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Oral COVID-19 Antiviral Uptake Among a Highly Vaccinated US Cohort of Adults With SARS-CoV-2 Infection Between December 2021 and October 2022

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Background. We described the oral nirmatrelvir/ritonavir (NMV/r) and molnupiravir (MOV) uptake among a subgroup of highly vaccinated adults in a US national prospective cohort who were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between 12/2021 and 10/2022.

Methods. We estimate antiviral uptake within 5 days of SARS-CoV-2 infection, as well as age- and gender-adjusted antiviral uptake prevalence ratios by antiviral eligibility (based on age and comorbidities), sociodemographic characteristics, and clinical characteristics including vaccination status and history of long coronavirus disease 2019 (COVID).

Results. NMV/r uptake was 13.6% (95% CI, 11.9%–15.2%) among 1594 participants, and MOV uptake was 1.4% (95% CI, 0.8%–2.1%) among 1398 participants. NMV/r uptake increased over time (1.9%; 95% CI, 1.0%–2.9%; between 12/2021 and 3/2022; 16.5%; 95% CI, 13.0%–20.0%; between 4/2022 and 7/2022; and 25.3%; 95% CI, 21.6%–29.0%; between 8/2022 and 10/2022). Participants age ≥65 and those who had comorbidities for severe COVID-19 had higher NMV/r uptake. There was lower NMV/r uptake among non-Hispanic Black participants (7.2%; 95% CI, 2.4%–12.0%; relative to other racial/ethnic groups) and among individuals in the lowest income groups (10.6%; 95% CI, 7.3%–13.8%; relative to higher income groups). Among a subset of 278 participants with SARS-CoV-2 infection after 12/2021 who also had a history of prior SARS-CoV-2 infection, those with (vs without) a history of long COVID reported greater NMV/r uptake (22.0% vs 7.9%; $P = .001$). Among those prescribed NMV/r (n = 216), 137 (63%; 95% CI, 57%–70%) reported that NMV/r was helpful for reducing COVID-19 symptoms.

Conclusions. Despite proven effectiveness against severe outcomes, COVID-19 antiviral uptake remains low among those with SARS-CoV-2 infection in the United States. Further outreach to providers and patients to improve awareness of COVID-19 oral antivirals and indications is needed.

Keywords. awareness of antivirals; CHASING COVID Cohort study; molnupiravir (MOV); nirmatrelvir-ritonavir (NMV/r); SARS-CoV-2.

Despite the availability of vaccination and boosters as a primary prevention strategy against coronavirus disease 2019 (COVID-19), there remains a large burden of severe disease and preventable deaths due to COVID-19. As of March 2023, >1.1 million deaths were attributed to COVID-19 in the United States [1]. A disproportionate number of COVID-19 hospitalizations and deaths in the United States are among high-risk and underserved populations, including people who are older (>65 years), who are unvaccinated or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) naive, who have comorbidities, who are socioeconomically disadvantaged, and who are racial or ethnic minorities [2, 3]. Oral antiviral treatments, such as oral nirmatrelvir-ritonavir (NMV/r) and molnupiravir (MOV), are effective at preventing hospitalization and death for those most susceptible to severe COVID-19 [4, 5].

In December 2021, oral COVID-19 antivirals received Food and Drug Administration (FDA) Emergency Use Authorization (EUA) [6, 7] based on clinical trials showing substantial reductions in hospitalizations and deaths among unvaccinated, SARS-CoV-2-naive individuals who were otherwise at high-risk for severe COVID-19 disease [5, 8]. In a randomized controlled trial (RCT) of high-risk, unvaccinated, SARS-CoV-2-naive, and nonhospitalized adults, oral NMV/r

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received within 5 days of symptom onset reduced the risk of COVID-19-related hospital admission by 86% [9]. Another RCT evaluating MOV showed a reduction in the risk of COVID-19-associated hospitalizations or deaths [5]. Real-world studies have since confirmed the effectiveness of SARS-CoV-2 antivirals in reducing COVID-19-related hospitalization and death in populations that have been previously vaccinated or infected [10–15], although the PANORAMIC trial conducted in the United Kingdom recently reported no effect of MOV for reducing COVID-19-associated hospitalizations or mortality among high-risk vaccinated adults [16, 17].

