



## **COVID-19 Investigational Treatments in Use Among Hospitalized Patients Identified Through the US Coronavirus Disease 2019-Associated Hospitalization Surveillance Network, March 1-June 30, 2020**

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# COVID-19 Investigational Treatments in Use Among Hospitalized Patients Identified Through the US Coronavirus Disease 2019–Associated Hospitalization Surveillance Network, March 1–June 30, 2020

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Using a coronavirus disease 2019 (COVID-19)–associated hospitalization surveillance network, we found that 42.5% of hospitalized COVID-19 cases with available data from March 1–June 30, 2020, received  $\geq 1$  COVID-19 investigational treatment. Hydroxychloroquine, azithromycin, and remdesivir were used frequently; however, hydroxychloroquine and azithromycin use declined over time, while use of remdesivir increased.

**Keywords:** coronavirus; hospitalization; therapeutics.

Numerous studies are currently in progress to examine the effectiveness of various potential coronavirus disease 2019 (COVID-19) treatments [1–5]. In the United States, it is unclear which investigational treatments are being selected in practice by clinicians to help manage the disease. Using data collected

from a national surveillance network for COVID-19-associated hospitalizations, we describe the type and frequency of inpatient COVID-19 investigational treatment (COVID-19 treatment) use over a 4-month period.

## METHODS

The COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) conducts population-based surveillance for laboratory-confirmed COVID-19-associated hospitalizations among persons of all ages in 99 counties in 14 states [6]. Laboratory-confirmed COVID-19-associated hospitalizations among residents in the surveillance catchment area who had a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) molecular test during hospitalization or up to 14 days before admission are included in surveillance. Using a standardized case report form, trained surveillance officers abstract data through medical chart review for all identified cases.

We analyzed a convenience sample of patients admitted from March 1 to June 30, 2020, for whom medical chart abstraction of COVID-19 treatments was complete as of the date of analysis; 13 states contributed data to these analyses. The primary analysis included a description of COVID-19 treatment use overall and by month across all surveillance sites. Sensitivity analyses included a similar assessment, limited to sites with the highest level of data completeness for COVID-19 treatment use or limited to sites with less complete data on COVID-19 treatment. All treatments were considered to be non-mutually exclusive. Proportions were compared using chi-square statistics.

From the initiation of COVID-NET, surveillance officers were instructed to routinely abstract data on some COVID-19 treatments (azithromycin, chloroquine, hydroxychloroquine, remdesivir); instruction for routine abstraction of other COVID-19 treatments (anakinra, atazanavir, baricitinib, convalescent plasma, darunavir, dexamethasone, infliximab, LY3127804, ribavirin, sarilumab, selinexor, tocilizumab) was implemented at varying times throughout the analytic period. In the absence of specific instructions, treatments may also have been identified and abstracted through a free-text field for COVID-19 treatments.

Data collected on use of protease inhibitors (atazanavir, darunavir, lopinavir/ritonavir) was specific to COVID-19 treatment only, and not to HIV. Azithromycin was not a recommended standalone treatment for COVID-19 during the analytic period. Therefore, we included it in the primary analysis only if administered in combination with another COVID-19 treatment. Because sites were not instructed to abstract dexamethasone as a specific COVID-19 treatment until June, we were not able to assess its use for the entire analytic period.

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## Patient Consent Statement

Patient consent was not required as the data used in this analysis were collected as part of routine public health surveillance and were determined to be nonresearch by the Centers for Disease Control and Prevention (CDC). Participating surveillance sites obtained approval for the COVID-NET surveillance protocol from their respective state and local institutional review boards, as required; no personnel identifiers are shared with the CDC in the transmitted surveillance data.

## RESULTS

From March 1 to June 30, 2020, 35 545 COVID-19-associated hospitalizations were reported in COVID-NET. At the time of analysis, medical chart abstraction on COVID-19 treatments was complete for 10 157 (28.6%) patients from 228 hospitals in 13 states. Of these 10 157 patients, the majority were >50 years of age, male, and either non-Hispanic White or non-Hispanic Black (Supplementary Table 1).

