

SARS-CoV-2 Reinfections as Compared with Primary Infections in Vaccinated People. Are there Clinical-Epidemiological Differences of Importance for Health Interventions between First Infection and Reinfection in Vaccinated People?

Jose Luis Turabian^{1,*}

¹ Specialist in Family and Community Medicine, Health Center Santa Maria de Benquerencia. Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain.

Research Article

*Corresponding author

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;
Email: jturabianf@hotmail.com.

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Abstract

Background

Although reinfections in vaccinated individuals should theoretically be lighter than primary infections in vaccinated individuals, the clinical-epidemiological differences and their importance regarding public health between cases of COVID-19 reinfection with vaccination and cases of COVID-19 primary infection with vaccination are not known.

Objective

To compare the clinical-epidemiological characteristics of the cases of COVID-19 reinfection with the cases of COVID-19 primary infection with 1, 2 or 3 doses of vaccine, to assess whether there are differences in health utility applicable to clinical work in general medicine.

Methodology

Comparison of secondary data from two observational, longitudinal, and prospective studies: A study of COVID-19 reinfection cases with vaccine (1, 2 or booster), and a set of studies of COVID-19 primary infections in vaccinated people (1 dose, 2 dose or booster), both from 2021 to June 2022, conducted on the same population, in a general medicine office in Toledo, Spain. For the statistical analysis, the bivariate comparisons were used Chi Square test, with Yates correction or Fisher Exact Test when necessary.

Results

We included 35 people with COVID-19 reinfection with vaccine (with 37 infections due to 2 cases with 2 reinfections: 2 women aged 17 and 19, with 2 and 1 dose of vaccine respectively), and 88 people with primary COVID-19 infections in vaccinated (1, dose, 2 doses 3 doses) from 2021 to June 2022. The cases of COVID-19 reinfection with vaccine vs. COVID-19 primary infections with vaccine, were younger, more women, with higher social-occupancy class, and with more chronic diseases of respiratory system. There were no significant differences by symptoms.

Conclusion

The cases of COVID-19 reinfection with vaccination vs. cases of COVID-19 primary infection with vaccine (1, 2 or 3 doses) are not differentiated by chronic diseases, except more chronic diseases of the respiratory system, nor by symptoms of infection, but by social variables, being younger, more women, with higher social-occupancy class, which probably associate other health behaviors. Given that in developed countries the majority of the population is vaccinated with at least one dose, if reinfections in vaccinated differ from primary infections in vaccinated in affecting a certain segment of the population, this could be the subject of special health measures public.

Keywords: COVID-19; SARS-CoV-2; Reinfections; COVID-19 Vaccine; Epidemiological characteristic; Secondary Analysis; General Practice.

Introduction

A reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurs when a person with COVID-19 recovers and acquires SARS-CoV-2 again. In the disease caused by the SARS-CoV-2 (COVID-19) it quickly became clear that naturally acquired immunity would not, in all cases, provide protection for months after the first infection [1]. After having presented COVID-19, most individuals will have some degree of protection, which is temporary because they may be susceptible to infection again; in fact, it has been found that 60% of patients still have SARS-CoV-2 antibodies at the time of reinfection diagnosis [2].

Therefore, coronavirus infection does not result in lifelong immunity, and reinfection is common. The natural course of coronavirus infection includes repeated exposure and repeated infection over a variable time course. Over time, SARS-CoV-2 is likely to transform into a seasonal coronavirus infection [3]. Evidence of infections with other seasonal coronaviruses suggests cycles of infection, with different coronavirus strains predominating every two to four years, and that complete immunity against symptomatic reinfection for at least a year if "reinfected" with the same strain, but only partial immunity occurs when exposed to a heterologous strain [3].

Data from vaccination studies show that protection declines over time, but lasts in most people for at least four months. Vaccination has been shown to be effective against all naturally circulating strains. Evidence continues to emerge on efficacy against the latest variant (omicron), although protection is definitely reduced. In any case, the immunity derived from vaccination diminishes over time [3], but these help protect against severe illness, hospitalizations, and death [4].