In March 2022, a national "Test to Treat" initiative was launched to increase access to SARS-CoV-2 antivirals at little or no cost [18]. The initiative expanded in May 2022 with an aim to ensure equitable access to SARS-CoV-2 antivirals by focusing on high-incident and high-risk COVID-19 communities [19]. A national analysis of antiviral dispensing data found that the number of antivirals dispensed substantially increased from March 2022 to May 2022, and the number of oral antivirals dispensed per 100 000 population increased from 3.3 to 77.4 in low–, from 4.5 to 70.0 in medium–, and from 7.8 to 35.7 in high–social vulnerability zip codes, coinciding with national efforts to increase access [20]. However, relative to the burden of infection, dispensing rates in the United States during March–May 2022 remained low overall, especially in neighborhoods with high social vulnerability [20].

The objective of this study was to estimate and describe uptake of NMV/r and MOV and factors associated with antiviral uptake among highly vaccinated adults in a large US national prospective cohort of individuals who reported a SARS-CoV-2 infection between December 2021 and October 2022. We also aimed to assess antiviral treatment completion and perceived reduction of COVID symptoms among participants who used antivirals.

METHODS

Participants

The Communities, Households, and SARS-CoV-2 Epidemiology (CHASING) COVID Cohort study is a national prospective cohort study launched on March 28, 2020, during the emergence of the COVID-19 pandemic in the United States. The cohort is a geographically and sociodemographically diverse sample of participants ≥18 years old residing in the United States or its territories. We used internet-based strategies to recruit a fully online cohort, with follow-up occurring approximately quarterly from March 2020 to October 2022. Additional recruitment and follow-up details are presented elsewhere [21].

For this analysis, we included the CHASING COVID Cohort participants who completed 2 follow-up assessments conducted in June 2022 and October 2022 and reported a SARS-CoV-2 infection since December 2021. The study was approved by the Institutional Review Boards of the City University Of New York (CUNY) Graduate School of Public Health and Health Policy (New York, NY, USA; protocol 2020-0256). Informed consent forms were completed in a web browser on participants' computers or mobile devices at baseline, at each round of serological testing, and at periodic follow-up assessments [21]. Participants may voluntarily discontinue participation at any time.

Outcomes: Antiviral Uptake, Eligibility, Treatment Completion, and Perceived Reduction of COVID-19 Symptoms

Antiviral uptake was defined based on whether participants reported being prescribed antiviral medications "for 5 days immediately after you were diagnosed." We defined eligibility according to the FDA NMV/r or MOV patient eligibility screening checklist tool for prescribers administered during the study period [6, 7]. We used the same criteria to define participants as eligible for both NMV/r and MOV. Specifically, we considered participants to be NMV/r or MOV prescription eligible if they self-reported any of the following conditions: age ≥65 or any age with a diagnosis of comorbidity, overweight or obese, physically inactive, pregnant, or a current cigarette or e-cigarette smoker. The comorbidities included asthma, cancer, chronic kidney diseases, lung diseases, liver diseases, type 2 diabetes, heart conditions, HIV, mental health disorders, and immunodeficiencies.

Among participants who reported NMV/r uptake, we assessed treatment completion and perceived reduction of COVID-19 symptoms. We considered participants who took NMV/r as prescribed to complete the treatment. Perceived reduction of COVID symptoms was defined based on an affirmative response to the question "Did you find [antiviral] helpful for reducing COVID-19 symptoms?"

Timing of SARS-CoV-2 Infection

To capture the impact of the national Test to Treat initiative launched in March 2022, we categorized the timing of SARS-CoV-2 infection relative to the launch of the initiative. Specifically, we looked at SARS-CoV-2 infections that occurred from December 2021 to March 2022, April to July 2022, and August to October 2022. For participants who reported more than 1 instance of SARS-CoV-2 antiviral use, we used the earliest instance.

COVID-19 Vaccination and Booster Status as of Infection

COVID-19 primary vaccine status was assessed between December 2020 and October 2022, with follow-up assessments approximately every 3 months. Participants reported vaccination manufacturer, dates, and number of doses of the primary vaccine series received. Participants who received 1 dose of a single-dose primary series (eg, Janssen) or 2 doses of 2-dose primary series (eg, Pfizer and Moderna) were considered vaccinated with a primary series. Between October 2021 and October 2022, we assessed COVID-19 booster status among

those who received a primary series. We defined vaccination and booster status based on doses received before each SARS-CoV-2 infection (Supplementary Figure 1).

