be a place for both anti-viral and anti-inflammatory medications in the treatment of COVID-19. In recent weeks, there has been an increasing number of trials testing and showing positive preliminary data using anti-inflammatory medications.

“You see a viral and an inflammatory part to this – people have more recently started thinking about using an anti-viral and an anti-inflammatory [drug for treatment]. We saw the first trial with Remdesivir and a JAK2 inhibitor. This combination might be what we need to treat this condition, but it would be expensive.” (Infectious Disease Specialist, New York City, NY)

One of the best benchmarks we have for understanding how to manage the viral component of SARS-CoV-2 is the way we have approached managing Type A and B influenza in the U.S. Granted, the main strategy for managing influenza is not to control the viral load with anti-viral therapies, but to prevent infection in the first place. This approach is exactly how experts view treatment development for COVID-19, prioritizing vaccination over exploration of other treatment options.

"Oral therapies may play a bigger role in the beginning – anti-viral [therapies] could control the transmission rate for a bit, but ultimately, we will need a vaccine to control the spread [of the coronavirus]." (Chief, Division of Infectious Diseases, Boston, MA)

Nonetheless, there are a handful of antiviral treatment options for influenza – oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir— which are all approved for use in the U.S. [1] However, Tamiflu (oral oseltamivir) is the primary CDC-recommended anti-viral therapy for patients with severe, complicated, or progressive illness who are not hospitalized and for hospitalized influenza patients. Despite being the primary recommended anti-viral therapy, Tamiflu has shown modest clinical efficacy in influenza treatment (time to first alleviation of symptoms reduced by less than one day) and very limited data on how the therapy affects viral load. [2] Given the modest efficacy of similar therapies, experts do not believe that anti-viral medications will ultimately have a large impact on the treatment of the novel coronavirus or its transmission.

"There aren't many good examples of successful viral interventions. The flu is tricky because anti-viral medications are not that effective. We have some data on Tamiflu, but we have the same problem in a way – there is no clear benchmark to measure how well these drugs work." (Infectious Disease Specialist, New York City, NY)

In general, viral infections must run their course in the human body and fortunately, many individuals can recover from the SARS-CoV-2 virus on their own. It is the other major component of COVID-19 which leads to significant mortality and morbidity: the human immune and inflammatory response. Though the exact immune signaling pathways triggered by SARS-CoV-2 infection are not currently well understood by researchers, there is clearly immune dysregulation transpiring, which ultimately leads to inflammation and severe clinical symptomology. [3]

"There is clearly a cytokine crisis later in the course of infection. We would hope we can prevent that in the first place with an anti-viral medication, but that is unlikely. We need broader cytokine targeting. IL-6 is too narrow and not cutting it. Maybe something like JAK inhibitors could show promise." (Infectious Disease Specialist, New York City, NY)

Although more research is needed to understand the exact role immune activation plays in the progression of COVID-19 in severe patients, data shows that changes in serum levels of various cytokines have been associated with several vascular alterations including permeability and clotting. [3] These findings, along with increasing evidence of thrombosis in COVID-19 patients, may suggest that a systematic immune process – along with the direct regulatory effects of severe acute respiratory distress syndrome – may underlie progression of life-threatening symptoms like stroke, late cerebrovascular disease, sepsis, and end-organ damage throughout the body. [4,5,6]

Fortunately, multiple anti-inflammatory therapies already exist for conditions with similar vascular manifestations in the autoimmune and hematology spaces, and the number of trials testing anti-inflammatory medications in COVID-19 is increasing steadily. Many treatments have shown at least modest clinical efficacy in COVID-19 patients as of July 2020. (See Figure 7 for details on each treatable component of COVID-19 and examples of potential treatments). Although the ability to manage this condition with anti-viral medications is currently unclear, there

