Symptomatology associated with the diffusion of the SARS-CoV-2

Lambda variant in Peru: An infodemiologic analysis

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Abstract

The SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) Lambda variant rapidly diffused across Peru following its identification in December 2020, and had now spread worldwide. In this study, we investigated infodemiologic trends in symptomatology associated with the Coronavirus Disease 2019 (COVID-19) following the spread of SARS-CoV-2 Lambda variant in Peru, enabling infodemiologic surveillance of SARS-CoV-2 in regions with high circulation of this new variant. Weekly Google Trends scores were obtained for key symptom keywords between March 1st, 2020 and July 4th, 2021, whilst case count data were obtained from Peruvian Ministry of Health. Multiple time series linear regression was used to assess trends in each score series, using the week of December 27th as cutoff for emergence of the Lambda variant. The significance of such trends was tested for each time period, before and after the cutoff date. A total 2,075,484 confirmed SARS-CoV-2 infections in Peru in relation to Google Trends data were analyzed. After Lambda variant emergence, searches for “diarrhea” demonstrated a change from a negative to positive correlation with weekly case counts and anticipated dynamic changes in case counts by 1-5 weeks. Searches for “shortness of breath” and “headache” remained consistently positively correlated to weekly case counts before and after Lambda emergence. No changes in searches for other common cold symptoms were observed, while no specific trends were observed for “taste loss” or “smell loss”. Diarrhea, headache, and shortness of breath appear to be the most important symptoms for infodemiologic tracking the current outbreak in Peru and other regions with high circulation of SARS-CoV-2 Lambda variant.

Keywords: coronavirus disease 2019; COVID-19; epidemiology; symptoms; infodemiology; Lambda variant
Introduction

The rapid emergence of novel variants of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) with potentially greater infectivity, transmissibility, severity, reduced neutralizing potential and/or ability to escape immune response poses a significant threat to global public health, especially in the face of continuing vaccine shortages. In December 2020, a new SARS-CoV-2 variant (lineage C.37) has been originally identified in Lima, Peru which has then been classified as “Lambda” by the World Health Organization (WHO). Early data suggest that this variant may have greater infectivity and capacity for immune escape from neutralizing antibodies from both naïve infection and vaccination, while changes in clinical severity remain to be determined. The lambda variant was classified in June 2021 by the WHO as “variant of interest”.

Over the course of the ongoing Coronavirus Disease 2019 (COVID-19) pandemic, we have shown that infodemiology, which utilizes the volume of Google web searches for specific COVID-19 symptoms (i.e. keywords), is effective and reliable for predicting regional epidemiological trends and anticipating demand for SARS-CoV-2 testing, assuming that symptomatology (i.e. the set of symptoms characteristic of a medical condition) of any emerging variants in the region remain consistent over time. In Peru, the Lambda variant accounted for 0.5% of cases in December 2020, then rapidly increased to 20.5% of cases in January 2021, 36.4% in February 2021, 79.2% in March 2021, up to 96.6% in April 2021. This dramatic trend in Peru presents the opportunity to investigate symptom keyword trends associated with case counts before and after emergence of this variant, given the homogenous spread within the country as opposed to other geographical regions which have experience the emergence and introduction of multiple variants over time. Here, we investigated infodemiologic trends in symptomatology associated with COVID-19 with
the spread of the Lambda SASR-CoV-2 variant in Peru, in order to enable infodemiologic virus surveillance in regions with high circulation of this variant.

**Methods**

Weekly Google Trends scores (Google Inc., Menlo Park, California, United States) were obtained for each symptom keyword between March 1st, 2020 and July 4th, 2021, for the geographic location Peru, which has approximately 31 million inhabitants and Spanish as its official language. The keywords searched were ‘fever’, ‘cough’, ‘shortness of breath’, ‘headache’, ‘smell loss’, ‘taste loss’, ‘fatigue’, ‘diarrhea’, ‘vomiting’, ‘nausea’, ‘nasal congestion’, ‘muscle pain’ and ‘stuffy nose’ in Spanish. A single unit in Google Trends reflects the relative search interest per week based on a 100-point scale, where the maximum value is established by the highest search volume for a particular term in the period studied. Weekly confirmed SARS-CoV-2 case counts in Peru were obtained from the Peruvian Health Ministry’s Open Data Repository. The case counts were then tabulated together with the Google Trend scores for the study period. Segmented linear regression for time series was used to assess trends in each score series, using the week of December 27th as cutoff for emergence of the SARS-CoV-2 Lambda variant, and the significance of these trends was tested for each time period, before and after the cutoff date. Trend coefficients, confidence intervals and p-values are presented, as well as visual representation of fitted models. A p-value <0.05 was considered significant. To verify the stationarity (mean, variance and autocorrelation structure that do not change over time) before applying the regression in the scores, the Phillips-Perron (PP) and Kwiatkowski-Phillips-Schmidt-Shin (KPSS) tests were performed. To the first test, p-value <0.05 indicate significant stationarity and, to the second, p-value >0.05. To verify the presence of autocorrelation after applying the regression, the Durbin-Watson test was used. When
the autocorrelation was significant, the adequacy of the model was used using the Cochrane-Orcutt method. To understand the relationship between case counts and Google Trend scores, time lagged cross correlations were calculated.

