

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

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Abstract

Background

It is not clear how the influence of host, environment, and agent on disease outcomes has varied throughout the covid-19 pandemic.

Objective

Assess the differences in the epidemiological triad between cases of covid-19 in unvaccinated (2020) and cases not fully vaccinated (2021).

Methodology

Comparison of secondary data of cases of covid-19 without vaccination of previous studies in 2020, with cases of covid-19 in not fully vaccinated people in 2021 (proxy of non-vaccinated persons), all of them carried out in the same population of patients treated in a general medicine office in Toledo, Spain (thus avoiding the confounding factor of comparing different places and environments).

Results

100 covid-19 cases were included in 2020, and 12 in 2021. Unvaccinated covid-19 cases during 2020 vs. partially vaccinated covid-19 cases (assimilated to unvaccinated) during 2021 did not differ in a statistically significant way, by age, sex, severity of covid-19, or chronic diseases, or presence of socio-health workers. In 2020 vs. 2021, the symptoms of Respiratory, Digestive, Neurological, Psychiatric and Skin predominated, but without statistical significance; and in 2021, General, and ENT symptoms predominated (the latter with statistical significance $p = .048019$).

Conclusion

The clinical presentation of covid-19 cases in 2020 was different than in 2021, and this difference does not seem to be due to the characteristics of the hosts or the context (which did not vary in the studies being compared), but to variables dependent on the virus itself.

Keywords: COVID-19; SARS-CoV-2; Symptoms; Epidemiology; Public Health; General Practice; Secondary Analysis

Introduction

The health crisis unleashed by covid-19 has evolved during the two years since its detection. The different health measures that have been taken have tried to influence

this evolution, while at the same time adapting to it. Knowledge of its epidemiology is essential to decide on these measures. For a communicable disease to appear and spread in the community, a set

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of factors must concur that, interacting with each other, give rise to the disease process; This set of factors is called the triad or ecological/epidemiological chain: causal agent, route of transmission/environmental or contextual factors, and susceptible host (1).

In coronavirus disease 2019 (covid-19), its epidemiological chain can be broken down as follows (2):

1. The agent is a virus called SARS-CoV-2, a Betacoronavirus. The coronavirus family is widespread in the animal kingdom, and is one of the most common causes of colds in humans. They produce pulmonary infections in specific epidemiological contexts such as epidemics in military compounds. The great aggressiveness of this new virus contrasts with the known species of this family. This family of viruses is characterized by an important capacity for mutability (3). SARSCov2 has a surface antigen (S) that allows it to enter cells by binding to the ACE2 receptor (4-7).

Among the characteristics of epidemiological agents, the following stand out: pathogenicity; Infectivity; diffusibility; virulence; toxigenicity; antigenic power or immunogenicity; lethality; specificity; and mutagenicity. The appearance of mutations is a natural and expected event within the evolution process of viruses. Since the initial genomic characterization of SARS-CoV-2, this virus has been divided into different genetic groups or clades. In fact, some specific mutations define the viral genetic groups (also called lineages) that currently circulate globally. Due to various processes of microevolution and selection pressures, some additional mutations may appear, generating differences within each genetic group (called variants) (8).

2. The 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. In this way, the environment as an element of the epidemiological triad includes both physical factors of the environment (soil, water, objects), as well as biotic factors (animals, food, or even human beings); which act as

vectors of disease transmission. On many occasions, a single change in the environmental and/or geographical conditions included within the environment, are capable of allowing or preventing the spread of infectious diseases (9). 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 (10, 11).

3. Human beings and some animals can be considered as epidemiological hosts, whose mechanisms of susceptibility, resistance and/or immunity at the time of infection are deficient or favor contracting a disease. Susceptibility may depend on different intrinsic characteristics of the hosts, such as age, sex, heredity, environmental conditions, nutrition, and hormonal imbalance. At the beginning of the covid-19 pandemic, emphasis was placed on the fact that the SARS-CoV-2 virus produces atypical pneumonia, sometimes fatal, but there are also many asymptomatic or paucisymptomatic cases. Similarly, at the beginning of the pandemic, cough, fever, and shortness of breath were reported as the main symptoms. Systemic and pulmonary manifestations predominated, with an increasing emphasis placed on gastrointestinal symptoms as both diagnostically and prognostically important (5).

