Open Forum Infectious Diseases

BRIEF REPORT

Post-severe Acute Respiratory Syndrome Coronavirus 2 Monoclonal Antibody Treatment Hospitalizations as a Sentinel for Emergence of Viral Variants in New York City

Kelsie Cowman,[1] Yi Guo,[2] Liise-anne Pirofski,[1,3] David Wong,[4] Hongkai Bao,[2] Victor Chen,[2] Una Hopkins,[5] Erin Andrews,[6] Joseph Hamel,[7] Marla Keller,[1] Eran Bellin,[8] Raja Thota,[6] Patricia Davis,[5] Edwin Torres Rodriguez,[10] Pooja Suthar,[2] Lauren Allen,[2] James Rossi,[1] Adam Haviland,[1] Erika Orner,[9] Wendy Szymczak,[9] Sadahf Shujauddin,[11] James McCarthy,[12] Barbara Binder,[12] Vanitha Pushparaj,[13] Linda Bard,[13] Vincent Frank Pierino,[13] Leslie Alsina,[13] David Esses,[14] Alicia McCaskie,[14] Caron Campbell,[14] Tabitha Madzura,[14] Andrew Wollowitz,[14] Kelly Basset,[14] Deborah White,[14] Rafael Ruiz,[6] Frank Sosnowski,[2] and Priya Nori[1]

[1]Division of Infectious Diseases, Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, USA, [2]Department of Pharmacy, Montefiore Medical Center, Bronx, New York, USA, [3]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York, USA, [4]Medical Officer, COVID-19 Therapeutics Team, US Department of Health and Human Services, Rockville, MD, USA, [5]Department of Nursing, Montefiore Medical Center, Bronx, New York, USA, [6]Network Performance Group, Montefiore Medical Center, Bronx, New York, USA, [7]Office of Strategy, Planning, Policy and Requirements, Assistant Secretary for Preparedness and Response, US Department of Health and Human Services, Washington, DC, USA, [8]Department of Epidemiology, Population Health and Medicine Albert Einstein College of Medicine, Montefiore Health System, Bronx, New York, USA, [9]Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA, [10]Division of Endocrinology, Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, USA, [11]Department of Pediatric Cardiology, Children's Hospital at Montefiore, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, USA, [12]Department of Oncology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York, USA, [13]Faculty Practice Group, Montefiore Health System, Bronx, New York, USA, [14]Department of Emergency Medicine Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York, USA

We partnered with the US Department of Health and Human Services to treat high-risk, nonadmitted coronavirus disease 2019 (COVID-19) patients with bamlanivimab in the Bronx, New York per Emergency Use Authorization criteria. Increasing posttreatment hospitalizations were observed monthly between December 2020 and March 2021 in parallel to the emergence of severe acute respiratory syndrome coronavirus 2 variants in New York City.

Keywords. antimicrobial stewardship; COVID-19; monoclonal antibodies; SARS-CoV-2 variants.

Since November 2020, the US Food and Drug Administration (FDA) has issued emergency use authorizations (EUA) for investigational monoclonal antibody therapies for treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in nonhospitalized high-risk patients. Early administration of these agents (bamlanivimab, bamlanivimab/etesevimab, and casirivimab/imdevimab) may reduce hospitalizations, viral shedding, and deaths [1–5]. On March 1, 2021, the Wadsworth Center, New York State Department of Health's public health reference laboratory, described a 484K variant in the B.1.526 lineage circulating in the New York metropolitan area [6]. Of concern, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies have reduced in vitro activity against variants detected in diverse New York City (NYC) neighborhoods, particularly among older, hospitalized patients [7–10].

The Bronx has higher rates of COVID-19 hospitalizations and deaths in NYC, as well as a lower median daily test rate per 100 000 population compared with other boroughs [11, 12]. In December 2020, the Montefiore Health System in the Bronx, New York was selected to participate in a US Department of Health and Human Services (HHS) pilot program to improve bamlanivimab access in underserved communities heavily impacted by COVID-19.

