

COVID-19 Symptoms Time Trend: Comparison Between 2020, 2021, 2022 and 2023 Years in a General Medicine Office in Toledo, Spain

Jose Luis Turabian

Specialist in Family and Community Medicine, Health Center Santa Maria de Benquerencia. Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain

Corresponding author

Jose Luis Turabian, Health Center Santa Maria de Benquerencia Toledo, Spain.

Received: November 03, 2023; **Accepted:** November 14, 2023; **Published:** November 20, 2023

ABSTRACT

Background: It is not well known if there have been changes in the clinical-epidemiological characteristics during the evolution of COVID-19 from 2020 to 2023.

Objective: To know the variations the clinical features of cases of COVID-19 from 2020 to 2023.

Methodology: Descriptive analysis and comparison of secondary data of cases of COVID-19 from previous studies in 2020, 2021, 2022 and 2023 years, all of them carried out in the same population of patients treated in a general medicine office in Toledo, Spain.

Results: 100 COVID-19 cases were included in 2020, 42 in 2021, 46 in 2022, and 76 in 2023. The statistically significant differences between the symptoms were: 1) ENT symptoms (anosmia / ageusia,odynophagia, dysphonia, rhinorrhea, sneezing, nasal congestion, pharyngeal dryness-mucus, ear pain, epistaxis) were significantly more frequent in 2021, 2022 and 2023 versus 2020. And 2) Digestive symptoms (anorexia, nausea / vomiting, diarrhea, abdominal pain) were significantly less frequent in 2022 and 2023 versus 2020 and 2021.

Conclusion: In the general practice setting in Toledo (Spain), from 2020 to 2023, a variation in the clinical presentation of COVID-19 is observed, with a tendency to predominate ENT symptoms and to present fewer digestive symptoms from 2021. This trend clinical presentation carries the risk that it can make one forget prevention measures, the careful evaluation of symptoms, and epidemiological control.

Keywords: COVID-19, SARS-CoV-2, Epidemiological Characteristic, Symptoms, General Practice, Public Health Practice, Secondary Analysis

Introduction

In epidemiology there are 3 classic models or schemes that serve as a basis for the study and analysis of infectious diseases: 1) Epidemiological Triad (host, agent and environment); 2) Natural History of the Disease (the process of a disease from the prepathogenic period in which the stimulus occurs and infection begins, to the pathogenic period in which the disease develops and continues its course until its resolution, chronification or death); And 3) Epidemiological Chain (with which the components that participate in the disease process are analyzed) [1,2].

Thus, the epidemiology of the coronavirus disease 2019 (COVID-19) has evolved during the four years since its detection [3]. The causal agent, the severe acute respiratory syndrome coronavirus (SARS-CoV-2), has evolved giving rise to different variants that have been predominant over time, and this has caused different degrees of virulence, pathogenicity, immunogenicity, affecting the ease of spread, the severity of the associated disease or the effectiveness of vaccines, treatment

medications, diagnostics or other public health measures, and social changes [4,5]. When the Omicron variant of SARS-CoV-2 began to spread rapidly and outperform other variants in late 2021, it became clear that this variant was quite different from previous ones; It caused less severe disease, but the number of cases broke records largely because a series of mutations in the virus's spike protein make vaccines much less effective at stopping infection than previous variants [6]. The effectiveness of the COVID-19 vaccine against severe diseases remained high; In contrast, vaccine efficacy against infection and symptomatic disease clearly decrease at 6 months [7]. The appearance of multiple variants of SARS-CoV-2 with greater transmissibility, different virulence and different capacity for immune escape represents a change that may give rise to clinical-epidemiological aspects different from previous ones [8].