SARS-CoV-2, like all viruses, are constantly changing. These changes occur over time and can lead to the emergence of variants that may have new characteristics. In the course of the covid-19 pandemic, SARS-CoV-2 has mutated enough to escape first-line immune defences, specifically antibodies (12, 13).

Any human being who does not have prior immune protection can be a host. There are some who are at higher risk of

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complications: Older people and people with pre-existing health conditions: High blood pressure, heart conditions and diabetes, People who care for the health of an infected patient (either in a clinical setting or at home) and who They have a greater exposure to the virus, such as the health workers or the relatives of a case, people who live overcrowded, or in situations of poverty or immunosuppression (4). Therefore, the likelihood that a person with pre-existing immunity will develop a productive infection (and clinical features of that infection) is likely a function of both viral and host properties. In the covid-19 pandemic, it has been said that it must be taken into account that the symptoms may not depend so much on the variant, but on how the organism reacts to the virus (14). It may be that not everything depends on the pathogen, but also on the host and environment (15, 16).

Research of covid-19 symptoms in 190 countries during 2020 showed that the frequency of symptoms of cough, fever, and loss of smell, was different depending on the country and the presence of underlying health conditions such as asthma and diabetes (17). In addition, it seems that the symptoms with which covid-19 manifested itself at the beginning of the pandemic are no longer the same. Fever seems not to be the most permanent symptom; 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 (18). The UK's official list of covid-19 symptoms was recently updated to include sore throat, fatigue, headache which are now commonly associated with the virus (14).

In this scenario, it is extremely important to study the ecological triad in covid-19, and the correlation and relative importance between the 3 elements, since from this the patterns that appear can be located, and thus have the possibility of intervening in its spread or even prevent it.

In this context, we present a study comparing unvaccinated covid-19 cases in

2020 with not fully vaccinated covid-19 cases in 2021, using secondary data from the same population attended in a general medicine consultation in two 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).

Material and Methods

A secondary analysis of data collected and published for purposes other than this research objectives, was conducted to compare clinical-epidemiological characteristics between cases of covid-19 in 2020 without vaccination, and covid-19 breakthrough infections in not fully vaccinated people in general medicine.

Therefore, this study compares data from previous studies:

1. The set of two previous studies on covid-19 cases. A study of covid-19 cases from March 1 to May 31, 2020 (19), and another study from March 15 to November 15, 2020 (20). These data were also used in a previous study (21). In 2020 there were still no vaccines against covid-19; they are therefore cases without vaccination. In this period, from March to April, in Spain, the A lineage of the coronavirus predominated, especially the SEC7 and SEC8, and from summer to December, 2020, the 20E (EU1) variant (22, 23).

2. A study of covid-19 infections in fully and not fully vaccinated people during 2021 (February 1 to November 30, 2021) (24). In this period, the dominant variant in Spain was first Delta and finally Omicrom (25).

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 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 (26). The methodology of all studies has been previously published (19-21, 24, 27)

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and here only the main elements will be repeated for the current study.

Current study objective

To compare selected clinical-epidemiological characteristics between cases of covid-19 in 2020 without vaccination, and covid-19 breakthrough infections in not fully vaccinated people, as a proxy indicator of cases of covid-19 in unvaccinated people, since experts suggested that a single dose of the COVID-19 vaccine from Moderna or Pfizer is not enough to reliably prevent infection (28).

During 2021 in Spain, the percentage of vaccinated with 1 dose and with 2 doses was very high. As of June 3, 87.1% of vaccinated with one dose, and 85.6% of vaccinated with a complete regimen (29) were reported. Therefore, the vast majority of the population was vaccinated, and it was not feasible to have covid-19 cases in the unvaccinated.

Collected variables

Variables for which data were available in all previous studies that were to be compared were: age, sex, socio-health worker, symptoms and 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" (30-32), classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 (33), and severity of the disease (34).

Statistic analysis

The bivariate comparisons were performed using the Chi Square test (X²) or Fisher Exact Test for percentages (according to the number the expected cell totals).