Use of ≥1 COVID-19 treatment was reported among 4313 (42.5%) patients with completed medical chart abstraction on COVID-19 treatments. Treatment use was greatest among patients aged 50–64 years (48.6%, 1298/2671), followed by patients aged ≥65 years (44.0%, 1724/3920) and patients aged 18–49 years (37.9%, 1275/3360). Children aged <18 years

received COVID-19 treatments infrequently (7.8%, 16/206). Of the 4313 patients who received treatments, 56.1% were male, 50.5% required intensive care unit (ICU) admission, 33.1% received mechanical ventilation, 28.7% required vasopressor support, and 19.2% died in-hospital (Supplementary Table 2). When examining race and ethnicity, similar proportions of patients received a COVID-19 treatment compared with those who did not (Supplementary Table 2).

Hydroxychloroquine was the most frequently reported COVID-19 treatment, followed by azithromycin, remdesivir, IL-6 inhibitors (sarilumab, tocilizumab), and convalescent plasma (Table 1). Protease inhibitors (atazanavir, darunavir, lopinavir/ritonavir) and dexamethasone were less commonly reported, although abstraction of dexamethasone use only began in June. The remaining agents were rarely reported. Of 2313 patients receiving azithromycin in combination with another COVID-19 treatment, 1663 (71.9%) received it with hydroxychloroquine.

Reported use of COVID-19 treatments varied by treatment setting (Table 1). IL-6 inhibitor, convalescent plasma, and dexamethasone use among patients treated in the ICU was >2-fold higher compared with patients treated in non-ICU settings. Azithromycin and remdesivir use were also significantly greater in the ICU compared with the non-ICU setting, while hydroxychloroquine was used less frequently in the ICU.

**Table 1. Use of Investigational Treatments<sup>a</sup> Among Hospitalized COVID-19 Patients Overall and by ICU Status—COVID-NET, March 1–June 30, 2020**

	Overall (n = 4313)		Non-ICU Setting <sup>b</sup> (n = 2128)		ICU Setting <sup>b</sup> (n = 2172)	
Hydroxychloroquine <sup>c,d</sup>	2862	66.4%	1461	68.7%	1390	64.0%
Azithromycin <sup>d,e</sup>	2311	53.6%	996	46.8%	1309	60.3%
Remdesivir <sup>c,d</sup>	1235	28.6%	555	26.1%	679	31.3%
IL-6 inhibitors (tocilizumab, sarilumab) <sup>c,d</sup>	480	11.1%	143	6.7%	336	15.5%
Convalescent plasma <sup>d</sup>	350	8.1%	106	5.0%	243	11.2%
Protease inhibitors (atazanavir, lopinavir/ritonavir, darunavir) <sup>f</sup>	216	5.0%	92	4.3%	124	5.7%
Dexamethasone <sup>d</sup>	145	3.4%	45	2.1%	100	4.6%
Vitamins/minerals (vitamin C, zinc)	77	1.8%	53	2.5%	24	1.1%
Baricitinib <sup>c</sup>	41	1.0%	23	1.1%	18	0.8%
Losartan <sup>c</sup>	31	0.7%	18	0.8%	13	0.6%
Chloroquine	28	0.6%	14	0.7%	14	0.6%
LY3127804 <sup>c</sup>	4	0.1%	4	0.2%	0	0.0%
Anakinra	3	0.1%	0	0.0%	3	0.0%
Ribavirin	3	0.1%	2	0.1%	1	0.0%
Infliximab	1	0.0%	0	0%	1	0.0%
Ivermectin	1	0.0%	0	0%	1	0.0%
Selinexor <sup>c</sup>	1	0.0%	1	0%	0	0.0%

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

<sup>a</sup>Assessed as non-mutually exclusive categories.

<sup>b</sup>ICU status not available for 13 patients included in this analysis.

<sup>c</sup>Includes treatments given as off-label or compassionate use or as part of randomized controlled trials where it could not be determined whether the patient received treatment vs placebo; the number who participated in randomized clinical trials included 78 for hydroxychloroquine, 70 for remdesivir, 25 for sarilumab, 36 for baricitinib, 27 for losartan, 4 for LY3127804, and 1 for selinexor.

<sup>d</sup>Significant difference of  $P \leq .001$  when comparing investigational treatment use by setting (non-ICU vs ICU).

<sup>e</sup>Only includes azithromycin when given in combination with another COVID-19-related treatment.

<sup>f</sup>Treatment specific to COVID-19; did not include treatment specific to HIV.