The SARS-CoV-2 human host in 2023 is different from those in 2020 in their vaccination status. Vaccines have been shown to be effective in reducing the severity of SARS-CoV-2 infection [9,10]. Currently, high levels of immunity to SARS-CoV-2 are beginning to limit its impact and reach [11]. The majority of patients with COVID-19 after vaccination usually has mild disease or even remains asymptomatic [12]. But, on the other

hand, there is increasing scientific evidence that shows that the protection generated by vaccination decreases over time, although it is reestablished with the inoculation of booster doses. In addition, the decrease in immunity as a result of the new variants must be taken into account [13]. Thus, it is accepted that it may be normal to be infected by SARS-CoV-2 several times throughout life [14-17]. In addition, available treatments can change the symptoms of COVID-19 [18].

Therefore, in this changing epidemiological framework (triad, natural history of the disease and epidemiological chain), it is to be expected that the symptoms of COVID-19 have also changed. However, although this change in COVID-19 symptoms is accepted, there is really little data and much remains to be clarified. Symptoms compatible with COVID-19 were initially defined as acute respiratory symptoms consisting of sudden onset in the last 10 days of any of the following symptoms: cough, dyspnea, sore throat, or runny nose, with or without fever. Likewise, official list of COVID-19 symptoms was later updated to include sore throat, fatigue, and headache [19]. Research of COVID-19 symptoms indicates that the symptoms of COVID-19 manifested itself at the beginning of the pandemic are no longer the same. Fever could not be the most permanent symptom now; loss of taste and smell also do not, and runny nose, sore throat or dry cough and headache appear as very frequent symptoms in people with the vaccine [20,21].

Understanding the variation of symptoms by location and temporality is crucial for clinical practice; it could help speed diagnosis, predict outcomes more accurately, and guide treatment, especially as new variants emerge. Likewise, the fact of being able to reflect this variation in symptoms in public health messages can contribute to prevention. It has been said that future work should focus on symptom profile variation in emerging SARS-CoV-2 virus variants [22].

In this context, we present a study comparing symptoms of COVID-19 cases in 2020, 2021, 2022 and 2023, using secondary data from the same population attended in a general medicine consultation in these time periods, with the goal of approaching the knowledge of the relative importance of the three elements of the epidemiological triad of COVID-19 (causal agent, environment, and host), of the natural history of the disease and of the epidemiological chain.

Material and Methods

Design and Emplacement

This study compares data from previous observational, longitudinal and prospective studies of COVID-19 infections from March, 2020 to October, 2023, already published:

1. A study that included unvaccinated COVID-19 cases in 2020 [23].
2. Two studies of COVID-19 cases in vaccinated people in 2021 [23,24].
3. A study of COVID-19 breakthrough infections in vaccinated people with vaccine booster in 2022 [25].
4. And a study of COVID-19 infections in 2023 [26].

All studies were conducted on the same population: patients saw in a general medicine office in Toledo, Spain, which has a list of 2,000 patients > 14 years of age (in Spain, GPs care for people >

14 years of age, except for exceptions). The GPs in Spain work within the National Health System, which is public in nature, and are the gateway for all patients to the system, and each person is assigned a GP [27]. The methodology of all studies has been previously published and here only the main elements will be repeated for the current study [23-26].

Outcome of Interest

To describes the variations in the clinical characteristics of cases of COVID-19 from March, 2020 to October, 2023.

Diagnosis of COVID-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing performed in health services or at home [28].

Collected Variables

Variables for which data were available in all previous studies were:

- Age and sex
- Chronic diseases (defined as "any alteration or deviation from normal that has one or more of the following characteristics: is permanent, leaves residual impairment, is caused by a non-reversible pathological alteration, requires special training of the patient for rehabilitation, and / or can be expected to require a long period of control, observation or treatment"), and symptoms of COVID-19, both classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [29,30].
- If they were Health Care Workers
- Disease severity (classified according to: 1. mild cases: clinical symptoms are mild and no manifestation of pneumonia can be found on images; 2. moderate cases: with symptoms such as fever and respiratory tract symptoms and the manifestation of pneumonia can be seen on the imaging tests; and 3. severe cases: respiratory distress, respiratory rate ≥ 30 breaths / min., pulse oxygen saturation $\leq 93\%$ with room air at rest, arterial partial pressure of oxygen / oxygen concentration ≤ 300 mmHg.) to simplify comparison, moderate and severe cases were counted together [31].