METHODS

One thousand bamlanivimab doses were allocated to Montefiore (December 2020–February 2021). Patient screening and treatment approval were incorporated into the antimicrobial stewardship preauthorization paradigm using EUA criteria [7–9, 13]. Referrals from providers, occupational health, and local urgent care centers were emailed to the stewardship team and answered 10 hours a day, 7 days per week. All direct viral tests were honored regardless of type (antigen or polymerase chain reaction) or location (internal or external). Montefiore nursing leadership rapidly deployed a cadre of trained nurses to administer infusions as per NYS regulations [14]. Administrations occurred in 3 Montefiore emergency departments (EDs) or an ambulatory infusion center within 48 hours of referral. All patients received a postinfusion phone call by infusion staff at 24–48 hours and an infectious diseases televisit at 2–6 weeks.

We conducted a retrospective observational study of patient outcomes after bamlanivimab treatment. Primary outcome was all-cause hospital admission 30 days postinfusion (either to Montefiore or elsewhere). The COVID-19-related admissions were defined by known COVID-19 symptoms or sequelae (eg, worsening respiratory status or thromboembolic complications), as determined by the study team.

Graphical abstract
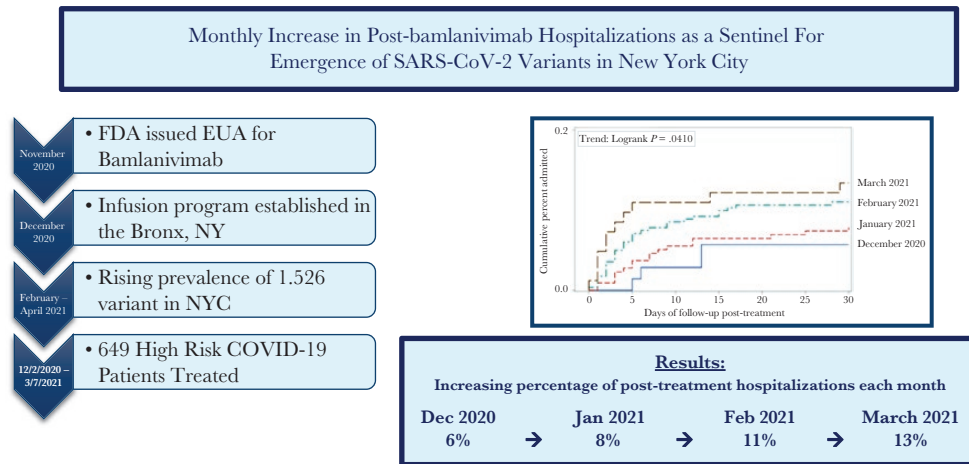
Bottom Line: Infusion programs need real-time data on local prevalence of SARS-CoV-2 variants and in-vitro susceptibilities to determine which monoclonal antibodies are best for their patients

Patients admitted on the same day as ED treatment due to disease progression were excluded, because they were not treated per EUA criteria. Bivariate analyses were conducted using χ^2 or t test. Kaplan-Meier analysis was conducted to assess cumulative percentage admitted posttreatment, and log-rank trend test was used to assess admissions by month of treatment. All statistical tests were 2-tailed and $P < .05$ were considered significant. Analyses were conducted using SAS, version 9.4 software (SAS Institute, Cary, NC).

Patient Consent Statement

The Albert Einstein College of Medicine institutional review board approved this study with waiver of informed consent.

RESULTS

Between December 2, 2020 and March 7, 2021, 665 patients received bamlanivimab. Sixteen patients treated and admitted during the same ED encounter were excluded. Of the remaining 649 patients, 63 (9.7%) were admitted within 30 days, and 46 (73%) of these were COVID-19 related. Median age was 61 years and 42% were male. Median duration from positive SARS-CoV-2 result to infusion was 18 hours (interquartile range [IQR], 6–43) and from infusion to admission was 4 days (IQR, 2–11). Seven patients (1.1%) died. Seventy percent lived in the Bronx; 42% were Hispanic, 20% were non-Hispanic black, and 21% non-Hispanic white. Admitted patients were more likely to be older (median age 65 vs 61 years; $P < .01$). There were no significant differences in sex or other high-risk categories (Table 1). Median pretreatment symptom duration was 5 days for both admitted and nonadmitted patients ($P = .20$) (Table 1). Eighteen patients were asymptomatic at time of treatment; exact symptom duration was unavailable for 22 patients; however, all

