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Tracking the SARS-CoV-2 variants associated with long-COVID in the United States using infodemiology

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Evidence in Context

- Google Trends was used to link SARS-CoV-2 variant surges with U.S. population interest in Long-COVID symptoms.
- Significant Google search increases for Long-COVID were noted during Alpha and Omicron variant surges.
- Joinpoint regression and Jonckheere-Terpstra tests confirmed rising Long-COVID interest with the dominance of some variants in the U.S.
- Results suggest that Delta or Original/wild variants are most likely associated with the occurrence of Long-COVID symptoms.
- Infodemiology can be an effective tool for real-time public health surveillance of the impact of disease outbreaks.

To view Article

Abstract

Background: The COVID-19 pandemic caused profound socioeconomic disruption in addition to claiming millions of lives worldwide. Beyond the infection-related mortality, a chronic and morbid condition known as "Long-COVID" is now getting increasing attention. Scholars and clinicians around the world are still trying to ascertain which COVID-19 variants could be linked with Long-COVID mostly from clinic or healthcare facility-based studies.

Methods: We conducted a nationwide assessment in the U.S. using an Infodemiological analysis to explore COVID-19 variants potentially linked with Long-COVID. Long-COVID search-related data were collected from Google Trends from January 1st, 2020, to January 10th, 2023 (the peak phase of the pandemic in the U.S.). Variants prevalent in this period were analyzed in relation to the searches on Long-COVID.

Results: A total of 2.2 million x 10^7 online searches for Long-COVID were observed during the analytic period. The highest average searches recorded were during the Omicron variant surge followed by the surge of the Alpha variant. Given these findings and reports from clinical studies, Delta or Original/wild variants are most likely associated with the occurrence of Long-COVID symptoms among the U.S population.

Conclusions: Delta or original wild variants may have the highest tendency to cause Long-COVID symptoms in the general public. Additional population-based surveillance studies are needed to validate Infodemiology methods on Long-COVID prevalence and occurrence.

Keywords: *Long-COVID, surveillance, infodemiology, information seeking behavior, search engines*

Introduction

In December 2019, the first case of pneumonia-like symptoms caused by the novel coronavirus SARS-CoV-2 (subsequently termed COVID-19) was detected in China. By March 2020, more than 100,000 cases and 4000 deaths in more than 100 countries had been observed and the World Health Organization (WHO) officially declared the COVID-19 outbreak as a pandemic [1-4]. By the end of 2024, COVID-19 infections claimed more than a million lives in the U.S. and more than 7 million lives worldwide.

Beyond the widespread mortality, it is estimated that more than 700 million individuals have been infected with COVID-19 globally by the end of 2024 [3, 4]. It is now well established that since the declaration of the pandemic in 2020, multiple COVID-19 variant strains emerged, as SARS-CoV-2 has consistently mutated throughout the pandemic [5, 6]. The original virus has been replaced by several variants over the past four years, but five major global variants of concern (VOC) have been identified so far (i.e., Alpha, Beta, Gamma, Delta, and Omicron). Additional variants of interest (VOI) include Epsilon (B.1.427 and B.1.429); Kappa (B.1.617.1); Zeta (P.2); Theta (P.3); Eta (B.1.525); Iota (B.1.526); Lambda (C.37) and Mu (B.1.621) [7, 8]. In the U.S, the variants that caused widespread surges in infection and became dominant variants during these surges were SARS-CoV-2 original, Alpha, Delta, Omicron (and the subvariants of omicron such as BA.2, BA.4, and BA.5) [8-10].