Primary infections in vaccinated people (who have some immunity to COVID-19) are generally less severe than primary infections in unvaccinated people (who have no immunity); therefore, hospitalization rates are lower among those vaccinated. Therefore, it is reasonable to assume that, in general, reinfections must be less severe than primary infections, since the person who becomes reinfected will have some pre-existing immunity from their primary infection. And while immunity against coronavirus infection and the development of covid symptoms declines, protection against serious illness and death appears much longer lasting. So reinfections definitely seem less severe [5,6].

In this context, if the primary infection generates immunity in such a way that the reinfection would be milder than the primary infection, and the infected vaccinated would have a milder clinical picture than the unvaccinated, consequently, the reinfections in vaccinated should be milder than primary infections in vaccinated. So far, data on this topic is minimal. This study aims to provide data on this so that they can be of practical application at the level of general medicine.

Material and Methods

This study compares data from two set of previous published studies:

- 1) A study of COVID-19 reinfection cases with vaccine (1, 2 or 3 doses) from 2021 to June 2022 [7, 8].
- 2) A set of studies of COVID-19 primary infections in vaccinated people (1, 2 or 3 doses) from 2021 to June 2022 [9-11].

The studies were conducted on the same population: patients seen in a general medicine office in Toledo, Spain, which has a list of 2,000 patients > 14 years of age (in Spain, the general practitioners [GPs] care for people > 14 years of age, except for exceptions requested by the child's family and accepted by the GP). 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 [12]. The methodology of both studies has been previously published [7-11]. This methodology will only be partially mentioned here, to avoid repetition.

Outcome of interest

To compare the clinical-epidemiological characteristics of the cases of COVID-19 reinfection with vaccination with the cases of COVID-19 primary infection with 1, 2 or 3 doses of vaccine, to assess whether there are differences in health utility applicable to clinical work in general medicine.

Definition of primary infection and reinfection

Primary infection was defined as the first positive polymerase chain reaction (PCR) or antigen test. Reinfection was defined as the first positive PCR or antigen test obtained at least 90 days after the primary infection [6].

Collected variables

Age; Sex; symptoms; severity of the disease (primoinfección y reinfección) [13], chronic diseases [14], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [15]; social-occupancy class [16], and Health Care Workers.

Statistic analysis

The bivariate comparisons were performed using the Chi Square test (χ^2), χ^2 with Yates correction or Fisher Exact Test when necessary, (according to the number the expected cell totals).

Ethical aspects

Individual patient data is not used, but only aggregated statistical data.

Results

It was included 35 people with COVID-19 reinfection with vaccine (1, 2 or 3 doses), with 37 infections due to 2 cases with 2 reinfections: 2 women aged 17 and 19, with 2 and 1 dose of vaccine, respectively, from 2020 to June 2022, and 88 people with primary COVID-19 infections in vaccinated (1, dose, 2 dose and booster) from 2021 to June 2022. The cases of COVID-19 reinfection with vaccine vs. COVID-19 primary infections with vaccine were younger, more female, with a higher social-occupancy class, and with more chronic diseases of the respiratory system. There were no significant differences by symptoms (Table 1, 2 & 3).

Discussion

Main findings

We found that the cases of COVID-19 reinfection with vaccine vs. COVID-19 primary infections with vaccine, were younger, more women, with higher social-occupancy class, and with more chronic diseases of respiratory system. There were no significant differences by symptoms. These results suggest that it is the social variables (age, sex, social class) that differentiate the cases of covid reinfection from those of primary infection in vaccinated (1, 2 or 3 doses). Possibly, these social variables are associated with certain health behaviors.

Table 1: Comparison of COVID–19 Reinfections Versus Primary Infections with Vaccine (1, 2 or 3 Doses) from 2021 to June 2022.