	SARS-CoV-2 Virus	Dysregulated Immune Response
Symptoms:	▪ Flu-like	▪ Acute Lung Injury ▪ ARDS ▪ Cytokine Storm
Potential Treatment(s):	▪ Remdesivir ▪ lopinavir/ritonavir (combo with INFb-1b and ribavirin) ▪ Favipiravir ▪ Umifenovir ▪ NRTIs (abacavir, entecavir, stavudine)* ▪ Valganciclovir* ▪ Cidofovir*	▪ Steroids (e.g., dexamethasone, prednisone) ▪ JAK Inhibitors (e.g., ruxolitinib, baricitinib tofacitinib) ▪ IL-6 Inhibitors (e.g., tocilizumab, siltuximab, clazakizumab) ▪ TNF blockers (e.g., infliximab, adalimumab) ▪ BTK Inhibitors (e.g., acalabrutinib, ibrutinib) ▪ IL-1 inhibitors (e.g., anakinra) ▪ Interferons (e.g., INFb-1b)
Relative Risk of Death Without Treatment:	▪ Low	▪ Moderate to High
Relative Risk of Death With Treatment:	▪ Low	▪ Low to Moderate

**Pending scaled clinical testing*

Figure 7. Details on. Viral and Inflammatory Components of COVID-19

are many anti-inflammatory therapies on the market which have the potential to significantly impact the lives of patients who develop severe cases of COVID-19. As researchers learn more about treating this condition, there is vast potential for true innovation which could affect not only the infectious disease space, but any field in which patients are negatively impacted by autoinflammatory immune activation.

Overall, a standard treatment algorithm and stepwise clinical guidelines will substantially improve the outlook for severe COVID-19 patients. Many ongoing trials are expected to yield pivotal information on how best to treat patients with life-threatening symptoms. The CDC has been continuously updating treatment guidelines and recommendations, though there are insufficient data to inform recommendations for or against many products under investigation as of July 2020. The ongoing, multidisciplinary effort among academics and industry personnel to develop efficacious treatment guidelines across the U.S. and the world is a promising effort to devising the most effective treatment algorithm(s) throughout the course of infection.

SECTION 6: HOSPITAL CAPACITY AND LOGISTICS

Key Findings

• Healthcare providers have found that the biggest challenge in handling the COVID-19 pandemic has been the rate at which patients initially presented and the associated lack of capacity, protocol, and resources

• Regarding the sudden need for surge hospital capacity, experts admit the only comparable analogs to the peak of COVID-19 in recent history are acute events – such as bombings, shootings, and natural disasters – none of which were sustained over time; there is a clear need for centralization of resources and communication

• COVID-19 is projected to be a leading cause of inpatient hospitalization in the U.S. in 2020 – between the 5th and 9th top causes; even hospitals which were not heavily impacted should be flexible in their response strategies