were treated within 10 days, per EUA criteria. None were admitted for infusion-related adverse events, but 2 (.3%) patients developed immediate, posttreatment allergic reactions. Thirty-eight (60%) patients had cycle threshold (Ct) values available on admission SARS-CoV-2 testing. Of these, 9 (24%) were under 25, 18 (47%) were between 25–35, and 11 (29%) were >35 or not detected.

Kaplan-Meier analysis demonstrated an increasing trend in cumulative percentage of monthly admissions within 30-days of treatment ($P = .04$); 6% (4 of 70) in December 2020, 8% (17 of 216) in January 2021, 11% (31 of 281) in February 2021, and 13% (11 of 82) in March 2021 (Figure 1). Overall, 30-day admission for untreated, high-risk COVID-19 patients (defined by EUA criteria) at Montefiore was 8% (121 of 1457) from November 2020 through February 2021. This increased from 7% (26 of 383) in December to 10% (24 of 244) in February.
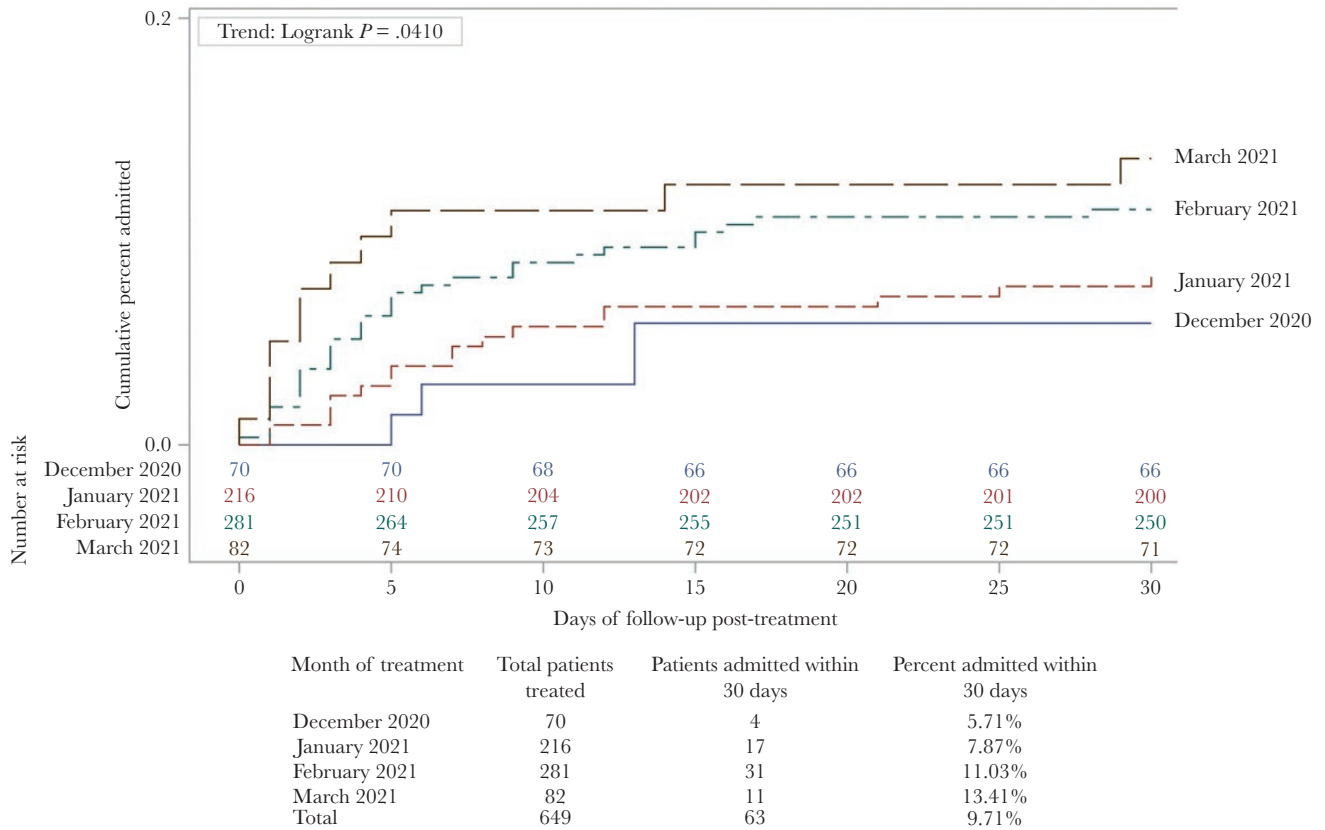
DISCUSSION

