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Epidemiological characterization of asymptomatic carriers of COVID-19 in Colombia

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ABSTRACT (187 words)

Introduction: Asymptomatic carriers (AC) of the new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) represent an important source of spread for Coronavirus Disease 2019 (COVID-19). Early diagnosis of these cases is a powerful tool to control the pandemic. Our objective was to characterize patients with AC status and identify associated sociodemographic factors.

Methods: Using a cross-sectional design and the national database of daily occurrence of COVID-19, we characterized both socially and demographically all ACs. Additional Correspondence Analysis and Logistic Regression Model were performed to identify characteristics associated with AC state (OR, 95% CI).

Results: 2338 ACs (11.8%; 95% CI, 11.3-12.2%) were identified, mainly in epidemiological week 18 [EW] (3.98; 3.24-4.90). Age ≤39 years (1.56; 1.42-1.72). Male sex (1.39; 1.26-1.53), cases imported from Argentina, Spain, Peru, Brazil, Costa Rica or Mexico (3.37; 1.47-7.71) and autochthonous cases (4.35 ; 2.12-8.93) increased the risk of identifying AC. We also identified groups of departments with moderate (3.68; 3.13-4.33) and strong (8.31; 6.10-7.46) association with AC.

Conclusion: Sociodemographic characteristics strongly associated with AC were identified, which may explain its epidemiological relevance and usefulness to optimize mass screening strategies and prevent person-to-person transmission.

Key words: COVID-19; Asymptomatic; Carrier States; Risk factors, Novel Coronavirus.

Article summary' section consisting of the heading: 'Strengths and limitations of this study', and containing up to five bullet points that relate specifically to the study reported. This should be placed after the abstract.

Article summary

- Asymptomatic carriers (AC) represent a silent source of spread for Coronavirus Disease 2019 (COVID-19).
- ACs have been included in epidemiological predictive models to estimate the second and third pandemic wave of COVID-19.

- Epidemiological reports of ACs are frequently biased given the inclusion of pre-symptomatic patients or the merge of ACs with patients with non-critical symptoms.
- Massive screening could improve current understanding of AC phenotype and thus provide useful information for predictive mathematical models.
- Recognizing the silent movement of COVID-19 through ACs could result in more effective public health strategies of containment and prevention.

TEXT (2481 words)

INTRODUCTION

In March 2nd, 2020, Colombia reported the first case of Coronavirus Disease 2019 (COVID-19), and as of May 23rd, more than 20,000 cases have been confirmed nationwide [1]. Asymptomatic carriers (AC) may be associated with the accelerated growth of cases in the initial phases of the pandemic, inadvertently spreading the infection to close contacts. In this case, transmission can only be limited until a diagnosis of SARS-CoV-2 infection is rendered after (i) isolation due to symptom onset, (ii) contact tracing or (iii) identification during massive screening strategies [2,3].

AC and pre-symptomatic cases are epidemiologically relevant since they represent a silent source of spread in various public settings (e.g. public transportation, emergency rooms, supermarkets, shelters) [4–6]. The proportion of ACs has been estimated at 15-25%, but seroprevalence studies have reported values of up to 43.2% (95% CI, 32.2-54.7%). Nonetheless, many pre-symptomatic patients are wrongfully classified as ACs during the incubation phase; to later become pauci-symptomatic or develop respiratory manifestations ranging from pneumonia to respiratory failure, or exhibit any other clinical symptoms within the COVID-19 spectrum [4–8].

Epidemiological predictive models have been developed and updated to incorporate silent mobility through AC phenotype in anticipation for the second and third epidemic waves of COVID-19. Such is the case for the SEIR model (Susceptible, Exposed, Infected and Recovered), recently updated to SEAIR (Susceptible, Exposed, Asymptomatic, Infected and Recovered) [9]. In China, estimates indicate that 60-65% of ACs remained undetected.

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Therefore, under the SEIR model and applying machine-learning-based transmission simulators (MLSim), including the number of undetected AC within its parameters and assuming 15 close contacts per day, estimates suggest that as of April 15th, 2020, the United States---the country contributing the majority of cases imported to Colombia---, could have presented 277,641-to-495,128 latent cases of COVID-19, potentially increasing the spread of the virus [10].

The assessment of ACs and the identification of sociodemographic characteristics associated with this subpopulation could be useful to estimate sample calculations in massive screening studies, as well as adjust control and mitigation measures---especially the intensity of isolation. Therefore, the objective of our study was to characterize ACs demographically and socially, as well as to identify individual characteristics in interaction models associated with ACs.

METHODOLOGY

Design and data selection.

We performed a cross-sectional study with information from the National Institute of Health (INS) database on COVID-19 cases updated until May 23, 2020. By INS protocol, suspected AC cases remained in quarantine for 7 days while monitoring the appearance of symptoms on a daily basis; on the eighth day, a nasal swab sample was collected to identify or rule out AC state. Records without health status information (symptomatic, asymptomatic) were excluded. The database is public, with de-identified patient data and IRB approval was thus exempt.

Patient and Public Involvement (PPI) statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Database and variables.

We used variables such as date of diagnosis, age, sex, country of origin, department, case type (imported, related), care setting (home, nursing home, hospital, intensive care unit) and outcome (recovered, convalescent, deceased). The date of diagnosis was adjusted into epidemiological weeks (EW), which were later grouped according to the pattern of AC occurrence (Figure S1) in EW 10-15, 16-17, 18, 19-21; additionally, the variable AC [yes, no] was established.

Statistical analysis

Data are presented in medians or proportions estimated with 95% CI due to the lack of massive screening for COVID-19 in certain areas of the country. The geographical origin and destination of imported cases was represented with a Sankey Plot (SankeyMATIC (BETA). Cumulative trends and case charts were created with the number of daily cases by Epid_weeks (RStudio Version 1.2.5042). In addition, a heatmap analysis was included to depict a dynamic representation of daily cases by Department from March 6th through May 23rd, 2020 (Orange Data Mining & Fruitful Fun, Version 3.25). The proportion of asymptomatic and symptomatic patients and the median age were compared with the Z and U Mann Whitney tests respectively (significant p-value <0.05, two tails) [Addinsoft. 2020.

XLSTAT statistical and data analysis solution. New York, USA. https://www.xlstat.com]. Age was dichotomized between 0-39 and ≥40 years due to its association with asymptomatic and symptomatic states respectively (preliminary exploratory analysis not shown).

Countries of origin and departments associated with ACs were identified with a Correspondence Analysis (CA). Additionally, with contribution coordinates of the columns (CCC-CA), groups with a variable level of association with ACs were created [Addinsoft. 2020. XLSTAT statistical and data analysis solution. New York, USA. https://www.xlstat.com].

To estimate the association between sociodemographic characteristics with CA (OR 95%), two Logistic Regression Models (LRM) were performed, the first to establish the main effects and the second a step-backward interaction model of the second level (p- value in <0.05; p-value out:> 0.1), which used the lowest Akaike criteria to select the best model (JASP Team (2020). JASP (Version 0.12.2))

RESULTS

General characteristics

We identified 2,388 ACs (11.8%; 11.3-12.2%) out of 20,177 cases reported in the database. Four cases were excluded due to lack of health status information. The occurrence of AC state in relation to symptomatic presented a slow growth phase between EW 10-15, moderate growth between EW 16-17, and a peak at EW 18, followed by a decrease between EW 19-21 (Figure 1A, 1B, S1). Daily cases ranged from 1 to 203 per day, and EWs 18 and 19 registered the highest number of cases per day: 172 and 203, respectively.

Additionally, we report department clusters with a high occurrence of daily COVID-19 cases, which follow different dynamic patterns for ACs and symptomatic patients (Figure 1C-1D). Meta reported the largest number of daily ACs (n: 151), with peak occurrences between April 23rd and May 10th; followed by Amazonas, Bogotá, and Caribbean departments with peak reports between May 11th and 12th,

More than half of the imported ACs came from Europe, specifically Spain, followed by North and South America. Those that arrived from Spain and USA were distributed mainly in Bogotá, Valle del Cauca and other departments of the Caribbean region. Amazonas department only received imported ACs from South American countries. The origin and distribution of imported symptomatic patients was more diverse; however, most cases originated from Spain, USA, Ecuador, Mexico, Brazil, or Panama, and were mainly distributed across Bogotá, Antioquia, and Valle del Cauca (Figure 2).

About half of the ACs were located in Meta and Bogotá, and a tenth in the Amazon (Table 1, Table S1). Median age was 32 years old, lower than the symptomatic patients. Most of them were males (Table 1). The domicile was the main place of care (85.7%; 84.3-87.1%) and 13.9% had recovered (95%, CI, 12.5-15.3%). Four of the admitted cases had fatal outcomes, two from the general wards and two from the Intensive Care Units (ICU). Possibly these last 8 cases were treated for symptoms unrelated to COVID-19, or were diagnosed post-mortem.

Factors associated with AC condition.

Using the CCC-CA, a group of six countries and three groups of departments were associated with AC state (Figure 3). To execute LRMs, the variables "age group 0-39 years" and "male sex" were transformed into dummi [0/1]. With a preliminary LRM, a higher β coefficient was estimated in relation to cases imported from countries associated with AC, therefore, the variable "geographical origin" was created, composed of the categories "imported from countries associated with symptomatic" [Imported CAS - referent], "imported from countries associated with asymptomatic" [Imported CA-AC] and "related cases". Additionally, a variable was created for the departments grouped with the CA [departments with low association - referent] and for the EW (EW 10-15 - referent). The first LRM (main effects) identified a significant association of all index sociodemographic categories with AC state (Table S2). The second model explores the following interactions: 1. Geographical origin and grouped departments, 2. Geographical origin and EW, 3. Age group (0-39 years) and gender, 4. Grouped departments and gender; and, 5. Age (0-39 years) and EW. We identified that the variables gender (males) and EW showed interaction with the grouped departments (Table 2).

Variables "0-39 years", "departments with strong association", "imported CA-AC" and "related cases" were found to increase the risk of identifying AC state. It was also determined that the risk increased with the interaction between men in the departments with a strong and moderate association. In isolation (without interaction), between EWs 19-21, the risk of identifying AC decreased, as did EWs 16-17 in departments with a strong association. However, the risk increased from EW 18 to EWs 19-21 when interacting, both with moderate and strong association departments (Table 2).

DISCUSSION

We found that, in an isolated fashion, age < 40 years old, imported cases from a group of 6 countries, autochthonous cases and the occurrence in groupings of departments were

194 associated with AC state. Additionally, the risk of being a male AC was only identified in departments with moderate or strong risk, and the risk was variable in the groupings of departments throughout specific epidemiological periods.

197 Additionally, our results show that the proportion of ACs in Colombia lays between 11-12% (Table 1), a lower estimate than previously described in other case series or mass screening studies with reported proportions between 5-80% [11–14]. Given the inclusion of presymptomatic patients or the unification of AC with non-critical symptoms in some reports, we cannot rule out that a non-differential classification bias influenced these estimates. An adapted definition for AC in Colombia may address this limitation.

203 Figure 1 shows that the majority of imported cases to Colombia came from Spain and USA, where AC rates have been estimated at 2.5% and 25%, respectively [14,15]. Although imported cases carry a distinctive genetic load that, population-wise, could manifest itself as a particular phenotype [16], currently there are no reports of genetic variants associated with AC in general or for any of the four AC subtypes described in the literature [17]. Subsequent research should be conducted on the possible association between ACs and phylogenetic variants (or other variables) to support the differential risk identified in imported cases from different regions of the world.

211 We identified that imported cases from a group of 6 countries were strongly associated with AC (Figure 2, Table S1, Table 2), and although no interaction was established between the country of import and the destination department (data not shown), we observed that departments strongly associated with AC had less diversity of import origin. Such is the case of Meta and Amazonas, which exclusively imported cases from USA and Brazil/Peru, respectively (Figure 2).

Among the demographic characteristics, the association between AC state and patients under 40 years of age stands out. Possible explanations for this observation include: (i) the lower presence of co-morbid conditions and baseline health issues within this age group and (ii) the higher risk of exposure through work activities which are greater in this age group [18]. However, clinical or social environment could also explain this finding, as a study in skilled nursing facility residents showed a high proportion of AC in those over 70 years of age, however this was a premature finding since most patients were later reclassified as pre-symptomatic or pauci-symptomatic [11].

We identified a higher frequency of men infected with COVID-19 consistent with reports from other countries around the world, except in Spain and Switzerland, where women ranked first [19]. Frequent occupations performed by men, as well as certain immunological and genetically susceptible backgrounds have been associated with this finding [19,20]. In particular, the risk of being an AC was higher in men, and increased in geographic areas associated with AC. This interaction is not uncommon given that professions regularly carried out by men, including those such as taxi driving, private security or prison guarding, among other work settings, can be distributed asymmetrically within countries, a pattern that would explain our findings [20].

The phases on the occurrence of cases throughout EWs and the interaction with groupings within departments associated with AC has been previously described in Chongqing, China, where researchers identified significant changes in the frequency of cases after implementation of geographic isolation measures. In Wuhan, a study showed that one group of ACs was linked to imported cases while others were linked mostly to autochthonous cases from geographically isolated areas of Wuhan [21]. We identified that in addition to being associated with a travel history to foreign countries, ACs were also associated with cases that appear spontaneously (related), occurring differentially as measures of geographic and social isolation were applied.

The lack of mass screening for COVID-19 in Colombia is the main limitation of our study since the actual AC ratio and the distribution of specific characteristics may differ from those estimated in this report. On the other hand, although a cross-sectional design is not ideal to identify risk factors, to the best of our knowledge this is the first study aimed at identifying factors associated with AC state with population data unbiased by the inclusion of pre-symptomatic cases.

The COVID-19 pandemic has had serious socioeconomic implications, including a collapse of healthcare systems, bankruptcy of companies as well as increasing trends in unemployment and crime rates [22–25]. This has forced countries with limited resources---such as Colombia---to perform massive screenings in order to prematurely lift quarantine and isolation measures despite the latent risk of successive outbreaks caused by a potential silent spread of COVID-19 through cases in the pre-symptomatic phase or AC state [26,27].

ACs transmit COVID-19 more efficiently than symptomatic patients for up to 21 days after the presumed date of infection [28,29]. This led to their inclusion in mathematical models intended to estimate the probability or expected number of person-to-person infections on repatriation trips from Wuhan, China [7,30]. Since then, ACs have become the target of mass screening in Asian and European countries effectively reducing economical losses due to unnecessary hospital care, controlling the spread in public or in-hospital settings, and allowing the execution of safe plans of social and work re-integration after quarantine and isolation [26,31–35].

To date, testing of asymptomatic individuals rests at the discretion of physicians when justified on a case-by-case basis. On the other hand, the utility of SARS-CoV-2 testing for broad screening of asymptomatic individuals remains to be determined given the limited sensitivity data available for most commercially available test kits [36].

CONCLUSION

Together, our findings demonstrate sociodemographic trends strongly associated with COVID-19 AC state in Colombia at a departmental and national level. We believe that the implementation of massive screening campaigns to detect AC and pre-symptomatic patients is paramount to further characterize this phenomenon and adequately guide public health measures of containment and prevention. Additional molecular analysis of viral and host genotypic characteristics should be conducted to determine possible associations with AC state.

Authors contributorship statement

AT, APM and JDR designed the study. AT, GC, RPG, CH, GH, LMP, LAP and AA conducted the statistical and descriptive analyses. CF, ECB provided the data for the analysis. AT, APM, LAP and JDR drafted the manuscript. All authors approved the final version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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Figure Legends

Figure 1. Daily accumulation and distribution of ACs by epidemiological week in Colombia. A. The y-axis represents the number of cumulative ACs transformed into a base 10 logarithm. The number of cumulative cases per day is located in points that increase in color intensity according to the occurrence of cases. **B.** The y-axis represents the number of daily ACs transformed into a base 10 logarithm. The number of daily cases per day is located in boxplots. **C.** Heatmap showcasing the number of ACs (top) and **B.** symptomatic patients (bottom) diagnosed in every Colombian department until May 23rd, 2020.

Figure 2. Origin and destination of imported asymptomatic and symptomatic cases. The left and right figures, respectively, represent the country of origin and destination department of ACs and symptomatic patients. The thickness of the link tapes corresponds to the number of reported cases.

Figure 3. Groups of countries and departments associated with AC state. The left figure shows the group of countries associated with asymptomatic carrier (AC) state identified with positive values of the CCC-CA. The right figure shows departments grouped according to three intervals of CCC-CA: low association (CCC-CA: negative values), moderate association (CCC-CA:> 0 - <0.05), and strong association (CCC-CA: ≥0.5).

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References.