This study was performed in conformation with the Declaration of Helsinki, under the terms of applicable local legislation. The analysis was conducted solely based on the searches of unrestricted, publicly available databases; thus, no informed consent or institutional review board approval were required.

**Results**

This study analyzed 2,075,484 total confirmed cases of SARS-CoV-2 infection in Peru in relation to Google Trends data throughout the study period (March 1st, 2020 to July 4, 2021). During this period, the number of new weekly SARS-CoV-2 cases ranged from 8 in the week of March 1st, 2020, to 63,558 in the week of April 4th, 2021. A total of 1,013,930 cases were observed in the months before December 27th, 2020, and 1,061,554 cases after that following emergence of the Lambda variant. Two major peaks in cases were observed in Peru, a pre-Lambda peak the first in the week of August 16th, 2020 and a Lambda peak in the second week of April 4th 2021.

Google trends data and case counts for each week over the study period for a given symptom keyword are presented in Figure 1. The weekly score series for “vomiting” and “diarrhea” both showed significant positive trends between March 1st, 2020 and December 27, 2020 ($p<0.001$; $p<0.01$, respectively), followed by significant negative trends ($p<0.001$; $p<0.05$, respectively) after that time period, indicating that search interest in those topics had been rising since the early weeks of the pandemic, reaching a peak around the end of 2020 and declining afterward. The scores for
“diarrhea” had significant and negative cross-correlation coefficients for weekly cases before the cutoff date, at no time lag as well as 1 through 5 weeks lag, meaning that higher scores were more likely to be followed by lower case counts. After the cutoff, the lagged “diarrhea” score series had mostly positive cross-correlations with the weekly case series, thus indicating a change in dynamics, where higher scores were more likely to be followed by higher case counts. The scores for “vomiting” also had mostly negative cross-correlations with the weekly case series before December 27th, but no significant cross-correlations after that date, thus signifying that higher scores were likely to be followed by lower case counts before the cutoff date, but had no significant association with case counts afterward.

The weekly score series for “cough” showed significant negative trend ($p<0.001$) before the end of 2020, and a significant positive trend ($p<0.001$) after that, indicating that Google search interest in the keyword had been declining since the beginning of the pandemic, but has been showing a significant increase since the cutoff date of December 27th. However, the scores had no significant cross-correlations with the weekly case series, thus indicating that no significant association of higher or lower scores with the number of cases in following weeks could be seen. Both “headache” and “shortness of breath” also had their peak Google search scores at the beginning of the pandemic, showing significant decline during the year 2020 ($p<0.01; p<0.05$, respectively), but no significant trend after December 27th. Both terms also had mostly positive cross-correlations with the weekly case series, both before and after the cutoff date, thus indicating that higher scores for these terms have been consistently associated with higher case counts in the following weeks.

The pathognomonic COVID-19 symptoms of “smell loss” and “taste loss” showed relative stability, with no significant trend variations before or after December 27th. Finally, no significant trends for fever were observed at any time point in the study period, while other general symptoms
of upper respiratory tract infections, such as “fatigue” (PP test $p<0.01$, KPPS test $p>0.05$), “nasal congestion” (PP test $p<0.01$, KPPS test $p>0.05$), “stuffy nose” (PP test $p<0.01$, KPPS test $p>0.05$), and “muscle pain” (PP test $p<0.01$, KPPS test $p>0.05$), all showed stationary behavior before applying linear regression. After applying the regression, the results did not show statistically significant trends of change, which was expected, considering the mean, variance and covariance of any stationary series do not change over time. Full results of the time series analysis are presented in Table 1, and cross-correlation coefficients in Table 2.

