Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Infectious Diseases Now 52 (2022) 110–121

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Letter to the editor

Are symptoms associated with SARS-CoV-2 infections evolving over time?

ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Signs and symptoms

Google Trends (GT), the open online tool developed by Google™ (Google Inc., Mountain View, CA, US) for infoveillance (i.e. syndromic surveillance that specifically uses information found online), has been extensively employed as a complement to conventional analyses [1], particularly during the ongoing SARS-CoV-2 pandemic [1–3]. GT does not quantify queries on a specific search term. It rather reports the users' web interest in a specific keyword through a normalized value ranging from 0 to 100 (i.e. "relative search volume", RSV), proportional to the ratio between the keyword-related queries and the total of web queries [1]. The search can also be focused on a specific geographical area and a specific timeframe, allowing for more accurate comparisons with conventional indicators [1–3]. For instance, a recent preprint based on a RSV analysis performed on UK data for the month of December 2021 [4] suggested that the recently emerged SARS-CoV-2 variant of concern (VOC) B.1.1.529 (i.e. "Omicron") may have elicited a marked increase in Google searches for symptoms such as conjunctivitis, chills, cough, aches, and fever compared to December 2020. Not coincidentally, there is evidence showing that Omicron may be associated with an increased prevalence of symptoms such as sore throat, fever, and cough with a marked reduction in reporting of loss of smell and taste in PCR-positive individuals [5].

Following the progressive spread of Omicron to other European countries, including Italy, we performed a GT-based RSV using a series of keywords (Table 1) derived from the aforementioned reports, plus the keyword "insomnia" [4–6].

To better cope with the background RSVs for symptoms that may be associated with common respiratory disorders, we used country option set to "Italy" – the first European country to be heavily impacted by the SARS-CoV-2 pandemic – while we opted for a broader search period (January 1, 2017–January 16, 2022).

Corresponding RSVs are reported in Fig. 1. Interestingly enough, symptoms such as anosmia and ageusia, but also conjunctivitis and dyspnea were characterized by a sustained surge in 2020, with a subsequent decrease in the following months. On the contrary, symptoms such as asthenia, coryza, sore throat, cough, diarrhea, headache, and nausea exhibited a sustained increase in 2021 compared to 2020. Despite significant outliers during the first months of the pandemic (i.e. spring 2020), visual inspection suggests that keywords such as cough, sore throat and even conjunctivitis (i.e. very common symptoms of upper airway infections) were associated with a COVID-19-independent seasonal trend, which was still ongoing at the time of the survey.

When RSVs were compared with the 7-day mobile average for notification rates for SARS-CoV-2 (https://github.com/pcm-dpc/COVID-19/blob/master/dati-andamento-nazionale/dpc-covid19-ita-andamento-nazionale.csv), a positive correlation calculated using Spearman's rank correlation coefficient was identified for all assessed search terms but conjunctivitis, sore throat, cough, and insomnia (Table 1). This stresses their substantial independence from the overall trend of the pandemic.

Eventually, RSVs for the timeframe December 1–January 16 were compared between the years 2020 and 2021 by means of Student's t test. An heterogeneous pattern was identified, with increased RSV for shivers/chills (+11.5%, $P=0.012$), pain/aches (+7.8%, $P<0.001$) and a substantial decrease for conjunctivitis (–17.7%, $P<0.001$), and even for sore throat (–10.2%, $P=0.005$) and headaches (–8.9%, $P=0.016$). However, no significant difference was scored for ageusia (+5.0%, $P=0.358$) and anosmia (–6.5%, $P=0.254$) as the Omicron VOC modified these clinical presentations compared to previous variants.