A major problem for survivors of COVID-19 infections now being discussed worldwide is Long-COVID [5, 8, 11-14]. As per the U.S. CDC, this condition can be broadly defined as signs, symptoms, and conditions that continue or develop after acute COVID-19 infection with features of these post-COVID conditions lasting for weeks, months, or even years [11]. The WHO defines Long-COVID more specifically as the continuation or development of new symptoms lasting for at least two months with no other explanation and beginning around three months after the initial SARS-CoV-2 infection [12]. Aiyegbusi and colleagues identified the 10 most common symptoms of Long-COVID as fatigue or myalgia, cough or dyspnea, joint or chest pain, altered smell or taste, headache, or diarrhea [13]. More recently, a comprehensive global review found that among 113 biomarkers from 28 studies, 69.9% (n=79) of the biomarkers were significantly increased, 25.7% (n=29) were decreased, and 4.4% (n=5) required further evaluation in those with Long-COVID [14]. The definitions, diagnostic criteria, and treatment guidelines for Long-COVID are still evolving [13-16]. Simultaneously, many healthcare facility-based studies and reviews have explored the association of Long-COVID symptoms with different variants of COVID-19 [15-18]. However, there is a lack of clarity among these studies on which variants could be associated with Long-COVID. Furthermore, as these are mostly healthcare facility-based studies of observations of individuals reporting Long-COVID symptoms, they are prone to biases (e.g. selection). Population-based studies from individuals experiencing Long-COVID symptoms without being hospitalized or actively being treated by a healthcare provider are needed to understand the broader scope of Long-COVID. Thus, the purpose of our analysis was to evaluate online information-seeking behavior among the general population of Americans on Long-COVID over time. Also, we investigated these Long-COVID-related online searches in proximation with the dominance of different variants of COVID-19 in the U.S. to understand if certain variant surges led to higher interest in the term Long-COVID. The technique used was Infodemiology, which has not yet been used to explore Long-COVID information-related interest among the general public in the U.S. Infodemiology is a technology-driven strategy for the assessment of the distribution of consumer information seeking in electronic mediums such as the Internet. Infodemiology methods explore consumer information-seeking behaviors on the internet to guide surveillance, inform public health practice, and develop public policies. During the COVID-19 pandemic, Infodemiology was used extensively to analyze the public's consumption of information from the Internet to monitor and predict public health issues and trends [6, 19, 20, 21].

Methods

For this investigation, we utilized the application programming interface of Google Health Trends (GHT-API). This is a novel approach to obtaining raw Google searches in a short search session without restrictions on the search volume index. Detailed methodological approaches to accessing data through GHT-API have already been published elsewhere [19-23]. From the Google Trends website, we collected multiple samples of '*Long Covid* + *Post Covid*' daily search data in the U.S. from January 1, 2020, to January 10, 2023, and averaged them to obtain better estimates of their true values. The GHT-API provides an estimated probability scale of the search scale of 10 million for readability [20-22]. Data collected were stratified according to COVID-19 variant timelines provided by the CDC [1,9]. We analyzed the data by plotting a line chart to describe the 'Long Covid' Google search trends in the U.S. following the COVID-19 variant timelines. A conservative approach (i.e., the Jonckheere-Terpstra test) was used to determine whether there were statistically significant trends in 'Long Covid' Google searches over time. Python 3.11.0 was used to obtain GH-API data and SPSS software was used for data processing and analysis. Ethical clearance

Was not required as no human subjects participated in this study, consent was not required, and data from Google was used to understand population searches for various terms on the internet.

Results

Figure 1 shows the temporal trends in 'Long Covid' online searches from the first case of COVID-19 in the U.S. to January 10th, 2023, as well as the timeline for the dominance of COVID-19 variants. During the study period, a total of 2,258,421.3 x 10^7 online searches were recorded, and the highest average number of Google searches were recorded during the surge of the Omicron variant (3800.1 x 10^7), followed by the surge of the Alpha variant (2470.7 x 10^7). The lowest number was recorded during the beginning of the pandemic (1543.6 x 10^7).

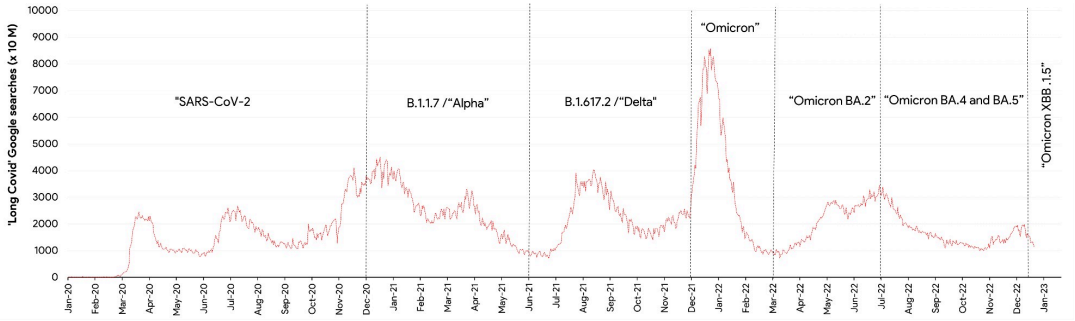

Figure 1: Long Covid searches on Google Corresponding with COVID-19 Variant Dominance in the United States, 2020-2023

