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Outpatient purchasing patterns of hydroxychloroquine and ivermectin in the United States and Canada during the COVID-19 pandemic: an interrupted time series analysis from 2016 to 2021

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Abstract

Background: Hydroxychloroquine and ivermectin received widespread attention after initial studies suggested that they were effective against COVID-19. However, several of these studies were later discredited.

Objectives: We explored the impact of scientific articles, public announcements, and social media posts on hydroxychloroquine and ivermectin purchases in the U.S. and Canada during the COVID-19 pandemic.

Methods: We conducted a retrospective, population-based time series analysis of retail hydroxychloroquine and ivermectin purchases in the U.S. and Canada from February 2016 through December 2021, using IQVIA's Multinational Integrated Data Analysis database. We fit the purchasing rates with interventional autoregressive integrated moving average models. We used Google Trends to identify the most influential interventions to include in the models.

Results: There were significant pulse increases in hydroxychloroquine purchases in March 2020 in both the U.S. ($p < 0.0001$) and Canada ($p < 0.0001$). For ivermectin, there were no significant changes in April 2020 in either the U.S. ($p = 0.41$) or Canada ($p = 0.16$); however, significant pulse increases occurred from December 2020 to January 2021 in both the U.S. ($p = 0.0006$) and Canada ($p < 0.0001$), as well as significant ramp increases from April to August 2021 in both the

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U.S. ($p < 0.0001$) and Canada ($p = 0.02$). The increases in ivermectin purchases were larger in the U.S. than in Canada.

Conclusions: Increases in hydroxychloroquine and ivermectin purchasing rates aligned with controversial scientific articles and social media posts. This highlights the importance of scientific integrity and disseminating accurate epidemiologic information during pandemics.

1. Introduction

Coronavirus disease 2019 (COVID-19) has been the subject of considerable scientific research and media attention. New agents for prevention or treatment take time to develop, and therefore much interest in the early parts of the pandemic was focused on the potential for drug repurposing for off-label use. In 2020 and 2021, speculation that hydroxychloroquine and ivermectin may prevent or treat COVID-19 led to their increasing popularity across North America despite a lack of rigorous data supporting their use.[1–3] As additional evidence emerged that called into question the effectiveness of hydroxychloroquine and ivermectin, several of the initial studies were discredited.[4,5]

Hydroxychloroquine is an antimalarial and antirheumatic drug that showed early potential against COVID-19 by inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *in vitro*.[6,7] In March 2020, a small, non-randomized study suggested that it reduced viral load in COVID-19 patients.[8] Then-President of the United States (U.S.) Donald Trump endorsed hydroxychloroquine, referencing this study.[9] The U.S. FDA subsequently issued an emergency use authorization for hydroxychloroquine in COVID-19.[10] However, there were soon reports of serious arrhythmia from its use.[11] When the interim results of several large randomized controlled trials showed no benefit in mortality in June 2020,[12–14] the FDA revoked the emergency use authorization.[10]

By contrast, the timeline of events for ivermectin was relatively protracted. Ivermectin is an antiparasitic drug that also showed early potential by inhibiting SARS-CoV-2 *in vitro*.[15] While some observational studies, randomized controlled trials, and meta-analyses reported its efficacy in COVID-19 patients throughout 2020 and 2021,[16–25] concerns were raised in late 2021 about randomization failure and potential fraud among published randomized controlled trials.[5] Several studies were subsequently retracted.[17,20,25] One of these, a meta-analysis, was re-analyzed and found no benefit in survival if high-risk-of-bias studies were excluded.[26]

Neither the FDA nor Health Canada has approved hydroxychloroquine or ivermectin to prevent or treat COVID-19. In fact, both federal regulators have recommended against their use based on results from large randomized controlled trials.[27–30] Nevertheless, over the course of the pandemic, these drugs received widespread attention. Controversial papers led to debate in the scientific community and, through the lay press and social media, influenced public opinion. Although some studies in the U.S. have described early trends in hydroxychloroquine and ivermectin prescribing,[1–3,31] the evidence and public discourse has continued to evolve. There is a great deal of shared media across the U.S.-Canada border, but little is known about how purchasing patterns compare between the two countries. Understanding the impact of scientific and social discourse on drug purchasing is important

for informing the conduct and dissemination of research. This is particularly relevant when considering the health risks of the widespread communication of studies with poor scientific rigour during a pandemic. Therefore, our objective was to evaluate the impact of influential scientific articles, public announcements, and social media posts on purchasing patterns of hydroxychloroquine and ivermectin in the U.S. and Canada.

