Letters

RESEARCH LETTER

Internet Searches for Unproven COVID-19 Therapies in the United States

There are no highly effective prescription drug therapies supported by any reliable evidence for the ongoing coronavirus disease 2019 (COVID-19) pandemic of severe acute respiratory syndrome coronavirus 2. However, fears among the public can lead to searches for unproven therapies. Therefore, when several high-profile figures, including entrepreneur Elon Musk and President Donald Trump, endorsed the use of chloroquine, a malarial prophylaxis drug, and hydroxychloroquine (with the antibiotic azithromycin), a lupus and rheumatoid arthritis treatment, to treat COVID-19, it drew massive public attention that could shape individual decision-making.

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This attention is especially troublesome because chloroquine and hydroxychloroquine (1) are thus far only known to inhibit severe acute respiratory syndrome coronavirus 2 in vitro,[1] (2) have potential cardiovascular toxic effects,[2] and (3) can be confused with commercially available chloroquine-containing products, such as aquarium cleaner. Poisonings, including 1 fatality, attributed to persons taking chloroquine to prevent or treat COVID-19 without the supervision of a licensed physician have already been reported.[3] To better understand the scope of demand for these drugs, we examined internet searches indicative of shopping for chloroquine and hydroxychloroquine.[4]

Methods | The fractions of Google searches (http://google.com/trends) originating from the United States that included the terms *buy*, *order*, *Amazon*, *eBay*, or *Walmart* (the latter being the top 3 e-commerce companies) in combination with *chloroquine* or *hydroxychloroquine* per 10 million total searches were monitored. Raw search volumes were inferred using Comscore estimates (https://comscore.com).

We examined daily searches from February 1, 2020, to March 29, 2020, using the date Musk endorsed the drugs on March 16 as the cut point for when knowledge of using chloroquine and hydroxychloroquine became widespread to compare observed search volumes with expected search volumes. We evaluated 2 postperiods of interest: (1) all days after March 16 (the entire period, including when President Trump first endorsed these drugs on March 19) and (2) all days after March 22 (when news reports on chloroquine-related poisonings were published). Expected volumes were calculated using Hyndman and Khandakar's algorithm,[5] and the ratio of observed and counterfactual volumes with bootstrap confidence intervals were computed using R Software, version3.6.3 (R Foundation for Statistical Computing).

Results | The query fraction (QF) of Google searches per 10 million for purchasing chloroquine on February 1, March 16, March 22, and March 29 were 4.78 (equivalent to 542 estimated searches), 26.90 (3052 estimated searches), 66.16 (7506 estimated searches), and 19.19 (2177 estimated searches), respectively. The QFs for purchasing hydroxychloroquine on February 1, March 16, March 22, and March 29 were 4.35 (494 estimated searches), 7.68 (871 estimated searches), 79.37 (9006 estimated searches), and 31.95 (3625 estimated searches), respectively. Queries for purchasing chloroquine were 442% (95% CI, 215%-1220%) higher following high-profile claims that these drugs were effective COVID-19 therapies (**Figure 1**). Similarly, searches for purchasing hydroxychloroquine were 1389% (95% CI, 779%-2021%) higher (**Figure 2**). The first and largest spike in searches corresponded directly with Musk's tweet and Trump's first televised endorsements, respectively, with the latter occurring on March 19 (chloroquine QF, 249.58 [28 319 estimated searches]; and hydroxychloroquine QF, 179.00 [20 311 estimated searches]). These changes represent about 93 000 and 96 000 more searches than expected for chloroquine and hydroxychloroquine, respectively, with 216 000 total searches for both drugs over just 14 days.

Following news reports of the first fatal poisoning, searches to buy chloroquine or hydroxychloroquine remained substantially above expected levels at 212% (95% CI, 66%-1098%) and 1167% (95% CI, 628%-1741%) higher, respectively.

Discussion | Demand for chloroquine and hydroxychloroquine increased substantially following endorsements by high-profile figures and remained high even after a death attributable to chloroquine-containing products was reported. In times of public health crises, therapies not supported by adequate evidence—such as would lead to US Food and Drug Administration approval—should not be touted by public figures. Endorsements can lead to unsupervised use of the products with dangerous consequences to the people who take them, and hoarding of these medications can result in shortages for those who require them for legitimate health reasons. These negative consequences are magnified in this circumstance because chloroquine-containing products are commercially available to the public through such sites as Amazon.