1. Coronavirus en Colombia. https://www.ins.gov.co/Noticias/Paginas/Coronavirus.aspx. Accessed May 10, 2020.

2. Rudan I. A cascade of causes that led to the COVID-19 tragedy in Italy and in other European Union co1. Rudan I. A cascade of causes that led to the COVID-19 tragedy in Italy and in other European Union countries. J Glob Health. 2020; 10(1):10335. untries. *J Glob Health*. 2020;10(1):10335. doi:10.7189/jogh-10-010335

3. Yi Y, Lagniton PNP, Ye S, Li E, Xu R-H. COVID-19: what has been learned and to be learned about the novel coronavirus disease. *Int J Biol Sci*. 2020;16(10):1753-1766. doi:10.7150/ijbs.45134

4. Tindale L, Coombe M, Stockdale JE, et al. Transmission interval estimates suggest pre-symptomatic spread of COVID-19. *medRxiv*. January 2020:2020.03.03.20029983. doi:10.1101/2020.03.03.20029983

5. Zhang W. Estimating the presymptomatic transmission of COVID19 using incubation period and serial interval data. *medRxiv*. January 2020:2020.04.02.20051318. doi:10.1101/2020.04.02.20051318

6. Rahimi F, Talebi Bezmin Abadi A. Challenges of managing the asymptomatic carriers of SARS-CoV-2. *Travel Med Infect Dis*. April 2020:101677. doi:10.1016/j.tmaid.2020.101677

7. Teherán AA, Camero G, Prado R, et al. Presumptive asymptomatic COVID-19

carriers' estimation and expected person-to-person spreading among repatriated passengers returning from China. *Travel Med Infect Dis*. April 2020:101688. doi:10.1016/j.tmaid.2020.101688

8. Lavezzo E, Franchin E, Ciavarella C, et al. Suppression of COVID-19 outbreak in the municipality of Vo, Italy. *medRxiv*. January 2020:2020.04.17.20053157. doi:10.1101/2020.04.17.20053157

9. Oliveira G. Refined compartmental models, asymptomatic carriers and COVID-19. *medRxiv*. January 2020:2020.04.14.20065128. doi:10.1101/2020.04.14.20065128

10. Yu Y, Liu Y-R, Luo F-M, et al. COVID-19 Asymptomatic Infection Estimation. *medRxiv*. January 2020:2020.04.19.20068072. doi:10.1101/2020.04.19.20068072

11. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2008457

12. Wong J, Abdul Aziz ABZ, Chaw L, et al. High proportion of asymptomatic and presymptomatic COVID-19 infections in travelers and returning residents to Brunei. *J Travel Med*. 2020. doi:10.1093/jtm/taaa066

13. Hijnen D, Marzano AV, Eyerich K, et al. SARS-CoV-2 Transmission from Presymptomatic Meeting Attendee, Germany. *Emerg Infect Dis*. 2020. doi:10.3201/eid2608.201235

14. COVID-19: What proportion are asymptomatic? - CEBM. https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/. Accessed June 16, 2020.

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15. Ministerio de Sanidad C. Estudio Nacional de sero-Epidemiología de la Infección por SARS-CoV-2 en España (ENE-Covid). Informe PRELIMINAR tras la primera ronda (13/05/2020). *Gob España*. 2020;(May 13).

16. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. *Proc Natl Acad Sci U S A*. 2020. doi:10.1073/pnas.2004999117

17. Zhou X, Li Y, Li T, Zhang W. Follow-up of asymptomatic patients with SARS-CoV-2 infection. *Clin Microbiol Infect*. 2020. doi:10.1016/j.cmi.2020.03.024

18. Yang R, Gui X, Xiong Y. Comparison of Clinical Characteristics of Patients with Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China. *JAMA Netw open*. 2020. doi:10.1001/jamanetworkopen.2020.10182

19. Márquez EJ, Trowbridge J, Kuchel GA, Banchereau J, Ucar D. The lethal sex gap: COVID-19. *Immun Ageing*. 2020;17(1):13. doi:10.1186/s12979-020-00183-z

20. Koh D. Occupational risks for COVID-19 infection. *Occup Med (Chic Ill)*. 2020;70(1):3-5. doi:10.1093/occmed/kqaa036

21. Tao Y, Cheng P, Chen W, et al. High Incidence of Asymptomatic SARS-CoV-2 Infection, Chongqing, China. *SSRN Electron J*. 2020. doi:10.2139/ssrn.3559583

22. Nussbaumer-Streit B, Mayr V, Dobrescu Ai, et al. Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. *Cochrane Database Syst Rev*. 2020;(4). doi:10.1002/14651858.CD013574

23. Nicola M, Alsafi Z, Sohrabi C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *Int J Surg*. 2020;78:185-193.

doi:https://doi.org/10.1016/j.ijsu.2020.04.018

24. Kalleberg AL, Wachter TM von. The U.S. Labor Market During and After the Great Recession: Continuities and Transformations. *RSF Russell Sage Found J Soc Sci*. 2017;3(3):1-19. doi:10.7758/rsf.2017.3.3.01

25. Sutherland M, McKenney M, Elkbuli A. Gun violence during COVID-19 pandemic: Paradoxical trends in New York City, Chicago, Los Angeles and Baltimore. *Am J Emerg Med*. 2020. doi:10.1016/j.ajem.2020.05.006

26. Gilbert M, Dewatripont M, Muraille E, Platteau JP, Goldman M. Preparing for a responsible lockdown exit strategy. *Nat Med*. 2020. doi:10.1038/s41591-020-0871-y

27. World Health Organisation. Considerations in adjusting public health and social measures in the context of COVID-19. *World Heal Organ*. 2020;(April):1-7. https://www.who.int/publications-detail/risk-.

28. Prather KA, Wang CC, Schooley RT. Reducing transmission of SARS-CoV-2. *Science (80-)*. 2020. doi:10.1126/science.abc6197

29. Huff H V, Singh A. Asymptomatic transmission during the COVID-19 pandemic and implications for public health strategies. *Clin Infect Dis*. May 2020. doi:10.1093/cid/ciaa654

30. Gostic K, Gomez ACR, Mummah RO, Kucharski AJ, Lloyd-Smith JO. Estimated effectiveness of symptom and risk screening to prevent the spread of COVID-19. Franco E, Ferguson NM, McCaw JM, eds. *Elife*. 2020;9:e55570. doi:10.7554/eLife.55570

31. Peto J, Alwan NA, Godfrey KM, et al. Universal weekly testing as the UK COVID-19 lockdown exit strategy. *Lancet*. 2020. doi:10.1016/S0140-6736(20)30936-3

32. Mallapaty S. Will antibody tests for the coronavirus really change everything? *Nature*. 2020. doi:10.1038/d41586-020-01115-z

33. The race against COVID-19. *Nat Nanotechnol*. 2020. doi:10.1038/s41565-020-0680-y

34. Mark K, Steel K, Stevenson J, et al. Coronavirus disease (COVID-19) community testing team in Scotland: A 14-day review, 6 to 20 February 2020. *Eurosurveillance*. 2020. doi:10.2807/1560-7917.ES.2020.25.12.2000217

35. Rosenthal PJ. The importance of diagnostic testing during a viral pandemic: Early lessons from novel coronavirus disease (CoVID-19). *Am J Trop Med Hyg*. 2020. doi:10.4269/AJTMH.20-0216

36. Woloshin S, Patel N, Kesselheim AS. False Negative Tests for SARS-CoV-2 Infection — Challenges and Implications. *N Engl J Med*. 2020. doi:10.1056/nejmp2015897

Table 1. Sociodemographic characteristics of the asymptomatic and symptomatic patients

Variables	Asymptomatic	Symptomatic	p-value
	n: 2388	**n:** 17785	
Age, years	32 (24-44)	37 (26-53)	<0.001
0-39	1603 (67.1)	9655 (54.2)	<0.001
≥40	785 (32.8)	8130 (45.7)	<0.001
Sex			
Male	1208 (75.2)	6220 (53.7)	<0.001
Female	399 (24.8)	5359 (46.3)	<0.001
Geographical source			
Related	2357 (98.7)	16972 (95.4)	<0.001
Imported	31 (1.30)	813 (4.57)	<0.001
Departments†			
Meta	749 (31.3)	219 (1.23)	<0.001

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Bogotá	437 (18.3)	65.4 (36.8)	<0.001
Amazonas	238 (9.97)	1150 (6.47)	<0.001
Atlántico	203 (8.50)	1068 (6.01)	<0.001
Barranquilla	117 (4.90)	1216 (6.84)	<0.001
Imported cases			
Spain	16 (51.6)	244 (30.0)	0.011
USA	7 (22.5)	202 (24.8)	0.774
Brazil	2 (6.45)	40 (4.92)	0.700
Mexico	2 (6.45)	49 (6.03)	0.922
Argentina	1 (3.23)	3 (0.37)	0.023
Peru	1 (3.23)	11 (1.35)	0.387
Puerto Rico	1 (3.23)	12 (1.48)	0.437
Turkey	1 (3.23)	27 (3.32)	0.977

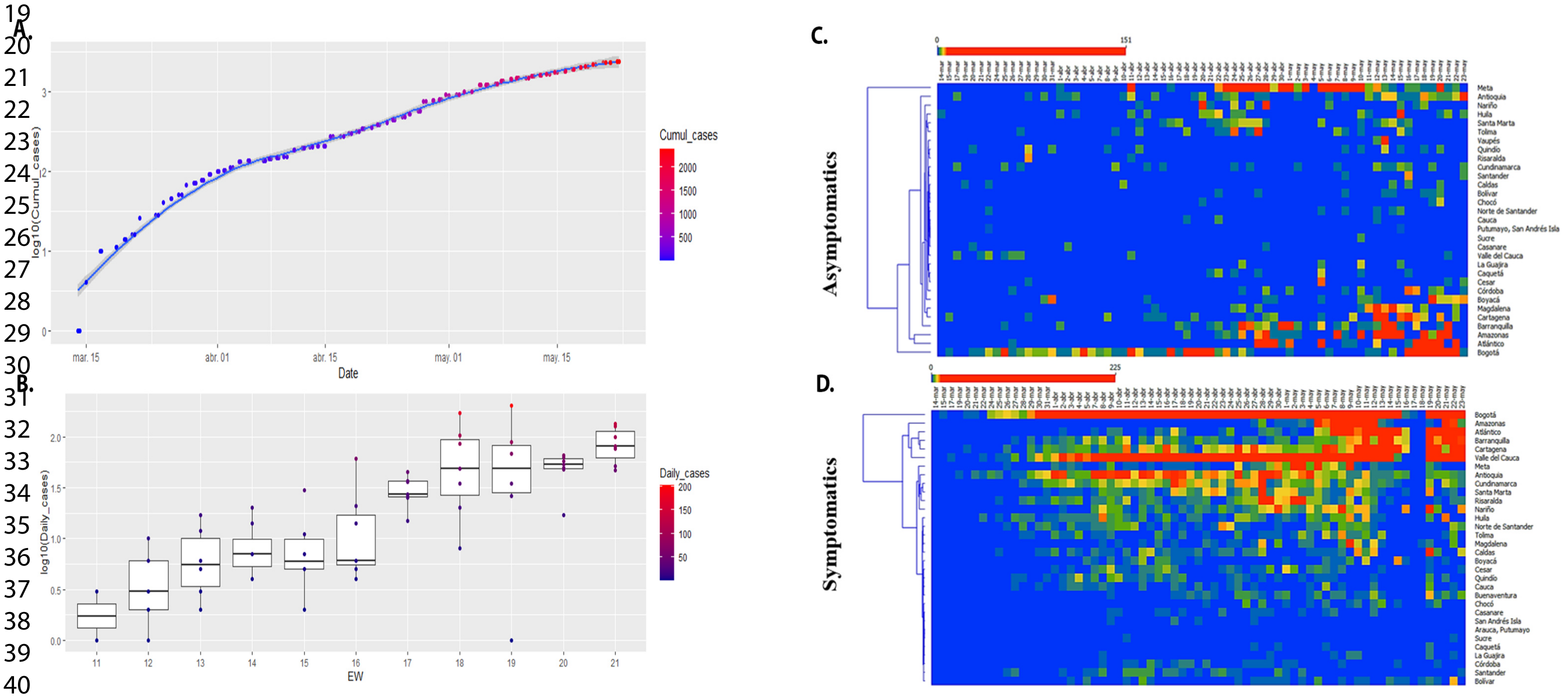
418 †: cases that appeared spontaneously in Colombia, ††: top 5 of the
419 departments with the highest frequency of AC.

420 **Table 2.** Factors associated with asymptomatic carrier (AC) state in Colombia

Variable	**Interaction model**		
	B	**ORc (95%, CI)**	**p-value**
Intercept	**-4.531**	-	**<0.001**
Age			
>40 years	**Ref.**	-	-
0-39 years	0.451	1.569 (1.422-1.732)	**<0.001**
Sex			

Female	**Ref.**	-	-
Male	-0.019	0.981 (0.850-1.132)	0.791
Department			
Low association [1]	**Ref.**	-	-
Moderate association [2]	0.210	1.234 (0.799-1.908)	0.344
Strong association [3]	1.130	3.095 (1.860-5.149)	**<0.001**
Geographical source			
Imported CAS†	**Ref.**	-	**-**
Imported CA-AC††	1.225	3.405 (1.491-7.775)	**<0.004**
Related cases†††	1.351	4.861 (1.885-7.910)	**<0.001**
EW			
10-15 [1]	**Ref.**	-	
16-17 [2]	0.657	1.410 (1.155-1.721)	**<0.001**
18 [4]	0.418	1.519 (1.087-2.122)	**<0.014**
19-21 [3]	-0.074	0.929 (0.758-1.138)	0.477
Department [2] + Male	0.363	1.438 (1.035-1.998)	**0.030**
Department [3] + Male	0.757	2.132 (1.723-2.638)	**<0.001**
EW [2] + Department [3]	-1.052	0.349 (0.198-0.616)	**<0.001**
EW [3] + Department [2]	1.474	4.368 (2.780-6.862)	**<0.001**
EW [4] + Department [2]	1.219	3.385 (1.631-7.023)	**0.001**
EW [4] + Department [3]	1.414	4.673 (2.273-7.447)	**<0.001**

†: CAS countries associated with symptomatic patients, ††: CA-AC countries associated with asymptomatic carriers (AC), †††: spontaneous cases, **EW:** epidemiological weeks.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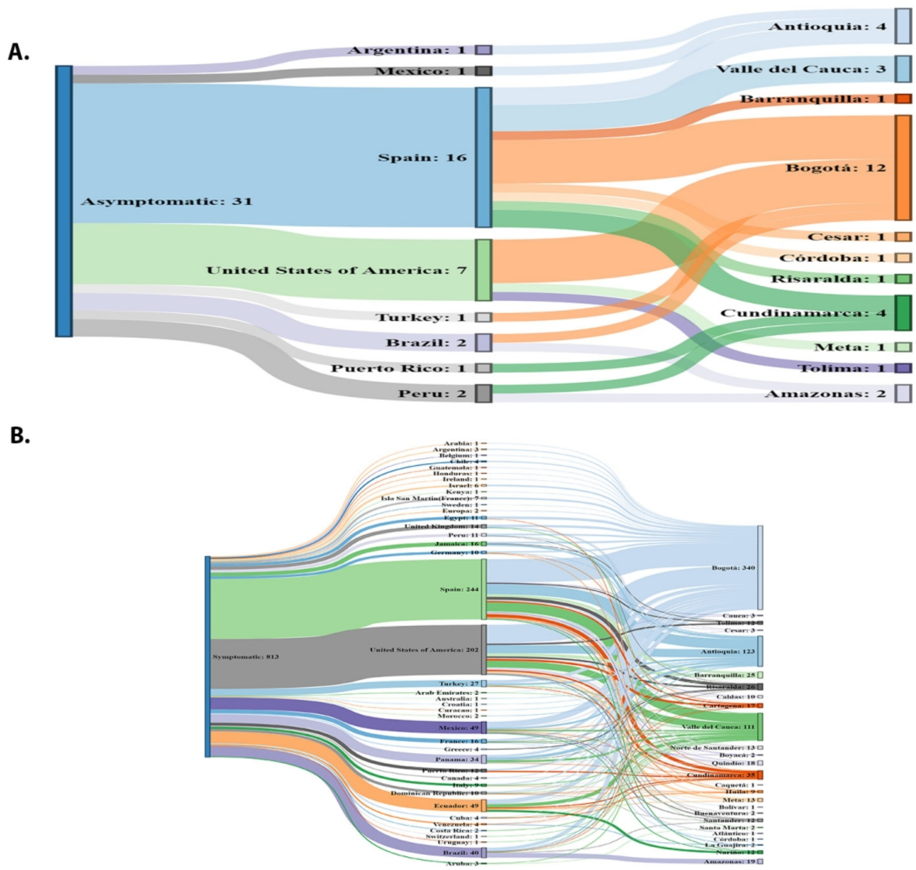

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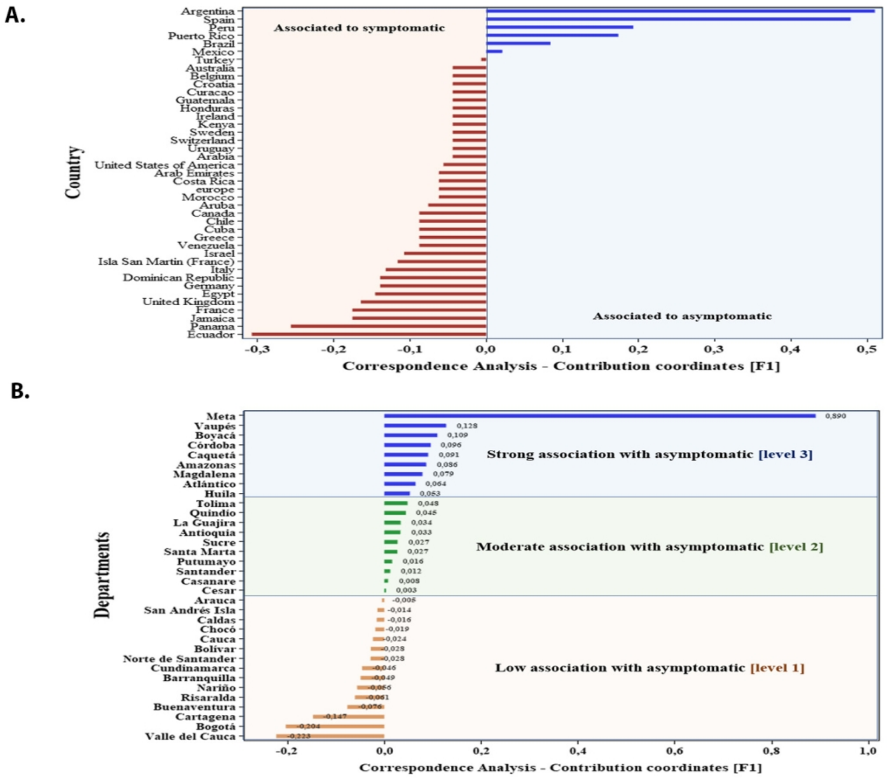

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Table S1. AC state frequency in Colombia by department

Department	Count	Proportion
Meta	749	31,37
Bogotá	437	18,3
Amazonas	238	9,97
Atlántico	203	8,5
Barranquilla	117	4,9
Antioquia	100	4,19
Cartagena	76	3,18
Magdalena	52	2,18
Boyacá	48	2,01
Huila	46	1,93
Nariño	44	1,84
Santa Marta	42	1,76
Tolima	37	1,55
Córdoba	31	1,3
Cundinamarca	28	1,17
Quindío	20	0,84
Valle del Cauca	14	0,59
Caquetá	12	0,5
Caldas	11	0,46
Cesar	11	0,46
La Guajira	11	0,46
Vaupés	11	0,46
Bolívar	9	0,38
Santander	9	0,38
Norte de	7	0,29
Risaralda	7	0,29
Chocó	6	0,25
Casanare	4	0,17
Cauca	4	0,17
Sucre	2	0,08
Putumayo	1	0,04
San Andrés Isla	1	0,04

The total number of ACs was used as the denominator to determine proportions.