2. Methods

2.1. Setting

We conducted a retrospective, population-based time series analysis of oral, solid units of hydroxychloroquine and ivermectin purchased in U.S. and Canadian outpatient settings between February 1, 2016 (earliest data available from IQVIA) and December 31, 2021. The start date for ivermectin in Canada was limited to November 2018 because it only entered the Canadian market then.[32] Ethical approval was granted by the University of Pittsburgh Institutional Review Board (Ref. STUDY21060160).

2.2. Data sources

We obtained the monthly outpatient purchase quantities of hydroxychloroquine and ivermectin using IQVIA's Multinational Integrated Data Analysis (MIDAS) database (Parsippany, NJ, USA). We restricted the data to oral, solid dosage forms, which were reported in units of single tablets for these two drugs. MIDAS includes all drug purchasing data for the U.S. and Canada, regardless of payer, by reporting annual transactions from pharmaceutical manufacturers to wholesaler distribution centers.[33] IQVIA internally validates their data annually against alternate sources through a standardized quality assurance program.[33] Data capture was 97% in the U.S. and 100% in Canada. We used monthly population estimates from the U.S. Census Bureau and Statistics Canada to population-adjust the drug purchasing data.[34–36] Population data in Canada was only available quarterly, and therefore we used linear interpolation to obtain monthly estimates.

To capture social discourse around these medications, we extracted monthly national web search data from Google Trends for the terms "hydroxychloroquine" and "ivermectin" in all search categories, for the U.S. and Canada, from February 2016 to December 2021. Google Trends creates a score for each month on a scale from 0 to 100, with 100 representing the month of maximum search interest during the study period.[37] This publicly available tool has been used to study social responses,[9,38–40] as well as correlation with prescription patterns,[41] during COVID-19. Finally, we obtained the number of monthly COVID-19 cases for the U.S. and Canada from the Johns Hopkins Coronavirus Resource Center.[42]

2.3. Outcomes

We measured the monthly rates of outpatient purchases of hydroxychloroquine and ivermectin in the U.S. and Canada, per 1000 population. These rates were overlaid against social discourse trends (using Google Trends) and COVID-19 case rates over the same period (see Table S1 for details on the dominant COVID-19 variants of concern during the study period).

2.4. Statistical analysis

For our interrupted time series analyses, we fit the monthly population-adjusted prescription purchasing rates with interventional autoregressive integrated moving average (ARIMA) models. ARIMA models can evaluate the impact of population-level health interventions.[43] We defined our interventions as major scientific articles, public announcements, or social media posts related to each drug. First, we compiled a list of influential articles, announcements, and posts about hydroxychloroquine or ivermectin from the literature and lay media; then, we plotted the Google Trends time series and used the peaks to identify the most influential interventions. All identified interventions are outlined in Tables 1 and 2. In cases where multiple interventions occurred in quick succession, we selected the date of the first intervention to fit in the models. We included pulse or ramp transfer functions to test for temporary or gradual changes, respectively, in purchasing rates after each intervention. A pulse function models a sudden change that returns to baseline afterwards. A ramp function models a gradual change that increases in magnitude linearly over time.

For each ARIMA model, we used differencing terms and the augmented Dickey-Fuller test to induce and confirm stationarity as well as seasonality. Seasonality refers to predictable fluctuations in rates that follow a repeated pattern, generally annually. Next, we selected model parameters using the autocorrelation function (ACF), partial autocorrelation function (PACF), and inverse autocorrelation function (IACF) plots. We chose the final model based on residual autocorrelation plots and the Ljung-Box chi-square test for white noise. Statistical analyses were conducted using SAS (Enterprise Guide 7.1, SAS Institute, Cary, NC) and a type 1 error rate of 0.05. To allow better visualization of interventions, we reported figures as of November 2018 (when ivermectin was first marketed in Canada). However, all ARIMA models were fit using the full data from February 2016 onwards.

3. Results

3.1. Hydroxychloroquine

During our study period from February 2016 to December 2021, U.S. outpatient pharmacies purchased 2,375,171,700 hydroxychloroquine tablets (average U.S. population 327,597,465; approximately 7 tablets per person over the entire study period), while Canadian outpatient pharmacies purchased 376,727,700 tablets (average Canadian population 37,255,419; approximately 10 tablets per person over the entire study period).