**Discussion**

Multiple previous studies, either by our group or by other teams which have investigated the trends in online search patterns within the context of regional COVID-19 outbreaks, have consistently shown that the frequency of Google searches of pathognomonic and non-pathognomonic (i.e., general) symptom keywords and SARS-CoV-2 surveillance data have a strong relationship, through which their temporal association enables predicting future trajectories of epidemic based on internet search volumes in a period of time, as well as the demand for SARS-CoV-2 testing and test positivity.\(^7\)\(^-\)\(^9\) However, this depends on consistency of symptoms over time and may also be influenced by emergence of novel SARS-CoV-2 variants with distinctive biological and clinical characteristics (i.e., higher virulence and/or pathogenicity, immune evasion, greater stability, and so forth).

In this investigation, we explored the symptomatology associated with diffusion of the SARS-CoV-2 Lambda variant in Peru, using a validated infodemiologic approach. A few interesting observations were found. First, shortness of breath is the most consistent symptom associated with
all the major variants circulating in the region during the study period as demonstrated by positive search correlations with case counts before and after Lambda variant emergence. Second, a significant change in behavior was observed for search data on diarrhea after emergence of the Lambda variant. Prior to December 27th 2020, negative correlations with case counts were observed but, after this date, searches for diarrhea positively correlated and anticipated spikes and drops in weekly case counts by 1-5 weeks. This suggests that diarrhea may be a more prominent feature, and perhaps early indicator of major circulation of the Lambda variant. No significant association was found with other gastrointestinal symptoms (i.e., nausea, vomiting) after Lambda variant emergence. Third, other generalized symptoms of upper respiratory tract infection, such as fever, cough, nasal congestion, fatigue, and muscle pain remained relatively stable over the study period, showing no change in their overall search trends following introduction of Lambda variant. Thus, we found no data to support that this emerging variant is more frequently presenting with common cold type of illness. Importantly, headache showed a rather consistent tracing across the study period, with positive search correlations, similar to shortness of breath, to weekly case counts. This is in line with previous findings in regard to the importance of headache in COVID-19 symptomatology.11. Finally, the pathognomonic COVID-19 symptoms of “smell loss” and “taste loss” displayed relative stability and no significant trend to suggest a positive correlation of these symptoms with the Lambda variant. This is in contrast to previous results published by our team, in which we have shown strong association between SARS-CoV-2 incidence and anosmia or dysgeusia7,8

Since being first identified in Peru in late 2020, this new SARS-CoV-2 lambda variant has now spread to countries across South America, with cases now being detected all around the world.12 Among the many mutations associated with the lambda variant, a novel spike protein mutation
(L452Q) within the receptor binding domain may offer greater capability to bind to the virus human host receptor (Angiotensin Converting Enzyme 2 (ACE2)) and escape neutralizing antibodies produced from naïve infection, vaccination, or therapeutic antibody cocktails. Another seven-amino-acid deletion in the N-terminal domain of spike protein (i.e., RSYLTPGD246-253N) seems to confer a substantial resistance to vaccine-induced neutralization, which may favor the major spread of Lambda variant among COVID-19 vaccine recipients, especially in those with lower vaccine-triggered immunogenicity. Therefore, further studies would be urgently needed to investigate the real-world clinical and public health implications of the lambda variant.

This study is limited by several factors. Though Spanish is the most spoken language in Peru, it is just one of many potentially limiting the search. Furthermore, limitations to internet access, especially in rural regions of the country may partially bias the results. Seasonal cold and influenza patterns with similar baseline symptoms could also in part bias the results. Finally, increasing familiarity with key COVID-19 symptoms among the general public, especially pathognomonic symptoms like loss of taste and smell, could be confounding our analysis. Nonetheless, this would have important implications for the use of such symptoms to infodemiologically monitor the evolving pandemic.

Conclusions

Following emergence of the SARS-CoV-2 Lambda variant in Peru, searches for diarrhea significantly increased and anticipated the dynamic changes in weekly case counts. Diarrhea, along with headache and shortness of breath, appear to be the most important infodemiologic symptoms for tracking the current outbreak in Peru and other regions with high Lambda variant circulation. On the other hand, common cold symptoms appear to be less frequently associated with searches
in a region with high circulation of Lambda variant, while similarly no trend was observed for loss of taste or smell. These results provide some insight into symptomatology of SARS-CoV-2 Lambda variant, and highlight the key search terms that should be used for infodemiologic surveillance of SARS-CoV-2 in regions with high circulation of this variant.

