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Evolution of throat symptoms during the COVID-19 pandemic in the US

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Abstract

Objectives: SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) structure and host tropism have changed over time, and so has the involvement of throat structures. This infodemiological analysis is hence aimed at investigating the evolution of throat symptoms during the COVID-19 pandemic in the US.

Methods: We searched Google Trends using the medical search terms “ageusia”, “hoarseness”, “dysphonia”, “pharyngitis” and “laryngitis”, setting geographical location to “United States”, within the past 5 years. The weekly Google Trends score for these symptoms, which reflects their national Web popularity, was divided in three parts, as “pre-COVID” (July 2017 to February 2020), COVID-19 “pre-Omicron” (March 2020 to November 2021), and COVID-19 “Omicron” (December 2021 to July 2022), and then compared.

Results: The volume of searches for ageusia increased in the pre-Omicron period and remained significantly higher also during Omicron prevalence, though a significant decrease (~30%) occurred with Omicron lineages compared to previous strains. The Google searches for hoarseness and dysphonia were relatively similar between the pre-COVID and pre-Omicron periods, but then significantly increased during Omicron predominance. The Google searches for pharyngitis and laryngitis decreased in the pre-Omicron period, but then considerably increased following Omicron emergence. Omicron endemic spread could be significantly

and independently predicted by the volume of searches for pharyngitis, laryngitis and hoarseness.

Conclusions: The epidemiological burden of throat symptoms has considerably changed after Omicron emergence, with a lower likelihood of developing chemosensory dysfunctions and enhanced risk of throat involvement.

Keywords: ageusia; COVID-19; dysphonia; laryngitis; pharyngitis; SARS-CoV-2.

Introduction

Coronavirus disease 2019 (COVID-19), a life-threatening infectious disease that emerged at the end of 2019 and that is sustained by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], is still placing a considerable burden on healthcare systems, societies, and economies, across the world. As with other types of viruses, SARS-CoV-2 is subjected to a strong selection pressure to escape natural or vaccine-induced immunity and contextually increase its capacity to colonize the human host [2]. As a result of this considerable evolutive pressure, SARS-CoV-2 has accumulated a vast array of mutations in its genome, that have gradually modified tropism, virulence and pathogenicity [3, 4].

Reliable evidence has been provided that the overall clinical severity of the recently emerged SARS-CoV-2 “Omicron” lineages seems lower compared to the previous variants (especially alpha, beta and the most recent delta strains), which is actually reflected in a lower risk of developing severe and/or critical illness and thus needing hospitalization and intensive care [5]. This lower pathogenicity of the Omicron lineages has been attributed to major propensity to colonize (and thereby reproduce in) the upper respiratory tract, which makes severe lung involvement and systemic complications less likely to occur [6]. It is hence inherently conceivable that the higher tropism of the Omicron lineages for the epithelia of the upper respiratory tract would be associated with major propensity to develop throat symptoms [7], the more common of which are certainly ageusia, pharyngitis, laryngitis, hoarseness and dysphonia [8]. This evidence has been highlighted in some preliminary reports [9–11],

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although no definitive data have been provided that Omicron lineages would cause a major burden of throat disturbances. To further define this important aspect in biology and clinical course of COVID-19, we conducted an infodemiological analysis aimed at describing the recent evolution of throat symptoms during the COVID-19 pandemic in the US.

Materials and methods

To investigate how throat symptoms may have changed throughout the ongoing COVID-19 pandemic, thus including the emergence of the highly mutated Omicron lineages, we have conducted an electronic search in Google Trends (Google Inc. Mountain View, CA, US), simultaneously using the medical search terms “ageusia”, “hoarseness”, “dysphonia” as well as “pharyngitis” and “laryngitis” (as synonymises of sore throat), with geographical location set to “United States”, within a period comprising the past 5 years (i.e., between July 2017 and July 2022). No further throat symptoms could be addressed, since Google Trends only enables the use of five search terms for direct comparisons. The weekly Google Trends score for each of these terms, which reflects their search popularity on the Web, was downloaded into a Microsoft Excel file (Microsoft, Redmond, WA, United States). The whole search period was then divided in three parts, i.e., as “pre-COVID” (from July 2017 to February 2020), COVID-19 “pre-Omicron” (from March 2020 to November 2021), and COVID-19 “Omicron” (from December 2021 to July 2022), based on US Centers for Disease Control and Prevention (CDC) information [12]. Results of the weekly Google Trends score were finally reported as median and interquartile range (IQR). Weekly Google Trends scores were analyzed with Spearman’s

correlation and multiple linear regression analysis, whilst differences in the volume Google searches for these five throat symptoms in the US across the three different periods were compared with the Mann–Whitney test (Analyse-it Software Ltd, Leeds, UK). The study was conducted in accordance with the Declaration of Helsinki, under the terms of relevant local legislation. This analysis was based on electronic searches in an open and publicly repository (Google Trends), and thus no informed consent or Ethical Committee approval were required.