History of SARS-CoV-2 Infection and Long COVID Status as of Infection

Participants were asked the number of times and dates they had a positive test or COVID-19 throughout the pandemic in the June 2022 assessment and any positive test between June and October 2022 in the October 2022 assessment. We classified participants as having a history of SARS-CoV-2 infection if they reported a SARS-CoV-2 infection before each SARS-CoV-2 infection separated by a median of 2.5 months (Supplementary Figure 1). Between November 2020 and October 2022, participants were asked if "they thought of themselves as having long COVID: having persistent coronavirus symptoms weeks and months after becoming sick." Among those with a history of SARS-CoV-2 infection, we defined long COVID status before each SARS-CoV-2 infection (Supplementary Figure 1).

Sociodemographic Characteristics

We used information on age, gender, race/ethnicity, education, household annual income, and presence of children in the household obtained at cohort enrollment (between March 2020 and July 2020). The responses from the most recent assessment completed through October 2022 were included for employment status, presence of comorbidities, current smoking status, health insurance status, and designation of residence [22].

Statistical Analysis

We estimated the proportion and 95% CIs of NMV/r or MOV uptake overall and by sociodemographic and clinical (vaccination, long COVID, and comorbidities) characteristics among (1) all participants who self-reported SARS-CoV-2 infection after December 2021 and (2) the subset that met the FDA eligibility criteria for COVID-19 oral antivirals [6, 7]. Participants reporting receipt of both antivirals at the same time were excluded. Additionally, NMV/r was treated as a competing event of MOV, and vice versa. Thus, we did not include participants who reported MOV uptake in the denominator when we assessed NMV/r uptake, and vice versa. Among participants who reported NMV/r uptake, we described treatment completion and the proportion that found NMV/r "helpful for reducing COVID symptoms." Crude and age- and gender-adjusted antiviral uptake prevalence ratios were estimated using log-binomial models (outcome distribution: binomial; link function between covariates and outcome: log), which results in less bias by obtaining maximum likelihood estimates with higher power and smaller standard errors [23, 24]. Because of sparse data, we combined those with nonbinary gender with the largest group (female) to address convergence issues in some models. Models that relied on the 2- vs 3-level gender variable for adjustment were indicated in tables. Statistical analyses were conducted using SAS 9.4 (Cary, NC, USA).

RESULTS

NMV/r Uptake

From December 2021 to October 2022, 1622 participants reported a SARS-CoV-2 infection; among these, 16 (0.99%) participants reported receipt of NMV/r or MOV at multiple time points. The first instance was used in the analysis. Among 1622 participants, 244 (15.0%; 95% CI, 13.3%–16.8%) ever took NMV/r or MOV during December 2021 and October 2022. Eight participants who reported both NMV/r and MOV uptake for the same infection were excluded from the analysis of both NVM/r and MOV uptake. Among 1594 with a SARS-CoV-2 infection who did not use MOV, 1356 (85.1%) were eligible for NMV/r prescription, 1482 (93.0%) had received at least 1 dose of COVID-19 vaccine, and 1084 (68.0%) were boosted at the time of the current SARS-CoV-2 infection (Table 1). NMV/r uptake was 13.6% (95% CI, 11.9%–15.2%) among SARS-CoV-2-infected participants and 15.4% (95% CI, 13.5%–17.3%) among participants who were eligible for an NMV/r prescription.

NMV/r Uptake by Sociodemographic Characteristics

As shown in Table 1, among those with SARS-CoV-2 infection from December 2021 to October 2022, NMV/r uptake increased over time. Relative to participants with a SARS-CoV-2 infection in December 2021–March 2022, participants infected in April–July 2022 or August–October 2022 had increasingly greater uptake (adjusted prevalence ratio [aPR], 8.38; 95% CI, 4.61–15.25; and aPR, 11.78; 95% CI, 6.59–21.05; respectively). NMV/r uptake increased with age group, and in age- and gender-adjusted models, participants who were aged 65+, 50–64, and 40–49 years had 4.36 (95% CI, 2.79–6.82), 2.94 (95% CI, 1.92–4.49), 1.71 (95% CI, 1.07–2.75), and 1.58 (95% CI, 1.02–2.45) times the NMV/r uptake as those aged 18–29 years, respectively. Males had a higher NMV/r uptake than females (aPR, 1.32; 95% CI, 1.03–1.69). Black non-Hispanic and Hispanic participants reported nonsignificantly lower NMV/r uptake (aPR, 0.55; 95% CI, 0.28–1.10; and aPR, 0.82; 95% CI, 0.57–1.20; respectively) compared with White non-Hispanic individuals. Participants with an annual household income <$100 000 had ~40% lower NMV/r uptake than participants with a household income >$100 000 (aPRs ranging from 0.61 to 0.71). NMV/r uptake was higher among those with (vs without) children age <18 years in the household (aPR, 1.50; 95% CI, 1.14–1.99).