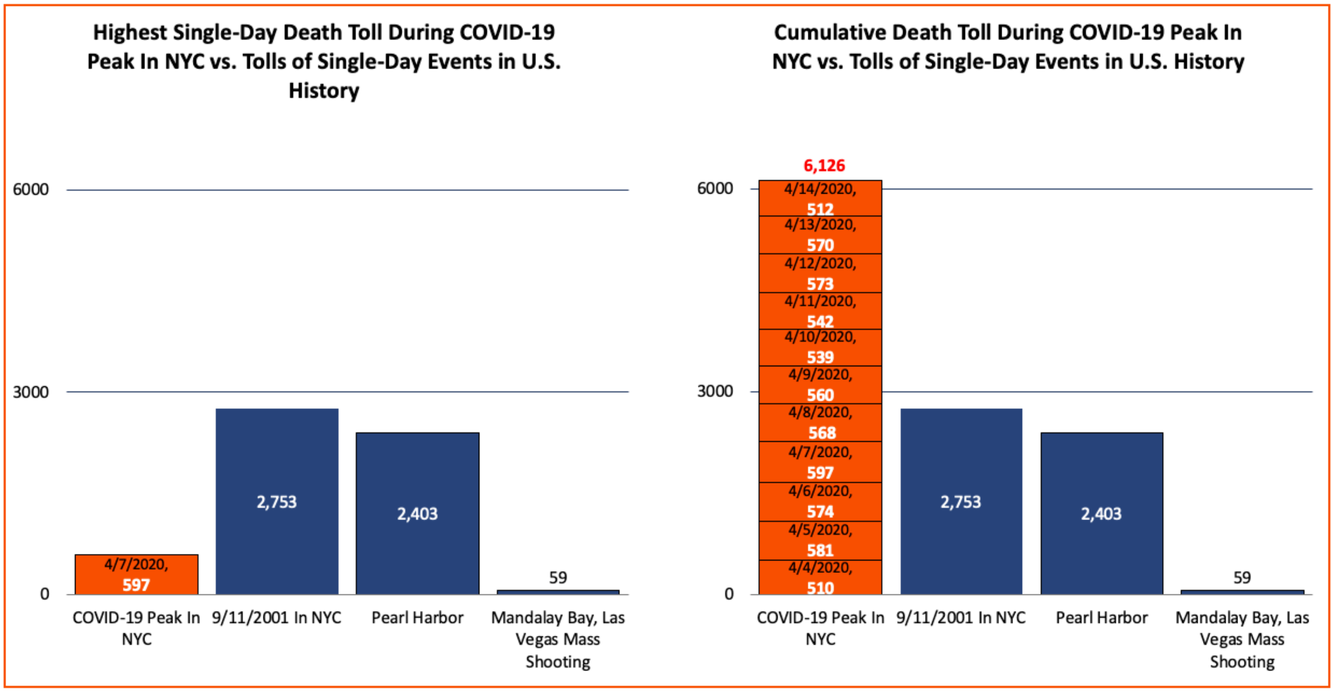

Figure 8. Death Tolls of Events in U.S. History vs. COVID-19 Peak in NYC

How Health Systems are Assessing and Addressing Strain

Given that we are dealing with a highly transmissible and lethal condition, hospital capacity becomes a major source of concern, especially with the understanding that these patients end up in the ICU far more frequently than patients with other leading causes of death. When thinking in terms of surge capacity needs in hospitals, experts in large, metropolitan areas compare the peak of the virus to acute unforeseeable tragedies – events like the Boston bombing or mass shootings in select cities. If the crisis were to last one or two days, experts believe that they may have had the capacity to handle the influx, but when the crisis lasts for weeks at a time, there becomes an unprecedented need for surge hospital capacity.

The rate at which patients became ill and ultimately died provides insight into how many hospital beds were likely needed at the time. At the single-day peak of COVID-19 in NYC, the death toll was 10% that of the 9/11 attack in 2001, but over the span of the 11 deadliest days during the NYC peak, the death toll from COVID-19 more than doubled that of the 9/11 attack. (See Figure 8 for death tolls at the peak of the coronavirus in NYC compared to U.S. historical events).

There are two major differences between those events and the reality faced during viral peaks of COVID-19: 1) this crisis remains sustained over many weeks rather than days, as discussed above, and 2) there is a significant need for single, negative-pressure rooms, which many older hospitals lack. Hospitals, especially those in large cities, are finding that asking employees to continuously work extra shifts is much more difficult than asking them to work an extra shift to cover a shorter-term major catastrophe like a shooting, bombing, or natural disaster. Limited human resources, along with a lack of available space to convert into negative-pressure rooms or floors, signals a need for a maintained, comprehensive system which allows us to adapt to the challenges associated with this type of longer-term national and global crisis.