Results

The main results of our infodemiological analysis are summarized in Figure 1. The median value of the weekly Google Trends score for the five common throat symptoms displayed considerable variations throughout the study period.

The volume of Google searches for ageusia increased from a median value of 2 (IQR, 2-2) in the pre-COVID-19 period, up to 16 (IQR, 12-21; $p<0.001$) in the pre-Omicron period, and remained significantly higher in the Omicron period compared to pre-COVID baseline (11; IQR, 8-14; $p<0.001$). Nonetheless, a significant decrease of nearly 31% in the volume of Google searches could be noted after the emergence of the Omicron lineages compared to previous SARS-CoV-2 waves.

The median value of the weekly Google Trends score for hoarseness did not vary significantly between the pre-

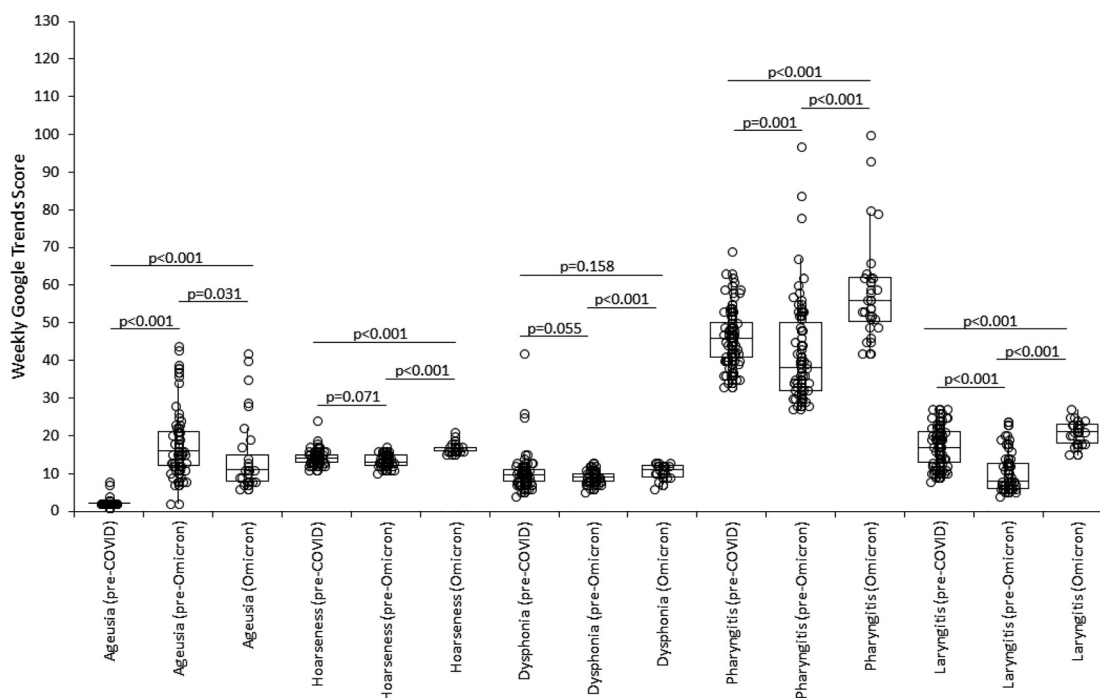


Figure 1: Weekly google trend score for ageusia, “hoarseness”, “dysphonia”, “pharyngitis” and “laryngitis”, in the US during and before the coronavirus disease 2019 (COVID-19) pandemic.

COVID-19 (14; IQR, 13-15) and the pre-Omicron (14; IQR, 12-15) periods ($p=0.071$), but significantly increased after emergence of the Omicron lineages (16; IQR, 16-17), becoming significantly higher compared to both the pre-COVID and pre-Omicron periods ($p<0.001$ for both comparisons).

A similar trend was noted in the volume of Google searches for dysphonia. Although the median Google Trends score did not apparently vary between the pre-COVID (9; IQR, 8-11) and pre-Omicron (9; IQR, 8-10; $p=0.055$) or Omicron (11; IQR, 9-12; $p=0.158$) periods, the volume of Google searches for this term was found to be significantly increased comparing the pre-Omicron and Omicron periods ($p<0.001$).

As concerns pharyngitis, the median weekly Google Trends score of this symptom significantly decreased from the pre-COVID (46; IQR, 41-50) to pre-Omicron (38; IQR, 32-50; $p=0.001$) periods, but then significantly increased during predominance of Omicron lineages (56; IQR, 51-62), reaching values that were significantly higher compared to both the pre-COVID and pre-Omicron periods ($p<0.001$ for both comparisons).