Our results are not only inconsistent with the previous report by Lippi et al. [4], but they also show limited consistency with available conventional studies on the Omicron VOC [5]. Several explanations may be suggested. First of all, available reports suggest that in December 2021, nearly 80% of British SARS-CoV-2 cases were associated with the Omicron VOC, while similar figures in Italy were only attained in the second week of January [5,6]. The Omicron VOC causes different clinical features, which in turn result in a different Internet search pattern, but a certain delay in RSV should be expected. Second, despite its potential significance, the predictive value of GT-based RSV analyses has been questioned by some studies [1,2] as they can be influenced by main media [1,7]. Not coincidentally, Fig. 1 suggests that some of the search terms were associated with substantial outliers during the first months of the pandemic. While cough and sore throat were reasonable queries based on the most common symptoms of SARS-CoV-2 infections, more conflicting evidence suggests the association between COVID-19 and specific ophthalmologic manifestations. Even though ocular pain (31.2%) and eye discharge (19.2%) may be quite common features in SARS-CoV-2 cases [8], redness and conjunctivitis are reported by around 1/10 of all cases, being relatively uncommon and unspecific signs. The sudden surge of new Internet searches may have actually been prompted by earlier claims [8].

In other words, earlier claims about the specificities of the Omicron VOC, and more specifically the higher occurrence of mild flu-like symptoms, may have prompted similar Internet searches in the UK, eventually impairing the reliability of overall estimates. Furthermore, it should be stressed that 2021 has been characterized by an unprecedented surge of infections sustained by the respiratory syncytial virus, mainly in children, newborns, and institutionalized elderly people [9,10]. Most search terms were characterized by a substantial seasonal trend, which in turn is reasonably associated with seasonal infectious diseases. We therefore cannot rule out that diseases other than SARS-CoV-2 may have influenced RSV estimates (either directly or indirectly) by inter-

Table 1
Search terms (Google Trends®) for signs and symptoms potentially associated with SARS-CoV-2 infection, reported by their correlation with corresponding 7-day average notification rates (Spearman's correlation tests) and the mean difference 2020 (i.e. December 1, 2020 to January 16, 2021) vs. 2021 (December 1, 2021 to January 16, 2022) (Student's *t* test).

Search terms	Correlation with the 7-day average of notification rates		Mean difference	2020 vs. 2021	
	R	*P* value	%	95% CI	*P* value
Ageusia	0.703	< 0.001	+ 5.0	– 5.8 to 15.7	0.358
Anosmia	0.705	< 0.001	– 6.5%	– 17.7 to 4.8	0.254
Asthenia	0.480	< 0.001	+ 7.0%	– 3.4 to 17.4	0.182
Shivers/chills	0.271	< 0.001	+ 11.5%	2.6 to 20.3	0.012
Conjunctivitis/red eye	0.091	0.142	– 17.7%	– 27.5 to – 8.0	< 0.001
Diarrhea	0.271	< 0.001	– 1.4%	– 7.8 to 5.0	0.666
Dyspnea	0.567	< 0.001	– 3.5%	– 14.1 to 7.2	0.518
Pain/aches	0.234	< 0.001	+ 7.8%	3.8 to 11.8	< 0.001
Fever	0.434	< 0.001	– 3.6%	– 10.6 to 3.4	0.310
Sore throat	0.053	0.394	– 10.2%	– 17.2 to 3.2	0.005
Headaches	0.501	< 0.001	– 8.9%	– 16.2 to 1.7	0.016
Nausea	0.143	0.021	+ 6.6%	– 0.5 to 13.6	0.069
Coryza/runny nose	0.489	< 0.001	+ 3.5%	– 8.7 to 15.6	0.572
Cough	– 0.087	0.160	+ 4.4%	– 1.5 to 10.2	0.146
Insomnia	– 0.084	0.178	+ 0.6%	– 6.6 to 7.8	0.875

