

#### **COVID-19** Crisis Timeline: The Warning and the Surge

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#### 1 Chapter 2

## 2 COVID-19 crisis timeline: The 3 warning, and the surge

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#### 5

6 Abstract After an initial warning, an infectious health crisis, especially a viral one, can 7 surge rapidly from a small outbreak to an overwhelming epidemic or even a pandemic. 8 A surge usually consists of a rapid escalation phase, a peak phase and a slow de-9 escalation phase. A surge may include an increase of all categories of patients, 10 emergency room visits, in-patient admissions and critically-ill patients with multi-organ 11 failure requiring ventilation, hemodialysis and other intensive care measures. There is 12 an accumulative effect of the rapid successive waves of patients admitted into the 13 hospital, with a severe strain on the human and material resources of the hospital. In 14 many health crises, as with the COVID-19 pandemic, the majority of the patients are 15 hospitalized for a long time. Such a long hospitalization slows down the recovery from 16 the crisis significantly. There is a disruptive effect of a health crisis on regular hospital 17 functions and services, such as elective surgery, ambulatory clinics, and care and follow 18 up of patients with diseases other than the cause of the infectious crisis. This disruption 19 may result in worsening of chronic diseases, such as diabetes, asthma, mental illnesses 20 and others. It may also result in delay in diagnosis and treatment of various types of 21 cancers and later presentation of cancers at higher stages. Consequently, the disruption 22 places special requirements for resumption of regular services after the crisis and an 23 additional substantial burden on hospital capabilities. This chapter describes the initial

COVID-19 crisis at SBH Health System in the Bronx, New York, USA and show its
unfolding surge over time alongside an overview of our response. While the COVID19 crisis has unique characteristics, many lessons learned from this crisis can be applied
to other crises, especially infectious pandemics.

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#### 29 **2.1 Defining the COVID-19 Pandemic**

30 A pandemic is defined as is an epidemic of an infectious disease (in case of COVID-19 a viral disease), that has spread across a large region 31 or worldwide, affecting a large number of people. Over the past 100 32 years, viral and bacterial infections have shown the ability to spread 33 34 locally, regionally and even globally, crossing borders and barriers, causing disability and death in an increasingly globalized world [1]. 35 Pandemics frequently strain healthcare resources and sometimes 36 overwhelm them. After localized sporadic cases, an initial outbreak 37 occurs. Following the outbreak, a pandemic is characterized by 3 phases: 38 a rapidly escalating surge, a peak and a slow or very slow de-escalation. 39 Not infrequently, pandemics also feature a second or even multiple surges 40 after the first one. Such surges of a crisis, and particularly initial surges, 41 can potentially overwhelm healthcare institutions and resources, 42 especially in large densely populated urban areas and communities of low 43 44 socio-economic status.

Infectious health crises, compared to earthquakes, hurricanes and other
health crises, have the unique ability to infect and disable not only the
patients, but also the healthcare workers themselves; thus, multiplying

the potential of overwhelming healthcare institutions with the loss of 48 49 staffing. Resultantly, infectious health crises place special demands for the protection of healthcare workers and the preservation of healthcare 50 institutions' ability to continue to function. Best practices in such 51 protection as well as prevention and patient treatment require the rapid 52 sharing of knowledge and a united approach to understanding and 53 54 developing novel treatments to often newly emerged pandemic diseases. 55 A global health crisis requires a global response. This can be achieved through the strengthening of the global health system focusing on 56 57 improving collaboration and coordination across organizations (e.g., the 58 WHO, Gavi, CEPI, national centers for disease control, pharmaceutical manufacturers, etc.) [2]. 59

60

#### 61 2.1.1 Origins of COVID-19

62 The origins of the SARS-CoV-2 virus, which causes COVID-19, is still not definitively known. Many of the early cases of COVID-19 were 63 linked to the Huanan market in Wuhan [3,4] indicating a possibility that 64 an animal source at that location may be responsible for zoonotic 65 66 transfer of the virus. Indeed, it is likely that bats were the original animal hosts for the progenitor virus due to the similarity of SARS-67 68 CoV-2 to bat SARS-CoV-like coronaviruses [4], although an intermediate host may exist between bats and humans. It is possible that 69 70 the virus adapted into its current infectious and transmissible form

either in the animal host before jumping to humans, or first transferring
to humans and subsequently evolving via natural selection during
undetected human-to-human transmission [5].