Prior to March 2020, the monthly rate of U.S. hydroxychloroquine purchases ranged from 72 to 114 tablets per 1000 population. In March 2020, hydroxychloroquine was shown to inhibit SARS-CoV-2 *in vitro*,[6,7] appeared to reduce viral load in COVID-19 patients,[8] and was endorsed by then-President Trump.[9] That month, we observed a significant pulse change in the purchasing rate (increase of 117.50 tablets per 1000 population; 95% CI 102.03–132.97; $p < 0.0001$; Table 3), with the rate peaking at 231 tablets per 1000 population before returning to earlier trends in May 2020 (Figure 1A). The pattern was similar in Canada; prior to March 2020, the monthly rate of hydroxychloroquine purchases ranged from 119 to 151 tablets per 1000 population. In March 2020, there was also a significant pulse change in purchasing rate (increase of 111.55 tablets per 1000 population;

95% CI 95.60–127.50; $p < 0.0001$; Table 3), with the rate peaking at 246 tablets per 1000 population before returning to earlier trends in April 2020 (Figure 1B). Across both countries, there was a large spike in Google Trends in March and April 2020, and a smaller spike in July 2020. The purchasing spikes in March 2020 were aligned with the first COVID-19 case wave for both countries, but subsequent trends were not.

3.2. Ivermectin

During our study period, U.S. outpatient pharmacies purchased 54,239,000 ivermectin tablets (approximately 0.2 tablets per person over the entire study period), while Canadian outpatient pharmacies purchased 354,164 tablets (approximately 0.01 tablets per person over the entire study period).

The results of the interrupted time series analysis were consistent across countries. In April 2020, after Caly *et al.*'s *in vitro* study and Patel *et al.*'s multinational registry analysis, there was no significant pulse change in monthly purchasing rate in both the U.S. (increase of 0.85 tablets per 1000 population; 95% CI −1.17–2.87; $p = 0.41$) and Canada (increase of 0.07 tablets per 1000 population; 95% CI −0.03–0.16; $p = 0.16$). In December 2020 and January 2021, after Elgazzar *et al.*'s pre-print, we observed a significant pulse change in rate of ivermectin purchasing in the U.S. (increase of 6.16 tablets per 1000 population; 95% CI 2.66–9.65; $p = 0.0006$) and Canada (increase of 0.44 tablets per 1000 population; 95% CI 0.36–0.51; $p < 0.0001$). This was followed by a significant ramp change between April and August 2021, when a series of meta-analysis supported ivermectin use for COVID-19, in both the U.S. (increase of 1.94 tablets per 1000 population; 95% CI 1.11–2.75; $p < 0.0001$) and Canada (increase of 0.02 tablets per 1000 population; 95% CI 0.003–0.04; $p = 0.02$) (Table 3). Purchasing rate trends mirrored the Google Trends and COVID-19 case rate trends across both countries. Despite similarities in responses to interventions across the U.S. and Canada, the population-adjusted rates of ivermectin purchasing differed considerably between the countries. Specifically, the monthly rate of ivermectin purchases reached a high of 30 tablets per 1000 population in the U.S. (August 2021), compared to a high of 0.8 tablets per 1000 population in Canada (January 2021; Figure 2; Figure S1).

4. Discussion

In this large study comparing the U.S. and Canada, we observed significantly increased outpatient purchasing rates of hydroxychloroquine and ivermectin during the COVID-19 pandemic. For hydroxychloroquine, despite initially increased sales associated with early announcements and publications, later reports of serious arrhythmia and negative interim results from several large randomized controlled trials appeared to swiftly return purchasing rates to baseline levels. By contrast, ivermectin had protracted increases in sales tied to COVID-19 case counts and publications supporting ivermectin's efficacy, despite the later retraction of several of these articles due to concerns of fraudulent data.

The way in which scientific evidence emerged may explain the differences between hydroxychloroquine (abrupt, short-term increase) and ivermectin (gradual, more sustained increase) purchasing trends. As suggested by Englund *et al.*,[9] interest in hydroxychloroquine was likely driven by then-President Trump's endorsement. His tweet on March 21, 2020[9]

cited a non-randomized study by Gautret *et al.* which has been criticized for having numerous issues such as potential confounding, small sample size, and overinterpretation of results.[4,44] This weak evidence base may explain why, upon reports of serious arrhythmia[11] and results of several large randomized controlled trials that showed no benefit in mortality,[12–14] the hydroxychloroquine pulse quickly dissipated. Unlike hydroxychloroquine, ivermectin was initially supported by randomized controlled trials[17–22] and meta-analyses.[23–25] However, randomized controlled trials by Elgazzar *et al.*[17] and Samaha *et al.*[20] were retracted after concerns of fraudulent data, and there have been concerns of randomization failure in the trial by Niaee *et al.*[5] While the article by Elgazzar *et al.*[17] was associated with higher ivermectin purchases, the highest peak in the U.S. was reached following the series of meta-analyses that incorporated the flawed data.[23–25] Ivermectin purchases declined after Lawrence *et al.*[5] published concerns about the quality of ivermectin trials in September 2021.