Variables	COVID–19 Reinfections with Vaccine (1, 2 or 3 Doses) from 2021 to June 2022 N=35	Primary Infections COVID–19 with Vaccine (1, 2 or 3 Doses) From 2021 to June 2022 N= 88	Statistical Significance
> = 65 years	2 (6)	22 (25)	X2= 5.9304. p= .014882. Significant at p < .05.
Women	29 (83)	47 (53)	X2= 9.1972. p= .002424. Significant at p < .05.
Social–occupancy class of patients (people with some type of labor specialization)	15 (43)	11 (12)	X2= 13.8431. p= .000199. Significant at p < .05.
Health Care Workers	7 (20)	20 (33)	X2= 0.1087. p= .741615. NS
Moderate–severe severity of reinfection	0	0	Fisher exact test= 1. NS
Moderate–severe severity of primary infection	3 (9) (pneumonias)	5 (6) (pneumonias)	Fisher exact test= 0.6869. NS
Chronic diseases presence	22 (63)	57 (65)	X2= 0.04. p= .841495. NS
(): Denotes percentages; NS: Not significant.			

Table 2: Comparison of Chronic Diseases in COVID–19 Reinfections Versus Primary Infections with Vaccine (1, 2 Or 3 Doses) from 2021 To June 2022.

Chronic Diseases* According to WHO, ICD–10 Groups	COVID–19 Reinfections with Vaccine (1, 2 or 3 Doses) From 2021 to June 2022 N=35	Primary Infections COVID–19 with Vaccine (1, 2 or 3 Doses) from 2021 to June 2022 N= 88	Statistical Significance
–I Infectious	0	0	Fisher exact test= 1. NS
–II Neoplasms	1 (2)	6 (3)	Fisher exact test= 1. NS
–III Diseases of the blood	0	4 (2)	Fisher exact test= 0.5872. NS
–IV Endocrine	10 (17)	39 (17)	X2= 0.0061. p .937546. NS
–V Mental	3 (5)	13 (6)	X2 with Yates correction= 0.0372. p= .84704. NS
–VI–VIII Nervous and Senses	4 (7)	25 (11)	X2= 0.7759. p= .37841. NS
–IX Circulatory system	5 (9)	28 (12)	X2= 0.5471. p= .459503. NS
–X Respiratory system	10 (17)	11 (5)	X2 with Yates correction= 9.0128. p= .002681. Significant at p < .05.
–XI Digestive system	4 (7)	32 (14)	X2= 2.0297. p= .154246. NS
–XII Diseases of the skin	3 (5)	8 (3)	Fisher exact test= 0.4644. NS
–XIII Musculo–skeletal	7 (12)	36 (15)	X2= 0.4369. p= .508637. NS
–XIV Genitourinary	11 (19)	30 (13)	X2= 1.3919. p= .238083. NS
TOTAL chronic diseases**	58	232	—
(): Denotes percentages; NS: Not significant; *Patients could have more than one chronic disease. The percentages of chronic diseases are over the total of chronic diseases of symptomatic and asymptomatic patients.			

Table 3: Comparison of Symptoms in COVID–19 Reinfections Versus Primary Infections with Vaccine (1, 2 Or 3 Doses) from 2021 to June 2022.

Symptoms* According to WHO, ICD–10 Groups	COVID–19 Reinfections with Vaccine (1, 2 or 3 Doses) from 2021 to June 2022 N=37**	Primary Infections COVID–19 with Vaccine (1, 2 or 3 Doses) from 2021 to June 2022 N= 88	Statistical Significance
General (discomfort, asthenia, myalgia, fever, arthralgias)	37 (39)	62 (30)	X2= 2.3913. p= .122011. NS
Respiratory (cough, dyspnea, chest pain)	26 (27)	47 (23)	X2= 0.7725. p= .379448. NS
ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness–mucus, epistaxis)	23 (24)	71 (34)	X2= 3.0918. p= .07869. NS
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	3 (3)	10 (5)	X2 with Yates correction= 0.1295. p=.718938. NS
Neurological (headache, dizziness, mental confusion –brain fog)	6 (6)	17 (8)	X2= 0.333. p= .563918. NS
Psychiatric (Anxiety, insomnia)	0	0	Fisher exact test= 1. NS
Skin (chilblains, flictenas, rash)	0	0	Fisher exact test= 1. NS
Total symptoms*	95	207 (100)	—