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#### 75 2.1.2 Basics of SARS-CoV-2: the coronavirus

SARS-CoV-2 is a member of the coronavirus family, Coronaviridae, 76 related to those that were previously responsible for the outbreaks of 77 Severe Acute Respiratory Syndrome (SARS) from 2002-2004 78 predominantly in East Asia and Middle East Respiratory Syndrome 79 (MERS) in 2012. It has a similar structure and genome to the other 80 coronaviruses and possesses the spherical shape with spike proteins 81 protruding from their surface which gives them their typical appearance 82 (Figure 2.1). While the coronaviruses are made up of four structural 83 84 proteins, including the spike (S), membrane, envelop and nucleocapsid 85 proteins, it is the S protein which is recognized as particularly important for attachment to and penetration into host cells. There are 2 functional 86 87 domains of the S protein known as S1 which binds with the host cell 88 receptor, and S2 which mediates fusion of the virus with the host cell 89 membrane.

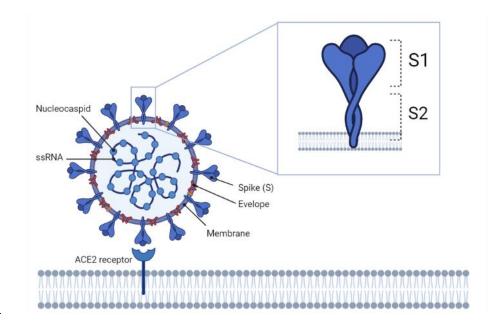




Figure 2.1: SARS-CoV-2 structure. The virus has a spherical shape 92 93 with spike proteins protruding from their surface which gives them their typical appearance. It is made up of four structural proteins, including 94 the spike (S), membrane, envelop and nucleocapsid proteins. The S 95 96 protein has 2 functional domains known as S1 and S2. S1 is recognized and binds to angiotensin-converting enzyme 2 (ACE2) receptor on host 97 cells allowing penetration of the virus and host cell infection. Created 98 with BioRender.com 99

100

Indeed, the entry of SARS-CoV-2 into host cells depends on the
recognition and binding of S protein to angiotensin-converting enzyme 2

103 (ACE2) receptor of the host cells indicating that organs and tissues that 104 have high expression of ACE2 receptor, particularly the lung alveolar epithelial cells but also enterocytes of the small intestine, are the primary 105 targets of SARS-CoV-2 [6]. Interestingly, S protein of SARS-CoV-2 is 106 demonstrated to possess a 10-20-fold higher affinity to ACE2 receptor 107 than that of SARS-CoV and likely contributes to the quick spreading of 108 109 virus [7]. Once inside the cell, the virus undergoes replication to form 110 new viral particles which can invade the adjacent epithelial cells while at the same time generating new infective viral particles for release out of 111 112 the host via respiratory droplets enabling community transmission. This 113 re-initiates the cycle in new cells and hosts.

Within the host SARS-CoV-2 activates an inflammatory immune 114 response, particularly in the lungs where the virus most commonly 115 116 resides, through the production of a milieu of cytokines, chemokines and 117 the activation of lymphocytes. Often this initial response is insufficient so the host amplifies the response to defend against the infection. It is this 118 amplification of the inflammatory immune response that gives rise to the 119 120 so-called "cytokine storm" which further acts to recruit neutrophils, CD4 helper T cells and CD8 cytotoxic T cells to the site. These cells are 121 responsible for fighting off the virus, but consequently the heightened 122 inflammation and excessive immune cell accumulation can injure the 123 lung. Alveolar epithelial cells undergo apoptosis (programmed cell death) 124 125 and release new viral particles which infect adjacent cells to continue the cycle. Diffuse alveolar damage ensues, and alveolar flooding can occur
as a result of insufficient resorption and capillary leakage of plasma
proteins and fluid. All of these features inhibit normal respiratory
function of the lungs and eventually culminate in an Acute Respiratory
Distress Syndrome (ARDS).