Despite the shared media across the U.S.-Canada border, there were differences between the two countries' trends in hydroxychloroquine and ivermectin purchasing. Between-country differences were more apparent for ivermectin than hydroxychloroquine. For ivermectin, after Elgazzar *et al.* posted their now-retracted pre-print in November 2020, we observed a 5-fold increase in purchases in the U.S. compared to a 2-fold increase in purchases in Canada. The U.S. had an even greater increase in purchases after the publication of several meta-analyses supporting ivermectin efficacy starting in April 2021. By August 2021, the U.S. reached 30 tablets sold per 1000 population, versus just 0.5 in Canada. The U.S.'s acceleration to much higher purchasing rates may be tied to the contrasting stances between healthcare bodies and the government regarding inappropriate prescribing. U.S. national healthcare bodies and state medical boards have discouraged ivermectin use for COVID-19.[28,45–48] However, some state legislatures have prohibited disciplinary action against physicians based on COVID-19 prescribing practices, such as in Tennessee and North Dakota.[49] Meanwhile, Canada's message has been more specific and actionable. Canadian national healthcare bodies and regulators have advised Canadians to not use ivermectin for COVID-19, and Health Canada has taken action against ivermectin advertisers.[30,50] Canadian medical, pharmacy, and nursing licensing bodies have also taken strong stances against ivermectin use, and have restricted or suspended licenses due to inappropriate ivermectin prescribing for COVID-19.[51,52] By contrast, between-country differences for hydroxychloroquine were relatively small (a slightly larger increase in March 2020 in the U.S. than in Canada), perhaps because interest only surged for one month, at the start of the pandemic when governments and health agencies were unprepared.

Most previous studies of hydroxychloroquine and ivermectin trends during the COVID-19 pandemic have focused on the first year of the pandemic and used descriptive analytic approaches. Nevertheless, our results are broadly consistent with purchasing and dispensing trends previously reported in the U.S.[1–3,31] as well as India,[53] Germany,[54] and Australia.[55] Unlike the U.S. and Canada, Latin America experienced a large ivermectin increase at the start of the pandemic, which appeared to be linked to Patel *et al.*'s now-retracted multinational registry analysis in April 2020.[56] This article was cited by researchers, clinicians, and governments in Latin America.[56] It may have influenced the Peruvian and Bolivian governments' decisions to recommend using ivermectin for COVID-19 in

May 2020.[57] This, combined with ivermectin not requiring a prescription[58] and increased production,[57] may explain why ivermectin use increased in Latin America.

There are many lessons to be learned from the increased use of hydroxychloroquine and ivermectin during the COVID-19 pandemic. High demand for these drugs have caused shortages in the U.S. and Canada.[59–61] Shortages place patients who need these drugs for on-label use at risk of uncontrolled disease. This has especially affected patients with lupus and arthritis, who chronically require hydroxychloroquine.[59] There have also been safety concerns. The FDA has noted reports of serious arrhythmia in patients with COVID-19 treated with hydroxychloroquine[11] and there have been large increases in the number of ivermectin poisonings.[46,62] Lastly, people may have been taking these drugs as a substitute for standard care, for example not being vaccinated or not seeking care after contracting COVID-19. This highlights the importance of consistent policies and evidence-based medicine during urgent, widespread public health crises, such as this pandemic. Furthermore, there are opportunities to improve the reporting of emerging research. For example, enhancing the ability for journals to request full disclosure of data for external review and accelerating the peer-review process may help facilitate high-quality, timely publications during crises. Media outlets can play an important role by being prudent with their coverage of pre-prints and emphasizing the uncertainty around findings that have not been peer-reviewed.[63]