The trend of Google searches for laryngitis mirrored that described for pharyngitis. Specifically, the median weekly Google Trends score of this symptom significantly decreased from the pre-COVID (17; IQR, 13-21) to pre-Omicron (8; IQR, 6-12; $p=0.001$) periods, but then significantly increased during predominance of Omicron lineages (21; IQR, 18-23), reaching values that were significantly higher than both the pre-COVID and pre-Omicron periods ($p<0.001$ for both comparisons).

The evolution over time of the weekly Google Trends score of all throat symptoms in the US based on the presumed epidemiological prevalence of the leading SARS-CoV-2 variants in the country is summarized in Table 2. A constant increase in the volume of Google searches over time could be noted for symptoms like hoarseness, dysphonia, pharyngitis and laryngitis, whilst a clear reduction could be seen for ageusia during the prevalence of Alpha and Omicron lineages.

The Spearman's correlation among the evolution of the different symptoms over time is reported in Table 1, which shows that significant associations could be found between laryngitis and ageusia ($r=-0.32$; $p<0.001$), hoarseness ($r=0.67$; $p<0.001$), dysphonia ($r=0.12$; $p=0.049$) and pharyngitis ($r=0.83$; $p<0.001$), as predictable, as well as between pharyngitis and hoarseness ($r=0.70$; $p<0.001$) and between dysphonia and hoarseness ($r=0.42$; $p<0.001$). In multiple linear regression analysis, where the pre-Omicron and Omicron periods were entered as dependent variable and the weekly Google Trends score of the five throat symptoms

Table 1: Spearman's correlation (and 95% confidence interval; 95% CI) between the Google Trends score of five common throat symptoms before and after the coronavirus disease 2019 (COVID-19) pandemic in the US.

Symptom	Hoarseness	Dysphonia	Pharyngitis	Laryngitis
Ageusia	0.01 (−0.11 to 0.13) $p=0.837$	−0.05 (−0.17 to 0.07) $p=0.396$	−0.07 (−0.19 to 0.05) $p=0.273$	−0.32 (−0.42 to −0.20) $p<0.001$
Hoarseness	–	0.42 (0.32 to 0.52) $p<0.001$	0.70 (0.63 to 0.76) $p<0.001$	0.67 (0.6 to 0.73) $p<0.001$
Dysphonia	–	–	0.07 (−0.05 to 0.19) $p=0.274$	0.12 (0.00 to 0.24) $p=0.049$
Pharyngitis	–	–	–	0.83 (0.79 to 0.87) $p<0.001$

as independent variable, Omicron predominance was significantly predicted by the volume of Web searches for pharyngitis ($p=0.01$), laryngitis ($p<0.001$) and hoarseness ($p=0.002$).

Discussion

The results of our infodemiological analysis provide a strong support to biological data suggesting that SARS-CoV-2 is capable of colonizing throat structures, suggesting viral tropism, virulence, pathogenicity and consequent symptoms have considerably changed over the course of the pandemic (Table 2).

As regards the specific analysis of the trend of the five throat symptoms that we have investigated, the most intriguing pattern seems that of ageusia, which is reflective of an increased burden of chemosensory dysfunctions that is known to be rather frequently associated with SARS-CoV-2 infection. Although we could not investigate the volume of Web searches for anosmia, since only five search terms can be simultaneously entered in Google Trends, the burden of these two symptoms is constantly associated, with a correlation up to 0.98, as we have showed in a preliminary investigation [13]. Not surprisingly, therefore, we found that the volume of Google searches for ageusia increased by 8-fold after emergence of the COVID-19 pandemic, though a nearly 30% decline in median weekly Google Trends score was observed after the Omicron lineages became dominant in the US. Notably, this evidence is in keeping with previous reports, which

Table 2: Evolution over time of the weekly Google Trends score (median and interquartile range) of throat symptoms in the US based on the presumed epidemiological prevalence of the leading severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants in the country.

Leading variants ^a	Period	Ageusia	Hoarseness	Dysphonia	Pharyngitis	Laryngitis
Ancestral	March 2020 to January 2021	17 (12–25)	13 (12–14)	2 (2–3)	34 (31–38)	6 (6–7)
Alpha	February 2021 to June 2021	11 (9–14)	13 (13–14)	2 (2–3)	40 (30–42)	10 (9–12)
Delta	July 2021 to November 2021	18 (15–21)	16 (15–16)	3 (2–3)	53 (51–55)	15 (13–19)
Omicron	December 2021 to July 2022	11 (8–14)	16 (16–17)	11 (9–12)	56 (51–62)	21 (18–23)

^aEstimated prevalence (i.e., >50%).

also emphasized that the risk of developing acute or persistent chemosensory dysfunctions may have decreased since when the Omicron variant has replaced previous SARS-CoV-2 strains [14, 15].