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#### 132 2.1.3 Symptoms

The SARS-CoV-2 virus is mainly spread from person to person via 133 respiratory droplet transmission, which occurs when a person is in close 134 contact with someone who is actively coughing or sneezing. Once the 135 virus is contracted an initial early viral response phase ensues before an 136 inflammatory second phase follows resulting in an overall biphasic 137 pattern of illness. The incubation period of COVID-19, which is the time 138 period from exposure to the virus to symptom onset, is 5-6 days, but can 139 140 be up to 14 days. During this period, also known as the 'pre-symptomatic' period, the infected individuals can be contagious and transmit the virus 141 142 to healthy individuals in the population.

Throughout both phases of the disease, in most symptoms are mild typically presenting as an influenza-like illness—which includes fever, cough, malaise, myalgia, headache, and taste and smell disturbance. However, approximately one in five patients infected with the virus progress to the severe pneumonia-like disease known as ARDS which displays extreme symptoms like high fever, severe cough, and shortness

of breath. These symptoms, particularly the difficulties in breathing,
require the patient to be hospitalized and in many cases, where high risk
comorbidities are present, can result in death.

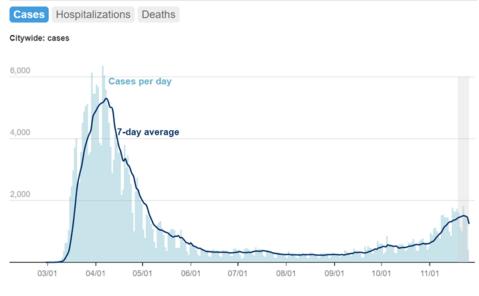
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#### 153 2.1.4 Classification as a pandemic

154 In December 2019, Wuhan city of Hubei province of China was overwhelmed by a series of acute atypical respiratory infections which 155 soon later were discovered to be caused by a novel coronavirus, SARS-156 CoV-2 and therefore the disease named COVID-19. COVID-19 was 157 158 broadcast as a public health emergency on January 30, 2020, on March 11, 2020, the World Health Organization (WHO) declared the novel 159 coronavirus outbreak a global pandemic [8]. Following accumulated data 160 161 that more than 118,000 cases were reported in 114 countries and 4,291 deaths worldwide, Dr. Tedros Adhanom Ghebreyesus the WHO 162 163 Director-General made clear his deep concerns regarding the alarming levels of spread and disease severity. Although some argue that COVID-164 165 19 is not a pandemic, but a syndemic - a concept to describe how epidemic disease clusters with pre-existing conditions, interacts with 166 167 them, and is driven by larger political, economic, and social factors [9]; it is universally acknowledged that this disease has caused a global health 168 169 crisis, like no other before it.

