Annals of Internal Medicine ORIGINAL RESEARCH

Use of Hydroxychloroquine, Remdesivir, and Dexamethasone Among Adults Hospitalized With COVID-19 in the United States

A Retrospective Cohort Study

Hemalkumar B. Mehta, MS, PhD; Huijun An, MS; Kathleen M. Andersen, MSc; Omar Mansour, MHS; Vithal Madhira, MS; Emaan S. Rashidi, MHS; Benjamin Bates, MD; Soko Setoguchi, MD, DrPH; Corey Joseph, MPH; Paul T. Kocis, PharmD, MPH; Richard Moffitt, PhD; Tellen D. Bennett, MD, MS; Christopher G. Chute, MD, DrPH; Brian T. Garibaldi, MD, MEHP; and G. Caleb Alexander, MD, MS; for the National COVID Cohort Collaborative (N3C)*

Background: Relatively little is known about the use patterns of potential pharmacologic treatments of COVID-19 in the United States.

Objective: To use the National COVID Cohort Collaborative (N3C), a large, multicenter, longitudinal cohort, to characterize the use of hydroxychloroquine, remdesivir, and dexamethasone, overall as well as across individuals, health systems, and time.

Design: Retrospective cohort study.

Setting: 43 health systems in the United States.

Participants: 137 870 adults hospitalized with COVID-19 between 1 February 2020 and 28 February 2021.

Measurements: Inpatient use of hydroxychloroquine, remdesivir, or dexamethasone.

Results: Among 137 870 persons hospitalized with confirmed or suspected COVID-19, 8754 (6.3%) received hydroxychloroquine, 29 272 (21.2%) remdesivir, and 53 909 (39.1%) dexamethasone during the study period. Since the release of results from the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial in mid-June, approximately 78% to 84% of people who have had invasive mechanical ventilation have received dexamethasone or other glucocorticoids. The use of hydroxychloroquine increased during March 2020, peaking at 42%, and started declining by April 2020. By contrast, remdesivir and dexamethasone use gradually increased over the study period. Dexamethasone and remdesivir use varied substantially across health centers (intraclass correlation coefficient, 14.2% for dexamethasone and 84.6% for remdesivir).

Limitation: Because most N3C data contributors are academic medical centers, findings may not reflect the experience of community hospitals.

Conclusion: Dexamethasone, an evidence-based treatment of COVID-19, may be underused among persons who are mechanically ventilated. The use of remdesivir and dexamethasone varied across health systems, suggesting variation in patient case mix, drug access, treatment protocols, and quality of care.

Primary Funding Source: National Center for Advancing Translational Sciences; National Heart, Lung, and Blood Institute; and National Institute on Aging.

Ann Intern Med. doi:10.7326/M21-0857 **Annals.org**

For author, article, and disclosure information, see end of text.

This article was published at Annals.org on 17 August 2021.

* For members of the National COVID Cohort Collaborative (N3C), see the **Appendix** (available at Annals.org).

As of 9 July 2021, more than 33 million infections and 598 000 deaths directly attributable to the COVID-19 pandemic have occurred in the United States (1). Because of this, major investments have been made to repurpose existing medications, as well as to develop new therapies, to prevent and treat COVID-19.

Although many investigational studies remain under way, 3 medications–hydroxychloroquine, remdesivir, and dexamethasone–have been subject to particular scientific scrutiny. Early interest in hydroxychloroquine, an antiinflammatory treatment of rheumatologic conditions and malaria, was based on evidence of in vitro activity against SARS-CoV-2 and small studies that assessed viral load and mortality (2). Although the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for hydroxychloroquine in March 2020 (3), that EUA was rescinded in June 2020 (4) on the basis of observational and randomized evidence failing to show benefit (5, 6). By contrast, remdesivir received an EUA in May 2020 on the basis of preliminary results from ACCT (Adaptive COVID-19 Treatment Trial) (7) and full FDA approval in October 2020 (8). Dexamethasone, already approved by the FDA for various indications, has been shown to reduce COVID-19 mortality among hospitalized patients requiring oxygen alone or mechanical ventilation (9, 10). Current clinical guidelines from the National Institutes of Health include both remdesivir and dexamethasone as treatments for some adults hospitalized with clinically suspected or laboratory-confirmed SARS-CoV-2 infection (11).

Despite rapidly accumulating evidence on safety and efficacy, far less is known about how treatments have been used in the United States. For example, although several studies have documented increases in use of hydroxychloroquine (12, 13) and remdesivir (14) and others have examined potential drivers of such use (14), analyses have generally been limited to aggregated,

See also:

Editorial comment

Web-Only
Supplement

 © 2021 American College of Physicians

national-level claims or single institutions. Furthermore, how much the use of these products has varied across patients and health systems is unclear (15, 16). We used the National COVID Cohort Collaborative (N3C), a large, multicenter, longitudinal cohort of persons with confirmed or suspected COVID-19 in the United States, to comprehensively characterize the use of hydroxychloroquine, remdesivir, and dexamethasone to treat COVID-19. In addition to quantifying adoption, we also characterized hydroxychloroquine de-adoption and variation in treatments across varied health systems.

METHODS

Data, Design, and Cohort Derivation

The N3C is a unique electronic health record repository supported by the National Institutes of Health whose structure, access, and analytic process have been previously described (17). In brief, the N3C represents the largest cohort of patients with COVID-19 in the United States to date and contains detailed, patient-level data for a racially, ethnically, and geographically diverse group of individuals. It queries electronic health record data from single- and multihospital health systems across the United States and stores data in a central location. As of 27 May 2021, the N3C included more than 2 million patients positive for COVID-19 (18). We used the limited data set, which contains deidentified data, patient ZIP codes, and exact dates of service use.

This retrospective cohort study included adults hospitalized with COVID-19 from 43 health centers between 1 February 2020 and 28 February 2021. We used the N3C definition to define COVID-19 (**Supplement Table**, available at Annals.org) (19–21). We limited our cohort to persons with an inpatient encounter and required the encounter to have occurred no longer than 21 days after the patient was designated as COVID-19–positive; we also allowed individuals to be diagnosed with COVID-19 within 5 days of their hospitalization to account for delays in access to testing and reporting. Given our interest in the use of therapeutics, we restricted analyses to people who remained hospitalized for at least 1 day. We considered only a first hospital stay related to COVID-19 and excluded subsequent inpatient encounters after initial discharge. Finally, we excluded 24 persons (0.02%) with missing information about sex, as well as all individuals younger than 18 years because of different treatment indications and COVID-19 trajectory in pediatric populations.