Voice disturbances, namely hoarseness, have not been constantly reported as potential side effects or complications of SARS-CoV-2 infection despite viral neurotropism [16, 17]. We showed here, however, that the volume of Google searches for hoarseness has apparently decreased after the spread of COVID-19, though the median weekly Google Trends score has instead increased during Omicron predominance, by 14% compared to the pre-COVID period, but up to 23% compared to the pre-Omicron period. It is then not surprising that the pattern of Google searches for dysphonia basically reflected that of hoarseness, with a substantial increase in the median weekly Google Trend score for this symptom reported during Omicron predominance (i.e., ~20% higher compared to the previous two pre-COVID and pre-Omicron periods). There is no comparable evidence for these two symptoms in the current scientific literature to the best of our knowledge, though it should now be acknowledged that infection by SARS-CoV-2 Omicron lineages may be associated with voice alterations during, and maybe even after, the infection period.

With respect to pharyngitis and laryngitis (used here as synonymies of “sore throat” to provide a broader picture), the evolution of the Google searches for these two symptoms is substantially comparable, mirroring a significant reduction of the median weekly Google Trends score after emergence of COVID-19, followed by a significant increase (especially for laryngitis) during Omicron predominance period. Specifically, the search volumes compared to the pre-Omicron period increased by 1.5- and 2.6-fold, respectively, with the spread of Omicron.

Taken together, the results of our analysis reveal that the volume of Google searches for throat symptoms has considerably varied during the past 5 years, as a consequence of SARS-CoV-2 spread and, more recently, Omicron predominance. Despite that chemosensory dysfunction seems to have decreased compared to the COVID-19 pre-Omicron period, the virus still poses important

clinical and psychological burdens in this regard within the general population, as revealed by our analysis which allows estimating a prevalence 5-fold higher compared to the pre-COVID period based on the volume of Google searches. In keeping with preliminary reports, we also found that the Web interest for other four common throat symptoms (hoarseness, dysphonia, pharyngitis and laryngitis) has consistently increased after Omicron lineages emerged and replaced the previous SARS-CoV-2 strains. Multiple linear regression analysis confirms this evidence, wherein Omicron predominance was found to be associated with a significantly higher volume of Google searches for pharyngitis, laryngitis and hoarseness compared to the previous pre-Omicron period. This inherently means that virulence, tropism and probably also pathogenicity may have indeed considerably changed as SARS-CoV-2 has accumulated genomic mutations since its first identification at the end of 2019.

There is certainly a plausible explanation for these findings. Besides the large bulk of clinical evidence testifying that the overall reduced severity of the Omicron lineages, reflected by the decreased risks for need of oxygen therapy, mechanical ventilation, intensive care, as well as the cumulative risk of death, after the Omicron lineages have become endemic worldwide, including in the US [5,18,19], and irrespective of the vaccination status [20] or previous natural immunity [21, 22]. Several lines of biological evidence attest that Omicron lineages display a lower replicative activity in the cells of the lower respiratory tract compared to the previous SARS-CoV-2 variants [23, 24].

The main reason underlying the higher tropism of Omicron lineages for the cells of the upper respiratory tract and the lower virulence in the lung tissue entails the fact that the spike protein of Omicron seems to be less efficiently cleaved compared to the Delta and ancestral SARS-CoV-2 strains, thus implying reduced lung infectivity [25]. Overall, what has become rather clear now is that some mutations in the S1/S2 cleavage site within the spike protein of the Omicron lineages cause suboptimal cleavage of these subunits, which is then associated with substantial

impairment of fusogenicity with host cells membrane, lower replication efficiency in host cells expressing Transmembrane Serine Protease 2 (TMPRSS2) and ultimately decreased pathogenicity in the lung tissue [26].

In conclusion, the results of our infodemiological analysis reveal that the epidemiological burden of throat symptoms has considerably changed after Omicron emergence, with lower likelihood of developing chemosensory dysfunctions and enhanced risk of throat involvement. This evidence would hence call for reinforced diagnostic, preventive and therapeutic measures, in order limit the unfavorable clinical and social consequences that may be caused by acute or chronic (COVID-19 related) involvement of the throat structure, but should also provide major awareness that sudden onset of ageusia, pharyngitis, laryngitis, hoarseness or dysphonia may be attributable to SARS-CoV-2 infection, thus enabling an earlier diagnosis and treatment of COVID-19, contextually contributing to limiting viral spread.

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