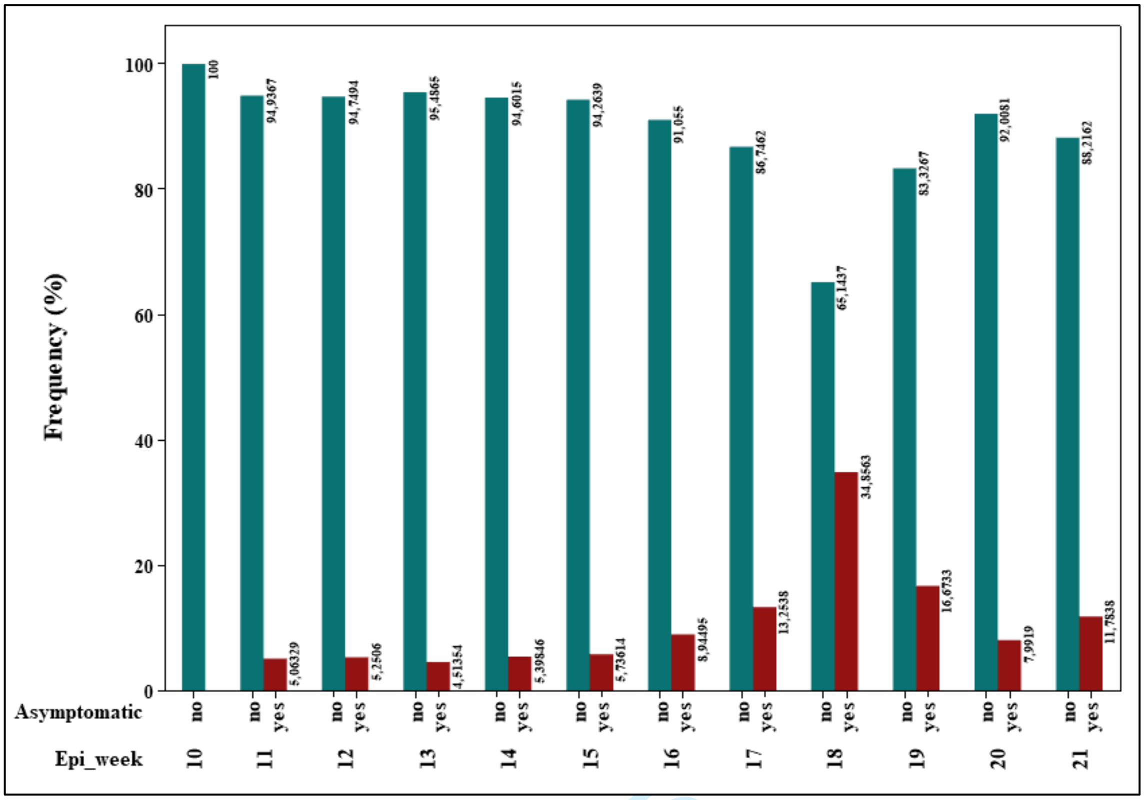
Table S2. Factors associated with AC state in Colombia.

Variable	**Main effects**		
	B	**ORa (95%, CI)**	**p-value**
Intercept	**-5.061**	-	**<0.001**
Age,			
≥40 years old	**Ref.**	-	**-**
0-39 years old	0.449	1.566 (1.421-1.726)	**<0.001**
Sex			
Female	**Ref.**	-	-
Male	0.322	1.393 (1.264-1.537)	**<0.001**
Department			
Low risk	**Ref.**	-	**-**
Moderate risk	1.304	3.372 (3.134-4.330)	**<0.001**
Strong risk	1.909	8.310 (6.101-7.464)	**<0.001**
Geographical origin			
Imported CAS†	**Ref.**	-	**-**
Imported CA-AC††	1.216	3.372 (1.474-7.716)	**<0.004**
Related cases†††	1.472	4.356 (2.123-8.939)	**<0.001**
EW			
10-15	**Ref.**	-	
16-17	0.344	1.410 (1.155-1.721)	**<0.001**
18	1.383	3.987 (3.243-4.902)	**<0.001**

19-21	0.264	1.302(1.095-1.548)	**<0.001**

†: CAS countries associated to symptomatic patients**, ††:** CA-AC countries associated to ACs**, †††: spontaneous cases**, **EW:** epidemiological week.

Figure S1. Proportion of ACs and symptomatic patients by epidemiological week in Colombia.



The number of reported ACs in Colombia by epidemiological week (EW) included: EW-11: 4/79, EW-12: 22/419, EW-13: 45/997, EW-14: 63/1167, EW-15: 60/1046, EW-16: 117/1308, EW-17: 211/1592, EW-18: 473/1357, EW-19: 421/2525, EW-20: 355/4442, EW-21: 617/5236.

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Epidemiological characterization of asymptomatic carriers of COVID-19 in Colombia: A cross-sectional study.

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ABSTRACT (187 words)

Introduction: Asymptomatic carriers (AC) of the new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) represent an important source of spread for Coronavirus Disease 2019 (COVID-19). Early diagnosis of these cases is a powerful tool to control the pandemic. Our objective was to characterize patients with AC status and identify associated sociodemographic factors.

Methods: Using a cross-sectional design and the national database of daily occurrence of COVID-19, we characterized both socially and demographically all ACs. Additional Correspondence Analysis and Logistic Regression Model were performed to identify characteristics associated with AC state (OR, 95% CI).

Results: 76.162 ACs (12.1%; 95%CI, 12.0-12.2%) were identified, mainly before epidemiological week 35 [EW]. Age ≤26 years (1.18;1.09-1.28), male sex (1.51;1.40-1.62), cases imported from Venezuela, Argentina, Brazil, Germany, Puerto Rico, Spain, United States of America or Mexico (12.6;3.03-52.5) and autochthonous cases (22.6;5.62-91.4) increased the risk of identifying ACs. We also identified groups of departments with moderate (1.23;1.13-1.34) and strong (19.8;18.6-21.0) association with ACs.

Conclusion: Sociodemographic characteristics strongly associated with AC were identified, which may explain its epidemiological relevance and usefulness to optimize mass screening strategies and prevent person-to-person transmission.

Key words: COVID-19; Asymptomatic; Carrier States; Risk factors, Novel Coronavirus.

3

Strengths and limitations:

- Cross-sectional studies are useful to identify possible variables associated with ACs.
- Weekly surveillance of potential cases reduced selection and classification bias of ACs.
- The large number of COVID-19 ACs included in this study allowed to draw precise estimates.
- The ongoing epidemic phase of COVID-19 in Colombia decreases the uncertainty of invisible subgroup occurrences.
- Estimates and characteristics associated with ACs may improve epidemiological surveillance in other countries.

TEXT (2481 words)

INTRODUCTION

In March 2nd, 2020, Colombia reported the first case of Coronavirus Disease 2019 (COVID-19), and as of September 22nd, more than 700,000 cases have been confirmed nationwide [1]. Asymptomatic carriers (AC) may be associated with the accelerated growth of cases in the initial phases of the pandemic, inadvertently spreading the infection to close contacts. In this case, transmission can only be limited until a diagnosis of SARS-CoV-2 infection is rendered after (i) isolation due to symptom onset, (ii) contact tracing or (iii) identification during massive screening strategies [2,3].

AC and pre-symptomatic cases are epidemiologically relevant since they represent a silent source of spread in various public settings (e.g. public transportation, emergency rooms, supermarkets, shelters) [4–6]. The proportion of ACs has been estimated at 15-25%, but seroprevalence studies have reported values of up to 43.2% (95% CI, 32.2-54.7%). Nonetheless, many pre-symptomatic patients are wrongfully classified as ACs during the incubation phase; to later become pauci-symptomatic or develop respiratory manifestations ranging from pneumonia to respiratory failure, or exhibit any other clinical symptoms within the COVID-19 spectrum [4–8].

Epidemiological predictive models have been developed and updated to incorporate silent mobility through AC phenotype in anticipation for the second and third epidemic waves of COVID-19. Such is the case for the SEIR model (Susceptible, Exposed, Infected and Recovered), recently updated to SEAIR (Susceptible, Exposed, Asymptomatic, Infected and Recovered) [9]. In China, estimates indicate that 60-65% of ACs remained undetected.

Therefore, under the SEIR model and applying machine-learning-based transmission simulators (MLSim), including the number of undetected AC within its parameters and assuming 15 close contacts per day, estimates suggest that as of April 15th, 2020, the United States---the country contributing the majority of cases imported to Colombia---, could have presented 277,641-to-495,128 latent cases of COVID-19, potentially increasing the spread of the virus [10].

The assessment of ACs and the identification of sociodemographic characteristics associated with this subpopulation could be useful to estimate sample calculations in massive screening studies, as well as adjust control and mitigation measures---especially the intensity of isolation. Therefore, the objective of our study was to characterize ACs demographically and socially, as well as to identify individual characteristics in interaction models associated with ACs.

METHODOLOGY

Design and data selection.

We performed a cross-sectional study with information from the National Institute of Health (INS) database on COVID-19 cases updated until August 31, 2020 (https://www.ins.gov.co/Noticias/Paginas/coronavirus-casos.aspx). By INS protocol, suspected AC cases remained in quarantine for 7 days while monitoring the appearance of symptoms on a daily basis; on the eighth day, a nasal swab sample was collected to identify or rule out AC state. Records without health status information (symptomatic, asymptomatic) were excluded. The database is public, with de-identified patient data and IRB approval was thus exempt.

Patient and Public Involvement (PPI) statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Database and variables.

We used variables such as date of diagnosis, age, sex, country of origin, department, case type (imported, related), care setting (home, nursing home, hospital, intensive care unit) and outcome (recovered, convalescent, deceased). The date of diagnosis was adjusted into epidemiological weeks (EW), which were later grouped according to the pattern of AC occurrence (Figure S1) in EW 10-34, ≥35; additionally, the variable AC [yes, no] was established.

Statistical analysis

Data are presented in medians or proportions estimated with 95% CI due to the lack of massive screening for COVID-19 in certain areas of the country; additionally, we estimated AC rates per 100.000 population by departments using Colombian demographic estimates for 2020 from the National Administrative Department of Statistics (DANE). The geographical origin and destination of imported cases was represented with a Sankey Plot (SankeyMATIC (BETA). Cumulative trends and case charts were created with the number of daily cases by Epid_weeks (RStudio Version 1.2.5042). In addition, a heatmap analysis was included to depict a dynamic representation of daily cases by Department from March 6th through August 31rd, 2020 (Orange Data Mining & Fruitful Fun, Version 3.25). The proportion of asymptomatic and symptomatic patients and the median age were compared with the Z and U Mann Whitney tests respectively (significant p-value <0.05, two tails) [Addinsoft. 2020. XLSTAT statistical and data analysis solution. New York, USA. https://www.xlstat.com]. Age was dichotomized between 0-26 and ≥27 years due to its association with asymptomatic and symptomatic states respectively (preliminary exploratory analysis not shown).

Countries of origin and departments associated with ACs were identified, respectively, with a Correspondence Analysis (CA) and Factorial analysis of mixed data using PCAmix. Raw data were used for CA while symptomatic and AC rates per 100.000 population were used for PCAmix . Additionally, with principal coordinates (PC) obtained with both CA (PC-CA) and PCAmix (PC-PCAmix), groups with a variable level of association with ACs were created. [Addinsoft. 2020. XLSTAT statistical and data analysis solution. New York, USA. https://www.xlstat.com].

To estimate the association between sociodemographic characteristics with ACs (OR 95%), two Logistic Regression Models (LRM) were performed, the first to establish the main effects and the second a step-backward interaction model of the second level (p- value in <0.05; p-value out:> 0.1), which used the lowest Akaike criteria to select the best model (JASP Team (2020). JASP (Version 0.12.2))

RESULTS

General characteristics

We identified 76.162 ACs (12.1%; 12.0-12.2%) out of 626.887 cases reported in the database. Four cases were excluded due to lack of health status information. The occurrence of AC state in relation to symptomatic presented a continuous growth phase between EW 10-17, and a peak at EW 18, followed by a newly increase between EW 19-34, and a steady state after EW 34 (Figure 1A, 1B, S1). Daily cases ranged from 1 to 4386 per day, and EW 34 registered the highest number of cases per day: 4141 and 4386.

Additionally, we report department clusters with a high occurrence of daily COVID-19 cases, which follow different dynamic patterns for ACs and symptomatic patients (Figure 1C-1D).

Throughout April, AC reports in Meta and Amazonas peaked; in May they peaked in Cartagena, Antioquia and Bogota, with Bogota's peak lasting until August 31st; in June-July, AC cases peaked in Atlantico, Barranquilla and Cordoba; and in August, they peaked in Santander and Cundinamarca. Overall, the frequency of ACs in Colombia has followed a dichotomic trend as shown in the lateral cluster of figure 1c: AC occurrences are distributed between the highly frequent profile in Bogota during most of the epidemic and the intermittent peak occurrences of the rest of Colombian departments.

More than half of the imported ACs came from Europe, specifically Spain, followed by North and South America. Those that arrived from Spain and USA were distributed mainly in Bogotá, Cundinamarca, Antioquia, and Valle del Cauca. Amazonas department only received imported ACs from South American countries. The origin and distribution of imported symptomatic patients was more diverse; however, most cases originated from Spain, USA, Ecuador, Mexico, Brazil, or Panama, and were mainly distributed across Bogotá, Antioquia, and Valle del Cauca (Figure 2).

More than 90% of ACs were located in Bogotá, Atlantico and Meta; However, Bogota, Amazonas and Putumayo reported the highest AC rates per 100.000 population (Table 1,

Table S1). Median age was 37 years old, lower than the symptomatic patients. Most of them were males (Table 1). By August 31st, most ACs were classified as recovered (85.8%; 85.6-86.1%) or in domiciliary isolation (13.6%; 13.4-13.8%), and 356 patients (0.46%; 0.42-052%) were diagnosed during their stay in ICUs (80 patients), general hospitalization services (185 patients) or in post-mortem phase (91 deceased). These 356 cases may have been treated for symptoms unrelated to COVID-19 or perhaps RT-PCR results arrived late, with some arriving even after the patient had already passed away.

Factors associated with AC condition.

Using the PC-CA and PC-PCAmix, a group of six countries and three groups of departments were associated with AC state (Figure 3). To execute LRMs, the variables "age group 0-26 years" and "male sex" were transformed into dummi [0/1]. With a preliminary LRM, a higher β coefficient was estimated in relation to cases imported from countries associated with ACs, therefore, the variable "geographical origin" was created, composed of the categories "imported from countries associated with symptomatic" [Imported CAS - referent], "imported from countries associated with ACs" [Imported CA-ACs] and "related cases". Additionally, a variable was created for the departments grouped with the PCAmix [departments with low association - referent] and for the EW (EW 10-34 - referent). The first LRM (main effects) identified a significant association of all index sociodemographic categories with ACs state (Table S2). The second model explores the following interactions: 1. Geographical origin and grouped departments, 2. Geographical origin and EW, 3. Age group (0-26 years) and gender, 4. Grouped departments and gender; and, 5. Age (0-26 years) and EW. We identified interactions between the variables "gender" (males), "age" (0-26 years), and "EW" and the grouped departments; and between the variables "gender" (males) and "age" (0-26 years) (Table 2).

Variables "age" (0-26 years), "gender" (male), "departments with moderate or strong association", "imported CA-ACs" and "related cases" were found to increase the risk of identifying ACs state. It was also determined that the risk increased for males (0-26 years), especially for those located in departments with a strong or moderate association since EW 35. However it should be noted that the risk of identifying ACs has decreased since EW 35 when only taking isolated estimates into account (Table 2).

DISCUSSION

We found that, in an isolated fashion, age <27 years old, imported cases from a group of 6 countries, autochthonous cases and the occurrence in groupings of departments were associated with AC state. Additionally, the risk of being a male AC was only identified in departments with moderate or strong risk, and the risk was variable in the groupings of departments throughout specific epidemiological periods.

Additionally, our results show that the proportion of ACs in Colombia lays between 12-12.2% (Table 1), a lower estimate than previously described in other case series or mass screening studies with reported proportions between 5-80% [11–14]. Given the inclusion of pre-symptomatic patients or the unification of AC with non-critical symptoms in some reports, we cannot rule out that a non-differential classification bias influenced these estimates. An adapted definition for AC in Colombia may address this limitation.

Figure 1 shows that the majority of imported cases to Colombia came from Spain and USA, where AC rates have been estimated at 2.5% and 25%, respectively [14,15]. Although imported cases carry a distinctive genetic load that, population-wise, could manifest itself as a particular phenotype [16], currently there are no reports of genetic variants associated with AC in general or for any of the four AC subtypes described in the literature [17]. Subsequent research should be conducted on the possible association between ACs and phylogenetic variants (or other variables) to support the differential risk identified in imported cases from different regions of the world.