Experts admit that the only national-level organization with the capacity to mobilize resources at the speed and volume required for this type of crisis is the U.S. military. The U.S.

military is structured to respond at this scale as it operates under central command and can communicate response measures through a central system, and resources and supplies are stored for future use. Conversely, the fragmented nature of the U.S. healthcare system makes it difficult to respond at scale to something nation-wide like the coronavirus pandemic. The CDC receives less than 2% of the funding the military receives on a yearly basis, which may explain the lack of resources and infrastructure in place to handle this type of crisis. [1]

“Hospitals need to have an adequate supply of PPE and supplies for something like this. To go through what we just went through, with such a high frequency and volume of patients, I would expect the government should be involved.” (Infectious Disease Specialist, New York City, NY)

Although individual hospitals have created their own best practices and handled the influx of COVID-19 patients well during peaks given their resources, healthcare providers would benefit from a well-supported centralized body of funding, resources, and knowledge throughout the pandemic.

“My job requires that I go to every floor and I saw different floors using different practices – we were updating our staff weekly and it wasn’t cutting it; the roll out of information needed to be faster. There was a lack of standardization because there was a lack of centralized knowledge.” (Infectious Disease Specialist, New York City, NY)

Adequately preparing the U.S. healthcare system for the peak of another pandemic would likely require comprehensive and coordinated federal government intervention, a much larger pool of available resources, and a scaled rapid response mechanism with centralized infrastructure.

It is important to recognize that hospitals across the U.S. have experienced a wide range of difficulty dealing with the influx of COVID-19 patients – some in metropolitan areas dealing with what feels like a natural disaster, as described above, while others, especially those in rural areas, barely feeling the impact of the first wave. On average, COVID-19 is expected to be a leading cause of hospitalization in 2020, with projections placing it somewhere between the 5th and 9th leading cause in the U.S. (See Figure 9 for projected leading causes of inpatient