Findings about the clinical efficacy of chloroquine and hydroxychloroquine were inconclusive at the time these drugs were promoted.[6] Until such time as these or other drugs are found to be effective for COVID-19 treatment, regulatory agencies and public-facing companies should be actively mitigating the negative consequences of this misinformation. The US Food and Drug Administration should warn the public against procuring unapproved therapies unless prescribed. Google responded to COVID-19 by integrating an educational website into search results related to the outbreak, and this could be expanded to include searches for unapproved COVID-19 therapies. Similarly, retailers must establish warnings or withhold

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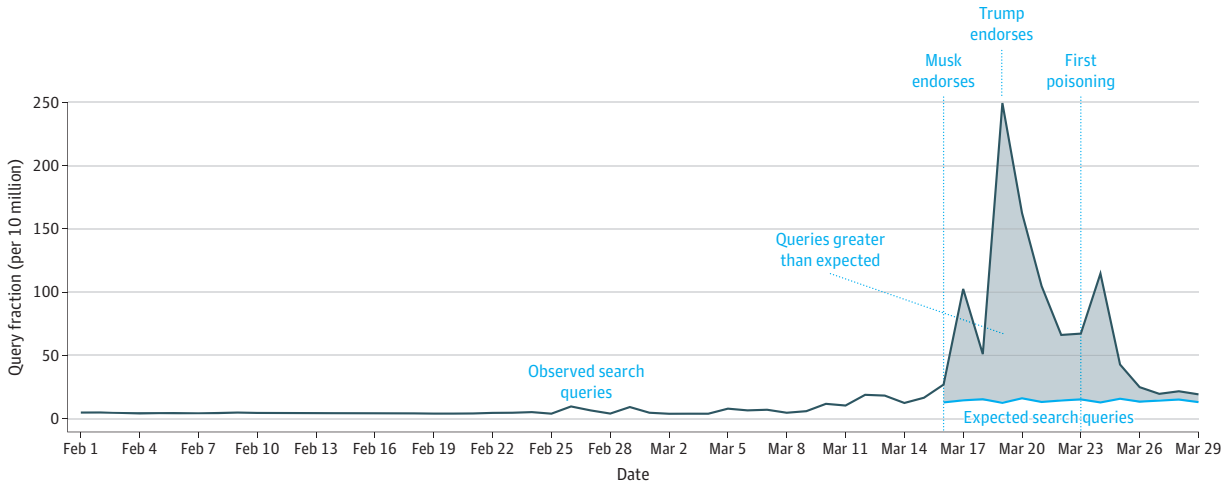
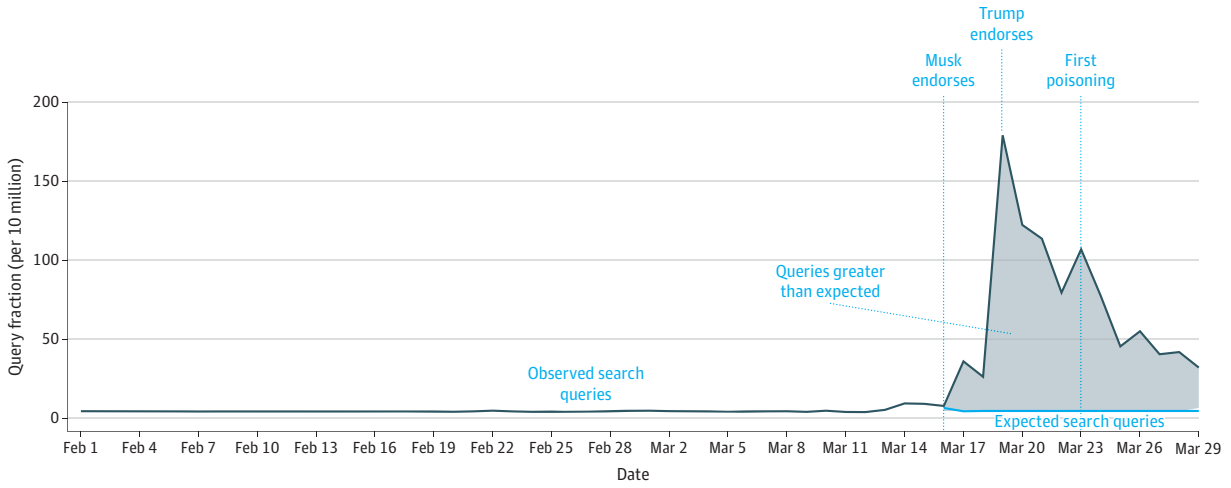
Figure 1. Internet Searches for Purchasing Chloroquine