We identified that imported cases from a group of 6 countries were strongly associated with AC (Figure 2, Table S1, Table 2), and although no interaction was established between the country of import and the destination department (data not shown), we observed that departments strongly associated with AC had less diversity of import origin. Such is the case of Meta and Amazonas, which exclusively imported cases from USA and Brazil/Peru, respectively (Figure 2).

Among the demographic characteristics, the association between AC state and patients under 27 years of age stands out. Possible explanations for this observation include: (i) the lower presence of co-morbid conditions and baseline health issues within this age group and (ii) the higher risk of exposure through work activities which are greater in this age group [18]. However, clinical or social environment could also explain this finding, as a study in skilled nursing facility residents showed a high proportion of AC in those over 70 years of age, however this was a premature finding since most patients were later reclassified as pre-symptomatic or pauci-symptomatic [11].

We identified a higher frequency of men infected with COVID-19 consistent with reports from other countries around the world, except in Spain and Switzerland, where women ranked first [19]. Frequent occupations performed by men, as well as certain immunological and genetically susceptible backgrounds have been associated with this finding [19,20]. In particular, the risk of being an AC was higher in men, and increased in geographic areas associated with AC. This interaction is not uncommon given that professions regularly carried out by men, including those such as taxi driving, private security or prison guarding, among other work settings, can be distributed asymmetrically within countries, a pattern that would explain our findings [20].

The phases on the occurrence of cases throughout EWs and the interaction with groupings within departments associated with AC has been previously described in Chongqing, China, where researchers identified significant changes in the frequency of cases after implementation of geographic isolation measures. The dynamic changes in the detection and distribution of ACs throughout EWs could be explained by the surveillance strategy executed in Colombia kwon as "PRASS" (in Spanish, tests, surveillance, and sustainable selective isolations); this can be particularly observed from EW 30 onwards (figure S1) [21]. In Wuhan, a study showed that one group of ACs was linked to imported cases while others were linked mostly to autochthonous cases from geographically isolated areas of Wuhan [22]. We identified that in addition to being associated with a travel history to foreign countries, ACs were also associated with cases that appear spontaneously (related), occurring differentially as measures of geographic and social isolation were applied.

The lack of mass screening for COVID-19 in Colombia is the main limitation of our study since the actual AC ratio and the distribution of specific characteristics may differ from those estimated in this report. On the other hand, although a cross-sectional design is not ideal to identify risk factors, to the best of our knowledge this is the first study aimed at identifying factors associated with AC state with population data unbiased by the inclusion of pre-symptomatic cases [23].

The COVID-19 pandemic has had serious socioeconomic implications, including a collapse of healthcare systems, bankruptcy of companies as well as increasing trends in unemployment and crime rates [24–27]. This has forced countries with limited resources---such as Colombia---to perform massive screenings in order to prematurely lift quarantine and isolation measures despite the latent risk of successive outbreaks caused by a potential silent spread of COVID-19 through cases in the pre-symptomatic phase or AC state [28,29].

ACs transmit COVID-19 more efficiently than symptomatic patients for up to 21 days after the presumed date of infection [30,31]. This led to their inclusion in mathematical models intended to estimate the probability or expected number of person-to-person infections on repatriation trips from Wuhan, China [7,32]. Since then, ACs have become the target of mass screening in Asian and European countries effectively reducing economical losses due to unnecessary hospital care, controlling the spread in public or in-hospital settings, and allowing the execution of safe plans of social and work re-integration after quarantine and isolation [28,33–37].

To date, testing of asymptomatic individuals' rests at the discretion of physicians when justified on a case-by-case basis. On the other hand, the utility of SARS-CoV-2 testing for broad screening of asymptomatic individuals remains to be determined given the limited sensitivity data available for most commercially available test kits [38].

CONCLUSION

283 Together, our findings demonstrate sociodemographic trends strongly associated with COVID-19 AC state in Colombia at a departmental and national level. We believe that the implementation of massive screening campaigns to detect AC and pre-symptomatic patients is paramount to further characterize this phenomenon and adequately guide public health measures of containment and prevention. Additional molecular analysis of viral and host genotypic characteristics should be conducted to determine possible associations with AC state.

Authors contributorship statement

AT, APM and JDR designed the study. AT, GC, RPG, CH, GH, LMP, LAP and AA conducted the statistical and descriptive analyses. CF, ECB provided the data for the analysis. AT, APM, LAP and JDR drafted the manuscript. All authors approved the final version of the manuscript.

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Data sharing statement: Data is freely available from the National Institute of Health (INS) database on COVID-19 cases updated until August 31, 2020 (https://www.ins.gov.co/Noticias/Paginas/coronavirus-casos.aspx).

Conflicts of Interest: The authors declare no conflict of interest.

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Figure Legends

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Figure 1. Daily accumulation and distribution of ACs by epidemiological week in Colombia. A. The y-axis represents the number of cumulative ACs transformed into a base 10 logarithm. The number of cumulative cases per day is located in points that increase in color intensity according to the occurrence of cases. **B.** The y-axis represents the number of daily ACs transformed into a base 10 logarithm. The number of daily cases per day is located in boxplots. **C.** Heatmap showcasing the number of ACs (top) and **B.** symptomatic patients (bottom) diagnosed in every Colombian department until August 31st, 2020.

Figure 2. Origin and destination of imported asymptomatic and symptomatic cases. The left and right figures, respectively, represent the country of origin and destination department of ACs and symptomatic patients. The thickness of the link tapes corresponds to the number of reported cases.

Figure 3. Groups of countries and departments associated with AC state. The left figure shows the group of countries associated with asymptomatic carrier (AC) state identified with positive values of the CCC-CA. The right figure shows departments grouped according to three intervals of CCC-CA: low association (CCC-CA: negative values), moderate association (CCC-CA:> 0 - <0.05), and strong association (CCC-CA: ≥0.5).

Supplementary materialTable S1. AC state frequency in Colombia by department

Table S2. Factors associated with AC state in Colombia

Figure S1. The stacked bar figure represents on the y-axis the epidemiological weeks (EW) and on the x-axis the proportion of symptomatic (green section of the bar) and the proportion of asymptomatic (purple section of the bar), as well as the result of a Chi square independence

326 test that shows statistical association between the EW variables and health status

327 (symptomatic/asymptomatic carrier).

328 **Table 1.** Sociodemographic characteristics of the asymptomatic and symptomatic patients

Variables	Asymptomatic n: 76162	Symptomatic n: 550725	p-value
Age, years	35 (25-49)	37 (27-52)	<0.001
0-26	21310 (27.9)	129529 (23.5)	<0.001
≥27	54852 (72.0)	421196 (76.4)	<0.001
Sex			
Male	38836 (50.9)	283068 (51.4)	0.035
Female	37326 (49.0)	267657 (48.6)	0.035
Geographical source			
Related†	76108 (99.9)	549789 (99.8)	<0.001
Imported	54 (0.07)	936 (0.170)	<0.001
Departments††			
Bogotá	68143 (89.4)	148258 (26.9)	<0.001
Atlántico	1455 (1.91)	26059 (4.73)	<0.001
Meta	836 (1.10)	8532 (1.55)	<0.001
Barranquilla	737 (0.97)	34262 (6.22)	<0.001
Cundinamarca	690 (0.91)	23222 (4.22)	<0.001
Imported cases†††	53	905	958
Spain	19 (35.8)	246 (27.2)	0.170

USA	14 (26.4)	208 (22.9)	0.565
Brazil	8 (15.1)	53 (5.86)	0.007
Mexico	3 (5.66)	51 (5.64)	0.994
Venezuela	3 (5.66)	8 (0.88)	0.002
Argentina	1 (1.89)	4 (0.44)	0.156
France	1 (1.89)	19 (2.10)	0.916
Germany	1 (1.89)	11 (1.22)	0.669
Peru	1 (1.89)	24 (2.65)	0.734
Puerto Rico	1 (1.89)	12 (1.33)	0.732
Turkey	1 (1.89)	27 (2.98)	0.645
Unknow	1	31	NA

†: cases that appeared spontaneously in Colombia, ††: top 5 of the departments with the highest frequency of AC. †††: the total number of imported asymptomatic and symptomatic cases was used as the denominator to estimate proportions by country of origin.

Table 2. Factors associated with asymptomatic carrier (AC) state in Colombia

Variable	Interaction model		
	β	**ORc (95%, CI)**	**p-value**
Intercept	**-7.316**	-	<0.001
Age			
>26 years	**Ref.**	-	-
0-26 years	0.172	1.188 (1.096-1.287)	<0.001

Sex			
Female	**Ref.**	-	-
Male	0.414	1.513 (1.408-1.625)	<0.001
Department			
Low association [1]	**Ref.**	-	-
Moderate association [2]	0.211	1.234 (1.137-1.340)	<0.001
Strong association [3]	2.986	19.81 (18.61-21.08)	<0.001
Geographical source			
Imported CAS†	**Ref.**	-	-
Imported CA-AC††(1)	2.536	12.62 (3.034-52.54)	<0.001
Related cases†††(2)	3.121	22.67 (5.620-91.47)	<0.001
EW			
10-34	**Ref.**	-	
≥35	-1.008	0.365 (0.320-0.415)	<0.001
0-26 years + Male	0.047	1.048 (1.010-1.089)	**0.014**
0-26 years + Department [2]	0.174	1.190 (1.069-1.325)	**0.001**
0-26 years + Department [3]	-0.005	0.995 (0.919-1.077)	0.898
Department [2] + Male	-0.387	0.679 (0.615-0.749)	**<0.001**
Department [3] + Male	-0.377	0.686 (0.637-0.737)	**<0.001**
EW ≥35 + Department [2]	-0.862	0.422 (0.315-0.567)	**<0.001**
EW ≥35 + Department [3]	2.217	9.182 (8.045-10.47)	**<0.001**

†: CAS countries associated with symptomatic patients, ††: CA-AC countries associated with asymptomatic carriers (AC), †††: spontaneous cases, **EW:** epidemiological weeks.

References.

1. Coronavirus en Colombia. https://www.ins.gov.co/Noticias/Paginas/Coronavirus.aspx. Accessed May 10, 2020.

2. Rudan I. A cascade of causes that led to the COVID-19 tragedy in Italy and in other European Union co1. Rudan I. A cascade of causes that led to the COVID-19 tragedy in Italy and in other European Union countries. J Glob Health. 2020; 10(1):10335. untries. *J Glob Health*. 2020;10(1):10335. doi:10.7189/jogh-10-010335

3. Yi Y, Lagniton PNP, Ye S, Li E, Xu R-H. COVID-19: what has been learned and to be learned about the novel coronavirus disease. *Int J Biol Sci*. 2020;16(10):1753-1766. doi:10.7150/ijbs.45134

4. Tindale L, Coombe M, Stockdale JE, et al. Transmission interval estimates suggest pre-symptomatic spread of COVID-19. *medRxiv*. January 2020:2020.03.03.20029983. doi:10.1101/2020.03.03.20029983

5. Zhang W. Estimating the presymptomatic transmission of COVID19 using incubation period and serial interval data. *medRxiv*. January 2020:2020.04.02.20051318. doi:10.1101/2020.04.02.20051318

359 6. Rahimi F, Talebi Bezmin Abadi A. Challenges of managing the asymptomatic
360 carriers of SARS-CoV-2. *Travel Med Infect Dis*. April 2020:101677.
361 doi:10.1016/j.tmaid.2020.101677

362 7. Teherán AA, Camero G, Prado R, et al. Presumptive asymptomatic COVID-19
363 carriers' estimation and expected person-to-person spreading among repatriated
364 passengers returning from China. *Travel Med Infect Dis*. April 2020:101688.
365 doi:10.1016/j.tmaid.2020.101688

366 8. Lavezzo E, Franchin E, Ciavarella C, et al. Suppression of COVID-19 outbreak in
367 the municipality of Vo, Italy. *medRxiv*. January 2020:2020.04.17.20053157.
368 doi:10.1101/2020.04.17.20053157

369 9. Oliveira G. Refined compartmental models, asymptomatic carriers and COVID-19.
370 *medRxiv*. January 2020:2020.04.14.20065128. doi:10.1101/2020.04.14.20065128

371 10. Yu Y, Liu Y-R, Luo F-M, et al. COVID-19 Asymptomatic Infection Estimation.
372 *medRxiv*. January 2020:2020.04.19.20068072. doi:10.1101/2020.04.19.20068072

373 11. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections
374 and transmission in a skilled nursing facility. *N Engl J Med*. 2020.
375 doi:10.1056/NEJMoa2008457

376 12. Wong J, Abdul Aziz ABZ, Chaw L, et al. High proportion of asymptomatic and
377 presymptomatic COVID-19 infections in travelers and returning residents to Brunei.
378 *J Travel Med*. 2020. doi:10.1093/jtm/taaa066

379 13. Hijnen D, Marzano AV, Eyerich K, et al. SARS-CoV-2 Transmission from
380 Presymptomatic Meeting Attendee, Germany. *Emerg Infect Dis*. 2020.

381 doi:10.3201/eid2608.201235

382 14. COVID-19: What proportion are asymptomatic? - CEBM.
383 https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/.
384 Accessed June 16, 2020.

385 15. Ministerio de Sanidad C. Estudio Nacional de sero-Epidemiología de la Infección
386 por SARS-CoV-2 en España (ENE-Covid). Informe PRELIMINAR tras la primera
387 ronda (13/05/2020). *Gob España*. 2020;(May 13).

388 16. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-
389 CoV-2 genomes. *Proc Natl Acad Sci U S A*. 2020. doi:10.1073/pnas.2004999117

390 17. Zhou X, Li Y, Li T, Zhang W. Follow-up of asymptomatic patients with SARS-
391 CoV-2 infection. *Clin Microbiol Infect*. 2020. doi:10.1016/j.cmi.2020.03.024

392 18. Yang R, Gui X, Xiong Y. Comparison of Clinical Characteristics of Patients with
393 Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China. *JAMA*
394 *Netw open*. 2020. doi:10.1001/jamanetworkopen.2020.10182

395 19. Márquez EJ, Trowbridge J, Kuchel GA, Banchereau J, Ucar D. The lethal sex gap:
396 COVID-19. *Immun Ageing*. 2020;17(1):13. doi:10.1186/s12979-020-00183-z

397 20. Koh D. Occupational risks for COVID-19 infection. *Occup Med (Chic Ill)*.
398 2020;70(1):3-5. doi:10.1093/occmed/kqaa036

399 21. Instituto Nacional de Salud – Ministerio de Salud y Protección Social. Orientaciones
400 para la Vigilancia en Salud Pública de la Covid19. ORIENTACIONES PARA LA
401 VIGILANCIA EN SALUD PÚBLICA DE LA COVID-19. Colombia: INS –

Minsalud;2020. Documento Técnico Científico.

22. Tao Y, Cheng P, Chen W, et al. High Incidence of Asymptomatic SARS-CoV-2 Infection, Chongqing, China. *SSRN Electron J*. 2020. doi:10.2139/ssrn.3559583

23. Sahu K, Kumar R. Preventive and treatment strategies of COVID-19: From community to clinical trials. *J Fam Med Prim Care*. 2020;9(5):2149-2157. doi:10.4103/jfmpc.jfmpc_728_20

24. Nussbaumer-Streit B, Mayr V, Dobrescu Ai, et al. Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. *Cochrane Database Syst Rev*. 2020;(4). doi:10.1002/14651858.CD013574

25. Nicola M, Alsafi Z, Sohrabi C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *Int J Surg*. 2020;78:185-193. doi:https://doi.org/10.1016/j.ijsu.2020.04.018

26. Kalleberg AL, Wachter TM von. The U.S. Labor Market During and After the Great Recession: Continuities and Transformations. *RSF Russell Sage Found J Soc Sci*. 2017;3(3):1-19. doi:10.7758/rsf.2017.3.3.01

27. Sutherland M, McKenney M, Elkbuli A. Gun violence during COVID-19 pandemic: Paradoxical trends in New York City, Chicago, Los Angeles and Baltimore. *Am J Emerg Med*. 2020. doi:10.1016/j.ajem.2020.05.006

28. Gilbert M, Dewatripont M, Muraille E, Platteau JP, Goldman M. Preparing for a responsible lockdown exit strategy. *Nat Med*. 2020. doi:10.1038/s41591-020-0871-y

29. World Health Organisation. Considerations in adjusting public health and social

measures in the context of COVID-19. *World Heal Organ*. 2020;(April):1-7. https://www.who.int/publications-detail/risk-.