### 171 2.2 COVID-19 pandemic in the USA and its epicenter New York 172 City; timeline of the crisis

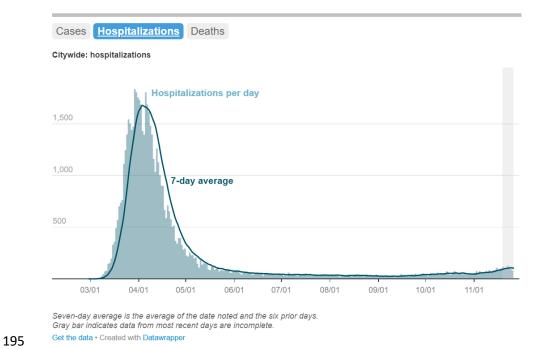
173 A remarkable feature of this particular threat was the fact that this was a completely new virus with lack of knowledge of its pathophysiology 174 and clinical effects and an absence of diagnostics, therapeutics and 175 vaccines at the time. After the subsequent news of the COVID-19 spread 176 177 through China, Italy and Europe, detection of cases started occurring in the USA at a very rapidly accelerating rate, most notably in its epicenter, 178 179 New York City. According to the New York City Department of Health, the first confirmed case in New York City was on February 29, 2020 and 180 181 although earlier cases in the USA had been confirmed, the numbers in New York City began to rise faster than other states and became the 182 worse affected area in the country. Figures 2.2-2.6 show the rapid surge 183 in cases, hospitalizations, mortality, emergency room visits and hospital 184 admissions through the emergency rooms in New York City. 185



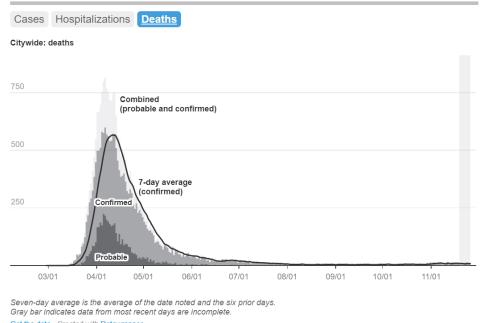
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Seven-day average is the average of the date noted and the six prior days. Gray bar indicates data from most recent days are incomplete.

- **Figure 2.2:** The number of COVID-19 cases per day and the 7 day
- 188 average over the period of March November 2020. Axis correspond
- to New York citywide cases (y axis) and the chronological date
- indicated by the  $1^{st}$  of each month (x axis). Source New York City
- 191 Department of Health website accessed on 11/29/2020
- 192 https://www1.nyc.gov/site/doh/covid/covid-19-data-trends.page.
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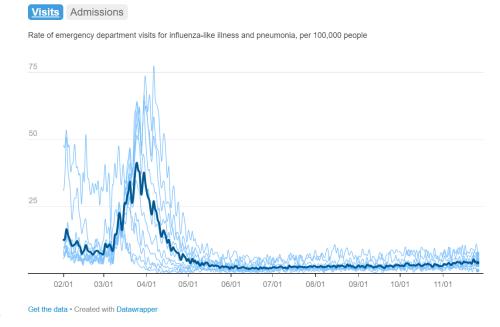


- 196 Figure 2.3: The number of COVID-19 hospitalizations per day and the
- 197 7-day average March November 2020. Source New York City
- 198 Department of Health website accessed on 11/29/2020
- 199 <u>https://www1.nyc.gov/site/doh/covid/covid-19-data-trends.page</u>.



202 Get the data • Created with Datawrapper

- Figure 2.4: The probable, confirmed and total number of COVID-19
- 204 deaths per day and the 7-day average March November 2020. Source
- New York City Department of Health website accessed on 11/29/2020
- 206 <u>https://www1.nyc.gov/site/doh/covid/covid-19-data-trends.page</u>.





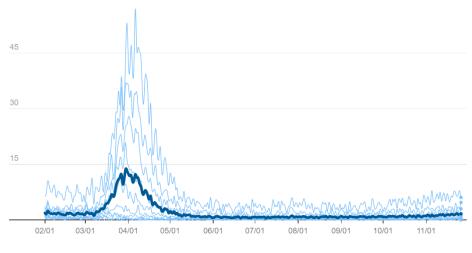
**Figure 2.5:** The rate of emergency department visits in New York City

210 hospitals for influenza-like illness and pneumonia per 100,000 people,

- 211 March November 2020. Source New York City Department of Health
- 212 website accessed on 11/29/2020
- 213 <u>https://www1.nyc.gov/site/doh/covid/covid-19-data-trends.page</u>.
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Rate of hospital admissions through emergency departments for influenza-like illness and pneumonia, per 100,000 people