(): Denotes percentages; NS: Not significant; * Patients could have more than one symptom. The percentages are over the total of symptoms; **N=37 (35 people, with 37 infections, for 2 cases with 2 reinfections: 2 women aged 17 and 19, with 2 and 1 dose of vaccine respectively).

As of January 2022, 60.5% of the world's population has received at least one dose of a COVID–19 vaccine. Vaccination rates continue to lag in low–income countries, where only 10% of the population have received at least one dose of a vaccine, while in high– and upper–middle–income countries, 77% of the population have received at least one dose of a vaccine [17].

In Spain, as of April 27, 2021, 23.7% of the population had received at least one dose [18]. And as of May 6, 2021, the percentage of vaccination with the complete schedule was 85.4% [19]. As of June 3, 2021, the percentage of vaccinated with 1 dose and with 2 doses was very high: 87.1% of vaccinated with one dose, and 85.6% of vaccinated with a complete regimen were reported [17]. In the community of Castilla–La Mancha (Spain), where this study was carried out, as of November 10, 2021, there were 76% with 2 doses and 79% with one dose [20]. In this way, the number of unvaccinated people (without any dose) was very low as the year 2021 progressed. In April 2022, in Spain there were only 6% of people without any dose [21].

Given that in developed countries the majority of the population is vaccinated with at least one dose of vaccine, if reinfections in vaccinated differ from primary infections in vaccinated in affecting a certain segment of the population (young women of low socioeconomic status) , this population could be the object of special public health measures.

Comparison with other studies

Vaccination may increase protection in previously infected persons [22]. It has been reported that vaccination after a previous infection may result in a further reduction in the risk of reinfection and hospitalization for up to 9 months [23]. That is, those who have better long–term immunity are those who were infected and then have been vaccinated. Likewise, the majority of patients with reinfection in non–vaccinated people had mild symptoms in both episodes [24]. Reinfections were 90% less likely to result in

hospitalization or death than primary infections [6]. In general, most studies suggest that the second SARS–CoV–2 infection is milder than the first. In fact, that is what should be expected from an immunological point of view [5, 25–28].

A single prior infection provides similar protection against infection with omicron as two doses of vaccine, but such immunity will still not be 100 percent protective [5, 6]. It is recognized that the reinfection may be milder than the primary infection. However, this may depend on when the infection occurs. Alpha reinfections are estimated to have given people symptoms only 20 percent of the time, while delta reinfections caused symptoms in 44 percent of cases and omicron in 46 percent. It has also been reported that people reinfected with alpha were much less likely to have symptoms the second time compared to their primary infection. While delta reinfections were somewhat more likely to give people symptoms compared to their primary infection. With an omicron reinfection, the rate of symptoms was almost the same in reinfection and primary infection [5, 6].

Our study covers from 2021 to June 2022. In the January 2021 period, the alpha variant predominated, and from the summer–autumn of 2021 there was an increase in the delta variant and a significant decrease in the Alpha variant [29, 30]. In November 2021 there was an almost total hegemony of the circulation of the delta variant with high population vaccination coverage. Although research suggests that COVID–19 vaccines are slightly less effective against the delta variant, they appear to offer protection against serious illness [31]. In March 2022, the BA.2 lineage of the omicron variant of COVID–19 predominated in Spain; at that time the prevalence of the alpha variant was declining [32, 33]. While people infected with delta are at risk of developing severe lung disease, infection with omicron often causes milder symptoms, especially in vaccinated people [34]. In our study, the fact of comparing reinfections with primary infections during the

same dates avoids the possible temporal bias due to the different variants.