30. Prather KA, Wang CC, Schooley RT. Reducing transmission of SARS-CoV-2. *Science (80-)*. 2020. doi:10.1126/science.abc6197

31. Huff H V, Singh A. Asymptomatic transmission during the COVID-19 pandemic and implications for public health strategies. *Clin Infect Dis*. May 2020. doi:10.1093/cid/ciaa654

32. Gostic K, Gomez ACR, Mummah RO, Kucharski AJ, Lloyd-Smith JO. Estimated effectiveness of symptom and risk screening to prevent the spread of COVID-19. Franco E, Ferguson NM, McCaw JM, eds. *Elife*. 2020;9:e55570. doi:10.7554/eLife.55570

33. Peto J, Alwan NA, Godfrey KM, et al. Universal weekly testing as the UK COVID-19 lockdown exit strategy. *Lancet*. 2020. doi:10.1016/S0140-6736(20)30936-3

34. Mallapaty S. Will antibody tests for the coronavirus really change everything? *Nature*. 2020. doi:10.1038/d41586-020-01115-z

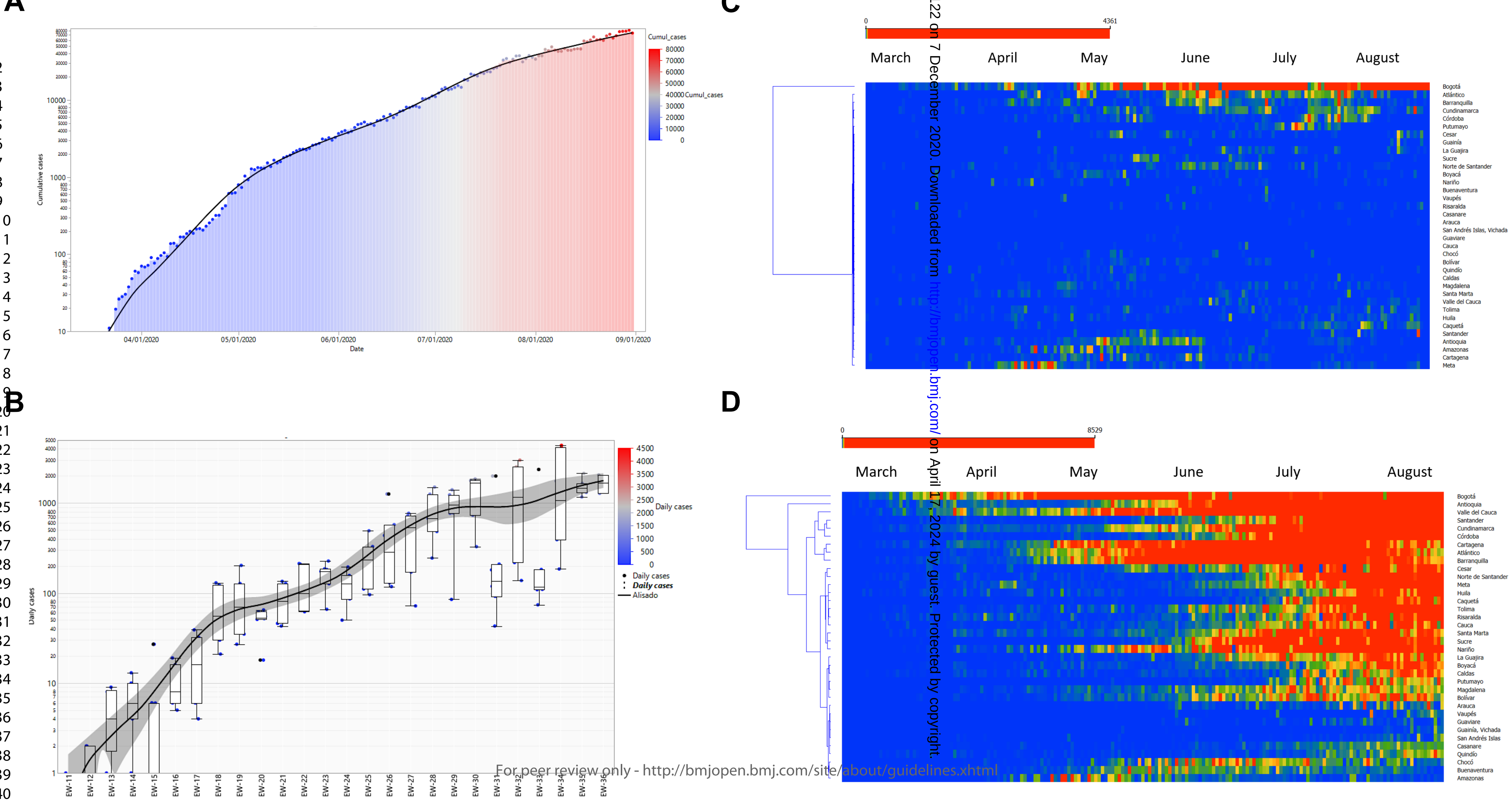
35. The race against COVID-19. *Nat Nanotechnol*. 2020. doi:10.1038/s41565-020-0680-y

36. Mark K, Steel K, Stevenson J, et al. Coronavirus disease (COVID-19) community testing team in Scotland: A 14-day review, 6 to 20 February 2020. *Eurosurveillance*. 2020. doi:10.2807/1560-7917.ES.2020.25.12.2000217

37. Rosenthal PJ. The importance of diagnostic testing during a viral pandemic: Early

lessons from novel coronavirus disease (CoVID-19). *Am J Trop Med Hyg*. 2020. doi:10.4269/AJTMH.20-0216

38. Woloshin S, Patel N, Kesselheim AS. False Negative Tests for SARS-CoV-2 Infection — Challenges and Implications. *N Engl J Med*. 2020. doi:10.1056/nejmp2015897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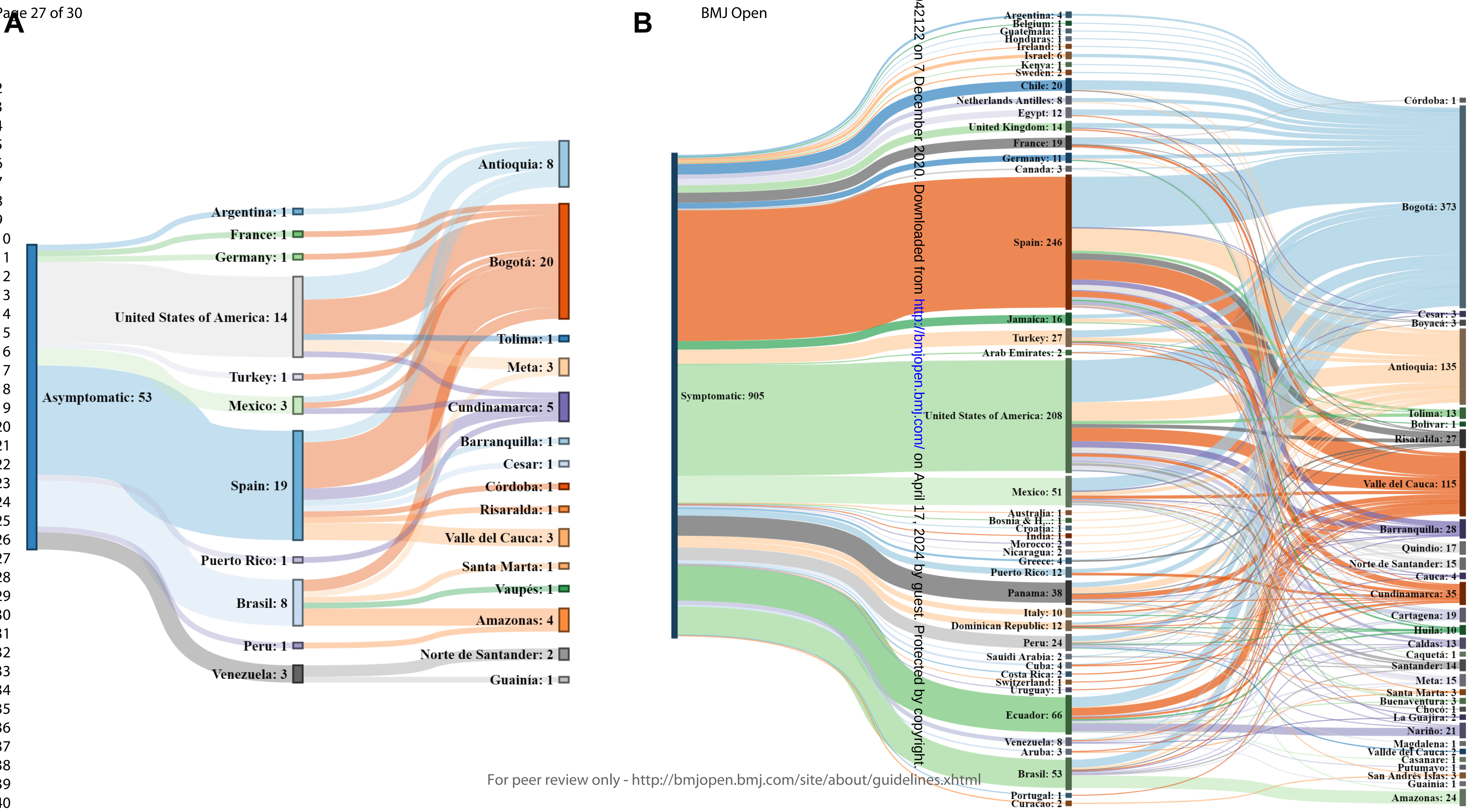
Chocó
Buenaventura
Amazonas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Santa Marta: 1
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Greece: 4
Puerto Rico: 12
Panama: 38
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Peru: 24
Sauidi Arabia: 2
Cuba: 4
Costa Rica: 2
Switzerland: 1
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Ecuador: 66
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La Guajira: 2
Nariño: 21
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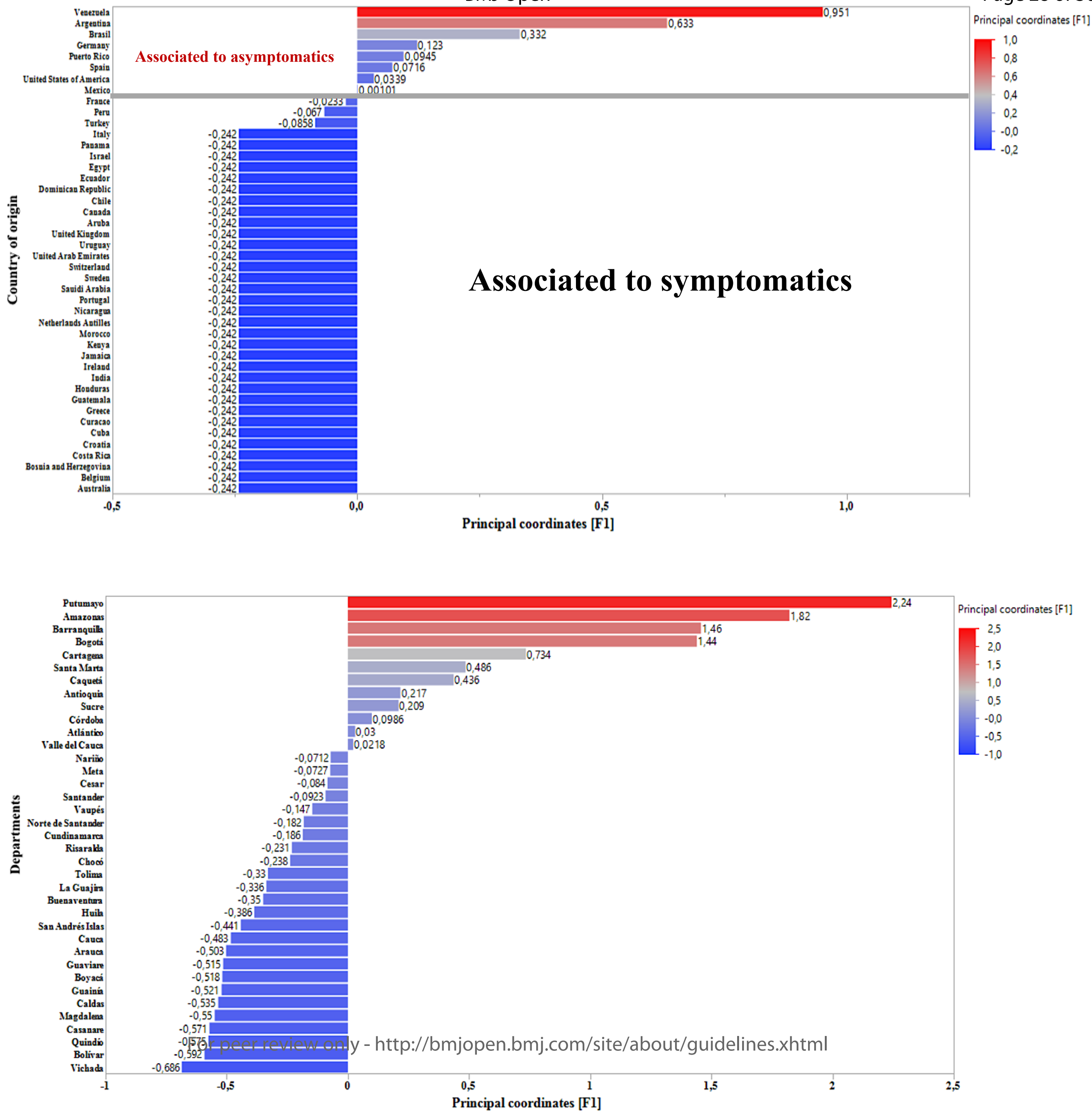
A

B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Associated to symptomatics
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Germany 0,123
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Spain 0,0716
United States of America 0,0339
Mexico 0,00101
France -0,0233
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Italy -0,242
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Dominican Republic -0,242
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Cartagena 0,734
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Caquetá 0,436
Antioquia 0,217
Sucre 0,209
Córdoba 0,0986
Atlántico 0,03
Valle del Cauca 0,0218
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Vaupés -0,147
Norte de Santander -0,182
Cundinamarca -0,186
Risaralda -0,231
Chocó -0,238
Tolima -0,33
La Guajira -0,336
Buenaventura -0,35
Huila -0,386
San Andrés Islas -0,441
Cauca -0,483
Arauca -0,503
Guaviare -0,515
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Guainía -0,521
Caldas -0,535
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No
Yes
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χ²: 14305.42 (p=0.000, dof=26)

Table S1. AC state frequency in Colombia by department

Department	Asympt_cases	%	Population	Asympt_rate*	Sympt_rate*
Bogotá	68143	89.5	7743955	880,0	1914.5
Atlántico	1455	1.91	2722128	53,5	957.3
Meta	836	1.10	1063454	78,6	802.3
Barranquilla	737	0.97	1243113	59,3	2756.1
Cundinamarca	690	0.91	3242999	21,3	716.1
Antioquia	518	0.68	6677930	7,8	1239.0
Córdoba	468	0.60	1828947	25,6	1072.0
Cartagena	437	0.57	1060577	41,2	1860.5
Amazonas	333	0.44	79020	421,4	2856.2
Putumayo	262	0.34	79020	331,6	3478.9
Norte de Santander	248	0.33	1620318	15,3	727.8
Caquetá	207	0.27	410521	50,4	1474.5
Cesar	195	0.26	1295387	15,1	851.6
Santander	190	0.25	2280908	8,3	847.8
Tolima	153	0.20	1339998	11,4	544.1
Huila	151	0.20	1122622	13,5	470.6
Sucre	151	0.20	949252	15,9	1221.6
La Guajira	140	0.18	965718	14,5	533.0
Boyacá	113	0.15	1242731	9,1	308.5
Magdalena	112	0.15	1427026	7,8	269.8
Valle del Cauca	111	0.15	4532152	2,4	997.9
Santa Marta	94	0.12	538612	17,5	1569.8
Nariño	69	0.09	1627589	4,2	878.5
Bolívar	57	0.07	2180976	2,6	221.9
Caldas	51	0.07	1018453	5,0	291.0
Risaralda	46	0.06	961055	4,8	675.6
Quindío	45	0.05	555401	8,1	236.9
Chocó	39	0.05	544764	7,2	664.9
Guainía	39	0.05	50636	77,0	237.0
Vaupés	27	0.04	44712	60,4	726.9
Buenaventura	20	0.03	440989	4,5	526.1
Cauca	18	0.02	1491937	1,2	360.9
Casanare	7	0.01	435195	1,6	248.9
Arauca	3	<0.01	294206	1,0	335.8
Guaviare	3	<0.01	86657	3,5	318.5
San Andrés Islas	2	<0.01	63692	3,1	411.4
Vichada	2	<0.01	112958	1,8	103.6

The total number of Asymptomatic carriers (ACs) was used as the denominator to determine proportions. **Asympt_cases:** asymptomatic cases, **Symptomatic cases:** see in supplementary file. ***Asympt_rate:** (Asympt_cases/population)*100.000 habitants. ***Sympt_rate:** (Asympt_cases/population)*100.000 habitants.

Table S2. Factors associated with AC state in Colombia.

Variable	**Main effects**		
	β	**ORa (95%, CI)**	**p-value**
Intercept	**-7.360**	-	**<0.001**
Age,			
>26 years old	**Ref.**	-	-
0-26 years old	0.205	1.227 (1.205-1.250)	**<0.001**
Sex			
Female	**Ref.**	-	-
Male	0.054	1.055 (1.038-1.073)	**<0.001**
Department			
Low risk	**Ref.**	-	-
Moderate risk	1.304	3.372 (3.134-4.330)	**<0.001**
Strong risk	1.909	8.310 (6.101-7.464)	**<0.001**
Geographical origin			
Imported CAS†	**Ref.**	-	-
Imported CA-AC††	2.541	12.68 (3.049-52.77)	**<0.001**
Related cases†††	3.255	25.90 (6.425-104.4)	**<0.001**
EW			
10-34	**Ref.**	-	
≥35	0.933	2.543 (2.484-2.603)	**<0.001**

†: CAS countries associated to symptomatic patients**, ††:** CA-AC countries associated to ACs**, †††: spontaneous cases**, **EW:** epidemiological week.

BMJ Open

Epidemiological characterization of asymptomatic carriers of COVID-19 in Colombia: A cross-sectional study.

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	Epidemiology < TROPICAL MEDICINE, VIROLOGY, INFECTIOUS DISEASES

Epidemiological characterization of asymptomatic carriers of COVID-19 in Colombia: A cross-sectional study.

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ABSTRACT (187 words)

Introduction: Asymptomatic carriers (AC) of the new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) represent an important source of spread for Coronavirus Disease 2019 (COVID-19). Early diagnosis of these cases is a powerful tool to control the pandemic. Our objective was to characterize patients with AC status and identify associated sociodemographic factors.

Methods: Using a cross-sectional design and the national database of daily occurrence of COVID-19, we characterized both socially and demographically all ACs. Additional Correspondence Analysis and Logistic Regression Model were performed to identify characteristics associated with AC state (OR, 95% CI).

Results: 76.162 ACs (12.1%; 95%CI, 12.0-12.2%) were identified, mainly before epidemiological week 35 [EW]. Age ≤26 years (1.18;1.09-1.28), male sex (1.51;1.40-1.62), cases imported from Venezuela, Argentina, Brazil, Germany, Puerto Rico, Spain, United States of America or Mexico (12.6;3.03-52.5) and autochthonous cases (22.6;5.62-91.4) increased the risk of identifying ACs. We also identified groups of departments with moderate (1.23;1.13-1.34) and strong (19.8;18.6-21.0) association with ACs.