The main strength of this study was its use of a large database that comprehensively captured hydroxychloroquine and ivermectin purchases in outpatient settings across the U.S. and Canada. Unlike many previous studies which were descriptive, we used ARIMA modeling to analyze the impact of interventions. These interventions were chosen based on peaks in Google Trends, which reflected surges in social interest of these two drugs. We also had a long follow-up period, until the end of 2021, allowing us to study multiple interventions. However, there were some limitations that require discussion. First, we did not have demographic, social, and clinical data on medication recipients, and thus could not explore variability in trends across ages, gender, vaccination status, or state/province. We also could not distinguish between off-label use of medications for COVID-19 versus on-label use, although the large increases in purchases compared to baseline in the absence of malarial or parasitic outbreaks supports the hypothesis that these were driven by off-label, COVID-19-related use. Second, we did not have data on veterinary ivermectin usage. The FDA received multiple reports of patients who required medical attention after taking veterinary ivermectin[45] meaning that we have likely underestimated the increase in ivermectin usage. Third, there were many competing events that occurred throughout the study period making it difficult to disentangle their individual impacts. For example, a scientific article may have been referenced at various stages of development, including as a pre-print, e-publication, full publication, and as part of a systematic review. Another example was the impact of COVID-19 waves on ivermectin use. Although scientific articles were tied to ivermectin purchasing and discourse trends, so were COVID-19 case rates. This ambiguity made it difficult to conclusively link specific interventions with ivermectin purchasing rates. For hydroxychloroquine, the March-2020 pulse may not only be explained by then-President Trump’s endorsement, but also by the stockpiling behaviour seen for other chronic medications.[54,55,64] However, the rapid increase in purchasing observed was

more dramatic than stockpiling patterns seen with other medications,[65] suggesting additional factors were at play. Finally, we only had purchasing data until December 2021 meaning that we were unable to explore the impacts of more recent interventions, such as the approval of nirmatrelvir/ritonavir (Paxlovid),[66,67] or the publication of the I-TECH and TOGETHER trials which did not support ivermectin use.[68,69] Future work can build on the findings of this study by exploring more recent trends and studying important patient subgroups (e.g. age, vaccination status).

Conclusion

We observed increased outpatient purchases in two purported treatments in the U.S. and Canada during the COVID-19 pandemic. The short-term increase in hydroxychloroquine purchases was associated with then-President Trump's endorsement, while the protracted increase in ivermectin purchases was aligned with the release of flawed scientific articles. Although the trends were similar across both countries, important differences were also present, with the U.S. exhibiting much higher increases in ivermectin purchasing rates compared to Canada. COVID-19 has not just been a pandemic, but also an infodemic that has ensnared primary research, meta-analyses, clinical practice, and health policy. It has reinforced the importance of evidence-based decision making and disseminating accurate information to the public in the face of urgent public health crises.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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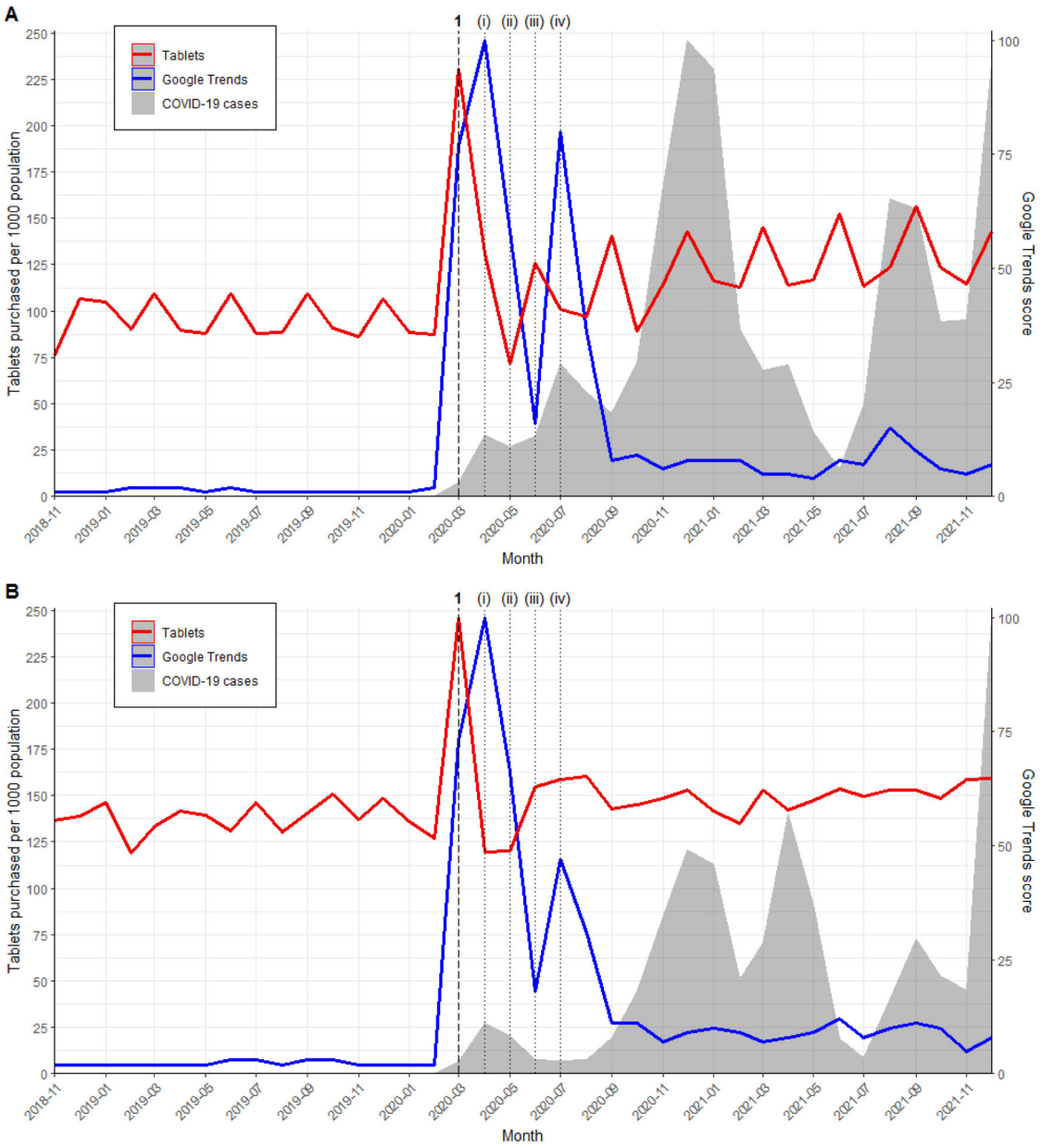