Our study describes outcomes from the real-world application of a novel COVID-19 therapeutics program in a dynamic environment. Despite rapid scale-up, improved staffing, and workflow efficiency, we observed a gradual increased percentage of postinfusion hospitalizations between December 2020 and March 2021. This was initially attributed to delayed access of testing, longer symptom duration before infusion, poor social determinants of health, insufficient public outreach, and older patient age, all of which may have contributed to reduced bamlanivimab effectiveness; however, median duration of symptoms before treatment was almost identical in both admitted and nonadmitted patients.

Although suspected but not confirmed in real-time, findings also raised concern for an increasing incidence of

Table 1. Characteristics of SARS-CoV-2-Positive Patients Treated With Bamlanivimab, Montefiore Health System, December 2020–March 2021

Characteristic	Admitted Within 30 Days n (%)	Nonadmitted n (%)	Total	P Value
Age, median (IQR)	65.0 (53–77)	60.0 (51–69)	61.0 (52–70)	<.01
Sex				
Male	32 (51)	241 (41)	274 (42)	.14
Female	31 (49)	345 (59)	376 (58)	
Race/Ethnicity				.72
Hispanic	33 (52)	240 (41)	273 (42)	
Non-Hispanic Black	11 (17)	117 (20)	128 (19)	
Non-Hispanic White	12 (19)	123 (21)	135 (21)	
Asian	2 (3)	22 (4)	24 (4)	
Other	3 (5)	44 (8)	47 (7)	
Unavailable	2 (3)	40 (7)	42 (6)	
High-Risk Comorbidities per EUA				
BMI ≥35	22 (35)	187 (32)	209 (32)	.67
Chronic kidney disease	9 (14)	86 (15)	95 (15)	>.99
Diabetes mellitus	11 (17)	92 (16)	103 (16)	.72
Immunocompromised condition	16 (25)	150 (26)	166 (26)	>.99
Currently receiving immunosuppressive treatment	12 (19)	71 (12)	83 (13)	.16
≥55 years with CAD, CHF, cardiomyopathy, HTN, COPD/emphysema	16 (25)	143 (24)	159 (24)	.88
Symptom Duration Before Treatment				
Days, median (IQR)	5 (4–7)	5 (4–8)	5 (4–8)	.20
Asymptomatic, n (%)	2 (3)	16 (3)	18 (3)	
Exact days unavailable, n (%)	1 (2)	21 (4)	22 (3)	

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; EUA, emergency use authorization; HTN, hypertension; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Number at risk	0	5	10	15	20	25	30
December 2020	70	70	68	66	66	66	66
January 2021	216	210	204	202	202	201	200
February 2021	281	264	257	255	251	251	250
March 2021	82	74	73	72	72	72	71

Trend: Logrank P = .0410

Month of treatment	Total patients treated	Patients admitted within 30 days	Percent admitted within 30 days
December 2020	70	4	5.71%
January 2021	216	17	7.87%
February 2021	281	31	11.03%
March 2021	82	11	13.41%
Total	649	63	9.71%

Figure 1. Cumulative percentage admitted posttreatment by month. March includes patients treated between March 1, 2021 and March 7, 2021.