The results from the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial on dexamethasone were released in mid-June and showed clinical benefit among patients who received invasive mechanical ventilation or oxygen (9). In subanalyses to determine dexamethasone use per the clinical evidence, we restricted our cohort to persons hospitalized between July 2020 and February 2021. Furthermore, except in **Figure 1**, we did analyses for dexamethasone stratified by invasive mechanical ventilation.

Key Variables of Interest

We used date-stamped records of inpatient medication to capture use of hydroxychloroquine, remdesivir, and dexamethasone. We examined sociodemographic and clinical characteristics, including age, sex, body mass index, comorbidity burden, and calendar week of hospital admission. We also examined race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, or another race), which are generally self-reported by patients or family members (24). We used information from COVID-19 admission and inpatient and outpatient data in the 1 year before the date of COVID-19 admission to characterize comorbid conditions using the Charlson Comorbidity Index, a validated measure that applies weights to 17 comorbid conditions (25). Severity of COVID-19 was measured by the development of acute kidney injury during hospitalization, use of invasive mechanical ventilation, or need for extracorporeal membrane oxygenation (20). All patients were classified into mutually exclusive categories of COVID-19 severity—for example, receipt versus no receipt of mechanical ventilation. For each center, we calculated weekly case volume of hospitalized patients with COVID-19 over the study period.

Statistical Analysis

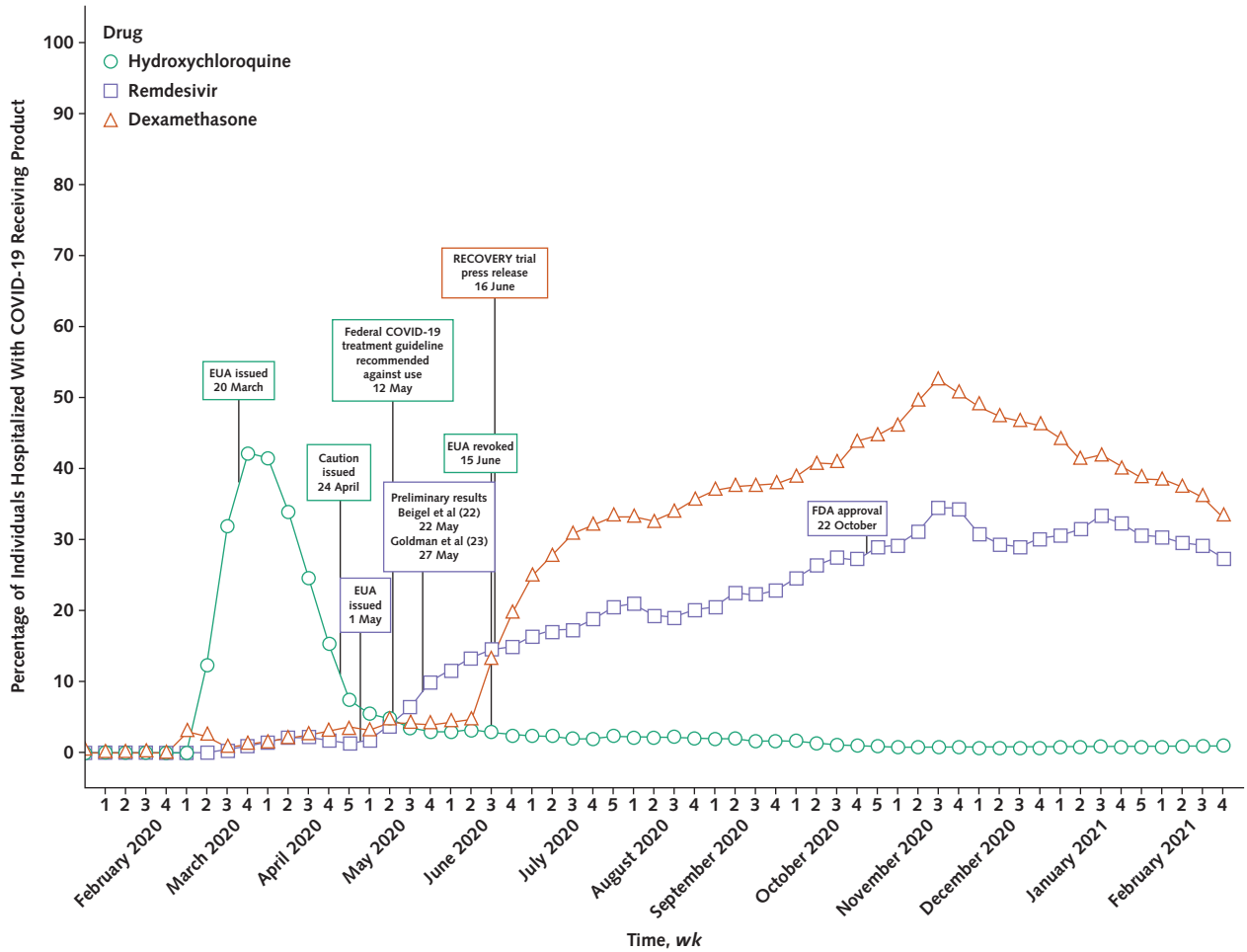
In the overall cohort, we used descriptive statistics to examine trends in product use. First, we separately quantified the weekly proportion of persons within each health system exposed to each product of interest. Here, the denominator included all persons who were hospitalized at any point during the week. Next, we characterized and visually inspected time trends for the 3 products of interest, looking for inflection points, influential outliers, and general trends. We superimposed selected events of interest, including FDA regulatory actions and publication of major clinical trial results, as we evaluated trends in use. We also used box plots to visually show variation in drug use across the centers.

Among ventilated patients who were hospitalized between July 2020 and February 2021, we used descriptive statistics to quantify potential underuse of dexamethasone. Because glucocorticoids other than dexamethasone may have been used (26), we included any oral glucocorticoid use among patients hospitalized with COVID-19 from July 2020 to February 2021. Furthermore, we restricted analysis to patients who remained hospitalized for at least 1 day to ensure that they were eligible to receive dexamethasone or other glucocorticoids. We plotted percentage of dexamethasone use for each center to visualize variation across centers, stratified by mechanical ventilation status.

We used 2-level hierarchical logistic regression models, nesting patients within health centers, to model the odds of a given individual receiving hydroxychloroquine, remdesivir, or dexamethasone. Health centers were included as random intercepts in the model, and we did not control for any patient or hospital characteristics. We quantified variation in use across health systems and used a latent variable approach to estimate intraclass correlation coefficients (ICCs) for each product of interest. The ICCs from these models represent the amount of variation in the underlying propensity to be prescribed medication due to systematic differences between health centers.