Figure 1. Population-adjusted hydroxychloroquine purchasing rates, Google Trends, and COVID-19 case rates in (A) the United States and (B) Canada.

The Google Trends score ranges from 0 to 100. The y-axes for COVID-19 case rates are not shown, but cases in the U.S. began in January 2020 and peaked in December 2020 (19.8 per 1000 population). COVID-19 cases in Canada began in January 2020 and peaked in December 2021 (11.1 per 1000 population). Vertical lines represent major events such as *in vitro* studies, clinical studies, public announcements, and social media posts (details in Table 1).

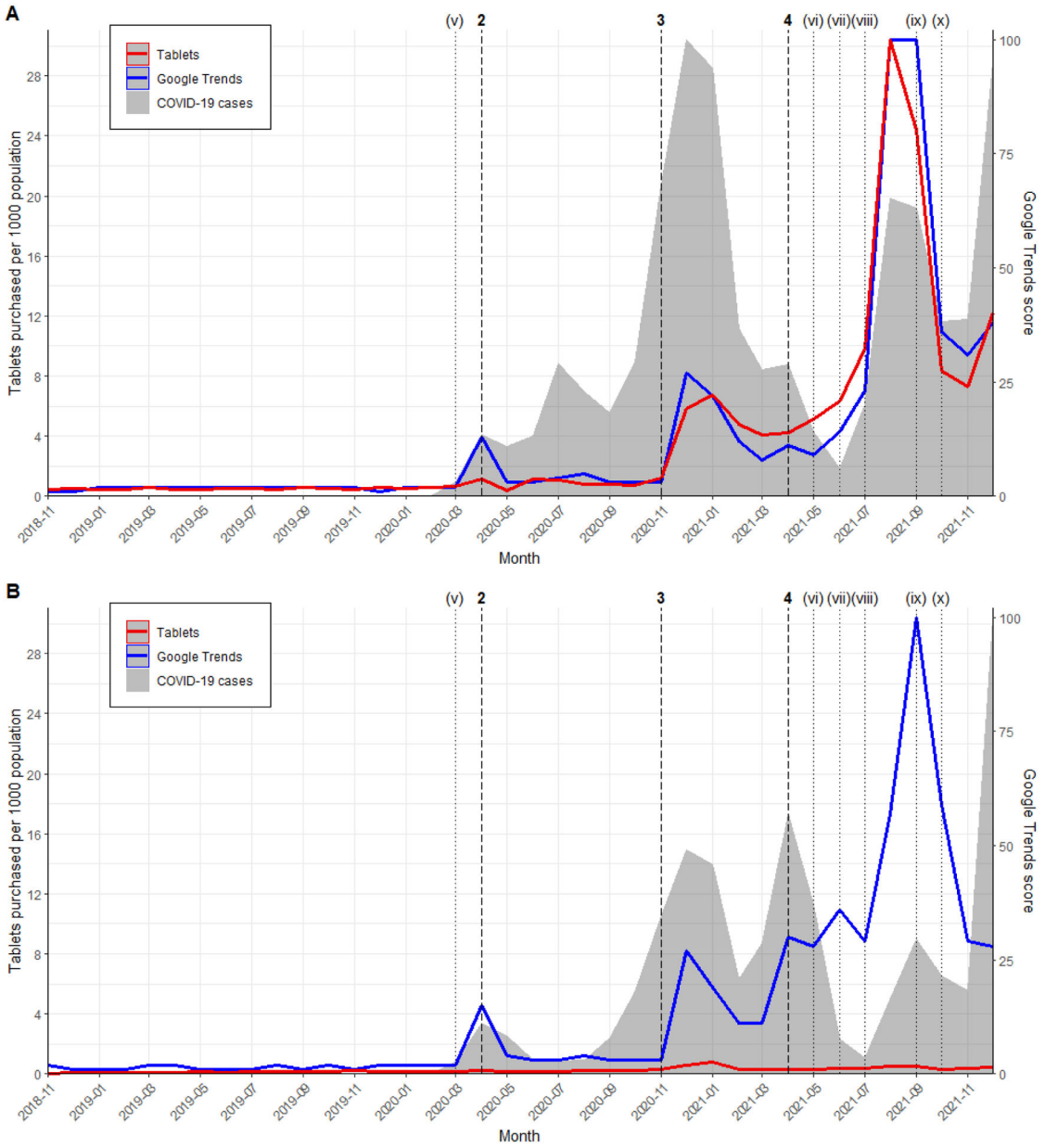

Figure 2. Population-adjusted ivermectin purchasing rates, Google Trends, and COVID-19 case rates in (A) the United States and (B) Canada.

The Google Trends score ranges from 0 to 100. The y-axes for COVID-19 case rates are not shown, but cases in the U.S. began in January 2020 and peaked in December 2020 (19.8 per 1000 population). COVID-19 cases in Canada began in January 2020 and peaked in December 2021 (11.1 per 1000 population). Vertical lines represent major events such as *in vitro* studies, clinical studies, review articles, and public announcements (details in Table 2). Figure S1 in the supplement is an expanded view of Figure 2B.

Table 1.

Major hydroxychloroquine events from the start of the COVID-19 pandemic to December 2021

Intervention in model		Date in 2020		Description
1	Pulse[a]	March	11	The World Health Organization (WHO) declared COVID-19 a pandemic.[70]
			9, 18	Yao *et al.* and Liu *et al.* suggested hydroxychloroquine inhibits SARS-CoV-2 *in vitro*.[6,7]