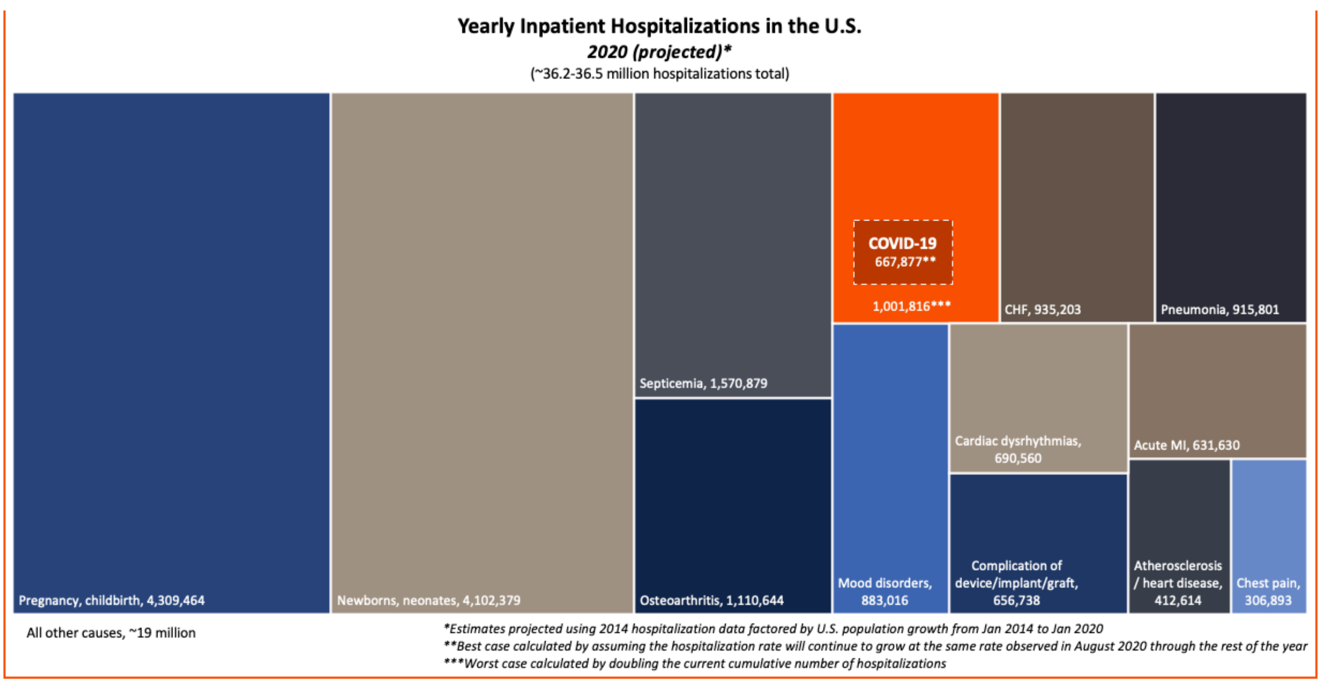

Figure 9. Leading Causes of Inpatient Hospitalization in the U.S. – *2020 (projected)*

hospitalization in the U.S. in 2020).

This highlights the need for flexibility in hospital response – even those hospitals which experienced little impact should have the capacity to accommodate another crisis; however, a national response strategy should incorporate learnings from the first wave of the COVID-19 pandemic as well as other previous events leading to heightened hospitalizations. For example, hospitals should implement strategies which allow for a wide range of responses and accommodations, while the federal government will likely need to be prepared to provide adequate resources in the most susceptible areas of the U.S. Hospitals should avoid narrowly looking only to solutions implemented to address prior outbreaks, such as the establishment of specialized Ebola treatment centers. Despite the unprecedented nature of the COVID-19 pandemic, a parallel can be drawn between its day-to-day logistical challenges and those of acute disaster or combat situations, keeping in mind the additional longer-term resources needed for extended health emergencies like the current pandemic. Hence, federal government officials should anticipate where future outbreaks are expected to be the worst and ensure response teams in those areas are prioritized and equipped with adequate resources before they become hotspots.

SECTION 7: INDIRECT MORTALITY AND MORBIDITY

Key Findings

• The indirect impacts of the COVID-19 pandemic are difficult to benchmark, though certain tools can measure the direct, long-term health effects of the virus including effects of reductions in administered care

• Although experts believe that there are clear declines in the quality of patient care in general as well as decreases in the incidence of care sought by non-COVID patients, it is difficult to identify reliable ways to quantify the impact of these changes

• Reducing indirect externalities of the COVID-19 pandemic will require collaboration across all healthcare stakeholders – suppliers, providers, and patients – to effectively collect rigorous data, communicate accurate information, and develop risk-mitigation strategies going forward

Characterizing the Indirect Impact of the COVID-19 Pandemic

One of the most difficult aspects of the COVID-19 pandemic to accurately benchmark is how the condition indirectly impacts both the long-term health of those who have been diagnosed with the condition and the overall health of the community at-large. Effectively managing risk in both settings will require collaboration and communication among suppliers, providers, and patients, as well as large-scale, coordinated efforts to collect and disseminate accurate data and implement effective risk-mitigation strategies.

Early research suggests that initial infection with SARS-CoV-2 may be associated with long-term effects on various organs, including the lungs, heart, liver, kidneys, and even the brain. However, further research is needed to understand the mechanisms behind these correlations and effective methods of mitigating long-term risk. [1,2] Collaborative academic efforts are expected to yield comprehensive, long-term data and proposed strategies for medical intervention.

Characterizing the impact of the pandemic on the health of the entire community is even more complex as it is difficult to attribute certain patient behaviors to the rise of the pandemic. Nonetheless, specific trends suggest a correlated shift in how patients manage their care. There are three different components to consider when assessing how the pandemic is impacting the community at-large: 1) Decreases in amount of medical care administered; 2) Declines in care quality; and 3) Decreases in the number of patients seeking medical care.

We can most easily track decreases in administered care which were mandated by hospitals and health systems, as we can account for any outpatient care, elective surgeries, or specialist appointments that have been cancelled, limited, or postponed due to the pandemic. Generally, these gaps are also associated with major economic losses for individual health systems, which may eventually lead to negative effects on hospital staff (though those effects are outside the scope of this research).