References

1. Lippi G, Henry BM. How will emerging SARS-CoV-2 variants impact herd immunity? *Ann Transl Med*. 2021;9(7):585. doi:10.21037/atm-21-893

2. Romero PE, Dávila-Barclay A, Salvatierra G, et al. The Emergence of SARS-CoV-2 Variant Lambda (C.37) in South America. *medRxiv*. Published online July 3, 2021;2021.06.26.21259487. doi:10.1101/2021.06.26.21259487

3. Tada T, Zhou H, Dcosta BM, Samanovic MI, Mulligan MJ, Landau NR. SARS-CoV-2 Lambda Variant Remains Susceptible to Neutralization by mRNA Vaccine-elicited Antibodies and Convalescent Serum. *bioRxiv*. Published online July 3, 2021;2021.07.02.450959. doi:10.1101/2021.07.02.450959

4. Tada T, Zhou H, Samanovic MI, et al. Comparison of Neutralizing Antibody Titers Elicited by mRNA and Adenoviral Vector Vaccine against SARS-CoV-2 Variants. *bioRxiv*. Published online July 21, 2021;2021.07.19.452771. doi:10.1101/2021.07.19.452771

5. Acevedo ML, Alonso-Palomares L, Bustamante A, et al. Infectivity and immune escape of the new SARS-CoV-2 variant of interest Lambda. *medRxiv*. Published online July 1, 2021;2021.06.28.21259673. doi:10.1101/2021.06.28.21259673

6. Tracking SARS-CoV-2 variants. Accessed July 25, 2021. https://www.who.int/activities/tracking-SARS-CoV-2-variants

7. Henry BM, Szergyuk I, Santos de Oliveira MH, Lippi G, Juszczyk G, Mikos M. Utility of Google Trends in anticipating COVID-19 outbreaks in Poland. *Pol Arch Intern Med*. 2021;131(4):389-392. doi:10.20452/pamw.15894

8. Lippi G, Henry BM, Mattiuzzi C, Sanchis-Gomar F. Google Searches for Taste and Smell Loss Anticipate Covid-19 Epidemiology. *medRxiv*. Published online November 12, 2020;2020.11.09.20228510. doi:10.1101/2020.11.09.20228510

9. Lippi G, Mattiuzzi C, Santos de Oliveira MH, Henry BM. Clinical Predictors of SARS-CoV-2 Testing Pressure on Clinical Laboratories: A Multinational Study Analyzing Google
Trends and Over 100 Million Diagnostic Tests. *Lab Med.* 2021;52(4):311-314. doi:10.1093/labmed/lmab013

10. Positive cases due to COVID-19 - [Peruvian Ministry of Health - MINSA] | National Open Data Platform. Accessed July 20, 2021. https://www.datosabiertos.gob.pe/dataset/casos-positivos-porcovid-19-ministerio-de-salud-minsa

11. Lippi G, Mattiuzzi C, Bovo C, Henry BM. Headache is an important symptom in patients with coronavirus disease 2019 (COVID-19). *Diagnosis.* 2020;7(4):409-411. doi:10.1515/dx-2020-0048

12. C.37 Lineage Report Updated as of July 25th, 2021. outbreak.info. Accessed July 25, 2021. https://outbreak.info/

13. Kimura I, Kosugi Y, Wu J, et al. SARS-CoV-2 Lambda variant exhibits higher infectivity and immune resistance. *bioRxiv.* Published online July 28, 2021:2021.07.28.454085. doi:10.1101/2021.07.28.454085
Figure 1. Weekly SARS-CoV-2 cases in Peru and Google Trend Scores for specific symptom keywords for searches conducted within the country from March 1st, 2020, to July 4th, 2021.

Blue line represents number of weekly confirmed SARS-CoV-2 cases reflected by the left-sided y-axis; Orange line represents weekly Google Trend score reflected by the right-sided y-axis; Dashed black line represents overall search trend before and after December 27th, 2020 which is demarcated by a red vertical line. Not shown is the plot for fatigue which had no significant trends with weekly case counts.
Table 1. Time Series Analysis results for key COVID-19 symptoms before and after emergence of the lambda SARS-CoV-2 strain in Peru.