Conclusion: Sociodemographic characteristics strongly associated with AC were identified, which may explain its epidemiological relevance and usefulness to optimize mass screening strategies and prevent person-to-person transmission.

Key words: COVID-19; Asymptomatic; Carrier States; Risk factors, Novel Coronavirus.

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Strengths and limitations:

- Cross-sectional studies are useful to identify possible variables associated with ACs.
- Weekly surveillance of potential cases reduced selection and classification bias of ACs.
- The large number of COVID-19 ACs included in this study allowed to draw precise estimates.
- The ongoing epidemic phase of COVID-19 in Colombia decreases the uncertainty of invisible subgroup occurrences.
- Estimates and characteristics associated with ACs may improve epidemiological surveillance in other countries.

63 **TEXT (2481 words)**

64 ## INTRODUCTION

65 In March 2nd, 2020, Colombia reported the first case of Coronavirus Disease 2019 (COVID-19), and as of September 22nd, more than 700,000 cases have been confirmed nationwide [1]. Asymptomatic carriers (AC) may be associated with the accelerated growth of cases in the initial phases of the pandemic, inadvertently spreading the infection to close contacts. In this case, transmission can only be limited until a diagnosis of SARS-CoV-2 infection is rendered after (i) isolation due to symptom onset, (ii) contact tracing or (iii) identification during massive screening strategies [2,3].

72 AC and pre-symptomatic cases are epidemiologically relevant since they represent a silent source of spread in various public settings (e.g. public transportation, emergency rooms, supermarkets, shelters) [4–6]. The proportion of ACs has been estimated at 15-25%, but seroprevalence studies have reported values of up to 43.2% (95% CI, 32.2-54.7%). Nonetheless, many pre-symptomatic patients are wrongfully classified as ACs during the incubation phase; to later become pauci-symptomatic or develop respiratory manifestations ranging from pneumonia to respiratory failure, or exhibit any other clinical symptoms within the COVID-19 spectrum [4–8].

80 Epidemiological predictive models have been developed and updated to incorporate silent mobility through AC phenotype in anticipation for the second and third epidemic waves of COVID-19. Such is the case for the SEIR model (Susceptible, Exposed, Infected and Recovered), recently updated to SEAIR (Susceptible, Exposed, Asymptomatic, Infected and Recovered) [9]. In China, estimates indicate that 60-65% of ACs remained undetected.

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Therefore, under the SEIR model and applying machine-learning-based transmission simulators (MLSim), including the number of undetected AC within its parameters and assuming 15 close contacts per day, estimates suggest that as of April 15th, 2020, the United States---the country contributing the majority of cases imported to Colombia---, could have presented 277,641-to-495,128 latent cases of COVID-19, potentially increasing the spread of the virus [10].

The assessment of ACs and the identification of sociodemographic characteristics associated with this subpopulation could be useful to estimate sample calculations in massive screening studies, as well as adjust control and mitigation measures---especially the intensity of isolation. Therefore, the objective of our study was to characterize ACs demographically and socially, as well as to identify individual characteristics in interaction models associated with ACs.

METHODOLOGY

Design and data selection.

We performed a cross-sectional study with information from the National Institute of Health (INS) database on COVID-19 cases updated until August 31, 2020 (https://www.ins.gov.co/Noticias/Paginas/coronavirus-casos.aspx). By INS protocol, suspected AC cases remained in quarantine for 7 days while monitoring the appearance of symptoms on a daily basis; on the eighth day, a nasal swab sample was collected to identify or rule out AC state. Records without health status information (symptomatic, asymptomatic) were excluded. The database is public, with de-identified patient data and IRB approval was thus exempt.

107 **Patient and Public Involvement (PPI) statement**

108 This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

112 **Database and variables.**

113 We used variables such as date of diagnosis, age, sex, country of origin, department, case type (imported, related), care setting (home, nursing home, hospital, intensive care unit) and outcome (recovered, convalescent, deceased). The date of diagnosis was adjusted into epidemiological weeks (EW), which were later grouped according to the pattern of AC occurrence (Figure S1) in EW 10-34, ≥35; additionally, the variable AC [yes, no] was established.

119 **Statistical analysis**

120 Data are presented in medians or proportions estimated with 95% CI due to the lack of massive screening for COVID-19 in certain areas of the country; additionally, we estimated AC rates per 100.000 population by departments using Colombian demographic estimates for 2020 from the National Administrative Department of Statistics (DANE). The geographical origin and destination of imported cases was represented with a Sankey Plot (SankeyMATIC (BETA). Cumulative trends and case charts were created with the number of daily cases by Epid_weeks (RStudio Version 1.2.5042). In addition, a heatmap analysis was included to depict a dynamic representation of daily cases by Department from March 6th through August 31rd, 2020 (Orange Data Mining & Fruitful Fun, Version 3.25). The

proportion of asymptomatic and symptomatic patients and the median age were compared with the Z and U Mann Whitney tests respectively (significant p-value <0.05, two tails) [Addinsoft. 2020. XLSTAT statistical and data analysis solution. New York, USA. https://www.xlstat.com]. Age was dichotomized between 0-26 and ≥27 years due to its association with asymptomatic and symptomatic states respectively (preliminary exploratory analysis not shown).

Countries of origin and departments associated with ACs were identified, respectively, with a Correspondence Analysis (CA) and Factorial analysis of mixed data using PCAmix. Raw data were used for CA while symptomatic and AC rates per 100.000 population were used for PCAmix . Additionally, with principal coordinates (PC) obtained with both CA (PC-CA) and PCAmix (PC-PCAmix), groups with a variable level of association with ACs were created. [Addinsoft. 2020. XLSTAT statistical and data analysis solution. New York, USA. https://www.xlstat.com].

To estimate the association between sociodemographic characteristics with ACs (OR 95%), two Logistic Regression Models (LRM) were performed, the first to establish the main effects and the second a step-backward interaction model of the second level (p- value in <0.05; p-value out:$>$ 0.1), which used the lowest Akaike criteria to select the best model (JASP Team (2020). JASP (Version 0.12.2))

RESULTS

General characteristics

We identified 76.162 ACs (12.1%; 12.0-12.2%) out of 626.887 cases reported in the database. Four cases were excluded due to lack of health status information. The occurrence of AC state in relation to symptomatic presented a continuous growth phase between EW 10-17, and a peak at EW 18, followed by a newly increase between EW 19-34, and a steady state after EW 34 (Figure 1A, 1B, S1). Daily cases ranged from 1 to 4386 per day, and EW 34 registered the highest number of cases per day: 4141 and 4386.

Additionally, we report department clusters with a high occurrence of daily COVID-19 cases, which follow different dynamic patterns for ACs and symptomatic patients (Figure 1C-1D).

Throughout April, AC reports in Meta and Amazonas peaked; in May they peaked in Cartagena, Antioquia and Bogota, with Bogota's peak lasting until August 31st; in June-July, AC cases peaked in Atlantico, Barranquilla and Cordoba; and in August, they peaked in Santander and Cundinamarca. Overall, the frequency of ACs in Colombia has followed a dichotomic trend as shown in the lateral cluster of figure 1c: AC occurrences are distributed between the highly frequent profile in Bogota during most of the epidemic and the intermittent peak occurrences of the rest of Colombian departments.

More than half of the imported ACs came from Europe, specifically Spain, followed by North and South America. Those that arrived from Spain and USA were distributed mainly in Bogotá, Cundinamarca, Antioquia, and Valle del Cauca. Amazonas department only received imported ACs from South American countries. The origin and distribution of imported symptomatic patients was more diverse; however, most cases originated from Spain, USA, Ecuador, Mexico, Brazil, or Panama, and were mainly distributed across Bogotá, Antioquia, and Valle del Cauca (Figure 2).

More than 90% of ACs were located in Bogotá, Atlantico and Meta; However, Bogota, Amazonas and Putumayo reported the highest AC rates per 100.000 population (Table 1,

Table S1). Median age was 37 years old, lower than the symptomatic patients. Most of them were males (Table 1). By August 31st, most ACs were classified as recovered (85.8%; 85.6-86.1%) or in domiciliary isolation (13.6%; 13.4-13.8%), and 356 patients (0.46%; 0.42-052%) were diagnosed during their stay in ICUs (80 patients), general hospitalization services (185 patients) or in post-mortem phase (91 deceased). These 356 cases may have been treated for symptoms unrelated to COVID-19 or perhaps RT-PCR results arrived late, with some arriving even after the patient had already passed away.

Factors associated with AC condition.

Using the PC-CA and PC-PCAmix, a group of six countries and three groups of departments were associated with AC state (Figure 3). To execute LRMs, the variables "age group 0-26 years" and "male sex" were transformed into dummi [0/1]. With a preliminary LRM, a higher β coefficient was estimated in relation to cases imported from countries associated with ACs, therefore, the variable “geographical origin” was created, composed of the categories “imported from countries associated with symptomatic" [Imported CAS - referent], "imported from countries associated with ACs" [Imported CA-ACs] and “related cases”. Additionally, a variable was created for the departments grouped with the PCAmix [departments with low association - referent] and for the EW (EW 10-34 - referent). The first LRM (main effects) identified a significant association of all index sociodemographic categories with ACs state (Table S2). The second model explores the following interactions: 1. Geographical origin and grouped departments, 2. Geographical origin and EW, 3. Age group (0-26 years) and gender, 4. Grouped departments and gender; and, 5. Age (0-26 years) and EW. We identified interactions between the variables "gender" (males), "age" (0-26 years), and "EW" and the grouped departments; and between the variables "gender" (males) and "age" (0-26 years) (Table 2).

Variables "age" (0-26 years), "gender" (male), "departments with moderate or strong association", "imported CA-ACs" and "related cases" were found to increase the risk of identifying ACs state. It was also determined that the risk increased for males (0-26 years), especially for those located in departments with a strong or moderate association since EW 35. However it should be noted that the risk of identifying ACs has decreased since EW 35 when only taking isolated estimates into account (Table 2).

As this is a cross-sectional study, the STROBE checklist was followed and can be revised in Table S3.

DISCUSSION

We found that, in an isolated fashion, age <27 years old, imported cases from a group of 6 countries, autochthonous cases and the occurrence in groupings of departments were associated with AC state. Additionally, the risk of being a male AC was only identified in departments with moderate or strong risk, and the risk was variable in the groupings of departments throughout specific epidemiological periods.

Additionally, our results show that the proportion of ACs in Colombia lays between 12-12.2% (Table 1), a lower estimate than previously described in other case series or mass screening studies with reported proportions between 5-80% [11–14]. Given the inclusion of pre-symptomatic patients or the unification of AC with non-critical symptoms in some reports, we cannot rule out that a non-differential classification bias influenced these estimates. An adapted definition for AC in Colombia may address this limitation.

Figure 1 shows that the majority of imported cases to Colombia came from Spain and USA, where AC rates have been estimated at 2.5% and 25%, respectively [14,15]. Although imported cases carry a distinctive genetic load that, population-wise, could manifest itself as a particular phenotype [16], currently there are no reports of genetic variants associated with AC in general or for any of the four AC subtypes described in the literature [17]. Subsequent research should be conducted on the possible association between ACs and phylogenetic variants (or other variables) to support the differential risk identified in imported cases from different regions of the world.

We identified that imported cases from a group of 6 countries were strongly associated with AC (Figure 2, Table S1, Table 2), and although no interaction was established between the country of import and the destination department (data not shown), we observed that departments strongly associated with AC had less diversity of import origin. Such is the case of Meta and Amazonas, which exclusively imported cases from USA and Brazil/Peru, respectively (Figure 2).

Among the demographic characteristics, the association between AC state and patients under 27 years of age stands out. Possible explanations for this observation include: (i) the lower presence of co-morbid conditions and baseline health issues within this age group and (ii) the higher risk of exposure through work activities which are greater in this age group [18]. However, clinical or social environment could also explain this finding, as a study in skilled nursing facility residents showed a high proportion of AC in those over 70 years of age, however this was a premature finding since most patients were later reclassified as pre-symptomatic or pauci-symptomatic [11].

We identified a higher frequency of men infected with COVID-19 consistent with reports from other countries around the world, except in Spain and Switzerland, where women ranked first [19]. Frequent occupations performed by men, as well as certain immunological and genetically susceptible backgrounds have been associated with this finding [19,20]. In particular, the risk of being an AC was higher in men, and increased in geographic areas associated with AC. This interaction is not uncommon given that professions regularly carried out by men, including those such as taxi driving, private security or prison guarding, among other work settings, can be distributed asymmetrically within countries, a pattern that would explain our findings [20].

The phases on the occurrence of cases throughout EWs and the interaction with groupings within departments associated with AC has been previously described in Chongqing, China, where researchers identified significant changes in the frequency of cases after implementation of geographic isolation measures. The dynamic changes in the detection and distribution of ACs throughout EWs could be explained by the surveillance strategy executed in Colombia kwon as "PRASS" (in Spanish, tests, surveillance, and sustainable selective isolations); this can be particularly observed from EW 30 onwards (figure S1) [21]. In Wuhan, a study showed that one group of ACs was linked to imported cases while others were linked mostly to autochthonous cases from geographically isolated areas of Wuhan [22]. We identified that in addition to being associated with a travel history to foreign countries, ACs were also associated with cases that appear spontaneously (related), occurring differentially as measures of geographic and social isolation were applied.

The lack of mass screening for COVID-19 in Colombia is the main limitation of our study since the actual AC ratio and the distribution of specific characteristics may differ from those estimated in this report. On the other hand, although a cross-sectional design is not ideal to identify risk factors, to the best of our knowledge this is the first study aimed at identifying factors associated with AC state with population data unbiased by the inclusion of pre-symptomatic cases [23].

The COVID-19 pandemic has had serious socioeconomic implications, including a collapse of healthcare systems, bankruptcy of companies as well as increasing trends in unemployment and crime rates [24–27]. This has forced countries with limited resources---such as Colombia---to perform massive screenings in order to prematurely lift quarantine and isolation measures despite the latent risk of successive outbreaks caused by a potential silent spread of COVID-19 through cases in the pre-symptomatic phase or AC state [28,29].

ACs transmit COVID-19 more efficiently than symptomatic patients for up to 21 days after the presumed date of infection [30,31]. This led to their inclusion in mathematical models intended to estimate the probability or expected number of person-to-person infections on repatriation trips from Wuhan, China [7,32]. Since then, ACs have become the target of mass screening in Asian and European countries effectively reducing economical losses due to unnecessary hospital care, controlling the spread in public or in-hospital settings, and allowing the execution of safe plans of social and work re-integration after quarantine and isolation [28,33–37].

To date, testing of asymptomatic individuals' rests at the discretion of physicians when justified on a case-by-case basis. On the other hand, the utility of SARS-CoV-2 testing for broad screening of asymptomatic individuals remains to be determined given the limited sensitivity data available for most commercially available test kits [38].

CONCLUSION

Together, our findings demonstrate sociodemographic trends strongly associated with COVID-19 AC state in Colombia at a departmental and national level. We believe that the implementation of massive screening campaigns to detect AC and pre-symptomatic patients is paramount to further characterize this phenomenon and adequately guide public health measures of containment and prevention. Additional molecular analysis of viral and host genotypic characteristics should be conducted to determine possible associations with AC state.

Authors contributorship statement

AT, APM and JDR designed the study. AT, GC, RPG, CH, GH, LMP, LAP and AA conducted the statistical and descriptive analyses. CF, ECB provided the data for the analysis. AT, APM, LAP and JDR drafted the manuscript. All authors approved the final version of the manuscript.

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Data sharing statement: Data is freely available from the National Institute of Health (INS) database on COVID-19 cases updated until August 31, 2020 (https://www.ins.gov.co/Noticias/Paginas/coronavirus-casos.aspx).

Conflicts of Interest: The authors declare no conflict of interest.

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Figure Legends

Figure 1. Daily accumulation and distribution of ACs by epidemiological week in Colombia. A. The y-axis represents the number of cumulative ACs transformed into a base 10 logarithm. The number of cumulative cases per day is located in points that increase in color intensity according to the occurrence of cases. **B.** The y-axis represents the number of daily ACs transformed into a base 10 logarithm. The number of daily cases per day is located in boxplots. **C.** Heatmap showcasing the number of ACs (top) and **B.** symptomatic patients (bottom) diagnosed in every Colombian department until August 31st, 2020.

Figure 2. Origin and destination of imported asymptomatic and symptomatic cases. The left and right figures, respectively, represent the country of origin and destination department of ACs and symptomatic patients. The thickness of the link tapes corresponds to the number of reported cases.

Figure 3. Groups of countries and departments associated with AC state. The left figure shows the group of countries associated with asymptomatic carrier (AC) state identified with positive values of the CCC-CA. The right figure shows departments grouped according to three intervals of CCC-CA: low association (CCC-CA: negative values), moderate association (CCC-CA:> 0 - <0.05), and strong association (CCC-CA: ≥0.5).

Supplementary material

Table S1. AC state frequency in Colombia by department

Table S2. Factors associated with AC state in Colombia

Table S3. STROBE checklist for cross-sectional studies

327 **Figure S1.** The stacked bar figure represents on the y-axis the epidemiological weeks (EW) and on the x-axis the proportion of symptomatic (green section of the bar) and the proportion of asymptomatic (purple section of the bar), as well as the result of a Chi square independence test that shows statistical association between the EW variables and health status (symptomatic/asymptomatic carrier).