NMV/r Uptake by Clinical Characteristics

Participants with (vs without) health conditions such as asthma (aPR, 1.59; 95% CI, 1.16–2.18), type 2 diabetes (aPR, 1.58; 95% CI, 1.14–2.20), obesity (aPR, 1.37; 95% CI, 1.07–1.75), mental health disorder (aPR, 1.55; 95% CI, 1.21–1.98), immunodeficiency

Table 1. Nirmatrelvir/Ritonavir Uptake by Sociodemographic and Clinical Factors—the United States CHASING COVID Cohort Study Participants With SARS-CoV-2 Infection From December 2021 to October 2022

	Total	NMV/r Uptake	NMV/r Uptake (95% CI)	Crude NMV/r Uptake Prevalence Ratio[a] (95% CI)	Adjusted NMV/r Uptake Prevalence Ratio[a] (95% CI)
Total, No. (%)	1594	216	13.6 (11.9–15.2)	…	…
Number eligible, No. (%)	1356	209	15.4 (13.5–17.3)	…	…
Infection timing, No. (%)					
Dec 2021–Mar 2022	637 (40.0)	12 (5.6)	1.9 (1.0–2.9)	Ref	Ref
Apr 2022–Jul 2022	431 (27.0)	71 (32.9)	16.5 (13.0–20.0)	**8.74 (4.80–15.92)**	**8.38 (4.61–15.25)**
Aug 2022–Oct 2022	526 (33.0)	133 (61.6)	25.3 (21.6–29.0)	**13.42 (7.52–23.96)**	**11.78 (6.59–21.05)**
Age category, No. (%)					
18–29 y	405 (25.4)	28 (13.0)	6.9 (4.4–9.4)	Ref	Ref
30–39 y	486 (30.5)	55 (25.5)	11.3 (8.5–14.1)	**1.64 (1.06–2.53)**	**1.58 (1.02–2.45)**
40–49 y	292 (18.3)	36 (16.7)	12.3 (8.6–16.1)	**1.78 (1.11–2.85)**	**1.71 (1.07–2.75)**
50–64 y	285 (17.9)	59 (27.3)	20.7 (16.0–25.4)	**2.99 (1.96–4.57)**	**2.94 (1.92–4.49)**
65+ y	126 (7.9)	38 (17.6)	30.2 (22.2–38.2)	**4.36 (2.79–6.81)**	**4.36 (2.79–6.82)**
Gender, No. (%)					
Male	703 (44.1)	111 (51.4)	15.8 (13.1–18.5)	**1.36 (1.06–1.75)**	**1.32 (1.03–1.69)**
Female	851 (53.4)	99 (45.8)	11.6 (9.5–13.8)	Ref	Ref
Non-Binary/transgender/other	40 (2.5)	6 (2.8)	15.0 (3.9–26.1)	1.29 (0.60–2.76)	1.67 (0.78–3.55)
Race/ethnicity, No. (%)					
Asian/American Indian/Pacific	135 (8.5)	11 (5.1)	8.2 (3.5–12.8)	**0.52 (0.29–0.92)**	0.81 (0.44–1.49)
Black NH	111 (7.0)	8 (3.7)	7.2 (2.4–12.0)	**0.46 (0.23–0.90)**	0.55 (0.28–1.10)
Hispanic	263 (16.5)	28 (13.0)	10.7 (6.9–14.4)	**0.67 (0.46–0.98)**	0.82 (0.57–1.20)
White NH	1037 (65.1)	164 (75.9)	15.8 (13.6–18.0)	Ref	Ref
Other/unknown	48 (3.0)	5 (2.3)	10.4 (1.8–19.1)	0.66 (0.28–1.53)	0.70 (0.30–1.61)
Education, No. (%)					