We did 2 sensitivity analyses. First, because patients with diabetes may have been less likely to receive glucocorticoids because they can increase blood glucose levels, we examined glucocorticoid use stratified by

Figure 1. Use of hydroxychloroquine, remdesivir, and dexamethasone among individuals hospitalized with COVID-19, 1 February 2020 to 28 February 2021 (n = 137 870).



Supplement Figure 2 (available at Annals.org) shows dexamethasone use among persons with and without mechanical ventilation. EUA = emergency use authorization; FDA = U.S. Food and Drug Administration; RECOVERY = Randomised Evaluation of COVID-19 Therapy.

diabetes status. Second, we determined variation in time to dexamethasone use and duration of use by race/ethnicity and health center.

We extracted data using queries in Spark SQL (Apache Software Foundation) and Python (Python Software Foundation) in the N3C Data Enclave and completed all analyses using R (R Foundation), version 3.5.1. The Johns Hopkins Medicine Institutional Review Boards waived the requirement for informed consent and deemed work in the N3C Data Enclave to be exempt research.

Role of the Funding Source

The funders had no influence on the study's design, conduct, or reporting.

RESULTS

Characteristics of the Study Sample

Among 1 109 631 persons with confirmed or suspected COVID-19 in the N3C cohort through 5 March 2021, a total of 162 150 (14.6%) were hospitalized during the study period. After excluding individuals from 2 sites because of data quality issues (n = 6336), those who were younger than 18 years (n = 5828), those whose length of stay was 0 days (n = 12 092), and those with missing information on sex (n = 24), we had a final cohort of 137 870 persons (**Appendix Figure**, available at Annals.org). The **Table** describes characteristics of the study cohort. Among the 137 870 hospitalized patients, the mean age was 59.4 years (SD, 18.8), 50.4% were male, and 47.8% were non-Hispanic White. Nearly 34.2% of hospitalized participants had none of the comorbid conditions assessed by the Charlson Comorbidity Index, whereas 19.8% had a score of one, 11.9% a score of two, 8.4% a score of three, and 25.8% a score of four or greater. Overall, 6.3% patients received hydroxychloroquine, 21.2% remdesivir, 39.1% dexamethasone, and 17.2% both remdesivir and dexamethasone during their COVID-19 hospitalization.

Table. Drug Use, by Patient Characteristics, Among Persons Hospitalized With COVID-19*

Characteristic	All Patients (*n* = 137 870), *n* (%)	Hydroxychloroquine (*n* = 8754 [6.3%]), %	Remdesivir (*n* = 29 272 [21.2%]), %	Dexamethasone (*n* = 53 909 [39.1%]), %
Age				
18–34 y	17 770 (12.9)	3.1	8.1	20.2
35–49 y	22 853 (16.6)	6.1	16.6	31.4
50–64 y	37 590 (27.3)	7.5	23.1	41.8
65–74 y	27 272 (19.8)	7.1	26.3	46.9
≥75 y	32 385 (23.5)	6.4	25.3	45.3
Sex				
Female	68 371 (49.6)	5.8	19.3	36.8
Male	69 499 (50.4)	6.9	23.1	41.3
Race/ethnicity				
Non-Hispanic White	65 945 (47.8)	4.1	24.4	45.4
Non-Hispanic Black	30 999 (22.5)	5.9	18.0	33.6
Hispanic	23 353 (16.9)	8.9	19.2	33.3
Asian	4632 (3.4)	8.5	16.9	32.1
Another race	1031 (0.8)	3.7	22.4	41.4
Missing	11 910 (8.6)	14.6	17.4	32.5
Charlson Comorbidity Index†				
0	47 139 (34.2)	6.4	14.2	53.2
1	27 238 (19.8)	7.0	23.6	26.4
2	16 409 (11.9)	6.5	25.3	31.4
3	11 556 (8.4)	6.3	26.0	32.5
≥4	35 528 (25.8)	5.7	25.4	35.8
Body mass index				
≤18.0 kg/m^2	17 159 (12.5)	7.4	20.1	34.8
18.1–25.0 kg/m^2	1514 (1.1)	6.1	17.0	34.1
25.1–30.0 kg/m^2	22 731 (16.5)	7.9	24.5	39.8
30.1–40.0 kg/m^2	27 794 (20.2)	7.4	28.7	43.9
40.1–45.0 kg/m^2	5212 (3.8)	6.8	30.5	46.8
≥45.1 kg/m^2	4920 (3.6)	6.6	34.3	49.3
Missing	58 540 (42.5)	4.9	14.9	36.4
AKI while in hospital				
No	112 390 (81.5)	5.1	20.4	37.3
Yes	25 480 (18.5)	11.7	25.1	47.0
Required mechanical ventilation				
No	124 519 (90.3)	5.9	20.0	37.3
Yes	13 351 (9.7)	10.4	32.9	55.9
ECMO				
No	137 109 (99.5)	6.3	21.2	39.0
Yes	761 (0.6)	6.7	28.5	55.5

AKI = acute kidney injury; ECMO = extracorporeal membrane oxygenation.
* Values in parentheses in the first column are column percentages; values in the second, third, and fourth columns are row percentages.
† Ranges from 0 to 33, where a higher score indicates greater likelihood of death within 1 y.