332 **Table 1.** Sociodemographic characteristics of the asymptomatic and symptomatic patients

Variables	**Asymptomatic** **n:** 76162	**Symptomatic** **n:** 550725	**p-value**
Age, years	35 (25-49)	37 (27-52)	<0.001
0-26	21310 (27.9)	129529 (23.5)	<0.001
≥27	54852 (72.0)	421196 (76.4)	<0.001
Sex			
Male	38836 (50.9)	283068 (51.4)	0.035
Female	37326 (49.0)	267657 (48.6)	0.035
Geographical source			
Related†	76108 (99.9)	549789 (99.8)	<0.001
Imported	54 (0.07)	936 (0.170)	<0.001
Departments††			
Bogotá	68143 (89.4)	148258 (26.9)	<0.001
Atlántico	1455 (1.91)	26059 (4.73)	<0.001
Meta	836 (1.10)	8532 (1.55)	<0.001
Barranquilla	737 (0.97)	34262 (6.22)	<0.001

Cundinamarca	690 (0.91)	23222 (4.22)	<0.001
Imported cases†††	53	905	958
Spain	19 (35.8)	246 (27.2)	0.170
USA	14 (26.4)	208 (22.9)	0.565
Brazil	8 (15.1)	53 (5.86)	0.007
Mexico	3 (5.66)	51 (5.64)	0.994
Venezuela	3 (5.66)	8 (0.88)	0.002
Argentina	1 (1.89)	4 (0.44)	0.156
France	1 (1.89)	19 (2.10)	0.916
Germany	1 (1.89)	11 (1.22)	0.669
Peru	1 (1.89)	24 (2.65)	0.734
Puerto Rico	1 (1.89)	12 (1.33)	0.732
Turkey	1 (1.89)	27 (2.98)	0.645
Unknow	1	31	NA

†: cases that appeared spontaneously in Colombia, ††: top 5 of the departments with the highest frequency of AC. †††: the total number of imported asymptomatic and symptomatic cases was used as the denominator to estimate proportions by country of origin.

Table 2. Factors associated with asymptomatic carrier (AC) state in Colombia

Variable	**Interaction model**		
	β	**ORc (95%, CI)**	**p-value**
Intercept	**-7.316**	-	<0.001

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Age			
>26 years	**Ref.**	-	-
0-26 years	0.172	1.188 (1.096-1.287)	<0.001
Sex			
Female	**Ref.**	-	-
Male	0.414	1.513 (1.408-1.625)	<0.001
Department			
Low association [1]	**Ref.**	-	-
Moderate association [2]	0.211	1.234 (1.137-1.340)	<0.001
Strong association [3]	2.986	19.81 (18.61-21.08)	<0.001
Geographical source			
Imported CAS†	**Ref.**	-	-
Imported CA-AC††(1)	2.536	12.62 (3.034-52.54)	<0.001
Related cases†††(2)	3.121	22.67 (5.620-91.47)	<0.001
EW			
10-34	**Ref.**	-	
≥35	-1.008	0.365 (0.320-0.415)	<0.001
0-26 years + Male	0.047	1.048 (1.010-1.089)	**0.014**
0-26 years + Department [2]	0.174	1.190 (1.069-1.325)	**0.001**
0-26 years + Department [3]	-0.005	0.995 (0.919-1.077)	0.898
Department [2] + Male	-0.387	0.679 (0.615-0.749)	**<0.001**
Department [3] + Male	-0.377	0.686 (0.637-0.737)	**<0.001**
EW ≥35 + Department [2]	-0.862	0.422 (0.315-0.567)	**<0.001**
EW ≥35 + Department [3]	2.217	9.182 (8.045-10.47)	**<0.001**

†: CAS countries associated with symptomatic patients, ††: CA-AC countries associated with asymptomatic carriers (AC), †††: spontaneous cases, **EW:** epidemiological weeks.

References.

1. Coronavirus en Colombia. https://www.ins.gov.co/Noticias/Paginas/Coronavirus.aspx. Accessed May 10, 2020.

2. Rudan I. A cascade of causes that led to the COVID-19 tragedy in Italy and in other European Union co1. Rudan I. A cascade of causes that led to the COVID-19 tragedy in Italy and in other European Union countries. J Glob Health. 2020; 10(1):10335. untries. *J Glob Health*. 2020;10(1):10335. doi:10.7189/jogh-10-010335

3. Yi Y, Lagniton PNP, Ye S, Li E, Xu R-H. COVID-19: what has been learned and to be learned about the novel coronavirus disease. *Int J Biol Sci*. 2020;16(10):1753-1766. doi:10.7150/ijbs.45134

4. Tindale L, Coombe M, Stockdale JE, et al. Transmission interval estimates suggest pre-symptomatic spread of COVID-19. *medRxiv*. January 2020:2020.03.03.20029983. doi:10.1101/2020.03.03.20029983

5. Zhang W. Estimating the presymptomatic transmission of COVID19 using incubation period and serial interval data. *medRxiv*. January 2020:2020.04.02.20051318. doi:10.1101/2020.04.02.20051318

6. Rahimi F, Talebi Bezmin Abadi A. Challenges of managing the asymptomatic carriers of SARS-CoV-2. *Travel Med Infect Dis*. April 2020:101677. doi:10.1016/j.tmaid.2020.101677

7. Teherán AA, Camero G, Prado R, et al. Presumptive asymptomatic COVID-19 carriers' estimation and expected person-to-person spreading among repatriated passengers returning from China. *Travel Med Infect Dis*. April 2020:101688. doi:10.1016/j.tmaid.2020.101688

8. Lavezzo E, Franchin E, Ciavarella C, et al. Suppression of COVID-19 outbreak in the municipality of Vo, Italy. *medRxiv*. January 2020:2020.04.17.20053157. doi:10.1101/2020.04.17.20053157

9. Oliveira G. Refined compartmental models, asymptomatic carriers and COVID-19. *medRxiv*. January 2020:2020.04.14.20065128. doi:10.1101/2020.04.14.20065128

10. Yu Y, Liu Y-R, Luo F-M, et al. COVID-19 Asymptomatic Infection Estimation. *medRxiv*. January 2020:2020.04.19.20068072. doi:10.1101/2020.04.19.20068072

11. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2008457

12. Wong J, Abdul Aziz ABZ, Chaw L, et al. High proportion of asymptomatic and presymptomatic COVID-19 infections in travelers and returning residents to Brunei.

21

382 *J Travel Med*. 2020. doi:10.1093/jtm/taaa066

383 13. Hijnen D, Marzano AV, Eyerich K, et al. SARS-CoV-2 Transmission from
384 Presymptomatic Meeting Attendee, Germany. *Emerg Infect Dis*. 2020.
385 doi:10.3201/eid2608.201235

386 14. COVID-19: What proportion are asymptomatic? - CEBM.
387 https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/.
388 Accessed June 16, 2020.

389 15. Ministerio de Sanidad C. Estudio Nacional de sero-Epidemiología de la Infección
390 por SARS-CoV-2 en España (ENE-Covid). Informe PRELIMINAR tras la primera
391 ronda (13/05/2020). *Gob España*. 2020;(May 13).

392 16. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-
393 CoV-2 genomes. *Proc Natl Acad Sci U S A*. 2020. doi:10.1073/pnas.2004999117

394 17. Zhou X, Li Y, Li T, Zhang W. Follow-up of asymptomatic patients with SARS-
395 CoV-2 infection. *Clin Microbiol Infect*. 2020. doi:10.1016/j.cmi.2020.03.024

396 18. Yang R, Gui X, Xiong Y. Comparison of Clinical Characteristics of Patients with
397 Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China. *JAMA*
398 *Netw open*. 2020. doi:10.1001/jamanetworkopen.2020.10182

399 19. Márquez EJ, Trowbridge J, Kuchel GA, Banchereau J, Ucar D. The lethal sex gap:
400 COVID-19. *Immun Ageing*. 2020;17(1):13. doi:10.1186/s12979-020-00183-z

401 20. Koh D. Occupational risks for COVID-19 infection. *Occup Med (Chic Ill)*.
402 2020;70(1):3-5. doi:10.1093/occmed/kqaa036

21. Instituto Nacional de Salud – Ministerio de Salud y Protección Social. Orientaciones para la Vigilancia en Salud Pública de la Covid19. ORIENTACIONES PARA LA VIGILANCIA EN SALUD PÚBLICA DE LA COVID-19. Colombia: INS – Minsalud;2020. Documento Técnico Científico.

22. Tao Y, Cheng P, Chen W, et al. High Incidence of Asymptomatic SARS-CoV-2 Infection, Chongqing, China. *SSRN Electron J*. 2020. doi:10.2139/ssrn.3559583

23. Sahu K, Kumar R. Preventive and treatment strategies of COVID-19: From community to clinical trials. *J Fam Med Prim Care*. 2020;9(5):2149-2157. doi:10.4103/jfmpc.jfmpc_728_20

24. Nussbaumer-Streit B, Mayr V, Dobrescu Ai, et al. Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. *Cochrane Database Syst Rev*. 2020;(4). doi:10.1002/14651858.CD013574

25. Nicola M, Alsafi Z, Sohrabi C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *Int J Surg*. 2020;78:185-193. doi:https://doi.org/10.1016/j.ijsu.2020.04.018

26. Kalleberg AL, Wachter TM von. The U.S. Labor Market During and After the Great Recession: Continuities and Transformations. *RSF Russell Sage Found J Soc Sci*. 2017;3(3):1-19. doi:10.7758/rsf.2017.3.3.01

27. Sutherland M, McKenney M, Elkbuli A. Gun violence during COVID-19 pandemic: Paradoxical trends in New York City, Chicago, Los Angeles and Baltimore. *Am J Emerg Med*. 2020. doi:10.1016/j.ajem.2020.05.006

28. Gilbert M, Dewatripont M, Muraille E, Platteau JP, Goldman M. Preparing for a

responsible lockdown exit strategy. *Nat Med*. 2020. doi:10.1038/s41591-020-0871-y

29. World Health Organisation. Considerations in adjusting public health and social measures in the context of COVID-19. *World Heal Organ*. 2020;(April):1-7. https://www.who.int/publications-detail/risk-.

30. Prather KA, Wang CC, Schooley RT. Reducing transmission of SARS-CoV-2. *Science (80-)*. 2020. doi:10.1126/science.abc6197

31. Huff H V, Singh A. Asymptomatic transmission during the COVID-19 pandemic and implications for public health strategies. *Clin Infect Dis*. May 2020. doi:10.1093/cid/ciaa654

32. Gostic K, Gomez ACR, Mummah RO, Kucharski AJ, Lloyd-Smith JO. Estimated effectiveness of symptom and risk screening to prevent the spread of COVID-19. Franco E, Ferguson NM, McCaw JM, eds. *Elife*. 2020;9:e55570. doi:10.7554/eLife.55570

33. Peto J, Alwan NA, Godfrey KM, et al. Universal weekly testing as the UK COVID-19 lockdown exit strategy. *Lancet*. 2020. doi:10.1016/S0140-6736(20)30936-3

34. Mallapaty S. Will antibody tests for the coronavirus really change everything? *Nature*. 2020. doi:10.1038/d41586-020-01115-z

35. The race against COVID-19. *Nat Nanotechnol*. 2020. doi:10.1038/s41565-020-0680-y

36. Mark K, Steel K, Stevenson J, et al. Coronavirus disease (COVID-19) community testing team in Scotland: A 14-day review, 6 to 20 February 2020. *Eurosurveillance*.

446 2020. doi:10.2807/1560-7917.ES.2020.25.12.2000217

447 37. Rosenthal PJ. The importance of diagnostic testing during a viral pandemic: Early
448 lessons from novel coronavirus disease (CoVID-19). *Am J Trop Med Hyg*. 2020.
449 doi:10.4269/AJTMH.20-0216

450 38. Woloshin S, Patel N, Kesselheim AS. False Negative Tests for SARS-CoV-2
451 Infection — Challenges and Implications. *N Engl J Med*. 2020.
452 doi:10.1056/nejmp2015897