Less than 12th grade	21 (1.3)	5 (2.3)	23.8 (5.6–42.0)	1.71 (0.78–3.73)	**2.30 (1.12–4.73)**
12th grade/GED	119 (7.5)	21 (9.7)	17.7 (10.8–24.5)	1.27 (0.84–1.92)	**1.54 (1.03–2.32)**
Some college (1–3 y)	369 (23.2)	39 (18.1)	10.6 (7.4–13.7)	0.76 (0.55–1.06)	0.81 (0.59–1.13)
College (4+ y)	1085 (68.1)	151 (69.9)	13.9 (11.9–16.0)	Ref	Ref
Employment status,[b] No. (%)					
Employed	1207 (75.7)	154 (71.3)	12.8 (10.9–14.6)	Ref	Ref
Out of work	79 (5.0)	7 (3.2)	8.9 (2.6–15.1)	0.69 (0.34–1.43)	0.76 (0.37–1.56)
Other	308 (19.3)	55 (25.5)	17.9 (13.6–22.1)	**1.40 (1.06–1.85)**	0.95 (0.67–1.34)
Household annual income, No. (%)					
<$35 000	341 (21.4)	36 (16.7)	10.6 (7.3–13.8)	**0.57 (0.40–0.82)**	0.71 (0.50–1.02)
$35 000–$49 999	163 (10.2)	17 (7.9)	10.4 (5.7–15.1)	**0.57 (0.35–0.92)**	**0.61 (0.38–0.99)**
$50 000–$69 999	232 (14.6)	26 (12.0)	11.2 (7.2–15.3)	**0.61 (0.41–0.91)**	0.68 (0.45–1.01)
$70 000–$99 999	286 (17.9)	34 (15.7)	11.9 (8.1–15.6)	**0.64 (0.45–0.93)**	**0.68 (0.47–0.96)**
$100 000+	537 (33.7)	99 (45.8)	18.4 (15.2–21.7)	Ref	Ref
Don't know	35 (2.2)	4 (1.9)	11.4 (0.9–22.0)	0.62 (0.24–1.59)	0.88 (0.35–2.22)
Any children <18 y, No. (%)					
No	1130 (70.9)	149 (69.0)	13.2 (11.2–15.2)	Ref	Ref
Yes	464 (29.1)	67 (31.0)	14.4 (11.2–17.6)	1.10 (0.84–1.43)	**1.50 (1.14–1.99)**
Health insurance,[c] No. (%)					
Yes	1459 (91.5)	207 (95.8)	14.2 (12.4–16.0)	Ref	Ref
No	102 (6.4)	5 (2.3)	4.9 (0.7–9.1)	**0.35 (0.15–0.82)**	0.44 (0.18–1.04)
Unknown	33 (2.1)	4 (1.9)	12.1 (1.0–23.3)	0.85 (0.34–2.16)	0.97 (0.39–2.39)
Designation of residence, No. (%)					
Urban	745 (46.7)	100 (46.3)	13.4 (11.0–15.9)	Ref	Ref
Suburban	413 (25.9)	58 (26.9)	14.0 (10.7–17.4)	1.05 (0.77–1.41)	1.01 (0.75–1.35)
Rural	407 (25.5)	53 (24.5)	13.0 (9.8–16.3)	0.97 (0.71–1.32)	0.95 (0.70–1.29)
Missing	29 (1.8)	5 (2.3)	17.2 (3.5–31.0)	Excluded from analysis	Excluded from analysis
Vaccine status as of infection,[d] No. (%)					
Boosted	1084 (68.0)	195 (90.3)	18.0 (15.7–20.3)	Ref	**Ref**
Vaccinated with at least 1 dose of primary vaccine, but not boosted	398 (25.0)	15 (6.9)	3.8 (1.9–5.6)	**0.21 (0.13–0.35)**	**0.24 (0.14–0.40)**
unvaccinated	112 (7.0)	6 (2.8)	5.4 (1.2–9.5)	**0.30 (0.14–0.66)**	**0.35 (0.16–0.77)**