In a systematic review of 17 cases of genetically confirmed COVID-19 reinfection, it was found that 69% of people had symptoms similar to those of their first episode, 19% had a more severe condition and 12% a milder one [35]. Other studies have already reported suspected reinfection rates in non-vaccinated were higher in females and people < 65 years [36, 37]. Our data on vaccinated people repeat the same findings.

It is recognized that people whose immune system is impaired, as well as those with conditions due to diabetes, cancer, HIV or another type of chronic disease, are more likely to suffer a reinfection by COVID-19. However, this depends on the immunity they have generated from the primary infection and/or vaccination. It currently seems to be accepted that underlying chronic respiratory diseases increase the predisposition to reinfection [38]. In the same population of our study, it has been previously published that the presence of chronic respiratory diseases was a moderate risk factor [8]. In the case of respiratory diseases, specifically, it has been seen that the representation of people with COPD or asthma with COVID-19 in relation to the population prevalence is strikingly low, however, COPD is associated with a worse clinical course and with a higher mortality from COVID-19, as well as a higher risk of admission to the ICU [39].

Not all social groups have been exposed to SARS-CoV-2 in the same way. Studies in various countries around the world, including Spain, have shown that the cumulative incidence of primary infection for COVID-19 has been higher in people of a lower socioeconomic position, perhaps due to greater exposure to the virus in people with fewer resources, especially in the workplace and housing [40–43]. On the other hand, it has been reported that people living in highly deprived areas were more likely to have post-vaccination infection after their first dose of vaccine [43]. However, we found more reinfections vs primary infections in people with a higher socio-occupational level.

Strengths and weaknesses 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) Samples were small, thus statistical significance of some variables could be obscured.
- 3) Studies were made with the same criteria, in the same general medicine practice, using the same reference population, and carried out by the same researcher, which gives coherence to the results.

Conclusion

The cases of COVID-19 reinfection with vaccination vs. cases of COVID-19 primary infection with vaccine (1, 2 or 3 doses) are not differentiated by chronic diseases, except more chronic diseases of the respiratory system, nor by symptoms of infection, but by psychosocial variables, being younger, and more women, with higher social-occupancy class, which probably associate other health behaviors. Given that in developed countries the majority of the population is vaccinated with at least one dose of vaccine, if reinfections in vaccinated differ from primary infections in vaccinated in affecting a certain segment of the population, this people could be subject to special measures of public health.

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None.

Conflict of interest

Author declares there is no conflict of interest.

References:

1. Brouqui P, Colson P, Melenotte C, et al. COVID-19 re-infection. *Eur J Clin Invest.* 2021;51(5): e13537.
2. Nguyen NN, Houhamdi L, Hoang VT, et al. SARS-CoV-2 reinfection and COVID-19 severity. *Emerg Microbes & Infect.* 2022;11(1): 894–901.
3. Johnston C, Hughes H, Lingard S, Hailey S, Healy B. Immunity and infectivity in covid-19. *BMJ.* 2022;378: e061402.
4. CDC. COVID-19 after Vaccination: Possible Breakthrough Infection. Last Updated June 23, 2022. Content source: National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases.
5. Hunter P. COVID reinfections: are they milder and do they strengthen immunity? *The Conversation;* 1 April, 2022.
6. Abu-Raddad LJ, Chemaitelly H, Bertollini R. National Study Group for COVID-19 Epidemiology. Severity of SARS-CoV-2 Reinfections as Compared with Primary Infections. *N Engl J Med.* 2021;385(26): 2487–2489.
7. Turabian JL. Characteristics of a case series of COVID -19 reinfection and its trend from 2020 to June 2022 in a general medicine office in Toledo (Spain). *International Journal of Epidemiology and Health Sciences.* In Press: <http://www.ijehs.com/>
8. Turabian JL. Incidence rates and risk factors of covid-19 reinfections from march 1, 2020 to July 1, 2022 in a general medicine office in Toledo, Spain. *Annals of Community Medicine and Primary Health Care.* In Press: <https://meddocsonline.org/annals-of-community-medicine-and-primary-health-care-press.html>
9. Turabian JL. Secondary infections in the family from primary cases of covid-19 breakthrough infections in fully vaccinated or not fully vaccinated people. Two doses modestly reduce family transmission but does not eliminate it. *Journal of SARS-CoV-2 Research.* 2022;2: 12–24.
10. Turabian JL. Risk Factors and Incidence Rates of Covid-19 Breakthrough Infections in Vaccinated People in General Medicine Practice in Toledo (Spain). *Arch Fam Med Gen Pract.* 2022;7(1): 183–192.
11. 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(2): 1–7.
12. Turabian JL. (1995) [Notebooks of Family and Community Medicine. An introduction to the principles of Family Medicine]. Madrid: Díaz de Santos: <http://www.amazon.co.uk/Cuadernos-medicina-familia-y-comunitaria/dp/8479781920>
13. Mao S, Huang T, Yuan H, et al. Epidemiological analysis of 67 local COVID-19 clusters in Sichuan Province, China. *BMC Public Health.* 2020;20: 1525.
14. Strauss AL. (1984) *Chronic illness and the quality of life.* St Louis: The C.V. Mosby Company.