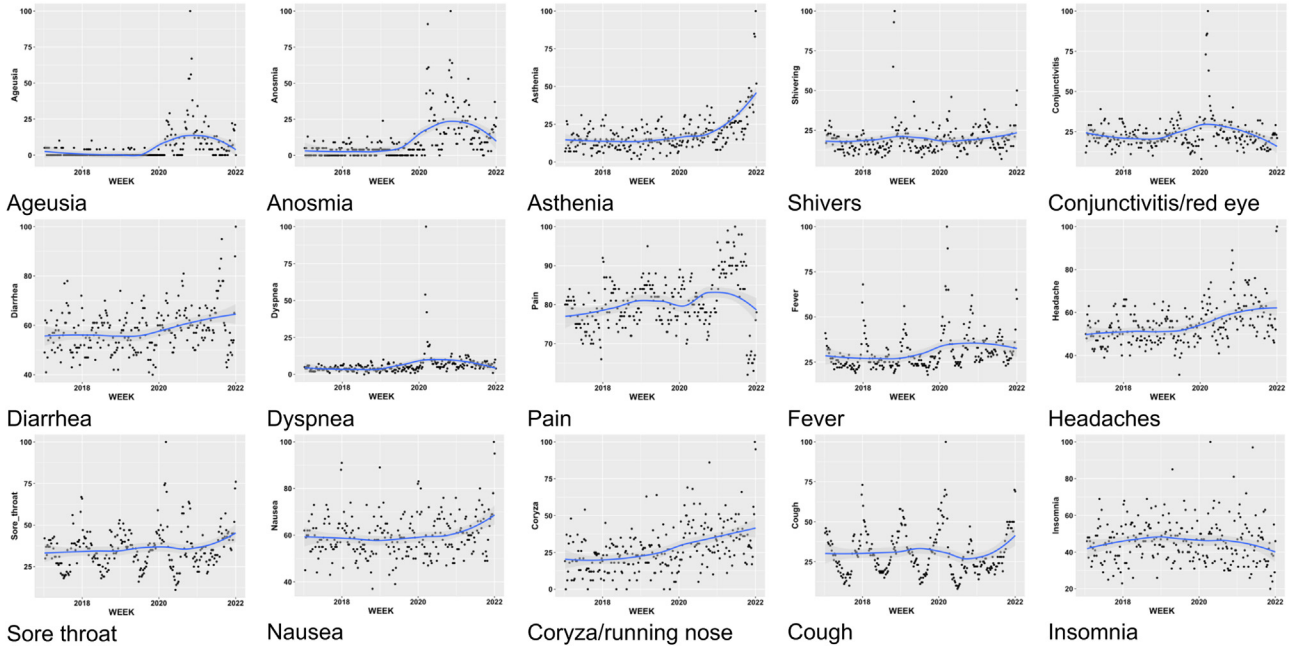

Fig. 1. Time trend of search terms (January 1, 2017–January 16, 2022).

fering with the basal Internet searches. In conclusion, even though our analysis showed interesting differences between RSV for symptoms potentially associated with SARS-CoV-2, GT-based surveys cannot reasonably sustain claims for a progressive evolution of symptoms over time. More extensive, conventional studies are required.

Disclosure of interest

The authors declare that they have no competing interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

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Received 17 January 2022

Accepted 26 January 2022
Available online 2 February 2022

https://doi.org/10.1016/j.idnow.2022.01.006

Exhaustive assessment of Reunion Island inpatients with COVID-19 during the first wave

On Reunion Island, a French overseas department of 860,000 inhabitants located in the Southwestern part of the Indian Ocean (SWIO), the first confirmed case of coronavirus disease 19 (COVID-19) was imported by March 11, 2020. Considering the intense air traffic, we hypothesized that importations would be a major source of COVID-19 cases on Reunion Island. It was even more likely given that high-level standard of care, regional organization and policies confer a central role to Reunion Island for receiving air-flight medical evacuations from the SWIO region (Mauritius, Madagascar, Mayotte, and The Comoros).

So far, limited information is available to describe the characteristics of inpatients from insular tropical settings. The Reunionese population is still relatively young but yet strongly affected by obesity (11%), diabetes (9.8%), and dengue, raising fear of increasing severe COVID-19 infections [1–3].

The purpose of this study was to describe the clinical severity of all COVID-19 inpatients presenting at the referral hospital of SWIO.