Table 1. Continued

	Total	NMV/r Uptake	NMV/r Uptake (95% CI)	Crude NMV/r Uptake Prevalence Ratio[a] (95% CI)	Adjusted NMV/r Uptake Prevalence Ratio[a] (95% CI)
History of SARS-CoV-2 infection,[b] No. (%)					
Yes	278 (17.4)	36 (16.7)	13.0 (9.0–16.9)	0.95 (0.68–1.32)	0.97 (0.70–1.35)
No	1316 (82.6)	180 (83.3)	13.7 (11.8–15.5)	Ref	Ref
History of long COVID among those with a prior SARS-CoV-2 infection,[e] No. (%)					
Yes	100 (36.0)	22 (61.1)	22.0 (13.9–30.1)	**2.80 (1.50–5.22)**	**3.88 (2.13–7.07)**[f]
No	178 (64.0)	14 (38.9)	7.9 (3.9–11.8)	Ref	Ref
Comorbidity[b]					
Asthma–current, No. (%)	174 (10.9)	34 (15.7)	19.5 (13.7–25.4)	**1.52 (1.10–2.12)**	**1.59 (1.16–2.18)**[f]
Cancer, No. (%)	82 (5.1)	18 (8.3)	22.0 (13.0–30.9)	**1.68 (1.09–2.57)**	1.06 (0.68–1.63)[f]
Kidney disease, No. (%)	20 (1.3)	7 (3.2)	35.0 (14.1–55.9)	**2.64 (1.43–4.85)**	1.55 (0.85–2.82)[f]
Lung disease, No. (%)	27 (1.7)	7 (3.2)	25.9 (9.4–42.5)	**1.94 (1.01–3.72)**	1.58 (0.83–3.01)[f]
Type 2 diabetes, No. (%)	111 (7.0)	32 (14.8)	28.8 (20.4–37.3)	**2.32 (1.68–3.21)**	**1.58 (1.14–2.20)**[f]
Obesity, No. (%)	462 (29.0)	80 (37.0)	17.3 (13.9–20.8)	**1.44 (1.12–1.86)**	**1.37 (1.07–1.75)**[f]
Mental health disorder, No. (%)	647 (40.6)	101 (46.8)	15.6 (12.8–18.4)	**1.29 (1.00–1.65)**	**1.55 (1.21–1.98)**[f]
Immunodeficiency, No. (%)	126 (7.9)	26 (12.0)	20.6 (13.6–27.7)	**1.59 (1.10–2.30)**	**1.55 (1.08–2.21)**[f]
Cardiovascular disease, No. (%)	45 (2.8)	21 (9.7)	46.7 (32.1–61.2)	**3.71 (2.64–5.20)**	**2.87 (2.06–4.00)**[f]
Current smoker or e-smoker,[g] No. (%)					
Yes	268 (16.8)	40 (18.5)	14.9 (10.7–19.2)	1.12 (0.82–1.54)	1.22 (0.89–1.67)[f]
No	1326 (83.2)	176 (81.5)	13.3 (11.5–15.1)	Ref	Ref
Took NMV/r as prescribed,[b] No. (%)					
Yes	…	192 (88.9)	…	…	…
Some, but not all	…	4 (1.9)	…	…	…
No	…	19 (8.8)	…	…	…
DK	…	1 (0.5)	…	…	…

The characteristics without a superscript were measured at baseline between March 2020 and July 2020.

[a]Bold font indicates statistical significance.

[b]Measured between June and October 2022.

[c]Measured between March and October 2022.

[d]Measured between February 2021 and January 2022.

[e]Measured between November 2020 and October 2022.

[f]Model adjusted for a 2-level gender.

[g]Measured between December 2021 and January 2022.

(aPR, 1.55; 95% CI, 1.08–2.21), and cardiovascular disease (aPR, 2.87; 95% CI, 2.06–4.00) had higher NMV/r uptake. Compared with participants who had received a booster before SARS-CoV-2 infection, NMV/r uptake was lower among participants who did not receive a booster or were unvaccinated (aPR, 0.24; 95% CI, 0.14–0.40; and aPR, 0.35; 95% CI, 0.16–0.77; respectively).

Among a subset of 278 participants with a history of SARS-CoV-2 infection, 100 (36.0%) self-identified as having a history of long COVID. NMV/r uptake was substantially higher among participants with vs without history of long COVID (aPR, 3.88; 95% CI, 2.13–7.07). The results were similar for all participants and a restricted subgroup of participants who were FDA-eligible for NMV/r (Supplementary Table 1).

NMV/r Completion and Perceived Reduction of COVID-19 Symptoms

As shown in Supplementary Table 3, among all participants who were prescribed NMV/r (n = 216), 192 (89%; 95% CI, 85%–93%) reported that they took NMV/r as prescribed, and 137 (63%; 95% CI, 57%–70%) indicated that NMV/r was helpful for reducing their acute COVID symptoms. The proportion taking NMV/r as prescribed and finding it helpful for reducing COVID symptoms varied by subgroup. However, due to sparse data in each subgroup, the confidence intervals were wide.