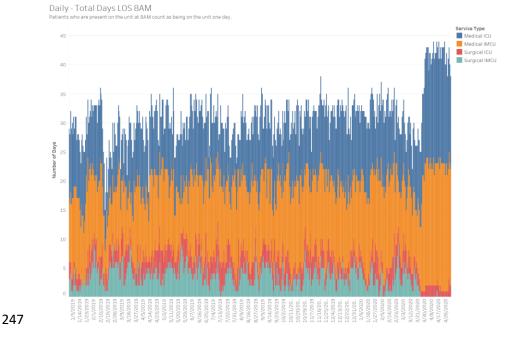


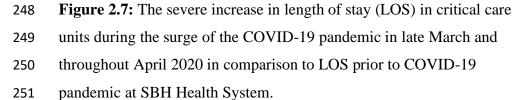


**Figure 2.6:** The rate of hospital admissions through emergency

- 218 departments in New York City hospitals for influenza-like illness and
- 219 pneumonia per 100,000 people, March November 2020. Source New
- 220 York City Department of Health website accessed on 11/29/2020
- 221 https://www1.nyc.gov/site/doh/covid/covid-19-data-trends.page.
- 222

There are several observations that can be noted from the data of the crisis as it happened in March, April and May 2020. The first observation of the timeline of the crisis is the rapid escalating increase of all categories of patients, emergency room visits, inpatient admissions and 227 critically ill patients requiring ventilation, dialysis and other intensive 228 care measures (Figures 2.3 and 2.5). The second observation is the accumulative effect of the rapid successive waves of patients coming to 229 hospitals, resulting in a rapidly reached peak of the surge in the first week 230 of April 2020. As severely ill patients accumulate in all parts of a hospital 231 and at all levels of care, regular, intermediate and intensive, the effect is 232 an acute severe strain on the human and material resources of a hospital. 233 The third observation is that disease progression occurs in a substantial 234 number of patients after admission, requiring transfer from regular care 235 to intermediate or intensive care. This progression of disease has an 236 237 additional additive and accumulative straining effect on top of the critically ill patients arriving in the emergency room and transferred 238 directly to intensive care. The fourth observation is that the majority of 239 240 patients have a long length of stay (LOS) in the hospital until either 241 recovery and discharge or death. Such long LOS slows down the recovery from the crisis and prolongs the strain on the human and 242 material resources of a hospital. The strain on the human resources is 243 particularly profound as the demand for care out-strips the capacity for 244 provision (Figure 2.7). 245





The fifth observation is the high mortality of the infectious pandemic. This high mortality has significant psychological impact on families and on the frontline hospital staff as well. The high mortality also requires substantial logistical effort to keep patient workflow in process and to free resources for other patients. In addition, prior to death, there is a highdemand for palliative care services and communications with families.

The sixth observation is that the peak of the surge of the crisis was 259 260 reached much earlier than the warning at the declaration of crisis had suggested. The epidemiologists of the various health authorities predicted 261 the peak of the surge to occur 6 weeks after declaration of the crisis. In 262 reality, the surge occurred in half that time, 3 weeks after the declaration 263 264 of the crisis, catching all New York City hospitals by surprise and shock. As a consequence, and the seventh observation, at the time of the first 265 266 surge, no hospital in the greater New York City metropolitan area was 267 adequately prepared for the magnitude of the COVID-19 health crisis. The magnitude and the rapidity of the surge of the COVID-19 crisis were 268 above and beyond the expectations and capacities of the usual and 269 270 customary hospital disaster planning. Modern healthcare is expensive. 271 Therefore, most hospitals function with tight lean staffing and capacities during peaceful regular times, with little reserve and ability to expand 272 rapidly. With a crisis hitting all hospitals in a large geographic area, it is 273 unrealistic to expect broad scale inter-hospital mutual help and support. 274