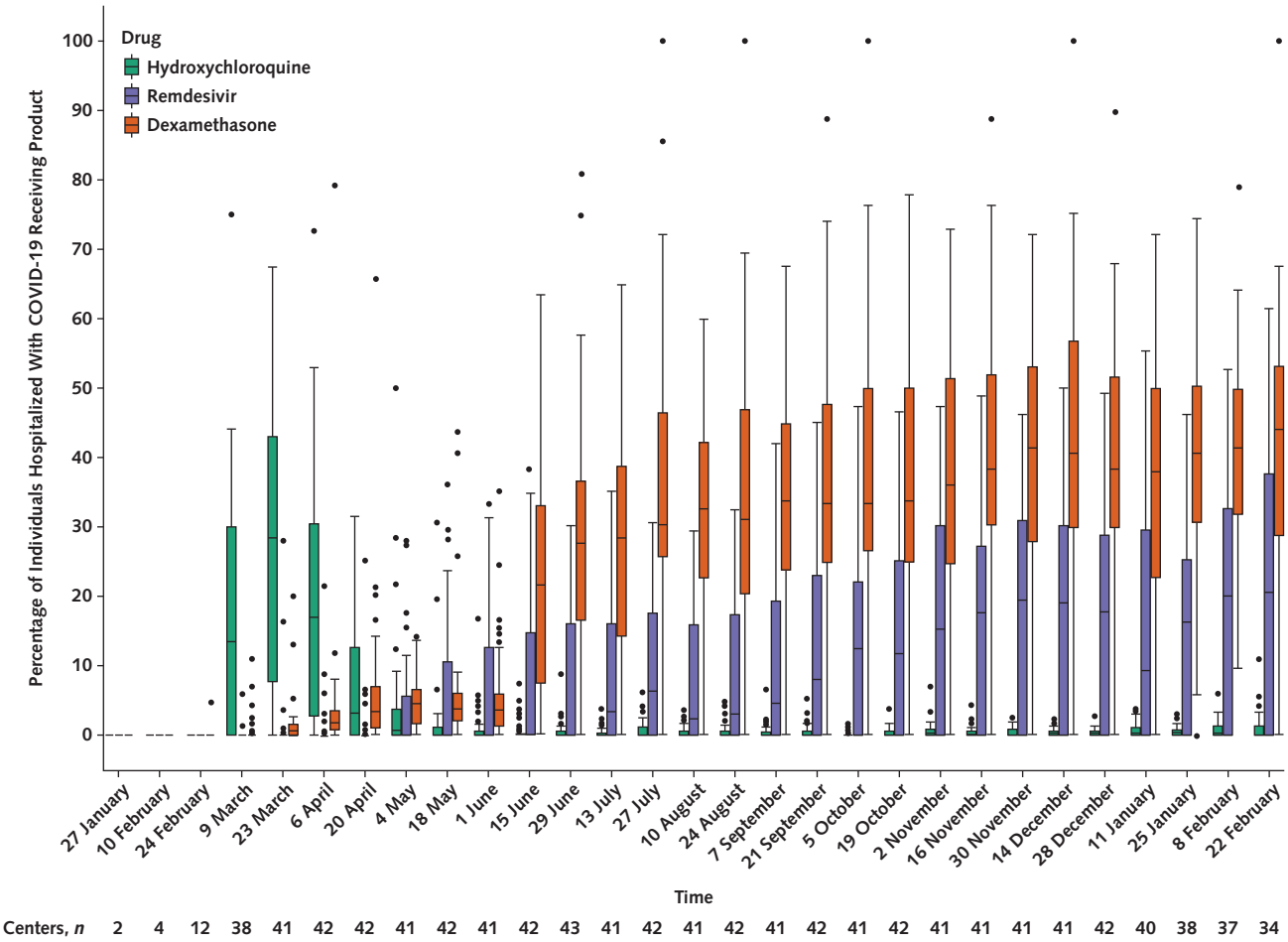
Trends in Hydroxychloroquine, Remdesivir, and Dexamethasone Use

Figure 1 shows trends in the use of hydroxychloroquine, remdesivir, and dexamethasone between February 2020 and February 2021. Beginning in March 2020, hydroxychloroquine use increased sharply, peaking at 42% of patients in late March before rapidly decreasing to approximately 7% by late April 2020 and subsequently to 0.6% by February 2021 among hospitalized individuals with COVID-19. By contrast, remdesivir use first increased rapidly in May 2020 from approximately 2% to 10% of patients, and since May 2020 it has increased gradually to 27% of those hospitalized in February 2021. Finally, about 4% of individuals or fewer used dexamethasone through May 2020; this percentage increased markedly during June and July 2020 to approximately 33%, continued to increase more gradually thereafter to about 53% of hospitalized individuals as of November 2020, and then declined to 33% by February 2021. Combined use of remdesivir and dexamethasone increased from 0.2% in May 2020 to 22.7% in February 2021 (Supplement Figure 1, available at Annals.org).

Characteristics of Persons Receiving COVID-19 Drugs

The Table shows the characteristics of persons in the cohort as well as those receiving each product. Dexamethasone was more commonly used among older adults (45.3% among those aged ≥75 years vs. 20.2% among those aged 18 to 34

Figure 2. Variation in hydroxychloroquine, remdesivir, and dexamethasone use across health centers over time, 1 February 2020 to 28 February 2021 (n = 137 870).



years), males (41.3% vs. 36.8%), non-Hispanic White compared with non-Hispanic Black persons (45.4% vs. 33.6%), and those requiring mechanical ventilation (55.9% vs. 37.3%). We saw similar patterns when examining remdesivir use, with greater use among patients who were older, male, non-Hispanic White, or obese and those with more severe COVID-19 or comorbid illness.

Over the study period, dexamethasone use was higher among those who received mechanical ventilation than among those who did not (**Supplement Figure 2**, available at Annals.org). From July 2020 to February 2021, between 70% and 77% of mechanically ventilated patients received dexamethasone. After other glucocorticoids were accounted for, the use of dexamethasone or other glucocorticoids ranged from 78% to 84% (**Supplement Figure 3** [*A*], available at Annals.org), and the results persisted when we restricted the analysis to patients who remained hospitalized for 2 days or more (**Supplement Figure 3** [*B*], available at Annals.org).

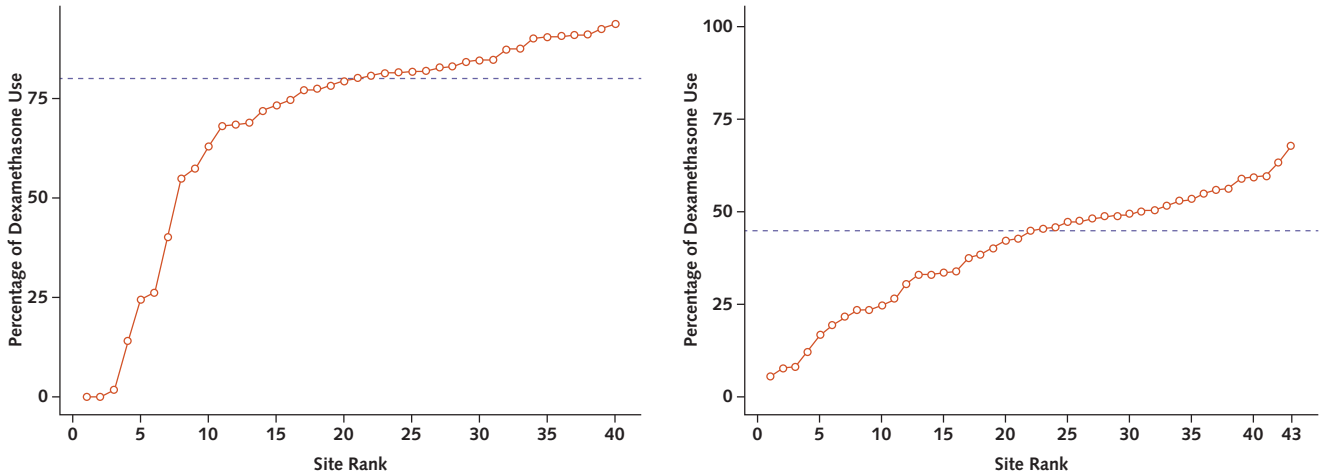
Variation in Drug Use Across Health Centers

Figure 2 characterizes variation in the use of each product across the 43 health centers included in the study. We found wide variation in hydroxychloroquine use across health centers in March 2020, with reductions in such variation by late April 2020 (ICC, 36.7%). Remdesivir use varied substantially across health centers (ICC, 84.6%), and variation persisted from May 2020 to February 2021. The ICC for dexamethasone was lower (14.2%), indicating lower variation across health centers over the study period (February 2020 through February 2021). We saw greater variation in dexamethasone use across health centers among those who received mechanical ventilation than those who did not (ICC, 25.7% vs. 13.0%) (**Figure 3** and **Supplement Figure 4**, available at Annals.org).