MOV Uptake

Among 1398 with a SARS-CoV-2 infection who did not use NMV/r, 1167 (83.5%) were eligible for MOV prescription, 1292 (92.4%) had received at least 1 dose of COVID-19 vaccine, and 906 (64.8%) were boosted as of infection (Supplementary Table 2). Crude MOV uptake was 1.4% (95% CI, 0.8%–2.1%) among those participants with a SARS-CoV-2 infection between December 2021 and October 2022 and 1.7% (95% CI, 1.0%–2.5%) among the subset of participants who had SARS-CoV-2 and were eligible for an MOV prescription. The sample of people reporting MOV uptake was small, which resulted in wide confidence intervals by subgroups and the inability to calculate adjusted prevalence ratios.

DISCUSSION

In our national community-based cohort of mostly vaccinated US adults with SARS-CoV-2 infection during December 2021–October 2022, antiviral uptake was low (NMV/r: 13.6%; MOV: 1.4%) despite most being eligible for an antiviral medication prescription (NMV/r: 85%; MOV: 84%). The contrast of high eligibility and low uptake in the national cohort is consistent with several other studies using different sampling methods [25–27]. In a population-representative probability sample of New York City (NYC) adults age 18 or older, 50% were eligible for antiviral prescription, but 15% received an antiviral [25]. NYC was the first city in the United States to offer free NMV/r at mobile testing sites in an attempt to address concerns over inequities in distributing antiviral treatments [28, 29]. NMV/r uptake in the NYC population-representative sample between April and May 2022 (15.1%; 95% CI, 7.1%–23.1%) was similar to our national cohort between April and July 2022 (16.5%; 95% CI, 13.0%–20.0%). In a convenience sample of Massachusetts and New Hampshire adult outpatients aged 50 or older who received health care service from Massachusetts General Brigham hospitals and clinics, 84% were eligible for a prescription considering potential drug interactions and contraindications and 19.9% were prescribed NMV/r [26]. In a convenience sample of adults who tested positive for SARS-CoV-2 between March 2021 and August 2022 at a large clinical laboratory that operates in 37 US states, antiviral uptake was 1.7% among individuals aged 65 and older who tested positive for SARS-CoV-2 [27]. Together, these findings underscore the low uptake of antivirals among those who are eligible in the United States. Our findings are unique, however, in that we measured antiviral uptake using methodology that minimizes the selection bias present in other studies that restrict the analysis to those with laboratory-confirmed evidence of SARS-CoV-2—which may miss many positive tests that are conducted at home and not reported.

There are several factors that may contribute to low antiviral uptake, including low awareness of antivirals, health care disparities, and barriers to health care and prescription access. A population-representative study in NYC found that 44% of adults were unaware of antivirals [25]. A cross-sectional convenience sample of adults who tested positive for SARS-CoV-2 between March 2021 and August 2022 at a large clinical laboratory that operates in 37 US states reported that 50% of adults aged 65 or younger were unaware of COVID-19 treatment [27]. Though federal and state efforts have aimed to increase antiviral accessibility, prescription barriers have remained [30]. The requirements of knowing patients' medical history, medication contraindications, clinical monitoring for side effects, and follow-up care might be beyond pharmacists' or mobile testing sites' scope, training, and capacity [8, 31]. Possible individual-level barriers to a prescription include patient access to testing, prescribers, and dispensing sites [20]. In addition, patients' concern about utilization, not perceiving oneself to be at high risk for severe COVID-19 [32], and believing they can recover quickly even without an antiviral might be the reasons for low antiviral uptake.

Health care disparities throughout the COVID-19 pandemic have been observed, specifically impacting people of color and those who are socioeconomically disadvantaged [22, 33–36]. Inequitable uptake of antivirals among those who are more vulnerable or experiencing a greater burden of severe COVID-19 disease may further exacerbate disparities that have been observed in COVID-19 morbidity and mortality. The Test to Treat initiative aims to reach communities that have been hardest hit by the COVID-19 pandemic [18]. However, similar to a NYC population-based study [25] and a US health system population-based cohort study of NMV/r uptake [26], we observed the lowest antiviral uptake among Black non-Hispanic participants (relative to other race/ethnic groups) and those in the lowest income groups (relative to higher income groups). Previously, we reported that Black non-Hispanic participants have more barriers to health care than White non-Hispanic participants in our national cohort, which may contribute to lower antiviral uptake [22].