antibody-resistant viral variants as evidenced by an increase in total admissions per month in both treated and nontreated high-risk patients at Montefiore. As of March 31, 2021, 7-day percentage of SARS-CoV-2 positivity in NYC remains at 6%–7% with a plateau of 3–4000 new cases per day and a slower rate of decline compared to the spring 2020 surge due to an increasing prevalence of B.1.526 and B.1.17 [6, 10, 11]. Thus, upon conclusion of the HHS pilot, Montefiore transitioned exclusively to combination monoclonal antibody therapies per Infectious Diseases Society of America and National Institutes of Health guidelines [15, 16]. In addition, distribution of bamlanivimab monotherapy was stopped and EUA was revoked shortly therafter [17].

On March 14, 2021, the NYC Department of Health (DOH) released data from Global Initiative on Sharing Avian Influenza Data on SARS-CoV-2 variants. As of March 23, 2021, of 7078 specimens sequenced from NYC residents, 1800 cases of B.1.526 and 590 of B.1.1.7 were identified [18]. Moreover, the number of variant cases increased weekly between February 8 and March 21 2021, when B.1.1.7 and B.1.526 accounted for 26.2% and 43% of cases, respectively [18]. On March 18, 2021, the FDA released pseudovirus neutralization data for variants of concern. No susceptibility reduction was reported for bamlanivimab alone or bamlanivimab/etesvimab with B.1.1.7 (key substitution N501Y) [7–9]. However, for B.1.526 (key substitution E484K), a >236-fold and 17-fold susceptibility reduction was reported for bamlanivimab and bamlanivimab/etesevimab, respectively. No susceptibility reductions were observed for B.1.1.7, B.1.526, or other lineages (B.1.351, P.1, and B.1.427/B.1.429) with casirivimab/indevimab [7–9].

It is not currently known how clinical outcomes in patients treated with bamlanivimab or bamlanivimab/etesimab are impacted by variants; nonetheless, these data raise concern that hospitalizations in our cohort may reflect an increasing number of bamlanivimab-resistant variants over time. Seventy-one percent of available Ct values on admission were <35. Although not a true estimate of viral load, this suggests a limited impact of bamlanivimab on viral replication [19].

New York City DOH data as of April 12, 2021 indicates that B.1.526 has been identified ubiquitously and is slightly more common in the Bronx, with multiple zip codes containing >60%–80% of sequenced cases [20]. Consequently, infusion programs located in regions with a high prevalence of resistant variants must adapt to rapidly evolving data.

One limitation is that our hospital does not conduct SARS-CoV-2 sequencing; therefore, data on bamlanivimab-treated patients is unavailable. In addition, although the study design did not include matched controls, the proportion of high-risk, untreated patients admitted within 30-days of a positive test was lower than that observed in treated patients (8.4% vs 9.7%). However, this unadjusted comparison does not account for untreated patients admitted to outside hospitals, whereas posttreatment telehealth follow-up of treated patients captured complete outcomes.

A strength of the study is the real-time correlation between bamlanivimab treatment failure and the rise of variants in NYC. Kaplan-Meier analysis demonstrated an increasing trend in hospitalizations by month. The monthly increase and more than doubling in hospitalizations of bamlanivimab-treated patients between December 2020 to March 2021 paralleled the rise of variants in NYC and served as an indicator for the emergence of B.1.526 in the Bronx. Hospitalizations to Montefiore peaked during the second week of February 2021; therefore, the study period encompassed the timeframe with maximal potential contribution from viral variants, before large-scale immunizations within the Bronx. Likewise, Bronx hospitalizations per 100 000 population increased from 105.3 in December 2020 to 167.9 in January 2021 and 169.2 in February 2021 [20].

CONCLUSIONS

Given the concerning reductions in in vitro susceptibilities of SARS-CoV-2 variants, there is an immediate need for viral sequence and clinical susceptibility data in real-time, given the complex workflows and infrastructures required to scale up infusion programs. National strategies to confront variants must include regional data for hospitals to maximally plan for future pandemic surges and determine which therapeutics are optimal for local patient populations. Lessons learned from the first NYC pandemic surge informed the global public health community. Likewise, ongoing SARS-CoV-2 transmission and rising posttreatment admissions due to viral variants in NYC should be considered another sentinel event.