Statistical Analysis

The bivariate comparisons were performed using the Chi Square test (X²) or test of Kruskal-Wallis, both with degrees freedom= 3.

Ethical Issues

No personal data of the patients were used, but only group results, which were taken from the clinical history.

Results

100 COVID-19 cases were included in 2020, 42 in 2021, 46 in 2022, and 76 in 2023. These cases from the respective samples differed in a statistically significant way in that they were older and had a greater number of chronic diseases in 2022 and 2023 versus 2020 and 2021. There were no statistically significant differences by sex, with respect to the presence of socio-health workers or with respect to Moderate-severe severity (Table 1). The statistically significant differences between symptoms were: 1) ENT symptoms (Anosmia/ageusia, odynophagia, dysphonia, rhinorrhea, sneezing, nasal congestion, pharyngeal dryness-

mucus, ear pain, and epixtasis) were significantly more frequent in 2021, 2022 and 2023 versus 2020. And 2) Digestive symptoms (anorexia, nausea / vomiting, diarrhea, abdominal pain) were significantly less frequent in 2022 and 2023 versus 2020 and 2021 (Table 2).

Table 1: Comparison of Selected Variables Among the Cases of the 4 Included Samples

Variables	COVID-19 Cases in 2020 N=100	COVID-19 Cases in 2021 N=42	COVID-19 Cases in 2022 N=46	COVID-19 Cases in 2023 N=76	Statistical Significance
>= 65 years	10 (10)	9 (21)	13 (28)	21 (28)	X2 (df=3)= 10.9998. p= .011727. Significant at p < .05.
Children and adolescents <= 22 years	11 (11)	1 (2)	1 (2)	2 (3)	X2 (df=3)= 8.5073. p= .036611. Significant at p < .05.
Women	54 (54)	20 (48)	27 (59)	48 (63)	X2 (df=3)= 3.0617. p= .382211. NS
Socio-health workers	11 (11)	7 (17)	13 (28)	13 (17)	X2 (df=3)= 6.7747. p= .079436. NS
Moderate-severe severity	3 (3)	4 (9)	1 (2)	2 (3)	X2 (df=3)= 4.5696. p= .206164. NS
Exitus	1 (1)	0	0	0	Test of Kruskal-Wallis (df=3): H= 1.45122. p= .69357. NS
Chronic diseases presence	51 (51)	22 (53)	35 (76)	48 (63)	X2 (df=3)= 9.5071. p= .023255. The result is significant at p < .05.

(): Denotes percentages; NS: Not significant; df= Degrees freedom

Table 2: Comparison of Symptoms between COVID-19 Cases from 2020, 2021, 2022 and 2023

Symptoms COVID-19 Infection* According to who, Icd-10 Groups	COVID-19 Cases in 2020 N=100	COVID-19 Cases in 2021 N=42	COVID-19 Cases in 2022 N=46	COVID-19 Cases in 2023 N=76	Statistical Significance
General (discomfort, asthenia, myalgia, fever, artralgiás)	24 (31)	28 (29)	34 (31)	95 (38)	X2 (df=3)= 3.5413. p= .315448. NS
Respiratory (cough, dyspnea, chest pain)	19 (25)	23 (24)	24 (22)	69 (27)	X2 (df=3)= 1.4894. p= .684724. NS
ENT (Anosmia / ageusia, odynophagia, dysphonia, rhinorrhea, sneezing, nasal congestion, pharyngeal dryness-mucus, ear pain, epixtasis)	8 (10)	30 (31)	41 (37)	64 (25)	X2 (df=3)= 17.808. p= .000482. Significant at p < .05.
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	9 (12)	7 (7)	3 (3)	6 (2)	X2 (df=3)= 13.7865. p= .003211. Significant at p < .05.
Neurological (headache, dizziness, photopsia, syncope, mental confusion -brain fog)	7 (9)	9 (9)	8 (7)	14 (6)	X2 (df=3)= 2.0467. p= .56278. NS
Psychiatric (anxiety, insomnia)	8 (10)	0	0	1 (1)	Kruskal-Wallis (df=3): H= .5482. p= .9082. NS
Skin (chilblains, flictenas, rash, petechiae)	2 (3)	0	0	0	Kruskal-Wallis (df=3): H= .175. p= .9815. NS
Urological (dysuria, frequency)	0	0	0	2 (1)	Kruskal-Wallis (df=3): H= .2308. p= .9725. NS
Total symptoms*	77 (100)	97 (100)	110 (100)	251 (100)	---