In March, the predominant COVID-19 treatments included hydroxychloroquine, azithromycin, protease inhibitors, and IL-6 inhibitors (Figure 1). However, by June, use of these treatments declined significantly, with the greatest absolute decline in hydroxychloroquine use, from 94.6% in March to 8.7% in June. In contrast, remdesivir use significantly increased from March to June (5.7% vs 78.6%). Convalescent plasma use increased from March to May but declined significantly in June. While data on dexamethasone use were not collected before June, 25.8% of hospitalizations reported its use during June (data not shown).

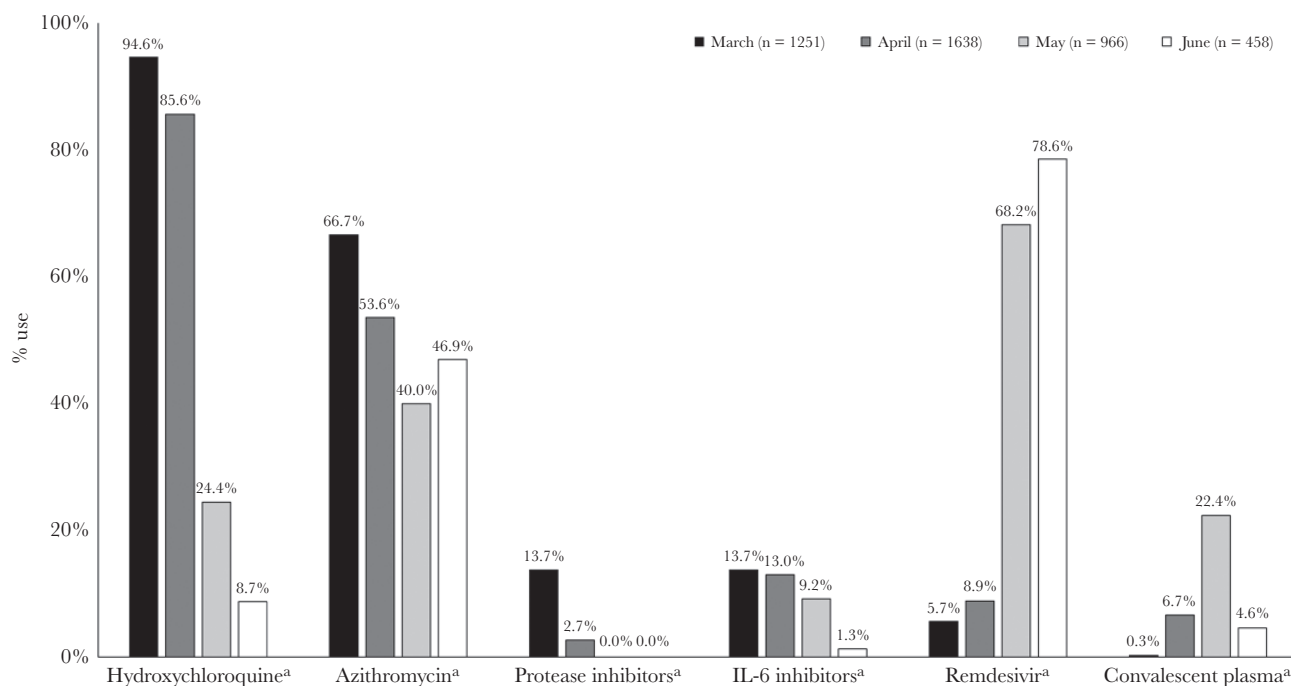
Medical chart abstraction for COVID-19 treatments was complete for 44.1% of COVID-NET hospitalizations in March, compared with 27.5% in April, 27.2% in May, and 20.5% in June. Data completeness by month also varied by COVID-NET site, ranging from 0% to 97.0%. To assess the impact of variable reporting, we performed sensitivity analyses of COVID-19 treatment use over time. We first limited the analysis to the 2 sites with the highest level of treatment data completeness (Supplementary Table 3). Data completeness for these 2 sites ranged from 94.5% to 99.7% by month and averaged 96.7% for the 4-month study period. These sites represented 44.4% (4512/10 157) of patients with data available on COVID-19 treatments; 35.7% (1610/4512) of these patients received  $\geq 1$  treatment. The temporal trends of COVID-19 treatment use

in these 2 sites mirrored the findings when including all sites (Supplementary Figure 1A). Because these 2 sites represented a large proportion of our primary analytic sample, we performed an additional sensitivity analysis of temporal COVID-19 treatment use excluding these 2 sites and including the remaining 11 sites; data completeness averaged 33.8% for the 4-month study period and included 55.6% (5645/10157) of patients with data available on COVID-19 treatments. The major temporal trends of COVID-19 treatment use in these 11 sites were similar to those for all sites and for the 2 sites with the highest level of data completeness (Supplementary Figure 1B).