“The clear gaps in care are those which also create a large economic toll on the system. These are things like elective surgeries – these procedures make money, but we had to stop those and anything else considered unnecessary.” (Infectious Disease Specialist, New York City, NY)

A more difficult aspect to measure is how the quality of care administered has declined because of the pandemic. Experts have expressed that the conversion of multiple spaces throughout their hospitals into COVID-19 areas has forced providers to shift attention away from patients hospitalized for other medical concerns. It is difficult to understand the totality of the impact of strained resources on the quality of patient care, as the metrics necessary to understand it will probably not be available for some time. Inpatient and long-term outcomes of patients treated for chronic and acute illnesses during the peak of the pandemic would need to be compared to outcomes of patients with the same concerns prior to the pandemic to assess impact. Patient-reported changes in care quality may also provide insight. Although the overall impact is unclear, expert input implies that it is significant, which is likely to drive shifts in health-system strategies around resourcing, surge capacity designation, more comprehensive on-call scheduling, and surplus supply stocking.

“Even if the death rate were the same as influenza, the issue would still be how quickly these people show up. If you must convert your hospital into a COVID hospital, other problems get ignored. We had 100 patients in the ICU with COVID-19 with 80 to 90 on ventilators. We cannot fix hips or do things like cardiac catheterization either. There is a huge knock-on effect. Then you can also have the people in the hospital get sick, both healthcare workers and staff – then you have a shortage. This paralyzes everything else we try to do in healthcare.” (Chief, Division of Infectious Diseases, Boston, MA)

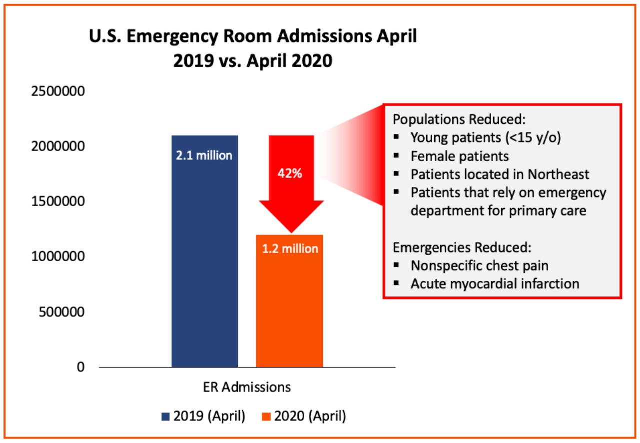

Figure 10. National ER Admissions April 2019 vs. 2020

The component for which we have the least data is the one that is driven by patient behavior: decreases in care sought. Trends demonstrate that fewer patients have been seeking general care since the pandemic became a major public health concern, though it is difficult to measure the effects this has had on patient mortality and morbidity. The CDC reported a 43% national decrease in ER visits during the first month of the pandemic outbreak in the U.S., and although we can measure these reductions, it is almost impossible to gauge exactly what they mean (e.g., how many people died of a heart attack that month who otherwise would not have, or how many strokes went untreated). [3] This, unfortunately, is not information we can expect to capture very reliably in the future. (See Figure 10 for U.S. ER admissions in April 2019 vs. April 2020).

The pandemic has also further brought the health disparities in the U.S. to light. Racial disparities in COVID-19 infection rates and deaths, for instance, have been highlighted at the forefront of social concerns surrounding healthcare equity and the COVID-19 pandemic. Granted, significant advancements are needed to fully understand and counter other potential factors (e.g., racial biology) contributing to these statistics. Nonetheless, it is an important area of exploration where findings could lead to a push for reform of the healthcare system to bridge major disparities. Continued and improved efforts to collect accurate and robust data on the racial, ethnic, and socioeconomic demographics of patients tested and affected by COVID-19— along with capturing any broader effects in general patient care across these subgroups— will be critical to assess the disproportionate impacts of pandemics and help inform future areas of improvement for response efforts during national crises.[4]