| Search Term       | PP test | KPSS test | Linear tendency before December 27 | p-value (Linear regression) | Trend | Linear tendency after December 27 | p-value (Linear Regression) | Trend |
|-------------------|---------|-----------|-----------------------------------|----------------------------|-------|-----------------------------------|----------------------------|-------|
| Fever             | >0.05   | <0.05     | -0.57 (-1.38; 0.23)               | >0.05                      |       | 0.44 (-1.33; 2.22)               | >0.05                      |       |
| Fatigue           | <0.01   | >0.05     | 0.26 (-0.12; 0.65)                | >0.05                      |       | -0.73 (-1.70; 0.22)              | >0.05                      |       |
| Headache          | >0.05   | <0.05     | -0.45 (-0.71; -0.19)              | <0.01                      | ↓     | 0.37 (-0.26; 1.02)               | >0.05                      |       |
| Nausea            | >0.05   | <0.05     | -0.32 (-0.86; 0.21)               | >0.05                      |       | 0.30 (-1.01; 1.62)               | >0.05                      |       |
| Vomiting          | >0.05   | <0.05     | 0.57 (0.20; 0.93)                 | <0.001                     | ↑     | -1.18 (-2.08; -0.29)             | <0.001                     | ↓     |
| Diarrhea          | >0.05   | <0.05     | 0.70 (0.19; 1.21)                 | <0.01                      | ↑     | -1.36 (-2.53; -0.18)             | <0.05                      | ↓     |
| Smell Loss        | >0.05   | <0.05     | -0.03 (-0.80; 0.73)               | >0.05                      |       | -0.31 (-2.09; 1.46)              | >0.05                      |       |
| Taste Loss        | >0.05   | <0.05     | -0.52 (-1.20; 0.15)               | >0.05                      |       | 0.60 (-1.0; 2.20)                | >0.05                      |       |
| Cough             | >0.05   | <0.05     | -0.78 (-1.11; -0.45)              | <0.001                     | ↓     | 1.43 (0.67; 2.20)                | <0.001                     | ↑     |
| Shortness of Breath | >0.05 | <0.05    | -0.65 (-1.23; -0.06)              | <0.05                      | ↓     | 0.58 (-0.80; 1.96)               | >0.05                      |       |
| Stuffy Nose       | <0.01   | >0.05     | -0.09 (-0.50; 0.33)               | >0.05                      |       | 0.44 (-0.58; 1.47)               | >0.05                      |       |
| Nose Congestion   | <0.01   | >0.05     | -0.31 (-0.69; 0.07)               | >0.05                      |       | 0.45 (-0.48; 1.38)               | >0.05                      |       |
| Muscle Pain       | <0.01   | >0.05     | 0.32 (-0.09; 0.73)                | >0.05                      |       | -0.85 (-1.86; 0.16)              | >0.05                      |       |

* PP - Phillips-Perron test: a p-value below 0.05 indicates stationary behavior; KPSS - Kwiatkowski-Phillips-Schmidt-Shin test: a p-value above 0.05 indicates stationary behavior.
Table 2. Cross-correlation coefficients for Google Trends scores series and weekly case counts, before and after December 27\textsuperscript{th}, 2020.

| Time lag (weeks) | Headache | Cough | Diarrhea | Shortness of Breath | Vomit |
|------------------|----------|-------|----------|---------------------|-------|
|                  | Before   | After | Before   | After              | Before | After | Before   | After | Before   | After |
| 0                | 0.102    | 0.364 | -0.14    | 0.281              | -0.565 | 0.226 | 0.214    | 0.384 | -0.202   | -0.277 |
| -1               | 0.16     | 0.357 | -0.044   | 0.224              | -0.551 | 0.312 | 0.333    | 0.391 | -0.334   | -0.168 |
| -2               | 0.24     | 0.351 | 0.032    | 0.127              | -0.493 | 0.364 | 0.352    | 0.378 | -0.248   | -0.008 |
| -3               | 0.335    | 0.255 | 0.145    | -0.032             | -0.484 | 0.386 | 0.371    | 0.279 | -0.306   | -0.079 |
| -4               | 0.387    | 0.397 | 0.157    | -0.166             | -0.362 | 0.482 | 0.395    | 0.213 | -0.321   | 0.256  |
| -5               | 0.387    | 0.313 | 0.241    | -0.313             | -0.339 | 0.449 | 0.358    | 0.185 | -0.268   | 0.246  |

* Values represent linear regression coefficient and 95\% CI.

PP - Phillips-Perron test: a \( p \)-value below 0.05 indicates stationary behavior; KPSS - Kwiatkowski-Phillips-Schmidt-Shin test: a \( p \)-value above 0.05 indicates stationary behavior.