(): Denotes percentages; NS: Not significant; df= Degrees freedom; * Patients could have more than one symptom. The percentages are over the total of symptoms

Comparison with other Studies

COVID-19 has evolved over the two years since its detection. The different health measures that have been taken have tried to influence this evolution, while adapting to it. It could be said that not everything depends on the pathogen, but also on the host and environment (Table 3) [32]. Thus, it must also be taken into account that the symptoms may not depend so much on the variant, but on how the body reacts to the virus [33].

Table 3: COVID-19 Epidemiology Has Evolved During the Four Years Since Its Detection

Epidemiological triad of COVID-19 (causal agent, host, environment)	With ongoing transmission cycles around the world, variants of SARS-CoV-2 have emerged with mutations throughout their genome, including in the spike protein gene. The rapid emergence of variants, the latest Omicron in November 2021, has raised concerns about how new mutations affect virus replication, infectivity, transmission and infection, and vaccine-induced immunity
	SARS-CoV-2 host has changed its immune status thanks to hybrid immunity from infection and vaccination. Likewise, the characteristics of the host have varied between 2020 and 2023, in variables such as sex, age, socioeconomic level and presence of chronic diseases, which may be biological risk factors or related to risk or prevention behaviors.
	Environment plays a very important role in the process of infection and propagation of diseases, since, depending on the environmental conditions, the infectious agents are capable or not of reaching the hosts. Environmental factors have varied according to behavioral changes related to the use of masks, safety distance and movements of people, among others.
Natural History of COVID-19	In COVID-19, viral transmission begins a few days before the clinical disease, and this period may vary since the beginning of the pandemic. Also, acute or chronic form (long-COVID-19), severity of the disease, and asymptomatic carrier state have been changing.
Epidemiological Chain of COVID-19	The Epidemiological Chain of COVID-19 has a sequential order that begins with the agent, continues with the reservoir, the agent's exit door, the transmission mechanism, the entry door and ends with the susceptible host. In COVID-19, viral transmission begins a few days before the clinical disease and its main mechanism is through droplets expelled when breathing, speaking, shouting, singing, etc. SARS-CoV-2 is transmitted by direct contact through droplets and by airborne transmission through exposure to aerosols. There is also transmission through hands and fomites contaminated by previous respiratory secretions. That is, it is transmitted primarily between people via respiratory droplets and contact routes.

Since the start of the pandemic, the coronavirus that causes COVID-19 has been mutating [5]. In the period from March to April, the A lineage of the coronavirus predominated in Spain, especially SEC7 and SEC8, and from summer to December 2020, the 20E (EU1) variant [34,35]. During 2021, the dominant variant in Spain was first Delta and finally Omicron [36]. The predominant variants in Spain during 2023 were those of the XBB family. The XBB.1.5 lineage became dominant globally in February 2023 and in March in Spain. The “Eris” variant (EG.5), a descendant of the omicron, also of the XBB family, has spread rapidly since the end of July 2023 throughout the United States, Europe (including Spain) and Asia. None of these variants have been shown to cause increased severity or increased escape from vaccines and symptoms remain largely similar to previous omicron variants [37-41]. However, experts are unclear whether comparing these differences in SARS-Co-2 reveals a general trajectory in the evolution of new variants [6].