References

1. Chen P, Nirula A, Heller B, et al; BLAZE-1 Investigators. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med **2021**; 384:229–37.

2. Weinreich DM, Sivapalasingam S, Norton T, et al; Trial Investigators. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med **2021**; 384:238–51.

3. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA **2021**; 325:632–44.

4. Dougon M, Nirula A, Gottlieb R, et al. Bamlanivimab +; etesevimab for treatment of COVID-19 in high-risk ambulatory patients [abstract]. CROI. Available at: https://www.croiconference.org/abstract/bamlanivimabetesevimab-for-treatment-of-covid-19-in-high-risk-ambulatory-patients/. Accessed 31 March 2021.

5. Regeneron. Phase 3 trial shows REGEN-COV (casirivimab with imdevimab) antibody cocktail reduced hospitalization or death by 70% in non-hospitalized COVID-19 patients. https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody. Accessed 31 March 2021.

6. Lasek-Nesselquist E, Pascal L, Erasmus S, Kirsten SG, Janice P. The localized rise of a B.1.526 SARS-CoV-2 variant containing an E484K mutation in New York State [preprint]. medRxiv **2021**:02.26.21251868

7. U.S. Food and Drug Administration. Fact sheet for health care providers, emergency use authorization (EUA) of bamlanivimab and etesevimab. Available at: https://www.fda.gov/media/145802/download. Accessed 31 March 2021.

8. U.S. Food and Drug Administration. Fact sheet for health care providers, emergency use authorization (EUA) of bamlanivimab. Available at: https://www.fda.gov/media/143603/download. Accessed 31 March 2021.

9. U.S. Food and Drug Administration. Fact sheet for health care providers, emergency use authorization (EUA) of REGEN-COV (casirivimab with imdevimab). Available at: https://www.fda.gov/media/145611/download. Accessed 31 March 2021.

10. Annavajhala MK, Mohri H, Zucker JE, et al. A novel SARS-CoV-2 variant of concern, B.1.526, identified in New York [preprint]. medRxiv **2021**. doi:10.1101/2021.02.23.21252259

11. COVID-19: Data. NYC Health website. Available at: https://www1.nyc.gov/site/doh/covid/covid-19-data-totals.page#boro. Accessed 31 March 2021.

12. Lieberman-Cribbin W, Tuminello S, Flores RM, Taioli E. Disparities in COVID-19 testing and positivity in New York City. Am J Prev Med **2020**; 59:326–32.

13. Patel PK, Nori P, Stevens MP. Antimicrobial stewardship and bamlanivimab: opportunities for outpatient preauthorization? Infect Control Hosp Epidemiol **2020**. doi:10.1017/ice.2020.1343

14. New York State Office of the Professions. Practice information: antibody therapy (intravenous or subcutaneous infusions). Available at: http://www.op.nysed.gov/prof/nurse/nurse-iv-monoclonal.htm. Accessed 1 March 2021.

15. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 14 March 2021.

16. National Institute of Health. COVID-19 treatment guidelines. Available at: www.covid19treatmentguidelines.nih.gov. Accessed 31 March 2021.

17. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab. Accessed 19 May 2021.

18. New York City COVID-19 cases caused by SARS-CoV-2 variants report. NYC Health website. Updated 3/23/2021. Available at: https://www1.nyc.gov/assets/doh/downloads/pdf/covid/covid-19-data-variants-032321.pdf. Accessed 31 March 2021.

19. IDSA and AMP joint statement on the use of SARS-CoV-2 PCR cycle threshold (Ct) values for clinical decision-making. IDSA website. Updated 3/12/2021. Available at: https://www.idsociety.org/globalassets/idsa/public-health/covid-19/idsa-amp-statement.pdf. Accessed 31 March 2021.

20. SARS-CoV-2 Variants: Report. NYC Health website. Available at: https://www1.nyc.gov/site/doh/covid/covid-19-data-archive.page#var. Accessed 14 April 2021.