Sensitivity Analyses

Among mechanically ventilated persons, use of dexamethasone or other glucocorticoids was more frequent among those with diabetes than those without (56.2% vs. 42.6%). The median time to initiation of dexamethasone therapy was 0 days (interquartile range, 0 to 1 days) among ventilated and nonventilated patients; median duration of use was 7 days (interquartile range, 1 to 10 days)

Figure 3. Variation in dexamethasone use across health centers, stratified by invasive mechanical ventilation, 1 July 2020 to 28 February 2021 (n = 106 039).



All individuals were classified into mutually exclusive categories of mechanical ventilation. **Left.** Among patients who were mechanically ventilated; 40 centers were included. The dotted line shows the overall median of 79.7% of hospitalized adults with COVID-19 who were mechanically ventilated and received dexamethasone. **Right.** Among patients who were not mechanically ventilated; 43 centers were included. The dotted line shows the overall median of 44.9% of hospitalized adults with COVID-19 who were not mechanically ventilated and received dexamethasone.

among ventilated patients and 3 days (interquartile range, 1 to 7 days) among nonventilated patients (**Supplement Figure 5**, available at Annals.org). Time to dexamethasone initiation and duration of dexamethasone use did not differ by race/ethnicity (**Supplement Figure 6**, available at Annals.org) or health center (**Supplement Figure 7**, available at Annals.org).

Discussion

Despite enormous investments in the development of therapeutics to address COVID-19, relatively little is known about how treatments to address coronavirus infection have been used in the United States. Using the N3C, a large, multicenter, longitudinal, U.S. cohort, we characterized the use of hydroxychloroquine, remdesivir, and dexamethasone, overall as well as across individuals, health systems, and time. We found that brisk uptake and abandonment of hydroxychloroquine early in the pandemic has been offset by increases in use of remdesivir and, to an even greater degree, dexamethasone. Despite this, approximately one fifth of patients who were mechanically ventilated after the release of the RECOVERY trial results in mid-June, and therefore were potentially eligible for use, did not receive dexamethasone or any other glucocorticoid, and substantial variation in dexamethasone use was observed across sites. These findings are important because of continued high levels of morbidity and mortality in the United States due to COVID-19, as well as a robust evidence base supporting the value of dexamethasone in reducing the likelihood of death among persons with COVID-19 who require mechanical ventilation (10, 11).

There are many potential drivers of the treatment trends that we described. In the case of hydroxychloroquine, early enthusiasm and media coverage about its potential benefit was rapidly followed by accruing evidence of its ineffectiveness (27) and potential harms (28, 29), ultimately leading the FDA to revoke the EUA governing its use to treat COVID-19 (30). By contrast, both remdesivir and dexamethasone are supported by a rapidly growing body of evidence. Among hospitalized patients, remdesivir use was far less common than dexamethasone use—an interesting finding that may be due in part to remdesivir shortages and cost in the United States (31).

We also found that despite treatment guidelines from the National Institutes of Health regarding the use of dexamethasone for COVID-19, approximately one fifth of mechanically ventilated patients during the most recent months of observation in our cohort did not receive a glucocorticoid, a finding that persisted after those who may not have been eligible because of early discharge or death were excluded. Drug shortages of dexamethasone have been reported (32), and hospital policies may restrict its use to subsets of patients who are critically ill with COVID-19. The relatively high mortality in the control group of the RECOVERY trial (26%) might also raise questions about the applicability of those results to patients in the United States, where the in-hospital mortality from COVID-19 has been closer to 8% (33).

We found marked treatment variation across the 43 centers that we examined, consistent with a large and constantly evolving evidence base from other settings documenting variation across systems beyond that explainable by observable patient or provider characteristics alone (34–36). The centers contributing to the N3C represent a diverse group of health systems that differ in geographic region, size, profit status, staffing ratio, and managerial structure; although our study was not designed to evaluate the independent effect of these and other center characteristics, including clinical

policies, they may nevertheless contribute to the variation that we found (37, 38). Clinicians may be reluctant to use corticosteroids in critically ill patients with COVID-19 because of the conflicting evidence for steroids in other forms of acute respiratory distress syndrome (39, 40). The fact that other trials of steroids in COVID-19 were stopped early and did not uniformly show the same mortality benefit may also contribute to the lack of universal use of steroids in mechanically ventilated patients with COVID-19 (41). Potential drug shortages, as well as a lack of clear and consistent communication about treatments in the context of an "infodemic," has likely compounded matters (42–44). As we expected, variation in use was largest for remdesivir, a product shown to reduce hospital length of stay but not mortality (22), and smallest for dexamethasone, which has an established mortality benefit (10). Although not the direct focus of our research, several questions remain regarding how individual-level and health system characteristics may account for the variations in drug use that we describe.

Our study has limitations. First, the N3C is a database of aggregate reports from health systems with differing common data models, and thus some data of interest, such as oxygen delivery, were not available. Second, although the N3C is the largest U.S. cohort of patients with COVID-19 that has been assembled to date, the centers it includes are clustered in the Southeast, Mid-Atlantic, and Midwest regions, and because most data contributors are academic medical centers, our findings may not generalize to community-based hospitals (18, 45). However, the distributions of age, sex, race, and ethnicity in the N3C indicate a cohort that is representative of many segments of the U.S. population (18, 21). Third, our information on prescription drug exposure is a combination of information about medication ordering and medication administration, depending on the contributing center, and we do not have information about drug dose. Fourth, no baseline inpatient or outpatient information was available for about one third of individuals, and our data likely underestimate their comorbidity burden. Fifth, some persons may not have received dexamethasone because of its antecedent use before hospitalization. Finally, because of imprecise information on the start date of mechanical ventilation, we classified individuals as mechanically ventilated if they received ventilation at any point during their hospitalization.