COVID-19 varies from asymptomatic or paucisymptomatic forms, to cases with mild-severe disease with non-pneumonia and mild pneumonia, and critical clinical conditions characterized by respiratory failure [42-45]. The first reports from China in 2020 showed that these patients had symptoms of a lower respiratory tract infection, including cough, fever, dyspnea, general pain, asthenia, nausea-vomiting, pneumonia. Later, with the significant expansion of this disease, reports indicated other prevalent symptoms of the upper respiratory tract, such as sore throat, nasal congestion, and rhinorrhea, in addition to headache, fatigue, myalgia, anosmia, and ageusia. In the early

stage of the pandemic, symptoms were related only to the initial strains of SARS-CoV-2 that circulated between April and September 2020 and were not related to later variants such as Delta or Omicron. Presentations of COVID-19 in unvaccinated people in this first period of the pandemic (In 2020 there were still no vaccines against COVID-19) have ranged from mild/asymptomatic symptoms to severe disease and mortality. Thus, the most frequently reported initial signs or symptoms in the first 12 US patients confirmed with COVID-19 from January 20 to February 5, 2020, were cough and fever; during the course of the disease reported cough, fever, diarrhea, and vomiting [46-51].

In an observational study evaluating reported clinical symptoms of 63,000 confirmed cases of COVID-19 over two time periods (June to November 2021 when the Delta variant predominated and December 2021 to January 2022 when Omicron predominated), showed that the most frequent were nasal congestion (80%), headache (80%), sneezing (65%) and sore throat (65%) [52]. Además, the symptoms with which COVID-19 manifested at the beginning of the pandemic are no longer the same as in the vaccinated population. The symptoms of COVID-19 change for those vaccinated: fever is no longer the most permanent symptom, neither is the loss of taste and smell, and rhinorrhea, sore throat or dry cough and headache appear as very frequent symptoms in people with the vaccine [53]. Among vaccinated adults symptoms are more closely related to the common cold; there are coughing, but also a higher prevalence of runny noses and sneezes; Headaches and sore throats are other top complaints. Fever and loss of taste and smell are being reported to a lesser

extent [54]. The omicron variant appears to replicate rapidly in the upper respiratory tract and their main symptoms include a runny nose, headache, fatigue, sneezing, and sore throat and generally other mild symptoms such as cough, congestion and fatigue [55-57].

Our study, in the context of general medicine in Toledo (Spain), shows homogeneous results with what has been published. Cases of COVID-19 from 2020 to 2023 are different, and these show a tendency to predominate symptoms of upper respiratory tract infection with fewer digestive symptoms. This change in symptoms, that causes COVID-19 to present itself as a common cold instead of the serious respiratory symptoms at the beginning of the pandemic, can do away with preventive precautions, so it is important to test to see what the symptoms mean [23,25].

Limitations and Strengths of the Study

1. The use of databases collected for specific purposes in the primary analysis, other than the secondary analysis, limits the analysis and interpretation of results.
2. The sample size may not meet the needs of the secondary analysis performed. The sample was small, so some data may cause misinterpretation.
3. Asymptomatic cases were missing because they did not attend in GP consultation, as no surveillance or systematic screening was done.
4. The lineages of the infections were not sequenced. Therefore, it cannot be completely ruled out of the causal variant
5. There may be an underreporting of infections to GP of patients with a positive test at home. But given the situation of the GP as the gateway to the health system, the vast majority of positive COVID-19 tests at home, is likely to be reported in GP office.
6. The study has the strength of its longitudinality, characteristic of work in general medicine.
7. All the studies were carried out in the same general medicine practice and carried out by the same researcher, which gives coherence to the results.