15. WHO. International Statistical Classification of Diseases and Health-Related Problems. ICD-10 Version:2019. <https://icd.who.int/browse10/2019/en>
16. Royal Collage of General Practitioners (1986) The Classification and Analisis of General Practice Data. Ocasional Paper 26.
17. Drouin O, Fontaine P, Arnaud Y, et al. Parental decision and intent towards COVID-19 vaccination in children with asthma: an econometric analysis. *BMC Public Health*. 2022;22: 1547.
18. GIV COVID-19 (2021) [Activity report. From December 27, 2020 to April 27, 2021]. Ministerio de Sanidad. Gobierno de España. https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Informe_GIV_comunicacion_20210428.pdf
19. Grasso D, Zafra M, Sevillano Pires L, Clemente Y. (2021) [This is how vaccination against covid evolves in Spain and in the world]. *El País*; 06 de mayo. <https://elpais.com/especiales/coronavirus-covid-19/asi-evolucion-la-vacunacion-en-espana-y-en-el-mundo/>
20. Fernández R. (2021) [Percentage of people vaccinated against the coronavirus (COVID-19) in Spain as of November 10, 2021, by vaccination pattern and autonomous community]. *Statista*. <https://es.statista.com/estadisticas/1258946/poblacion-vacunados-contrala-covid-19-por-numero-de-dosis-y-comunidad-autonoma-de-espana/>
21. García-Abadillo RR. (2022) [Almost 3 million people (2,974,889) are missing who have not received a single inoculation]. *El Mundo*; Jueves, 28 abril. <https://www.elmundo.es/ciencia-y-salud/salud/2022/04/28/62697e3afdddf18558b45a1.html>
22. Alkhatib M, Salpini R, Carioti L, et al. Update on SARS-CoV-2 Omicron Variant of Concern and Its Peculiar Mutational Profile. *Microbiology Spectrum*. 2022;10(2): 1-12.
23. Nordström P, Ballin M, Nordström A. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. *Lancet Infect Dis*. 2022;22(6): 781-790.
24. Fabiánová K, Kynčl J, Vlčková I, et al. COVID-19 reinfections. *Epidemiol Mikrobiol Imunol*. 2021;70(1): 62-67.
25. de Vrieze J. Reinfections, still rare, provide clues on immunity. *Science*. 2020;370(6519): 895-897.
26. Goel RR, Painter MM, Apostolidis SA, et al. mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. *Science*. 2021;374: abm0829.
27. Stokel-Walker C. What we know about covid-19 reinfection so far. *BMJ*. 2021;372: n99.
28. Pilz S, Theiler-Schwetz V, Trummer C, Krause R, Ioannidis JPA. SARS-CoV-2 reinfections: Overview of efficacy and duration of natural and hybrid immunity. *Environmental Research*. 2022;209: 112911.
29. Centro de Coordinación de Alertas y Emergencias Sanitarias (2021) [Update on the epidemiological situation of variant B.1.1.7 of SARS-CoV-2 and other variants of interest. February 08, 2021]. Ministerio de sanidad. Gobierno de España. https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/20210208_Variantes_de_SARS-CoV-2_en_Espana.pdf