Despite progress in identifying treatments of COVID-19, the pandemic continues to cause enormous morbidity and mortality in the United States. In this retrospective cohort study of the N3C, brisk uptake and abandonment of hydroxychloroquine early in the pandemic has been offset by increases in use of remdesivir and, to an even greater degree, dexamethasone. However, as many as one fifth of mechanically ventilated patients potentially eligible for dexamethasone did not receive it, and we noted substantial variation in remdesivir and dexamethasone use across sites.

From Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (H.B.M., H.A., K.M.A., E.S.R., C.J.); Monument Analytics, Baltimore, Maryland (O.M.); Palila Software, Reno, Nevada (V.M.); Rutgers Center for Pharmacoepidemiology and Treatment Science, New Brunswick, New Jersey (B.B., S.S.); Penn State Health, Milton S. Hershey Medical Center, Hershey, Pennsylvania (P.T.K.); Stony Brook University, Stony Brook, New York (R.M.); University of Colorado School of Medicine, University of Colorado, Aurora, Colorado (T.D.B.); Schools of Medicine, Public Health, and Nursing, Johns Hopkins University, Baltimore, Maryland (C.G.C.); Johns Hopkins University School of Medicine, Baltimore, Maryland (B.T.G.); and Johns Hopkins Bloomberg School of Public Health and Johns Hopkins School of Medicine, Baltimore, Maryland (G.C.A.).

Acknowledgment: The analyses described in this publication were done with data or tools accessed through the National Center for Advancing Translational Sciences N3C Data Enclave (ncats.nih.gov/n3c/about) and supported by NCATS U24 TR002306. This research was possible because of the patients whose information is included in the data and the organizations and scientists who have contributed to the ongoing development of this community resource: doi.org/10.5281/zenodo.3979622. The authors thank Harold Lehmann, Paul Nagy, Ken Wilkins, and Kunbo Wang for feedback on study design and analytic approach.

Financial Support: Dr. Mehta receives support from the National Institute on Aging (grant 1K01AG070329-01). Ms. Andersen and Mr. Joseph receive doctoral training support from the National Heart, Lung, and Blood Institute Pharmacoepidemiology T32 Training Program (grant T32HL139426-03). The authors also acknowledge assistance for clinical data coordination and retrieval from the Core for Clinical Research Data Acquisition, supported in part by the Johns Hopkins Institute for Clinical and Translational Research (grant UL1TR001079).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-0857.

Reproducible Research Statement: *Study protocol:* Available from Dr. Mehta (e-mail, hbmehta@jhu.edu). *Statistical code:* Available from Dr. Mehta (e-mail, hbmehta@jhu.edu) and Ms. An (e-mail, han13@jhmi.edu). *Data set:* Available at https://ncats.nih.gov/n3c.

Corresponding Author: G. Caleb Alexander, MD, MS, Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, 615 North Wolfe Street, W6035, Baltimore, MD 21205; e-mail, galexan9@jhmi.edu.

Current author addresses and author contributions are available at Annals.org.

References

1. **Center for Systems Science and Engineering at Johns Hopkins University.** COVID-19 Dashboard. 2021. Accessed at https://coronavirus.jhu.edu/map.html on 2 February 2021.
2. **Keyaerts E, Vijgen L, Maes P, et al.** In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004;323:264-8. [PMID: 15351731]
3. **Hinton DM.** Re: Request for emergency use authorization for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the Strategic National Stockpile for treatment of 2019 coronavirus disease. 28 March 2020. Accessed at www.fda.gov/media/136534/download on 2 February 2021.