The eighth observation is the disruptive effect of the crisis on regular hospital functions and services, such as non-COVID-19 emergencies, elective surgery, ambulatory clinics, trauma care, cancer care, and care and follow up on patients with chronic diseases other than COVID-19; such as diabetes, asthma and mental health disorders. This disruption undoubtedly resulted in deterioration and worsening of chronic disease
such as diabetes and heart failure and delayed diagnosis and treatment of
cancers potentially causing progression of cancer and consequently late
presentation of cases at higher clinical stages of disease. Furthermore,
this places special requirements for resumption of regular services after
the crisis and a substantial burden of services after the crisis.

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#### 287 **2.3 Timeline of the response at SBH Health System**

288 The first phase of the response of the SBH Health System was triggered by the public news of the spreading COVID-19 pandemic in addition to 289 290 information coming from the State and City Departments of Health. The leadership and senior administration officials of the hospital started early 291 292 preparations for the crisis. Once it was clear that the pandemic had broken 293 out significantly in the greater New York City metropolitan area, the 294 Departments of Health of New York State and New York City issued 295 orders to all hospitals to increase bed capacity by 50% and prepare for a 296 surge of the crisis.

Significantly, the first patient admitted to SBH Health System was on March 13, 2020. Table 2.1 shows a timeline of some of the key events that followed at the hospital during this surge of the crisis, highlighting the rapid escalation of the number and severity of illness of the admitted patients. The SBH Health System responded quickly with several

adjustments to normal practice across all departments. These included 302 303 primarily setting up a crisis command center with multiple daily briefings, meetings and communications. Multiple multidisciplinary 304 crisis teams and workgroups were also set up from all clinical and 305 administrative departments, to plan, prepare and manage the anticipated 306 health crisis and the surge of the pandemic. The teams of medical critical 307 care, surgical critical care and anesthesiology were combined into one 308 critical care team to cope with the influx of severely ill patients. Figures 309 2.8 and 2.9 show the surge of inpatient admissions and the surge of 310 critically-ill mechanically ventilated patients at SBH Health System. A 311 312 critical care committee and multidisciplinary tiered teams were set up, to serve the rapidly rising needs for critical care services of acceleratingly 313 increasing numbers admitted with severe respiratory failure and other 314 315 multi-organ failure. Daily briefings and meetings were conducted and 316 frequent communications were established. Human and material resources were mobilized maximally to allow provision of care in areas 317 under increased demand, and to aid in this, all elective surgery was 318 cancelled on March 17, 2020. 319

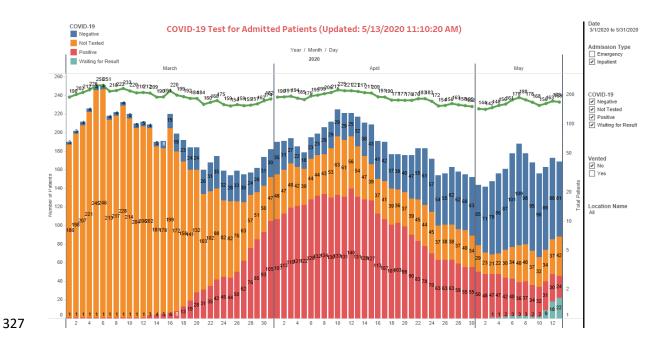
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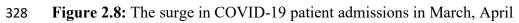
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- **Table 2.1**: timeline of the key events at SBH Health System during the
- 324 surge of the COVID-19 crisis