Although tracking the indirect impacts of the COVID-19 pandemic is difficult, what we can control is how we work together to reduce these impacts. Data collection and communication efforts between suppliers, providers, and patients must be comprehensive, collaborative, and coordinated at a national level. Patients must be informed on how forgoing an ER visit may affect them in the long-term; academic and commercial stakeholders must be aligned and informed on where certain interventions fit into long-term risk mitigation regimens for severe COVID-19 patients; and the data informing these initiatives must be continuously and rigorously updated. Managing the externalities of the pandemic will require buy-in from all healthcare stakeholders, so we can create a strong united front to ensure no patient falls through the cracks.

Conclusion

Although we are dealing with something unprecedented, the ability to benchmark individual attributes of SARS-CoV-2 and COVID-19 against other conditions and historical events can help elucidate strategies for managing the virus and the disease. Overall, we have the tools necessary to characterize, detect, and protect against the virus. However, it is the aspects for which we have no precedent – those which require large-scale, coordinated initiatives, infrastructure, and leadership – that create the opportunity for true innovation.

Key areas of opportunity include designating a central diagnostic authority for infectious diseases, capturing useful data on the impact of social regulation, forming the public infrastructure necessary to adequately respond to similar situations in the future, and facilitating collaboration among relevant experts necessary to create standardized, stepwise treatment guidelines for mass circulation. If we harness the uncertainty as an opportunity to innovate, we may have a full set of useful benchmarks for the next pandemic and the infrastructure to respond forcefully, swiftly, and effectively.

In summary, we have come away from this benchmarking exercise with three observations on critical factors that will drive progress in managing through COVID-19 and/or other future pandemics:

1 | Analyzing and Slowing the Population Death Rate: The United States has been following an ascending annual population death rate since 2009. Before COVID-19, the population death rate was expected to grow by 1.2% from 2019 to 2020. Now, as a direct contribution from COVID-19, the population death rate is expected to grow between 9% and 14% from 2019 to 2020. This does not account for the numerous other preventable deaths that could be occurring as an indirect consequence of COVID-19's disruption to the healthcare system and the economy. Although

the experts we consulted believe that SARS-COV-2 is more vaccinatable relative to other human viruses, the acceleration in aggregate population death triggered by COVID-19 will likely last for years to come. It will therefore be critical to examine how COVID-19 has directly impacted other leading causes of death, such as Cancer and Heart Disease, to fully understand the magnitude of impact that a pandemic can cause, and to allow health systems to develop nuanced approaches to managing the spillover impact on specific diseases and populations.

2 | Establishing Diagnostic Leadership: The COVID-19 pandemic has exposed some harsh realities within the world of diagnostics. The challenges of establishing diagnostic accuracy to guide medical decisions, coupled with conflicting or misaligned incentives have likely contributed to the void in diagnostic leadership that we still see at the time of this writing, more than 8 months into the pandemic. Looking to benchmark models in disease areas like Oncology can help both private sector and public policy decision makers to establish prospective models for what the future of diagnostic leadership in infectious disease can and should look like.

3 | Embracing the Virtual Model: Flex capacity and surge management have become top priority for hospital and health systems following the severe capacity crises seen in major outbreak centers during the height of COVID-19's first wave. The entire model of matching and delivering care to people in acute need will require rapid evolution. The United States Military provides some interesting and useful benchmarks to consider when designing a system to stand at virtual readiness and flex to evolving areas of need. Rapid deployment forces like the US Army's 75th Ranger Regiment are concepts that provide benchmark concepts to consider in health system planning. A more virtually-integrated and flexible healthcare system will likely start to evolve at every level – from staffing and personnel organization, to flex-facility design and equipment, to urban planning and infrastructure. Successful management of current or future pandemics will require a health system that is less tethered to physical and hard-wired operational models, and that stands ready to flex and mobilize. Virtual planning and integration are keys to achieving this future state.

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