Conclusion

In the general practice setting in Toledo, Spain, from 2020 to 2023, a variation in the clinical presentation of COVID-19 is observed, with a tendency to predominate ENT symptoms and to present fewer digestive symptoms from 2021. The data show a clear evolution to presentations with milder symptoms of COVID-19, possibly due both to the evolution of the virus itself, and also due to vaccines and immunity after passing the disease. However, given the history of the virus in terms of mutations, a resounding projection cannot be established about its future behavior. This trend towards milder symptoms does not mean that more serious symptoms cannot appear: a more thrombogenic approach with cardiovascular problems in the future, or with increased risk of type 1 diabetes, and possibly dementia. Only time will tell if this was a feature of the previous variants or not. This change in symptoms that causes COVID-19 to present itself like a common cold, instead of the severe respiratory symptoms at the beginning of the pandemic, carries the risk that it can make people forget prevention measures, and physician forget the careful evaluation of symptoms and the epidemiological surveillance.

References

1. Rosales Ortega JC. Curso Precongreso: Epidemiología Aplicada Historia Natural de Enfermedad, Niveles de Prevencion Cadena Epidemiológica. VII Congreso Internacional DE Epidemiologia San Andrés Cholula, Puebla. 2005.
2. Castillo Acosta M. Epidemiología. Ciudad de la Habana: Editorial Pueblo y Educación. 1984.
3. Kolifarhood G, Aghaali M, Mozafar Saadati H, Taherpour N, Rahimi S, et al. Epidemiological and Clinical Aspects of COVID-19; a Narrative Review. Archives of academic emergency medicine. 2020. 8: e41.
4. DeGrace MM, Ghedin E, Frieman MB, Krammer F, Grifoni A, et al. Defining the risk of SARS-CoV-2 variants on immune protection. Nature. 2022. 605: 640-652.
5. Ingrassia V. Alpha, Beta, Gamma, Delta and Omicron: differences and lethality of the COVID-19 variants that marked the pandemic. Infobae. 2021. 26.
6. Robitzski D. How Mild Is Omicron Really? Early reports that Omicron causes less-severe disease than Delta seem to be borne out, but it's not yet clear to what extent that's due to the variant itself versus the populations it's infecting. The Scientist. 2022.
7. Feikin DR, Higdon MM, Abu-Raddad LJ, Vaux S, Montagnat C, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. Lancet. 2022. 399: 924-944.
8. Kumar A, Narayan RK, Prasoon P, Kumari C, Kaur G, et al. Mechanisms of COVID-19 in the human body: What we know so far]. Kompass Neumol 2022. 4: 3-20.
9. Dagan N, Barda N. BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021 384: 1412-1423.
10. Grange Z, Buelo A, Sullivan C, Moore E, Agrawal U, et al. Characteristics and risk of COVID-19-related death in fully vaccinated people in Scotland. Lancet. 2021 398: 1799-800.
11. Mayor SJ, Welte T. From Pandemic to Endemic: How Do Influenza and SARS-CoV-2 Compare? Medscape CME & EDUCATION. 2023.
12. Pérez-Cortés Villalobos A. A new disease that we must know: COVID-19 after being vaccinated. Medscape. 28. 2021.
13. Crist C. Unvaccinated People Likely to Catch COVID Repeatedly. Medscape. 2021.
14. Kojima N, Klausner JD. Protective immunity after recovery from infection. Lancet Infect Dis. 2021. 22: 12-14.
15. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman LS, et al. Protection and Waning of Natural and Hybrid Immunity to SARS-CoV-2. N Engl J Med. 2022. 386: 2201-2212.
16. Williams S. Cold-Causing Coronaviruses Don't Seem to Confer Lasting Immunity. The Scientist. 2020.
17. Johnston C, Hughes H, Lingard S, Hailey S, Healy B. Immunity and infectivity in COVID-19. BMJ. 2022. 378: e061402.
18. Lenharo M. New pill helps COVID smell and taste loss fade quickly. The antiviral drug ensitrelvir, which shortens sensory problems, is one of the few COVID-19 drugs available to people not at high risk of grave illness. Nature. 2023.