			19	Then-President Trump endorsed hydroxychloroquine in a White House press briefing.[9]
			20	Gautret *et al.* suggested hydroxychloroquine efficiently clears nasopharyngeal carriage of SARS-CoV-2 in a small, open-label, non-randomized clinical trial.[8]
			21	Then-President Trump cited Gautret *et al.* in a tweet supporting hydroxychloroquine use.[9]
			28	The FDA issued an emergency use authorization for hydroxychloroquine.[10]
(i)	Not included[a]	April	24	The FDA issued a drug safety communication for hydroxychloroquine (reports of serious arrhythmia).[11]
(ii)	Not included[a]	May	18	Then-President Trump said he was taking hydroxychloroquine prophylactically.[9]
			22	Mehra *et al.* suggested hydroxychloroquine increased in-hospital mortality in a large, multinational registry analysis (retracted on June 4).[71]
(iii)	Not included[a]	June	4	Mehra *et al.* retracted their paper because they were unable to independently verify their data set.[72]
			5, 19, 19	Three large randomized controlled trials (RECOVERY, Solidarity, and ORCHID) closed enrolment early because of no observed benefit in mortality.[12–14]
			15	The FDA revoked the emergency use authorization for hydroxychloroquine.[10]
(iv)	Not included[a]	July	27	Then-President Trump tweeted a viral video supporting hydroxychloroquine use that was later removed by major social media platforms.[9]

[a]Major hydroxychloroquine events occurred every month from March to July 2020. It is difficult to model and interpret interventions when there are few or no time points separating them. Hence, we only included the first intervention (March 2020) in the models.