30. García Marín AM, Chiner Oms A, González Candelas F, Comas Espadas I, López MG, Coscolla Devis M. (2021) [What genomic epidemiology teaches us about the waves of COVID-19 in Spain (and how to avoid a new wave)]. *The Conversation*; 11 de Julio. <https://theconversation.com/lo-que-nos-ensena-la-epidemiologia-genomica-sobre-las-olas-de-covid-19-en-espana-y-como-evitar-una-nueva-ola-155401>
31. DeSimon DC. (2022) COVID-19 variants: What's the concern? *Mayo Clinic*. <https://www.mayoclinic.org/diseases-conditions/coronavirus/expert-answers/covid-variant/faq-20505779>
32. Evaluación rápida de riesgo (2022) [SARS-CoV-2 variants in Spain: Ómicron lineages BA.2.12.1, BA.4 and BA.5 11th update, June 28, 2022]. Centro de Coordinación de Alertas y Emergencias Sanitarias. Ministerio de sanidad. España. <https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/20220628-ERR.pdf>
33. Centro de Coordinación de Alertas y Emergencias Sanitarias (2022). [Update of the epidemiological situation of SARS-CoV-2 variants in Spain. May 17, 2022]. Ministerio de Sanidad. España. https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Actualizacion_variantes_20220517.pdf
34. Suryawanshi RK, Chen IP, Ma T, et al. Limited cross-variant immunity from SARS-CoV-2 Omicron without vaccination. *Nature*. 2022;607: 351-355.
35. Wang J, Kaperak C, Sato T, et al. COVID-19 reinfection: a rapid systematic review of case reports and case series. *JIM*. 2021;69: 1253-1255.
36. Slezak J, Bruxvoort K, Fischer H, Broder B, Ackerson B, Tartof S. Rate and severity of suspected SARS-CoV-2 reinfection in a cohort of PCR-positive COVID-19 patients. *Clin Microbiol Infect*. 2021;27(12): 1860.e7-1860.e10.
37. Murillo-Zamora E, Trujillo X, Huerta M, Ríos-Silva M, Aguilar-Sollano F, Mendoza-Cano O. Symptomatic SARS-COV-2 reinfection: healthcare workers and immunosuppressed individuals at high risk. *BMC Infect Dis*. 2021;21(1): 923.
38. Vila N (2021) [If I have already had covid, can I get it again?]. *ARA*; 29/12. https://es.ara.cat/sociedad/salud/he-pasado-covid-volver-contagiar_1_4226444.html
39. Villar-Álvarez F, Martínez-García MA, JiménezD, et al. SEPAR Recommendations for COVID-19 Vaccination in Patients With Respiratory Diseases. *Open Respiratory Archives*. 2021;3: 100097.
40. Gullón Tosio P (2021) [The covid-19 does understand social classes]. *The Conversation*; 5 julio. <https://theconversation.com/la-covid-19-si-entiende-de-clases-sociales-163443>

41. Ontario Agency for Health Protection and Promotion (Public health Ontario) (2020) COVID-19 – What we know so far about... social determinants of health. Toronto. Queen's Printer for Ontario; 24 May. <https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2020/05/what-we-know-social-determinants-health.pdf?la=en>
42. Abrams EM, Szeffler SJ. COVID-19 and the impact of social determinants of health. *Lancet Respir Med.* 2020;8(7): 659–661.
43. Antonelli M, Penfold, RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis.* 2022;22(1): 43–55.