Table 1 demonstrates the trend analysis of online searches for 'Long Covid' during the surge of different variants of COVID-19. During the study period, the average online searches for 'Long Covid' increased significantly from 0.0 to 8558.5 and the Johckheere-Terpstra trend analysis found that there were statistically significant trends of higher searches related to 'Long Covid' with changing variants of COVID-19 (T_{JT} = 288,782.0, z = 5.770, p<.001). There was a significant 'Long Covid' search trend change observed during the early COVID-19 variant (Z_{TJ} = 13.008, p<.001), Alpha variant (Z_{TJ} = 9.639, p<.001), and Omicron variant (Z_{TJ} = 5.389, p<.001) surges.

Table 1: Trends analysis for Long COVID Google searches from 2020 – 2023

	Long Covid (mean ± SD)	Minimum	Maximum	TJT	ZJT	P-value
Overall	2041.9 (1312.8)	0.0	8558.5	288782.0	5.770	<.001
SARS-CoV-2	1543.6 (1110.4)	0.0	4494.9	20510.0	13.008	<.001
Alpha variant	2470.7 (791.5)	881.1	4403.5	42921.0	9.639	<.001
Delta variant	2074.4 (923.1)	712.3	4029.1	10116.0	-4.462	<.001
Omicron variant	3800.1 (2487.1)	865.8	8558.5	12812.0	5.389	<.001
Omicron BA.2	1928.9 (754.3)	726.9	3052.6	3499.0	-5.113	<.001
Omicron BA.4 and BA.5	1747.9 (629.1)	989.8	3453.1	10087.0	-1.170	0.242

The searches for Long-COVID are in multiples of 10^7. SD indicates standard deviation.

Discussion

In this Infodemiology study, we found that Google searches for Long-COVID in the U.S. started increasing towards the end of the surge of the original SAR COV-2 variant and a notable peak in searches was observed during the surge of the Alpha and Omicron variant. The timing and volume of searches are likely to reflect an increase in interest in Long-COVID due to personal affliction with the condition rather than a generalized interest in the concept. Also, several clinical studies have suggested that multiple SARS-COV-2 variants are associated with Long-COVID symptoms [15-17]. Our analysis indicates that two major variants need further exploration concerning the occurrence of Long-COVID symptoms (i.e., original/wild and Delta); immediately after the dominance of these

Two variants in the U.S., online searches for Long-COVID surged among the general public. One of the earliest and largest clinical studies from a Spanish hospital included more than 200 hospitalized patients infected per variant with the original, Alpha, and Delta. The researchers found that upon a 6-month follow-up among these non-vaccinated patients, the average number of Long- COVID symptoms was more than 2 for those infected with original and delta variants, but less than 2 for individuals infected with other variants [24].

Persistent symptoms of the original and Delta variant emerged a few weeks to months after the initial infection (by which time, the Alpha and Omicron variants had become dominant in the U.S. population) [1, 10, 16, 24]. Specifically, Delta variant is of notable interest as the highest online searches for "Long- COVID" related terms by Americans occurred shortly after Delta variant's infection dominance in the U.S. (overlapping with the surge of Omicron infections for almost a month between 2021-2022) [10, 16] Diexer and colleagues (2023) analyzed a sample of 48,826 individuals (17,008 infected with SARS COV-2 at least once) and found that the risk of developing Long-COVID symptoms was the highest for Delta and original variants regardless of vaccination status or prior infection history [25]. Similarly, a UK-based study of people with self-reported positive COVID-19 tests included those with Omicron infection (n=56,003) and Delta infection (n=41,361) and found that more than a tenth of the people (10.8%) with Delta infection had Long-COVID symptoms compared to 4.5% of those with Omicron infection who experienced such symptoms. The authors also reported a consistent reduction in the risk of Long-COVID symptoms with the Omicron variant versus the Delta variant, depending on the time since vaccination [26]. A prospective study on more than 2500 individuals in Spain utilizing hospital cases admitted from March 2020- to July 2022 found that Long-COVID symptoms persisted for more than a month in more than a third of the cases (35.2%) and certain viral lineages (i.e., Delta lineages AY.126 and AY.43) consistently correlated with higher-severity Long-COVID symptoms [17]. Conversely, a case-control study from Japan found the number of patients with at least one Long-COVID symptom 90 days after diagnosis of COVID-19 in the Omicron group was 5.6% versus 38.9% of those with infection from other variants [27]. For the original variant, a study of more than 2500 healthcare workers who did not require hospitalization after infection found the highest prevalence of Long-COVID symptoms among those infected in the first wave of the pandemic (coinciding with the wild/original variant) [28]. Also, a Meta-Analysis of clinical studies found that the highest prevalence of Long-COVID symptom-related CT scan abnormalities (60.5%; 95% CI= 40.4-80.6) was seen in those infected with the original/wild strain of SAR-COV-2 [29]. An Italian investigation on children who received at least one dose of vaccination (median age = 7.25) found that those infected with the original/wild variant had the highest risk of developing Long-COVID symptoms, and children infected with all other variants were more likely to experience Long-COVID symptoms at 6, 12, and 18 months after initial infection compared to those infected with the Omicron variant [30].