Table 2.

Major ivermectin events from the start of the COVID-19 pandemic to December 2021

Intervention in model		Date in 2020		Description
(v)	Not included	March	11	The World Health Organization (WHO) declared COVID-19 a pandemic.[70]
2	Pulse	April	3	Caly *et al.* suggested ivermectin inhibits SARS-CoV-2 *in vitro*.[15]
			6	Patel *et al.* suggested ivermectin effectively reduces mortality in a multinational registry analysis (pre-print) (retracted for "further analysis" in May – exact date uncertain).[16,56]
3	Pulse (December to January)[a]	November	13	Elgazzar *et al.* suggested ivermectin effectively reduces mortality in a large, randomized controlled trial (pre-print) (version 1 on November 13, version 2 on November 16, version 3 on December 28, 2020, and retracted on July 14, 2021).[17]
Intervention in model		**Date in 2021**		**Description**
4	Ramp (April to August)[b]	April	22	Kory *et al.*'s meta-analysis on ivermectin (which used pre-print data by Elgazzar *et al.* and Niaee *et al.*) suggested large reductions in mortality, time to clinical recovery, and time to viral clearance.[23]
(vi)		May	26	Samaha *et al.* suggested ivermectin reduces symptoms, viral load, and hospital admissions in a randomized controlled trial (retracted on October 26).[20]
(vii)		June	21	Bryant *et al.*'s meta-analysis of ivermectin (which used pre-print data by Elgazzar *et al.* and Niaee *et al.*, and published data by Samaha *et al.*) suggested large reductions in mortality.[24]
			25	Niaee *et al.*'s article was published, which suggested ivermectin reduces mortality in a randomized controlled trial (there have been concerns of randomization failure, though).[5,19]
(viii)		July	6	Hill *et al.*'s meta-analysis of ivermectin (which used data by Elgazzar *et al.*, Samaha *et al.*, and Niaee *et al.*) suggested large reductions in mortality (retracted in 2022; their re-analysis after excluding high risk of bias studies showed no benefit in survival).[25,26]
			14	Elgazzar *et al.*'s pre-print version 3 was retracted by the pre-print platform after concerns of fraudulent data emerged.[17]
			15	The Guardian covered Lawrence *et al.*'s concerns about Elgazzar *et al.*'s study, such as duplicated patient records.[73]
Intervention in model (continued)		**Date in 2021**		**Description**
(viii)	Ramp (April to August)[b]	July	28	Popp *et al.*'s Cochrane systematic review did not support ivermectin use outside of randomized trials.[74]
(ix)	Not included[c]	September	22	Lawrence *et al.*'s letter to Nature Medicine's editor about the Elgazzar *et al.* (potentially fraudulent data) and Niaee *et al.* (potential randomization failure) papers was published.[5]
(x)	Not included[c]	October	26	Samaha *et al.* retracted their paper after it was found that blocks of patient records were duplicated.[75]

[a] Although their first version was posted in November 2020, based on the delayed Google Trends spike, we modeled this pulse from December 2020 (their third and last version was posted on December 28) to January 2021.

[b] We ended the ramp function before September 2021 because Lawrence *et al.*'s debunking article was published that month.

[c] We did not model these events because there were not enough data points after them to know if their effects were sustained.

Table 3.

Results of the interventional ARIMA analyses

	Model 1: Hydroxychloroquine U.S.		**Model 2: Hydroxychloroquine Canada**		**Model 3: Ivermectin U.S.**		**Model 4: Ivermectin Canada**	
ARIMA model	(2,1,0) no intercept		(4,1,1) no intercept		$(2,1,0) \times (0,1,0)_{12}$ no intercept		(2,1,0) no intercept	
Intervention:	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
1 (pulse)[a]	117.50 (102.03, 132.97)	<0.0001	111.55 (95.60, 127.50)	<0.0001	–	–	–	–
2 (pulse)[a]	–	–	–	–	0.85 (−1.17, 2.87)	0.41	0.07 (−0.03, 0.16)	0.16
3 (pulse)[a]	–	–	–	–	6.16 (2.66, 9.65)	0.0006	0.44 (0.36, 0.51)	<0.0001
4 (ramp)[a]	–	–	–	–	1.94 (1.11, 2.75)	<0.0001	0.02 (0.003, 0.04)	0.02

[a]Interventions are described in Tables 1 and 2. Intervention 1 is for hydroxychloroquine, while interventions 2–4 are for ivermectin. Results that are not applicable to the model are marked with a dash (–).