Date	Event
3/4/2020	Hospital leadership COVID-19 emergency
	management call started 3 times/week
3/13/2021	First symptomatic COVID-19 patient admitted to
	SBH Health System
3/16/2020	Health crisis declared with predicted peak in the 3 <sup>rd</sup> or
	4 <sup>th</sup> week of April
3/17/2020	All elective surgery cancelled
3/18/2020	Multidisciplinary critical care committee established
3/23/2020	Hospital command center opened
3/26/2020	First body collection-point refrigerated truck on site
4/2/2020	Second body collection-point refrigerated truck on
	site
4/6/2020	Peak of surge reached lasting 4 days
4/7/2020	Intermittent partial diversion from the hospital
	emergency room over 7 days
4/9/2020	Peak of number of ventilated COVID-19 inpatients
4/12/2020	Peak of total COVID-19 inpatients, ventilated and
	non-ventilated

4/13/2020	Start of slow decline in total COVID-19 inpatients;
	slower decline in critical care patient
4/16/2020	Quietest day in ED in the past 4 weeks with only 1
	ventilated patient in the ED
5/1/2020	Continuation of slow decline of COVID-19
	admissions and number of inpatients





and early May 2020 at SBH Health System.

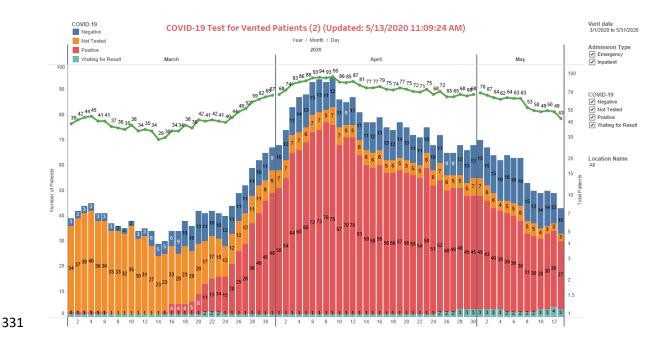


Figure 2.9: The surge in COVID-19 critically ill ventilated patients in
March, April and early May 2020 at SBH Health System.

Once the peak of the surge started to pass from April 13, 2020, the various teams returned very slowly, carefully and gradually to regular functions. Ultimately, elective surgery was resumed, and other functions were restarted, albeit with new rules and processes, including infection prevention measures. The details of the hospital response are recounted in the subsequent chapters of this book with explanations specific to each clinical or administrative department described along with the lessons

learned from critical reflection. These highly valuable lessons may guide
preparation, planning and management of future crises, here at SBH
Health System and potentially elsewhere at hospitals and primary health
care providers across the world.

Although the above describes in detail the acute first surge of the COVID-19 crisis, it should be emphasized that the crisis continued well beyond the surge with slow recovery and second and third surges, albeit less intense than the first surge. The recovery from the crisis has taken a long time and major efforts.

#### 351 **2.4 Key lessons learnt from the surge at SBH**

An infectious health crisis can surge rapidly from a small outbreak to 352 an overwhelming epidemic or even a pandemic. This surge may include 353 354 an increase of all categories of patients, emergency room visits, in-patient admissions and critically-ill patients with multi-organ failure. There is an 355 356 accumulative effect of the waves of patients coming to the hospital, with a severe strain on the human and material resources. Long hospitalization 357 358 of the majority of patients slows the recovery from the crisis. Consequently, there is undoubtedly a disruptive effect of a health crisis 359 on regular hospital functions and services, such as elective surgery, 360 ambulatory clinics, cancer care, mental health, and care and follow up on 361 patients with diseases other than infectious crisis. This places special 362 requirements for resumption of regular services after the crisis and a 363

substantial burden of services after the crisis, therefore strategic plans tominimize this recovery burden are needed.

A collaborative culture and teamwork are very important for any hospital system at time of a health crisis to overcome extreme adversity. Furthermore, it is important for a hospital to establish collaborative relationships with other health institutions for future health crises.

It became clear that there are a number of vulnerabilities, during peaceful regular times, in hospital systems that could hamper crisis efforts, including low capacities, shortages in equipment and supplies, shortages in staffing, and inadequacies of the physical facilities. In particular, redundancy of suppliers of essential items is very prudent and the hospital should include into its planning mitigation the difficulty in accessing and affording such resources.