19. Iacobucci G. COVID-19: UK adds sore throat, headache, fatigue, and six other symptoms to official list. *BMJ*. 2022. 377: o892.
20. Redacción. Alfredo Corell warns that the symptoms of COVID-19 have changed for those vaccinated. *La Ventana. Cadena SER*. 2021.
21. Ministerio de Sanidad. Surveillance and control strategy against COVID-19 after the acute phase of the pandemic. *Gobierno de España*. 2022.
22. Kadirvelu B, Burcea G, Quint J, Costelloe CE, Faisal AA. Variation in global COVID-19 symptoms by geography and by chronic disease: A global survey using the COVID-19 Symptom Mapper. *Eclinical Medicine*. 2022. 45: 101317.
23. Turabian JL. Sars-Cov-2 Dependent Variables are most important in Epidemiological Triad during COVID-19 Pandemic Evolution. A Comparison Study of Unvaccinated COVID-19 Cases in 2020 with Not Fully Vaccinated COVID-19 Cases in 2021. *Archives of Health Science*. 2022. 6: 1-11.
24. Turabian JL. COVID-19 Breakthrough Infections in Vaccinated People Versus COVID-19 Infections People without Vaccination: Secondary Data Analysis of Clinical-Epidemiological Characteristics in a General Medicine Practice in Toledo (Spain). *J Community Prev Med* 2022. 4: 23-31.
25. Turabian JL. COVID-19 Breakthrough Infections In Vaccinated People With Vaccine Booster In 2022 Versus COVID-19 Cases In Unvaccinated People In 2020: A New Disease Whose Clinic We Should Know Or Another Cause Of The Old Symptoms Of The Common Cold?. *J General medicine and Clinical Practice*. 2022. 5: 1-7.
26. Turabian JL. Clinical-Epidemiological COVID-19 Case Series Study in Endemic Period, from October 2022 to October 2023, in a General Medicine Office, in Toledo (Spain): Mild Symptoms should not Imply Mild Epidemiological Surveillance. *Int Jr Infect Dis & Epidemlgy*. 2023. 4: 1-6.
27. Turabian JL. Notebooks of Family and Community Medicine. An introduction to the principles of Family Medicine. Madrid: Díaz de Santos. 1995.
28. Ministerio de Sanidad. COVID-19 early detection, surveillance and control strategy. 2021.
29. Strauss AL. Chronic illness and the quality of life. St Louis: The C.V. Mosby Company. 1984.
30. WHO. International Statistical Classification of Diseases and Health-Related Problems. ICD-10 Version: 2019. <https://icd.who.int/browse10/2019/en>
31. Mao S, Huang T, Yuan H, Li M, Huang X, et al. Epidemiological analysis of 67 local COVID-19 clusters in Sichuan Province, China. *BMC Public Health*. 2020. 20: 1525.
32. Ledford H. How severe are Omicron infections? As cases spread and countries plan their response, researchers await crucial data on the severity of the disease caused by the coronavirus variant. *Nature*. 2021. 600: 577-578.
33. Iacobucci G. COVID-19: Runny nose, headache, and fatigue are commonest symptoms of omicron, early data show. *BMJ*. 2021. 375: n3103.
34. López MG, Chiner-Oms Á, García de Viedma D, Ruiz-Rodríguez P, Bracho MA, et al. The first wave of the COVID-19 epidemic in Spain was associated with early introductions and fast spread of a dominating genetic variant. *Nature Genetics*. 2021.
35. Hodcroft EB, Zuber M, Nadeau S, et al. (2020) Spread of a SARS-CoV-2 variant through Europe in the summer of 2020, *Nature*. 2020. 595: 707-712.
36. Centro de Coordinación de Alertas y Emergencias Sanitarias. Update of the epidemiological situation of SARS-CoV-2 variants in Spain. *Ministerio de Sanidad. Gobierno de España*. 2021.
37. Centro de Coordinación de Alertas y Emergencias Sanitarias. Update on the epidemiological situation of SARS-CoV-2 variants in Spain. *Ministry of Health. Spain*. 2023.
38. Viciosa M. If you have COVID today, the new variant O EG.5 or 'Eris' may have something to do with it (and it is not more serious). 2023.
39. Pérez B. The new eris variant, more contagious, already alerts doctors to the rebound in COVID. *El Periódico*. 2023.
40. Looi M. COVID-19: Hospital admissions rise in England amid fears of new variant and waning immunity. *BMJ*. 2023. 382: p1833.
41. Smith DG. What to Know About the New Dominant COVID Variant. EG.5 is spreading quickly, but experts say it's no more dangerous than previous versions. Another new variant, called BA.2.86, is being closely watched because of its mutations. *The New York Times*. 2023.
42. CDC. Symptoms of Coronavirus. 2020. <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>
43. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Napoli RD. Features, Evaluation and Treatment Coronavirus (COVID-19). In: *StatPearls. Treasure Island (FL): StatPearls Publishing*. 2020.
44. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 102433. 2020.
45. Lescure F-X, Bouadma L, Nguyen D, Clinical and virological data of the first cases of COVID-19 in Europe: a case series. et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet*. 2020. 20: e116.
46. Stawicki SP, Jeanmonod R, Miller AC, Paladino L, Gaiiski DF, et al. The 2019-2020 Novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2) Pandemic: A Joint American College of Academic International Medicine-World Academic Council of Emergency Medicine Multidisciplinary COVID-19 Working Group Consensus Paper. *J Glob Infect Dis*. 2020. 12:47-93.
47. Kentab OY, Ibrahim AAA, Soliman KR, Alanazi M, Alsunaid A, et al. Testing for anosmia and ageusia in patients presenting to the emergency department with suspected coronavirus disease 2019 in Saudi Arabia. *J Int Med Res*. 2022. 50.
48. Turabian JL. Clinical-Epidemiological Characteristics That May Help the General Practitioner to Consider COVID-19 Diagnosis in Acute Respiratory Infections When Diagnostic Tests Are Not Accessible. *Epidemol Int J*. 2020. 4: 000143.
49. Ellis R. CDC Says Three COVID-19 Symptoms Are Most Common. *Medscape*. 2020.
50. The COVID-19 Investigation Team. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *Nat Med*. 2020 26: 861-868.