4. **U.S. Food and Drug Administration.** FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Updated 1 July 2020. Accessed at www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or on 2 February 2021.
5. **Rosenberg ES, Dufort EM, Udo T, et al.** Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA. 2020;323:2493-2502. [PMID: 32392282] doi:10.1001/jama.2020.8630
6. **Tang W, Cao Z, Han M, et al.** Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020;369:m1849. [PMID: 32409561] doi:10.1136/bmj.m1849
7. **National Institute of Allergy and Infectious Diseases.** NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. 29 April 2020. Accessed at www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19 on 2 February 2021.
8. **Hinton DM.** Veklury (remdesivir) EUA letter of approval. 22 October 2020. Accessed at www.fda.gov/media/137564/download on 2 February 2021.
9. **Ledford H.** Coronavirus breakthrough: dexamethasone is first drug shown to save lives. Nature. 2020;582:469. [PMID: 32546811] doi:10.1038/d41586-020-01824-5
10. **Horby P, Lim WS, Emberson JR, et al; RECOVERY Collaborative Group.** Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693-704. [PMID: 32678530] doi:10.1056/NEJMoa2021436
11. **National Institutes of Health.** Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2021. Accessed at www.covid19treatmentguidelines.nih.gov on 2 February 2021.
12. **Shehab N, Lovegrove M, Budnitz DS.** US hydroxychloroquine, chloroquine, and azithromycin outpatient prescription trends, October 2019 through March 2020. JAMA Intern Med. 2020;180:1384-1386. [PMID: 32628242] doi:10.1001/jamainternmed.2020.2594
13. **Bull-Otterson L, Gray EB, Budnitz DS, et al.** Hydroxychloroquine and chloroquine prescribing patterns by provider specialty following initial reports of potential benefit for COVID-19 treatment – United States, January–June 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1210-1215. [PMID: 32881845] doi:10.15585/mmwr.mm6935a4
14. **Lin KJ, Schneeweiss S, Tesfaye H, et al.** Pharmacotherapy for hospitalized patients with COVID-19: treatment patterns by disease severity. Drugs. 2020;80:1961-1972. [PMID: 33151482] doi:10.1007/s40265-020-01424-7
15. **McPherson K, Wennberg JE, Hovind OB, et al.** Small-area variations in the use of common surgical procedures: an international comparison of New England, England, and Norway. N Engl J Med. 1982;307:1310-4. [PMID: 7133068]
16. **Chassin MR, Brook RH, Park RE, et al.** Variations in the use of medical and surgical services by the Medicare population. N Engl J Med. 1986;314:285-90. [PMID: 3510394]
17. **Haendel MA, Chute CG, Bennett TD, et al; N3C Consortium.** The national COVID Cohort Collaborative (N3C): rationale, design, infrastructure, and deployment. J Am Med Inform Assoc. 2021;28:427-443. [PMID: 32805036] doi:10.1093/jamia/ocaa196
18. N3C Cohort Exploration. Accessed at https://covid.cd2h.org/dashboard on 21 April 2021.
19. N3C Phenotype Documentation. Updated 14 April 2020. Accessed at https://covid.cd2h.org/phenotyping on 2 February 2021.
20. COVID-19 phenotype documentation, version 3.0. Updated 12 November 2020. Accessed at https://github.com/National-COVID-Cohort-Collaborative/Phenotype_Data_Acquisition/wiki/Latest-Phenotype on 2 February 2021.
21. **Bennett TD, Moffitt RA, Hajagos JG, et al; National COVID Cohort Collaborative (N3C) Consortium.** Clinical characterization and prediction of clinical severity of SARS-CoV-2 infection among US adults using data from the US National COVID Cohort Collaborative. JAMA Netw Open. 2021;4:e2116901. [PMID: 34255046] doi:10.1001/jamanetworkopen.2021.16901
22. **Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members.** Remdesivir for the treatment of Covid-19 – final report. N Engl J Med. 2020;383:1813-1826. [PMID: 32445440] doi:10.1056/NEJMoa2007764
23. **Goldman JD, Lye DCB, Hui DS, et al; GS-US-540-5773 Investigators.** Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020;383:1827-1837. [PMID: 32459919] doi:10.1056/NEJMoa2015301
24. **Hasnain-Wynia R, Baker DW.** Obtaining data on patient race, ethnicity, and primary language in health care organizations: current challenges and proposed solutions. Health Serv Res. 2006;41:1501-18. [PMID: 16899021]
25. **Charlson ME, Pompei P, Ales KL, et al.** A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83. [PMID: 3558716]
26. **Angus DC, Derde L, Al-Beidh F, et al; Writing Committee for the REMAP-CAP Investigators.** Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA. 2020;324:1317-1329. [PMID: 32876697] doi:10.1001/jama.2020.17022
27. **Horby P, Mafham M, Linsell L, et al; RECOVERY Collaborative Group.** Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med. 2020;383:2030-2040. [PMID: 33031652] doi:10.1056/NEJMoa2022926
28. **Mercuro NJ, Yen CF, Shim DJ, et al.** Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:1036-1041. [PMID: 32936252] doi:10.1001/jamacardio.2020.1834
29. **Chorin E, Wadhwani L, Magnani S, et al.** QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Heart Rhythm. 2020;17:1425-1433. [PMID: 32407884] doi:10.1016/j.hrthm.2020.05.014
30. **Hinton DM.** Letter revoking EUA for chloroquine phosphate and hydroxychloroquine sulfate. 15 June 2020. Accessed at www.fda.gov/media/138945/download on 2 February 2021.
31. **Boodman E.** From Houston to Miami, hospitals running short of remdesivir for Covid-19 patients. STAT. 10 July 2020. Accessed at www.statnews.com/2020/07/10/hospitals-running-short-of-remdesivir-for-covid19-patients on 2 February 2021.
32. **Silverman E.** Hospitals see shortages of a cheap steroid that one study says helps Covid-19 patients. STAT. 25 June 2020. Accessed at www.statnews.com/pharmalot/2020/06/25/covid19-coronavirus-dexamethasone-shortages on 2 February 2021.
33. **Asch DA, Sheils NE, Islam MN, et al.** Variation in US hospital mortality rates for patients admitted with COVID-19 during the first 6 months of the pandemic. JAMA Intern Med. 2021;181:471-478. [PMID: 33351068] doi:10.1001/jamainternmed.2020.8193
34. **Wennberg J, Gittelsohn A.** Variations in medical care among small areas. Sci Am. 1982;246:120-34. [PMID: 7079718]
35. **Zhang Y, Baicker K, Newhouse JP.** Geographic variation in the quality of prescribing. N Engl J Med. 2010;363:1985-8. [PMID: 21047217] doi:10.1056/NEJMp1010220
36. **Zhang Y, Steinman MA, Kaplan CM.** Geographic variation in outpatient antibiotic prescribing among older adults. Arch Intern Med. 2012;172:1465-71. [PMID: 23007171] doi:10.1001/archinternmed.2012.3717
37. FACTBOX-U.S. hospitals differ on best use of hydroxychloroquine for coronavirus. Reuters. 6 April 2020. Accessed at www.reuters.com/article/health-coronavirus-usa-hydroxychloroquin-idUSL1N2BU1K5 on 2 February 2021.

38. **Morgan SG, Cunningham CM, Hanley GE.** Individual and contextual determinants of regional variation in prescription drug use: an analysis of administrative data from British Columbia. PLoS One. 2010;5:e15883. [PMID: 21209960] doi:10.1371/journal.pone.0015883
39. **Venkatesh B, Finfer S, Cohen J, et al; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group.** Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med. 2018;378:797-808. [PMID: 29347874] doi:10.1056/NEJMoa1705835
40. **Villar J, Ferrando C, Martínez D, et al; Dexamethasone in ARDS Network.** Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med. 2020;8:267-276. [PMID: 32043986] doi:10.1016/S2213-2600(19)30417-5
41. **Carlet J, Payen D, Opal SM.** Steroids for sepsis and ARDS: this eternal controversy remains with COVID-19 [Letter]. Lancet. 2020. [PMID: 33045189] doi:10.1016/S0140-6736(20)32132-2
42. **Eysenbach G.** How to fight an infodemic: the four pillars of infodemic management [Editorial]. J Med Internet Res. 2020;22:e21820. [PMID: 32589589] doi:10.2196/21820
43. **Zarocostas J.** How to fight an infodemic. Lancet. 2020;395:676. [PMID: 32113495] doi:10.1016/S0140-6736(20)30461-X
44. **Saag MS.** Misguided use of hydroxychloroquine for COVID-19: the infusion of politics into science [Editorial]. JAMA. 2020;324:2161-2162. [PMID: 33165507] doi:10.1001/jama.2020.22389
45. **National Center for Advancing Translational Sciences.** Data Transfer Agreement Signatories. Accessed at https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories on 2 February 2021.

Current Author Addresses: Dr. Mehta: Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, E7640, Baltimore, MD 21205.
Ms. An, Ms. Andersen, Ms. Rashidi, and Mr. Joseph: 615 North Wolfe Street, W6021, Baltimore, MD 21205.
Mr. Mansour: PO Box 20862, Baltimore, MD 21209.
Mr. Madhira: Palila Software, 10890 Rushing Flume Drive, Reno, NV 89521.
Dr. Bates: Rutgers Institute for Health, Health Care Policy, and Aging Research, 112 Paterson Street, Room 318, New Brunswick, NJ 08901.
Dr. Setoguchi: 112 Paterson Street, Institute for Health, New Brunswick, NJ 08901.
Dr. Kocis: Penn State Health, Milton S. Hershey Medical Center Anticoagulation Clinic, Mail Code EC079, 30 Hope Drive, Entrance B, Suite 1003, PO Box 859, Hershey, PA 17033-0859.
Dr. Moffitt: Stony Brook University, MART L7-0810, Stony Brook, NY 11794.
Dr. Bennett: University of Colorado School of Medicine, 13199 East Montview Boulevard, Suite 300, Mail Stop F443, Aurora, CO 80045.
Dr. Chute: Johns Hopkins University, Division of General Internal Medicine, 2024 East Monument Street, Suite 1-200, Baltimore, MD 21287.
Dr. Garibaldi: Division of Pulmonary and Critical Care, Johns Hopkins, 1830 East Monument Street, 5th Floor, Baltimore, MD 21205.
Dr. Alexander: Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, 615 North Wolfe Street, W6035, Baltimore, MD 21205.