Queries included *chloroquine* in combination with *buy*, *order*, *Amazon*, *eBay*, or *Walmart* (the latter being the top 3 e-commerce companies). The first dotted vertical line corresponds to entrepreneur Elon Musk's tweet on March 16, the second corresponds to President Donald Trump's endorsement on March 19, and the third corresponds to the first reported chloroquine poisoning on March 23.

Figure 2. Internet Searches for Purchasing Hydroxychloroquine



Queries included *hydroxychloroquine* in combination with *buy*, *order*, *Amazon*, *eBay*, or *Walmart* (the latter being top 3 e-commerce companies). The first dotted vertical line corresponds to entrepreneur Elon Musk's tweet on March 16, the second corresponds to President Donald Trump's endorsement on March 19, and the third corresponds to the first reported chloroquine poisoning on March 23.

products that might be linked to use for COVID-19 treatment, as was exemplified by eBay's removing chloroquine sales from its site.

Additional surveillance will clarify this study's findings, including estimating the number of sales of chloroquine-containing products. Nonetheless, the present analysis suggests that in times of public health crises, demand for unproven and potentially hazardous COVID-19 treatments is massively increased by endorsements. Public health leaders, regulatory agencies, media, and retailers must amplify accurate information.

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Disclaimer: The content of this article is solely the responsibility of the authors and does not necessarily reflect the position or policy of their employers and collaborating institutions.

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Editor's Note

The Risks of Prescribing Hydroxychloroquine for Treatment of COVID-19—First, Do No Harm

On March 21, 2020, President Donald Trump tweeted that hydroxychloroquine and azithromycin have "a real chance to be one of the biggest game changers in the history of medicine."[1] The president later said of hydroxychloroquine, "What do you have to lose? I'll say it again: What do you have to lose? Take it."[2]

Although the president acknowledged that physicians should be involved in the decision to use these medications, the message to patients with coronavirus disease 2019 (COVID-19), and people worried about becoming infected, was clear. Within days, a man in Arizona died after ingesting a chloroquine-containing aquarium product that did not require a prescription.[3] Federal regulators facilitated use of prescription hydroxychloroquine and chloroquine by immediately issuing an Emergency Use Authorization.

One way of quantifying the influence of these high-profile statements is to examine internet search behaviors. In this issue of *JAMA Internal Medicine,* Liu and colleagues[4] examined internet searches for purchasing chloroquine or hydroxychloroquine online. From March 16 to 29, 2020, searches increased 442% and 1389% for chloroquine and hydroxychloroquine, respectively, compared with the preceding 6 weeks.

Although testing of hydroxychloroquine for treatment of COVID-19 is underway, available data do not support its widespread use. The study[5] referenced by President Trump may have methodologic flaws. A small randomized trial suggesting benefit was unblinded, and some patients received concomitant steroids or antivirals.[6] Nevertheless, some physicians have begun prescribing hydroxychloroquine widely, which prompted at least 12 states to pass emergency prescribing restrictions.

The potential harms are substantial. Hydroxychloroquine is QT prolonging, which poses a risk of sudden cardiac death in certain populations. People with autoimmune conditions, disproportionately women and people of color, could face disease flares owing to medication shortages.[7] The burden may fall hardest on the most vulnerable; low-income patients worldwide could be the first to lose access to hydroxychloroquine therapy.

Given the toll of COVID-19, the pressure to *do something* is enormous and understandable. But that must not prompt clinicians to jettison the tenets of evidence-based medicine and the admonition to *do no harm*. As health care providers, we should inform patients about the evidence behind experimental therapies, work to enroll patients in randomized clinical trials, and consider the needs of patients without COVID-19 who may be affected by drug shortages. It is vital that we do not give in to nonevidence-based calls to embrace unproven therapies. Although we may be tempted to bypass enduring principles in this time of uncertainty and fear, the best way to protect patients is to stay grounded in evidence and to fight misinformation.