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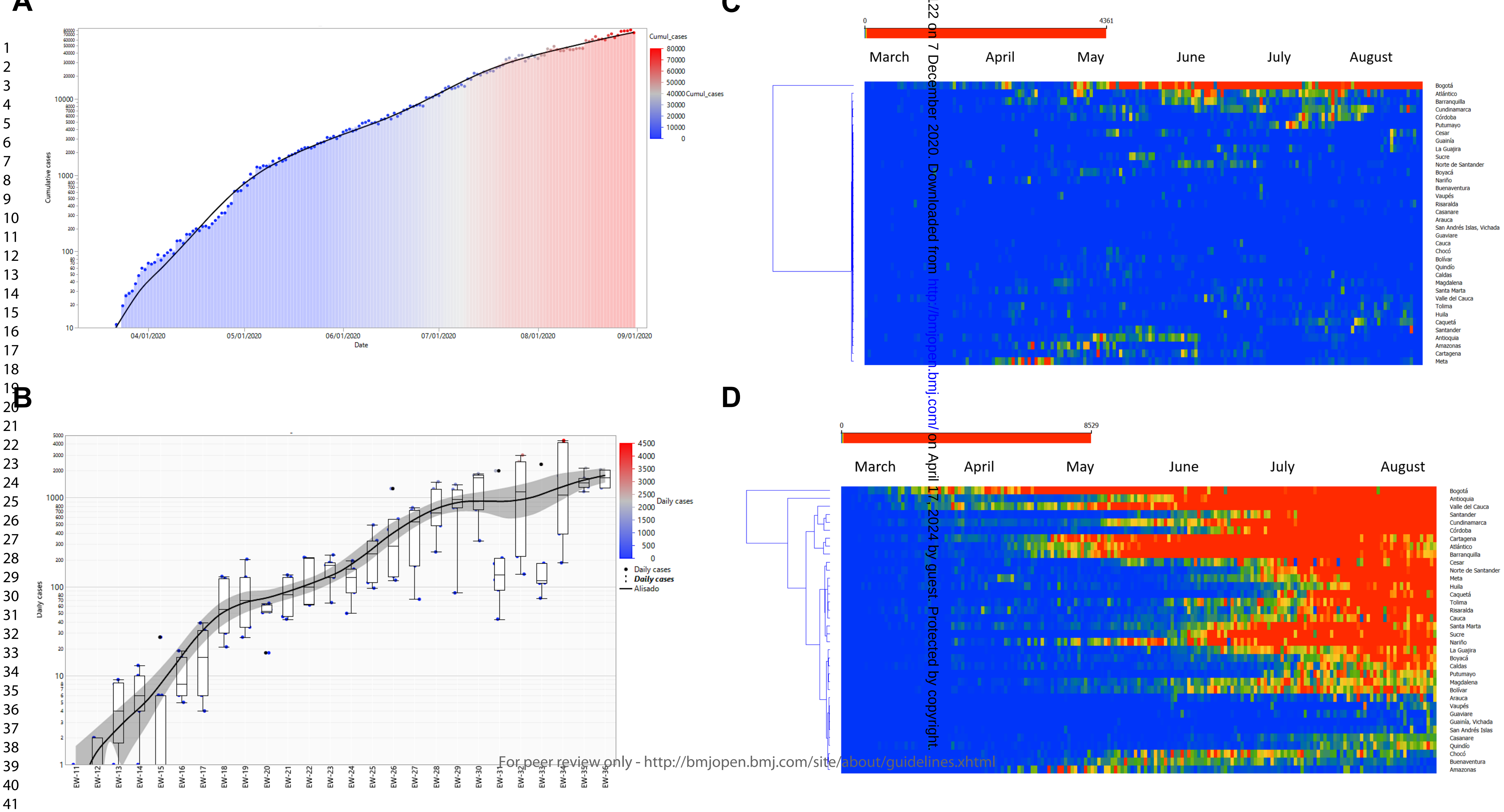
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Date
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06/01/2020
07/01/2020
08/01/2020
09/01/2020
Cumul_cases
80000
70000
60000
50000
40000 Cumul_cases
30000
20000
10000
0
B
Daily cases
Daily cases
Daily cases
Alisado
4500
4000
3500
3000
2500
2000
1500
1000
500
0
EW-11 EW-12 EW-13 EW-14 EW-15 EW-16 EW-17 EW-18 EW-19 EW-20 EW-21 EW-22 EW-23 EW-24 EW-25 EW-26 EW-27 EW-28 EW-29 EW-30 EW-31 EW-32 EW-33 EW-34 EW-35 EW-36
C
0
4361
March
April
May
June
July
August
Bogotá
Atlántico
Barranquilla
Cundinamarca
Córdoba
Putumayo
Cesar
Guainía
La Guajira
Sucre
Norte de Santander
Boyacá
Nariño
Buenaventura
Vaupés
Risaralda
Casanare
Arauca
San Andrés Islas, Vichada
Guaviare
Cauca
Chocó
Bolívar
Quindío
Caldas
Magdalena
Santa Marta
Valle del Cauca
Tolima
Huila
Caquetá
Santander
Antioquia
Amazonas
Cartagena
Meta
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March
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Bogotá
Antioquia
Valle del Cauca
Santander
Cundinamarca
Córdoba
Cartagena
Atlántico
Barranquilla
Cesar
Norte de Santander
Meta
Huila
Caquetá
Tolima
Risaralda
Cauca
Santa Marta
Sucre
Nariño
La Guajira
Boyacá
Caldas
Putumayo
Magdalena
Bolívar
Arauca
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Guaviare
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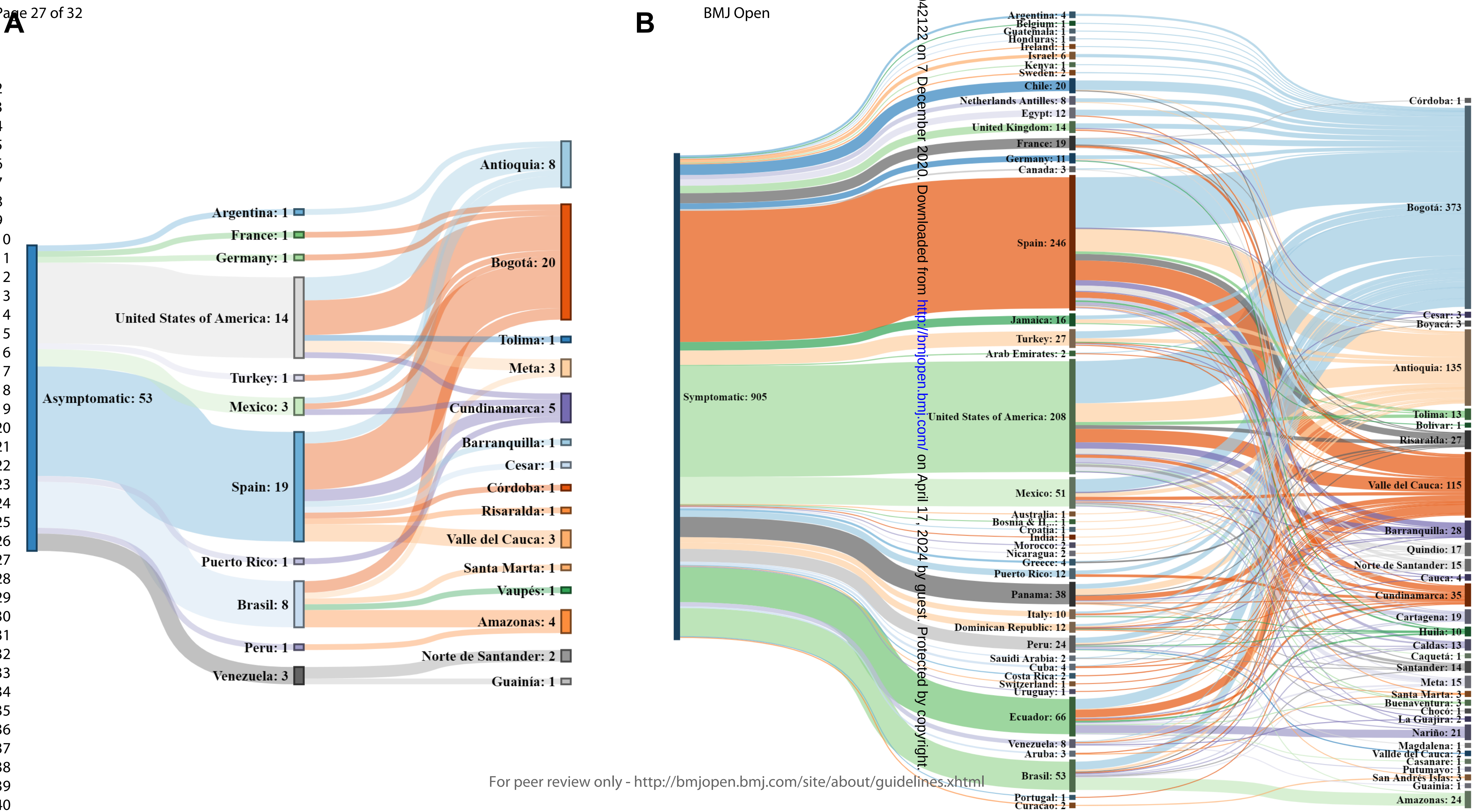
Casanare
Quindío
Chocó
Buenaventura
Amazonas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Puerto Rico: 1
Brasil: 8
Peru: 1
Venezuela: 3
Antioquia: 8
Bogotá: 20
Tolima: 1
Meta: 3
Cundinamarca: 5
Barranquilla: 1
Cesar: 1
Córdoba: 1
Risaralda: 1
Valle del Cauca: 3
Santa Marta: 1
Vaupés: 1
Amazonas: 4
Norte de Santander: 2
Guainía: 1
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Symptomatic: 905
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Guatemala: 1
Honduras: 1
Ireland: 1
Israel: 6
Kenya: 1
Sweden: 2
Chile: 20
Netherlands Antilles: 8
Egypt: 12
United Kingdom: 14
France: 19
Germany: 11
Canada: 3
Spain: 246
Jamaica: 16
Turkey: 27
Arab Emirates: 2
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Mexico: 51
Australia: 1
Bosnia & H...: 1
Croatia: 1
India: 1
Morocco: 2
Nicaragua: 2
Greece: 4
Puerto Rico: 12
Panama: 38
Italy: 10
Dominican Republic: 12
Peru: 24
Sauidi Arabia: 2
Cuba: 4
Costa Rica: 2
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Venezuela: 8
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Curacao: 2
Córdoba: 1
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Boyacá: 3
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Tolima: 13
Bolívar: 1
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Cundinamarca: 35
Cartagena: 19
Huila: 10
Caldas: 13
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Santa Marta: 3
Buenaventura: 3
Chocó: 1
La Guajira: 2
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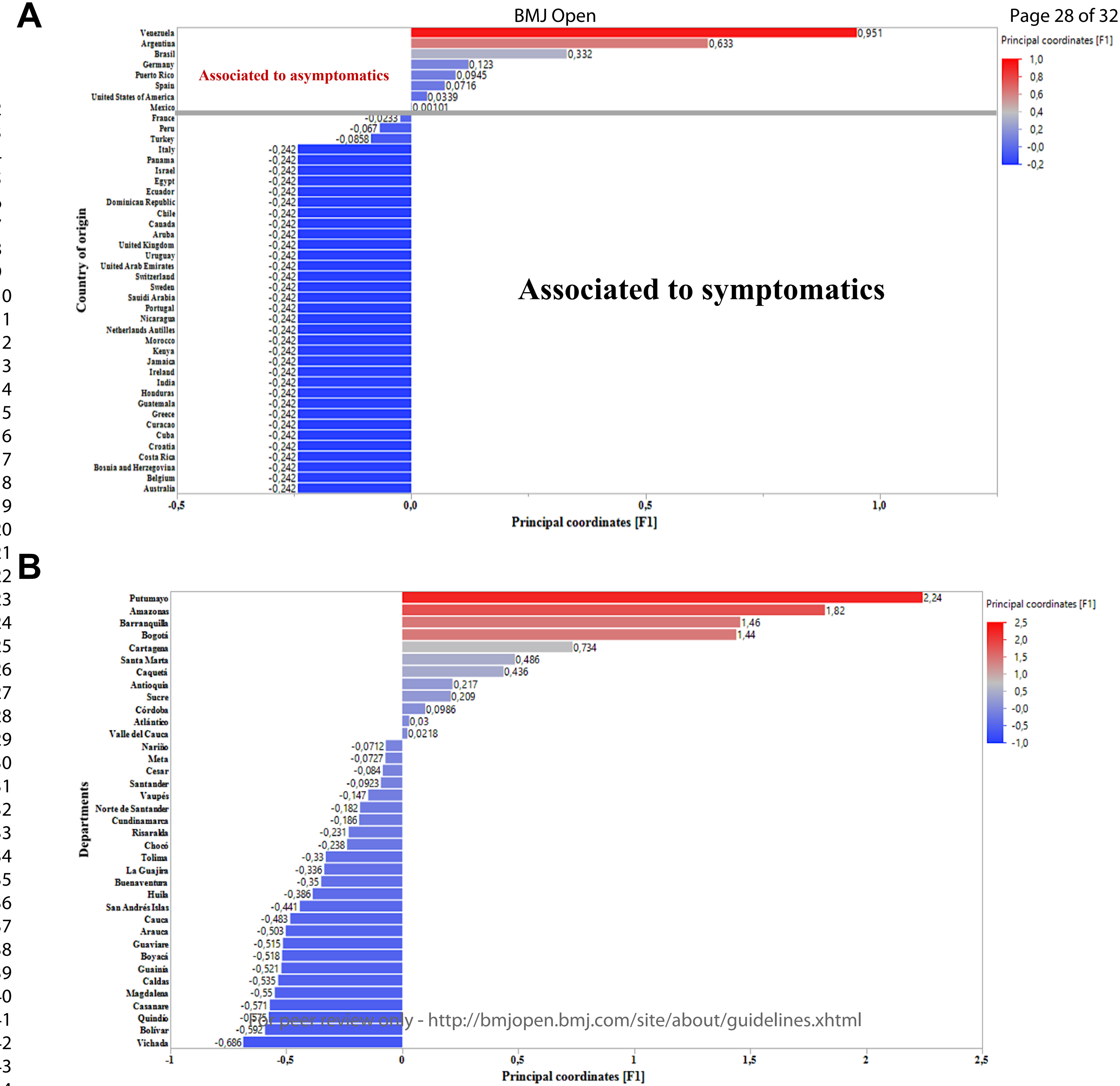
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Associated to asymptomatics
Associated to symptomatics
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Puerto Rico
Spain
United States of America
Mexico
France
Peru
Turkey
Italy
Panama
Israel
Egypt
Ecuador
Dominican Republic
Chile
Canada
Aruba
United Kingdom
Uruguay
United Arab Emirates
Switzerland
Sweden
Sauidi Arabia
Portugal
Nicaragua
Netherlands Antilles
Morocco
Kenya
Jamaica
Ireland
India
Honduras
Guatemala
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Belgium
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Departments
Putumayo
Amazonas
Barranquilla
Bogotá
Cartagena
Santa Marta
Caquetá
Antioquia
Sucre
Córdoba
Atlántico
Valle del Cauca
Nariño
Meta
Cesar
Santander
Vaupés
Norte de Santander
Cundinamarca
Risaralda
Chocó
Tolima
La Guajira
Buenaventura
Huila
San Andrés Islas
Cauca
Arauca
Guaviare
Boyacá
Guainía
Caldas
Magdalena
Casanare
Quindío
Bolívar
Vichada
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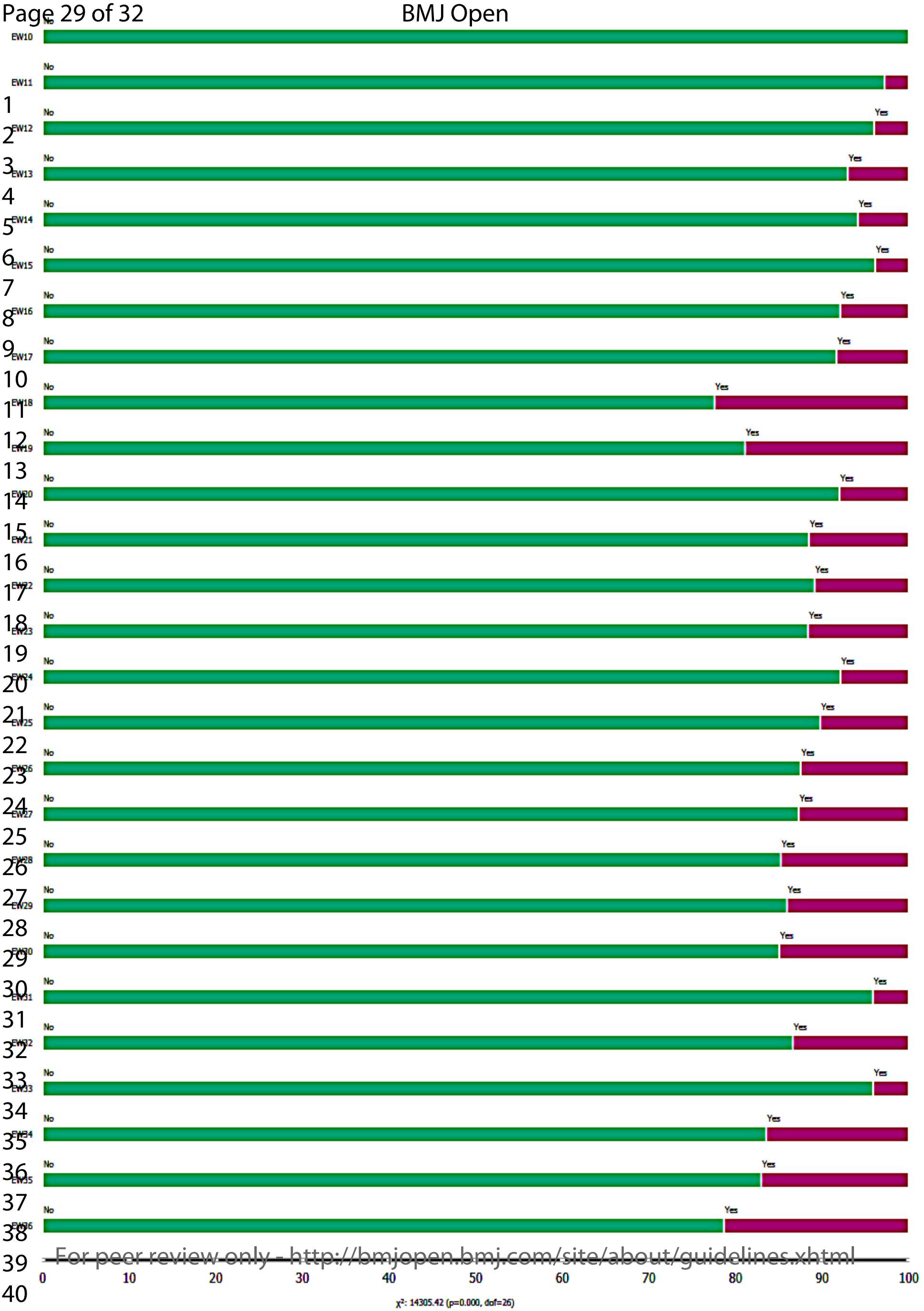
EW10
EW11
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EW33
EW34
EW35
EW36
No
Yes
0 10 20 30 40 50 60 70 80 90 100
χ²: 14305.42 (p=0.000, dof=26)

Table S1. AC state frequency in Colombia by department

Department	Asympt_cases	%	Population	Asympt_rate*	Sympt_rate*
Bogotá	68143	89.5	7743955	880,0	1914.5
Atlántico	1455	1.91	2722128	53,5	957.3
Meta	836	1.10	1063454	78,6	802.3
Barranquilla	737	0.97	1243113	59,3	2756.1
Cundinamarca	690	0.91	3242999	21,3	716.1
Antioquia	518	0.68	6677930	7,8	1239.0
Córdoba	468	0.60	1828947	25,6	1072.0
Cartagena	437	0.57	1060577	41,2	1860.5
Amazonas	333	0.44	79020	421,4	2856.2
Putumayo	262	0.34	79020	331,6	3478.9
Norte de Santander	248	0.33	1620318	15,3	727.8
Caquetá	207	0.27	410521	50,4	1474.5
Cesar	195	0.26	1295387	15,1	851.6
Santander	190	0.25	2280908	8,3	847.8
Tolima	153	0.20	1339998	11,4	544.1
Huila	151	0.20	1122622	13,5	470.6
Sucre	151	0.20	949252	15,9	1221.6
La Guajira	140	0.18	965718	14,5	533.0
Boyacá	113	0.15	1242731	9,1	308.5
Magdalena	112	0.15	1427026	7,8	269.8
Valle del Cauca	111	0.15	4532152	2,4	997.9
Santa Marta	94	0.12	538612	17,5	1569.8
Nariño	69	0.09	1627589	4,2	878.5
Bolívar	57	0.07	2180976	2,6	221.9
Caldas	51	0.07	1018453	5,0	291.0
Risaralda	46	0.06	961055	4,8	675.6
Quindío	45	0.05	555401	8,1	236.9
Chocó	39	0.05	544764	7,2	664.9
Guainía	39	0.05	50636	77,0	237.0
Vaupés	27	0.04	44712	60,4	726.9
Buenaventura	20	0.03	440989	4,5	526.1
Cauca	18	0.02	1491937	1,2	360.9
Casanare	7	0.01	435195	1,6	248.9
Arauca	3	<0.01	294206	1,0	335.8
Guaviare	3	<0.01	86657	3,5	318.5
San Andrés Islas	2	<0.01	63692	3,1	411.4
Vichada	2	<0.01	112958	1,8	103.6

The total number of Asymptomatic carriers (ACs) was used as the denominator to determine proportions. **Asympt_cases:** asymptomatic cases, **Symptomatic cases:** see in supplementary file. ***Asympt_rate:** (Asympt_cases/population)*100.000 habitants. ***Sympt_rate:** (Asympt_cases/population)*100.000 habitants.

Table S2. Factors associated with AC state in Colombia.

Variable	Main effects		
	β	**ORa (95%, CI)**	**p-value**
Intercept	**-7.360**	-	**<0.001**
Age,			
>26 years old	**Ref.**	-	-
0-26 years old	0.205	1.227 (1.205-1.250)	**<0.001**
Sex			
Female	**Ref.**	-	-
Male	0.054	1.055 (1.038-1.073)	**<0.001**
Department			
Low risk	**Ref.**	-	-
Moderate risk	1.304	3.372 (3.134-4.330)	**<0.001**
Strong risk	1.909	8.310 (6.101-7.464)	**<0.001**
Geographical origin			
Imported CAS†	**Ref.**	-	-
Imported CA-AC††	2.541	12.68 (3.049-52.77)	**<0.001**
Related cases†††	3.255	25.90 (6.425-104.4)	**<0.001**
EW			
10-34	**Ref.**	-	
≥35	0.933	2.543 (2.484-2.603)	**<0.001**

†: CAS countries associated to symptomatic patients**, ††:** CA-AC countries associated to ACs**, †††: spontaneous cases**, **EW:** epidemiological week.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Page and relevant text from manuscript
Title and abstract	1	(Page 1) A cross-sectional study
		(Page 2) It is reported in the abstract
Introduction		
Background/rationale	2	(Page 4-5)
Objectives	3	(Page 5)
Methods		
Study design	4	(Page 5)
Setting	5	(Page 5)
Participants	6	(Page 5-7)*Cross-sectional study*
Variables	7	(Page 6)
Data sources/ measurement	8*	(Page 6-7)
Bias	9	(Page 7)
Study size	10	(Page 5)
Quantitative variables	11	(Page 6)
Statistical methods	12	(Page 5-7)

Continued on next page

Results		
Participants	13*	(Page 7-8)
Descriptive data	14*	(Page 7-9)
Outcome data	15*	(Page 7-10)
Main results	16	(Page 7-10)
Other analyses	17	NA
Discussion		
Key results	18	(Page 10-11)
Limitations	19	(Page 11-12)
Interpretation	20	(Page 11-13)
Generalisability	21	(Page 13)
Other information		
Funding	22	(Page 14)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.