Based on the aforementioned clinical studies and our analysis, we can reasonably conclude that certain SARS-CoV-2 variants have a higher likelihood of causing Long-COVID symptoms (e.g., original and Delta). Conversely, infection with other SARS-CoV-2 variants has a lower likelihood of causing Long-COVID symptoms. A recent review also summarized that prevalence rates of Long-COVID symptoms could be less than 25% in people infected with the Omicron variant versus a rate of more than 50% for other variants (e.g. Delta and original) [31]. Biomolecular and immunological studies need to be understaken with urgency to understand the role of various variants of SARS-CoV-2 in causing Long-COVID symptoms with an emphasis on the original/wild variants and Delta variants as these two types seem to be heavily dominating the scientific discourse on Long-COVID symptoms. Given these observations, our analysis also has major implications for public health practice [32, 33]. Monitoring search trends on epidemic-related health topics can help policymakers and public health professionals better understand emerging health concerns and how the public perceives and acts upon them. Infodemiology, the emerging science of using internet information as a surveillance tool to inform public health professionals in a timely way, should be deployed widely for epidemic outbreaks and applications for other population health concerns should be explored [20-23]. Using such information (e.g., the one provided by our analysis) can help deploy public health promotion initiatives, emergency preparedness measures, and resource allocation for population health needs. Knowing how individuals use readily available resources, such as search engines like Google, during international health emergencies can be useful in creating informational materials that are specific to public health needs [20-23, 32,33].

The results of our analysis are subject to potential limitations [19-23]. First, we only used one search engine (i.e. Google) based on its widespread use globally. It could be possible that individuals search for Long-COVID symptoms through other websites; if so, this limits the external validity of our findings. Second, individuals may have repeated searches using different terms for Long-COVID; this could limit the reliability of our findings. Third, individuals with Long-COVID in the general population may be different from those who are hospitalized or actively getting treatment on symptoms severity, the timing of onset, the variant causing infection, and above all, online search behavior. If so, additional studies are needed to define subgroups of individuals with Long-COVID symptoms and their information-seeking behaviors. Similarly, it is unclear what proportion of the populations around the world are affected by Long-COVID versus how many of them are aware that their symptoms could be due to Long-COVID; this would also influence overall search volumes. Finally, while the U.S. is a relatively well-connected country as it relates to internet access, there could be representation biases. For example, it is well known that racial and ethnic minorities were the worst affected by COVID-19 infections and mortality and they are also less likely to have quality internet connections and access to technology. This could have limited the number of searches that could have occurred in the absence of such representation biases.

Conclusions

In this Infodemiology study from the U.S., we tracked the surge of SARS-CoV-2 variants from years 2000-2023 and assessed them in proximation with the public's online searches for the term "Long-COVID". The analysis in this study along with the evidence from prior healthcare facility-based studies indicates that certain SARS-CoV-2 variants are more likely to cause Long-COVID (e.g. Delta and original/wild variant). Future studies should focus on other parts of the world where people continue to struggle with COVID-19 infection surges or Long-COVID to better understand the spectrum of variants associated with Long-COVID. Such infodemiological information can help prepare for future outbreaks of COVID-19 and understand the burden of Long-COVID symptoms corresponding with different SARS-CoV-2 strains. Finally, biomolecular and immunological studies are needed, specifically for Delta and Original/Wild variants to understand why these variants may have a higher tendency to cause long-lasting symptoms due to COVID-19 infections.

Abbreviations

VOC: variants of concern

VOI: Variants of interest

WHO: World Health Organization

Supporting information: None

Ethical Considerations: Not applicable

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Data availability statement: All data used in this study are publicly available at:

Https://trends.google.com/trends/

Additional information: No additional information is available for this paper.

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