The highest uptake of NMV/r in our study was among those aged 65 and over (30.2%; 95% CI, 22.2%–38.2%), which is similar to a study conducted in Massachusetts and New Hampshire, whereby a greater proportion of NMV/r users were >65 years old (54.5% vs 38.1%; $P < .001$) [21]. Higher uptake among the older adult population is encouraging, given that breakthrough SARS-CoV-2 infections and hospitalizations and COVID-19-related mortality are more likely to occur among the older adult population [24]; however, only a third of the eligible participants with SARS-CoV-2 infection in our study over 65 years received NMV/r. These findings suggest the need for awareness and education strategies targeting the vulnerable populations who can most benefit from SARS-CoV-2 antivirals.

Participants with a self-reported history of long COVID reported higher NMV/r uptake than those with a history of infection who did not report long COVID. This finding suggests that individuals with a history of long COVID may be more proactively seeking health care treatment. Though there is no experimental evidence of antivirals' effectiveness in easing long COVID symptoms, experimental trials have started [37, 38], and one cohort study using the health care databases of the US Department of Veterans Affairs found that NMV/r uptake was associated with a 26% reduced risk of long COVID [39].

The patient-reported outcomes suggest that NMV/r was helpful for reducing acute COVID symptoms, reported among 63% (95% CI, 57%–70%) of our mostly vaccinated study participants, which is consistent with other observational studies [11, 26]. Though randomized clinical trials found a

nonsignificant 57% reduction in hospitalization and death in NMV/r-treated vaccinated individuals with at least 1 risk factor for severe COVID-19 [40], observational studies with patient-reported outcomes on symptom relief could potentially help providers and patients understand more about whether they might benefit from antivirals [26].

Our study has several limitations. We included all SARS-CoV-2 infections that occurred since December 2021 in the denominator for assessing uptake. However, some of the individuals infected in December (n = 117) may not have been eligible for antivirals as EUA approval occurred on December 22, 2021 [41]. The findings remained consistent after removing infections that occurred in December 2021 in sensitivity analyses. In addition, as our cohort participants tend to be more socioeconomically advantaged compared with the general US population, the antiviral uptake in the general US population may be even lower. The sample of participants with SARS-CoV-2 infection and reporting antiviral uptake was small in some subgroups, which reduced the precision of estimates of uptake in stratified analyses (eg, race/ethnicity, education, comorbidity). Information on perceived reduction of COVID-19 symptoms of NMV/r was missing for 35 (16% of 216) NMV/r users, further reducing the sample size for that analysis. The sample size of participants reporting MOV was small; therefore, we were unable to draw detailed conclusions or estimate adjusted prevalence ratios for MOV. We did not capture information on all antiviral eligibility criteria, such as some comorbidities (eg, cerebrovascular disease, disabilities, cystic fibrosis, dementia), nor did we collect medication information to be able to assess contraindicated concomitant medications (eg, drugs that are primarily metabolized by CYP3A [42]). This may result in underestimation of the proportion of participants who were eligible for SARS-CoV-2 antivirals. Imperfect recall of SARS-CoV-2 infection timing, vaccination status, or other data (eg, symptom recall) may impact the accuracy or classification of the temporal sequence of events.

Despite proven effectiveness against severe outcomes of NMV/r [8–11, 14, 15] in a geographically and sociodemographically diverse national cohort of highly vaccinated adults, NMV/r and MOV uptake were low among eligible participants with a SARS-CoV-2 infection. Because of the community-based nature of our cohort, antiviral uptake measured in our study is likely lower than studies of SARS-CoV-2 patients who present to a health care facility for testing. Disparities in uptake were observed by racial/ethnic group and income level. Although antiviral uptake increased over time, coinciding with national outreach efforts, the highest uptake of NMV/r reported was only about one-third of eligible participants, even among those 65 years and older. Despite low uptake, among participants prescribed NMV/r, the majority reported that the antiviral was helpful for reducing symptoms. Our findings suggest that additional outreach strategies to providers and patients to increase awareness of antiviral medication and reduce COVID-19 disparities and barriers to health care and antiviral access are important given the continued burden of preventable COVID-19 deaths and the demonstrated benefit of NMV/r.

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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Patient consent. Informed consent forms were completed in a web browser on participants' computers or mobile devices at baseline, at each round of serological testing, and at periodic follow-up assessments. The study was approved by the Institutional Review Boards of the City University of New York (CUNY) Graduate School of Public Health and Health Policy (New York, NY, USA; protocol 2020–0256).

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