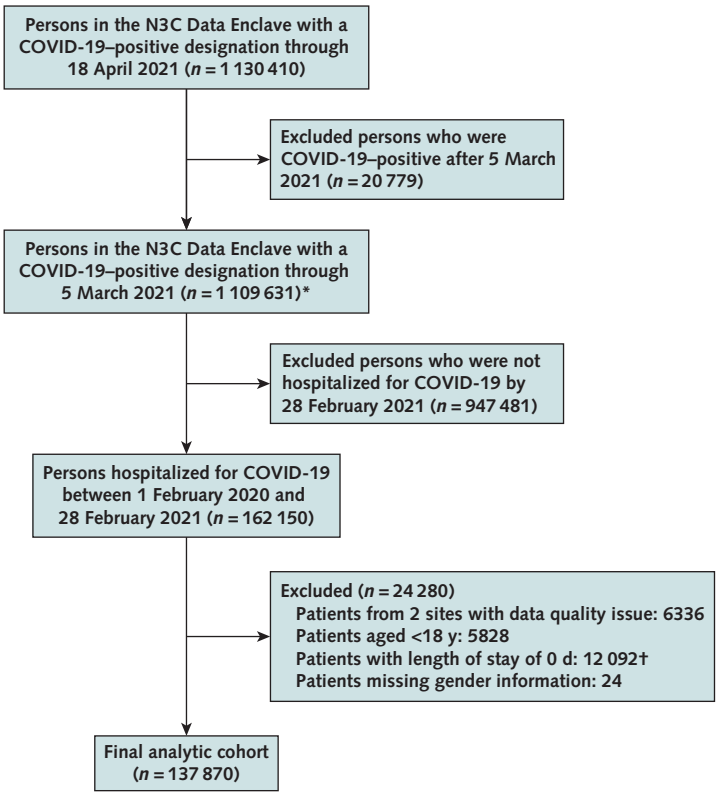
Author Contributions: Conception and design: H.B. Mehta, K.M. Andersen, O. Mansour, S. Setoguchi, C. Joseph, C.G. Chute, B.T. Garibaldi, G.C. Alexander.
Analysis and interpretation of the data: H.B. Mehta, H. An, K.M. Andersen, O. Mansour, E.S. Rashidi, B. Bates, S. Setoguchi, C. Joseph, T.D. Bennett, B.T. Garibaldi, G.C. Alexander.
Drafting of the article: H.B. Mehta, K.M. Andersen, E.S. Rashidi, B. Bates, C. Joseph, P.T. Kocis, C.G. Chute, B.T. Garibaldi, G.C. Alexander.
Critical revision of the article for important intellectual content: H.B. Mehta, K.M. Andersen, O. Mansour, E.S. Rashidi, S. Setoguchi, R. Moffitt, T.D. Bennett, B.T. Garibaldi, G.C. Alexander.
Final approval of the article: H.B. Mehta, H. An, K.M. Andersen, O. Mansour, V. Madhira, E.S. Rashidi, B. Bates, S. Setoguchi, C. Joseph, P.T. Kocis, R. Moffitt, T.D. Bennett, C.G. Chute, B.T. Garibaldi, G.C. Alexander.
Provision of study materials or patients: K.M. Andersen, E.S. Rashidi.
Statistical expertise: H.B. Mehta, K.M. Andersen, O. Mansour.
Obtaining of funding: C.G. Chute.
Administrative, technical, or logistic support: H.B. Mehta, K.M. Andersen, E.S. Rashidi, C.G. Chute, G.C. Alexander.
Collection and assembly of data: K.M. Andersen, V. Madhira, P.T. Kocis, C.G. Chute.

Appendix: Members of the National COVID Cohort Collaborative (N3C)

Members of the N3C who authored this work: Hemalkumar B. Mehta, MS, PhD, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Huijun An, MS, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Kathleen M. Andersen, MSc, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Omar Mansour, MHS, Monument Analytics, Baltimore, Maryland; Vithal Madhira, MS, Palila Software, Reno, Nevada; Emaan S. Rashidi, MHS, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Benjamin Bates, MD, Rutgers Center for Pharmacoepidemiology and Treatment Science, New Brunswick, New Jersey; Soko Setoguchi, MD, DrPH, Rutgers Center for Pharmacoepidemiology and Treatment Science, New Brunswick, New Jersey; Corey Joseph, MPH, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Paul T. Kocis, PharmD, MPH, Penn State Health, Milton S. Hershey Medical Center, Hershey, Pennsylvania; Richard Moffitt, PhD, Stony Brook University, Stony Brook, New York; Tellen D. Bennett, MD, MS, University of Colorado School of Medicine, University of Colorado, Aurora, Colorado; Christopher G. Chute, MD, DrPH, Schools of Medicine, Public Health, and Nursing, Johns Hopkins University, Baltimore, Maryland; Brian T. Garibaldi, MD, MEHP, Johns Hopkins University School of Medicine, Baltimore, Maryland; and G. Caleb Alexander, MD, MS, Johns Hopkins Bloomberg School of Public Health and Johns Hopkins School of Medicine, Baltimore, Maryland.

Members of the N3C who contributed to this work but did not author it: Melissa A. Haendel, PhD, Center for Health AI, University of Colorado Anschutz Medical Campus, Aurora, Colorado; Christopher G. Chute, DrPH, MPH, MD, Schools of Medicine, Public Health, and Nursing, Johns Hopkins University, Baltimore, Maryland; Carolyn Bramante, MPH, MD, University of Minnesota, Minneapolis, Minnesota; Farrukh M. Koraishy, PhD, MD, Stony Brook University, Stony Brook, New York; Stephanie S. Hong, BS, Johns Hopkins University School of Medicine, Baltimore, Maryland; and Richard L. Zhu, MD, MS, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Appendix Figure. Study flow diagram.



N3C = National COVID Cohort Collaborative.

* Our cohort definition allowed for persons to be designated as COVID-19–positive up to 5 d after admission, to account for delays in test reporting. For this reason, the first step allowed COVID-19–positive designation through 5 March 2021 and hospitalization through 28 February 2021.

† Of 12 092 individuals discharged on the same day who were excluded from the analysis, 188 (1.6%) died on that day.