The COVID-EPI retrospective cohort study was conducted within Félix Guyon University Hospital, the only referral facility allowed to treat patients with COVID-19 on Reunion Island. Between March 11 and May 10, 2020, we enrolled all consecutive COVID-19 inpatients either diagnosed by a positive SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab specimen or positive antibodies. We divided our study period into two periods: Stage-1 period (introduction of an emergent pathogen into the territory) for admissions between March 11 and March 24, 2020, and Stage-2 period (start of its autochthonous spread) between March 25 and May 10, 2020 (end of lockdown). Hospitalization policy changed to comply with national and local guidelines according to the stage of the outbreak.

Consent to participate was obtained orally for each patient before enrolment in the cohort after written information had been handed out.

Epidemiological, clinical, sociodemographic characteristics and outcomes were collected from electronic medical records. Length of stay was provided by the Medical Informatics Department, blood group by the French blood establishment, and health insurance status by the administrative department of the hospital.

Clinical outcomes included the length of hospital stay, intensive care unit (ICU) admission, vital status at discharge [4], type of discharge for patients discharged alive, readmission, and vital status on day 28 post admission.

Continuous variables were described using median and interquartile range (IQR) values and categorical variables as percentages. Comparison between Stage-1 and Stage-2 periods were performed using Student's *t* test or Mann-Whitney test or Chi2 or Fisher's exact test, as appropriate. Two-sided tests and a significance threshold set at $p \leq 0.05$ were used. All statistical analyses were performed using the SAS® software (v9.4, SAS Institute, Cary, NC, USA, 2013).

Out of 436 COVID-19 cases diagnosed on the island, 171 (39%) required hospitalization. Among these, 168 were enrolled in the COVID-EPI cohort.

The median age of inpatients was 50 years (IQR: 35-63, range 3-86 years). Half were females, of whom five were pregnant. Eighty-two inpatients (50%) had one or more comorbidities (including age and obesity), 70 (43%) excluding age. The most common comorbidities were hypertension, obesity, and diabetes mellitus (Table 1).

Stage-2 inpatients were more likely autochthonous than Stage-1 inpatients. However, there were no significant differences between imported and autochthonous cases regarding age, comorbidities, severity of illness, and time from symptom onset to RT-PCR and from symptom onset to admission. Importantly, most imported cases (82%) were permanent residents of the island. Among 159 symptomatic people, the five most common symptoms at onset of illness were fever, dry cough, asthenia, myalgia, and headache.

Median time between fever onset and apyrexia was 9 days (IQR: 6-13 days).

Forty (23%) inpatients had a severe to critical COVID-19 presentation. There was a trend towards more severe forms of COVID-19 in Stage-2 compared with Stage-1 ($P = 0.059$). None of the patients have been included in an interventional research study protocol (Table 2).

The median length of stay was seven days (IQR: 3-13 days). Seventeen (10%) patients required admission to the ICU. One patient died in the ICU, 12 days after admission (death attributable to COVID-19). He was an 82-year-old man with hypertension and chronic kidney failure, who had been medically evacuated from Mayotte Island. Evacuated patients from Mayotte or Comoros Islands ($n = 9$) more frequently presented with comorbidities (89% vs. 47%; $P = 0.034$) and were more likely to be admitted to the ICU (33% vs. 9%; $P = 0.050$).

Our data highlight the low severity of the illness on our territory during the first wave of the COVID-19 epidemic (low infection fatality rate: 0.6%). Several factors may influence SARS-CoV-2 severity here. First, COVID-19 severity can be modulated by age [5]. Compared to some other European hospital-based studies, our population was about 10 to 20 years younger [6–8]. People under 20 years of age represent 31% of the Reunionese population [9]. Second, the health service has never been overburdened. Postponement of non-urgent care was implemented in the hospital as soon as March 11, 2020 (6 days prior to the national lockdown), thus increasing hospital bed capacity. Treatment has evolved during this period according to new scientific knowledge. In addition, early