51. Burke RM, Killerby ME, Newton S, Ashworth CE, Berns AL, et al. Symptom Profiles of a Convenience Sample of Patients with COVID-19 - United States, January-April 2020. *MMWR Morb Mortal Wkly Rep.* 2020. 69: 904-908.
52. ABC Sociedad. These are the most frequent symptoms of coronavirus in vaccinated people. ABC. 2021. https://www.abc.es/sociedad/abci-sintomas-frecuentes-coronavirus-personas-vacunadas-nsv-202107221213_noticia.html#ancla_comentarios
53. Mejía L. Immunologists warn: "We have to maximize precautions until there are no more vaccinated". *La Ventana.* 2021.
54. Caron C. What are the symptoms of the delta variant like and what precautions should you take? We ask experts to describe the predominant symptoms they are detecting among people with COVID-19. *The New York.* 2021.
55. ZOE COVID Study. What are the new top 5 COVID symptoms? 2021. https://COVID.joinzoe.com/post/new-top-5-COVID-symptoms#part_1
56. Roy M. Most Reported U Omicron Cases Have Hit the Fully Vaccinated: CDC. *Medscape;* 2021.
57. Turabian JL. Case Series of 46 COVID-19 Breakthrough Infections in Vaccinated People with Vaccine Booster Shot in General Medicine for the Period December 2021 to February 2022, in Toledo, Spain. *J Community Prev Med.* 2022. 5: 11-20.