In reflection of the surge at SBH, some pertinent questions arose that
solidify some of the key lessons that were, and need to, be learnt from a
healthcare crisis of this magnitude and nature.

380 What is unique about an infectious, possibly viral health crisis? There

are many characteristics unique to an infectious crisis versus other

382 crisis, such as a hurricane, an earthquake or a mass casualty event. An

infectious crisis has an accumulative rapidly escalating surge with an

acute burden on healthcare systems. Furthermore, an infectious crisis

385 can affect the healthcare workers themselves, thus threatening hospitals'

ability to cope with the crisis and deliver care to patients.

# *Can a hospital count on pre-setting a maximal capacity and executing a diversion to other hospitals in case of high demand during a surge of a crisis?* Yes and No! Depending on the magnitude of the surge and the availability of other receptive hospitals, a hospital may or may not be able to divert to other hospitals. In the case of an extraordinary surge, maximal capacity may frequently have to be "stretched".

393 *Can the triage of the various acuity of patient conditions and the* 

394 designation of levels of care be preset prior to an infectious health

*crisis?* While it is very important to include, in crisis preparedness
plans, criteria for triage and designation of levels of care, such practices
should be subject to frequent review and dynamic adjustment during a
crisis, in order to achieve practical flexibility, maximal efficiency and
prompt response to a continuously changing situation.

The reflections on these questions and the key features of the SBH Health System response to the surge can provide lessons to develop a culture of preparedness in healthcare settings to lessen the impact on hospital services and workers, and hopefully mitigate the devastating impact on patient lives health crises can bring.

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#### 407 **References**

- 408 1. Frenk J, Gómez-Dantés O, Knaul FM. Globalization and infectious
- diseases. Infect Dis Clin North Am. 2011;25(3):593-9, viii. doi:

410 10.1016/j.idc.2011.05.003. Epub 2011 Jul 2. PMID: 21896360;

- 411 PMCID: PMC7135545.
- 412 2. Bloom DE, Cadarette D. Infectious Disease Threats in the Twenty-First
- 413 Century: Strengthening the Global Response. Front Immunol.
- 414 2019;10:549. doi: 10.3389/fimmu.2019.00549. PMID: 30984169;
- 415 PMCID: PMC6447676.
- 416 3. Zhou P, Yang XL, Wang XG, Hu B, Zhang W, et al. A pneumonia
- 417 outbreak associated with a new coronavirus of probable bat origin.
- 418 Nature. 2020;579, 270–273. https://doi.org/10.1038/s41586-020-2012-
- 419 7
- 420 4. Wu F, Zhao S, Yu B, Chen Y, Wang W, Song Z, et al. A new
- 421 coronavirus associated with human respiratory disease in China.
- 422 Nature. 2020;579, 265–269. https://doi.org/10.1038/s41586-020-2008-
- 423 3.
- 424 5. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The
- 425 proximal origin of SARS-CoV-2. Nat Med. 2020;26, 450–452.
- 426 https://doi.org/10.1038/s41591-020-0820-9

- 427 6. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data 428 analysis on the receptor ACE2 expression reveals the potential risk of 429 different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185-192. doi: 10.1007/s11684-020-0754-0. Epub 430 431 2020 Mar 12. PMID: 32170560; PMCID: PMC7088738. 432 7. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion 433 434 conformation. Science. 2020;367(6483):1260-1263. doi: 10.1126/science.abb2507. Epub 2020 Feb 19. PMID: 32075877; 435 PMCID: PMC7164637. 436 437 8. Ghebreyesus TA. WHO Director-General's opening remarks at the media briefing on COVID-19-2020. https://www.who.int/director-438 439 general/speeches/detail/who-director-general-s-opening-remarks-at-440 the-media-briefing-on-covid-19---11-march-2020
- 441 9. Horton R. Offline: COVID-19 is not a pandemic. Lancet. 2020; 396:
  442 874.