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Change in Traffic Fatality Rates in the First 4 States to Legalize Recreational Marijuana

Marijuana use impairs driving,[1] but researchers have not yet conclusively determined if a state's legalizing recreational marijuana is associated with traffic fatality rates. Two early studies reported no significant change in roadway deaths following legalization in Colorado and Washington,[2,3] whereas a study including Oregon reported a temporary increase.[4] A more recent study, including 2017 data, found a statistically significant increase in fatal crashes only after commercial stores opened, suggesting that the effect of legalization may take more time to observe.[5]

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Following the recent release of 2018 roadway fatality reports by the US Department of Transportation, we analyzed data from more states over a longer period of commercial sales to get a better understanding of the relationship between legalization of recreational marijuana and traffic fatalities.

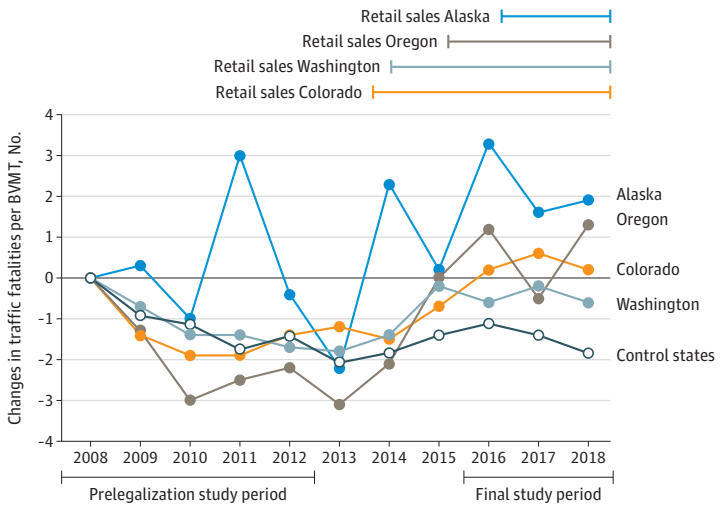
Methods | Traffic fatality rates were obtained from the National Highway Traffic Safety Administration's Fatality Analysis Reporting System.[6] The first 4 states to legalize recreational marijuana (Colorado, Washington, Oregon, and Alaska) comprised the experimental group. These states are the only ones for which there are at least 2 full years of traffic fatality data available following the opening of retail stores. All 20 states that did not legalize recreational or medical marijuana as of the beginning of 2018 served as controls.

First, parallel fatality trends in both groups of states during the 18 years preceding legalization were confirmed by graphing and inspecting the data. Then, we performed a difference-in-difference analysis with a random effects model to compare the change in traffic fatality rates between the 2 groups from the prelegalization to the postcommercialization period. The prelegalization panel data were from the 5 years preceding legalization in any state (2008-2012), and the postcommercialization data were from the years that included commercial sales in all 4 experimental states (2016-2018). Unemployment rate, maximum speed limit, and presence of a primary seatbelt law were included as covariates. We calculated our estimates using the xtreg function in Stata MP statistical software (version 16.0, StataCorp). Robust standard errors were used to generate confidence intervals. Data were analyzed from December 22, 2019 to February 29, 2020. Because the study used deidentified publicly available data, no review board approval was needed.

Results | The changes in fatality rates for the control group and each experimental state are displayed in the **Figure**. Our unadjusted difference-in-difference analysis showed an increase of 2.1 (95% CI, 1.2-2.9; $P < .001$) traffic fatalities per billion vehicle miles traveled (BVMT) in experimental states relative to control states in the postcommercialization study period. Including covariates, the increase was 2.1 (95% CI, 1.3-3.0; $P < .001$) traffic fatalities per BVMT.

Discussion | By analyzing additional experimental states over a more recent time period, we have provided additional data

Figure. Change in Traffic Fatality Rate From 2008



BVMT indicates billion vehicle miles traveled. Rates are indexed to 2008. Data points represent the change in the annual traffic fatality rate since 2008 for each experimental state and the 20-state control group mean. Colorado and Washington voted to legalize recreational marijuana in November 2012. Retail stores opened in January and July of 2014, respectively. Oregon and Alaska voted to legalize in November 2014. Retail stores opened in October 2015 and October 2016, respectively.

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