## DISCUSSION

Early COVID-NET surveillance data demonstrated frequent use of hydroxychloroquine, azithromycin, and remdesivir as COVID-19 treatments. They also identified significant evolution in treatment patterns over the surveillance period, including declining use of hydroxychloroquine, azithromycin, protease inhibitors, and IL-6 inhibitors and increasing use of remdesivir.

These temporal changes in COVID-19 treatment use may reflect the impact of federal and medical expert guidance, in addition to a growing knowledge base on treatment effectiveness. At the start of the pandemic, treatment choice relied upon



**Figure 1.** Percentage of hospitalized COVID-19 patients with reported use of investigational treatments by month—COVID-NET, March 1–June 30, 2020. Investigational treatments were assessed as non-mutually exclusive. Data for hydroxychloroquine, remdesivir, and IL-6 inhibitors included when given as off-label or compassionate use or as part of randomized controlled trials where it could not be determined whether the patient received treatment or placebo. Data for azithromycin only included when given in combination with another COVID-19-related treatment. Data included for protease inhibitors were specific to COVID-19 treatment and did not include treatment specific to HIV; protease inhibitors included atazanavir, darunavir, and lopinavir/ritonavir. IL-6 inhibitors included sarilumab and tocilizumab. <sup>a</sup>Significant difference of  $P < .0001$  in treatment use from March to June. Abbreviations: COVID-19, coronavirus disease 2019; IL-6, interleukin 6.



findings from in vitro studies [7], studies evaluating treatments for other coronaviruses [8], or hypothetical effectiveness based on presumed COVID-19 pathogenesis [9], pushing the hydroxychloroquine and azithromycin combination, protease inhibitors, and IL-6 inhibitors to the forefront of observational and clinical trials. This information, along with the emergency use authorization issued in March by the US Food and Drug Administration (FDA) for hydroxychloroquine [10], likely contributed to these treatments' initial frequent use. Subsequent publication of guidelines on COVID-19 treatments by the National Institutes of Health [11] in May, withdrawal of the emergency use authorization for hydroxychloroquine [12] in June, and data on the limited effectiveness of these treatments [1, 2, 13] may have influenced a decline in their use. Similarly, FDA issuance of emergency use authorization for remdesivir in May [14] and recent publications suggesting that remdesivir may reduce time to recovery [3] and that dexamethasone may reduce mortality [4] may have led to their increasing use over time. Use of convalescent plasma fluctuated over time, which may reflect difficulties in accessing this treatment or represent concerns about its effectiveness, as definitive findings are not yet available [5]. Increased use of some COVID-19 treatments in the ICU setting might suggest that these treatments are reserved for last-ditch efforts in resuscitation, perhaps due to the uncertainty of their effectiveness. While the overall use of azithromycin declined, its use was more sustained than that of hydroxychloroquine. This may be secondary to its function as an empiric treatment for presumed bacterial pneumonia, before a COVID-19 diagnosis is confirmed. COVID-NET does not abstract the timing of each treatment, and therefore it is possible that azithromycin was detected as a COVID-19 treatment when it was not being used as such, especially in later months of the analytic period. In general, these surveillance data suggest that clinicians are aware of the evolving information on investigational treatments and have adjusted treatment practice to be consistent with the currently available evidence and guidance.

Several limitations of these findings should be considered. This population-based surveillance network represents ~10% of the US population, and therefore these findings may not be generalizable to the entire country. In addition, due to the shifting nature of treatment availability and knowledge on treatment effectiveness, COVID-NET protocols on medical chart abstraction for COVID-19 treatments have evolved over time. This may have resulted in under-reporting of some treatments. Finally, our findings may be influenced by missing data on COVID-19 treatment use, and our convenience sample may not be representative of the entire COVID-NET network. However, results from sensitivity analyses were similar to those of the overall primary analysis, regardless of whether we limited to sites with more or less complete data.

This analysis of COVID-19 treatment use offers insight into treatment practices over the early stages of the COVID-19

pandemic in the United States. Given the rapidly evolving information on potential treatments for COVID-19, it is reassuring that clinicians appear to be choosing treatments based on the available evidence. As additional data on emerging COVID-19 treatments become available, continued monitoring of treatment use is merited.

### Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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