Results

100 covid-19 cases were included in 2020, and 12 in 2021. The unvaccinated covid-19 cases during 2020 vs. partially vaccinated covid-19 cases (assimilated to unvaccinated) during 2021 did not differ in a statistically significant way, by age, sex, severity of covid-19, or chronic diseases, or presence of socio-health workers. In 2020 vs. 2021, symptoms predominated Respiratory (cough, dyspnea, chest pain), Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain), Neurological (headache, dizziness, mental confusion - brain fog), Psychiatric (Anxiety, insomnia), and of Skin (chilblains, phlyctenas, rash, petechiae), but without statistical significance; and in 2021, General symptoms (discomfort, asthenia, myalgia, fever, arthralgia), ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis) predominated [the latter with statistical significance: X²= 3.9093. p= .048019] (TABLE 1, TABLE 2, TABLE 3).

Table 1: Comparison of Selected Variables between Unvaccinated Covid-19 Cases in 2020 with Not Fully Vaccinated Covid-19 Cases In 2021

VARIABLES	UNVACCINATED COVID-19 CASES IN 2020 N=100	NOT FULLY VACCINATED COVID-19 CASES IN 2021 N=12	STATISTICAL SIGNIFICANCE
> = 65 years	10 (10)	1 (8)	Fisher exact test= 1. NS
Children and adolescents <= 22 years	11 (11)	1 (8)	Fisher exact test= 1. NS
Women	54 (54)	4 (33)	X ² = 1.8328. p= .175796. NS
Socio-health workers	11 (11)	2 (17)	Fisher exact test= 0.629. NS
Moderate-severe severity	3 (3) [3 pneumonias]	2 (17) [2 pneumonias]	Fisher exact test= 0.088. NS
Exitus	1 (1)	0	Fisher exact test= 1. NS
Chronic diseases presence	51 (51)	5 (42)	X ² = 0.3733. p= .541193.

(): Denotes percentages; NS: Not significant

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Table 2: Comparison of Chronic Diseases between Unvaccinated Covid-19 Cases in 2020 with Not Fully Vaccinated Covid-19 Cases In 2021

CRHONIC DISEASES ACCORDING TO WHO, ICD-10 GROUPS*	UNVACCINATED COVID-19 CASES IN 2020 N=100	NOT FULLY VACCINATED COVID-19 CASES IN 2021 N=12	STATISTICAL SIGNIFICANCE
-II Neoplasms	3 (3)	1 (11)	Fisher exact test= 0.2689. NS
-II Diseases of the blood	1 (1)	1 (11)	Fisher exact test= 0.1438. NS
-IV Endocrine	26 (23)	2 (23)	Fisher exact test= 1. NS
-V Mental	11 (10)	1 (11)	Fisher exact test= 1. NS
-VI-VIII Nervous and Senses	9 (8)	1 (11)	Fisher exact test= 0.5527. NS
-IX Circulatory system	16 (14)	0	Fisher exact test= 0.6051. NS
-X Respiratory system	12 (10)	0	Fisher exact test= 0.5964. NS
-XI Digestive system	11 (10)	2 (22)	Fisher exact test= 0.2487. NS
-XII Diseases of the skin	3 (3)	0	Fisher exact test= 1. NS
-XIII Musculo-skeletal	10 (9)	0	Fisher exact test= 1. NS
-XIV Genitourinary	10 (9)	1 (11)	Fisher exact test= 0.589. NS
TOTAL*	112 (100)	9 (100)	---

(): 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

Table 3: Comparison of Symptoms between Unvaccinated Covid-19 Cases in 2020 with Not Fully Vaccinated Covid-19 Cases In 2021

SYMPTOMS * ACCORDING TO WHO, ICD-10 GROUPS	UNVACCINATED COVID-19 CASES IN 2020 N=100	NOT FULLY VACCINATED COVID-19 CASES IN 2021 N=12	STATISTICAL SIGNIFICANCE
General (discomfort, asthenia, myalgia, fever, arthralgias)	24 (31)	13 (48)	X2= 2.5145. p=.112803. NS
Respiratory (cough, dyspnea, chest pain)	19 (25)	4 (15)	X2= 1.1284. p=.288111. NS
ENT (Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis)	8 (10)	7 (26)	X2= 3.9093. p=.048019. Significant at p < .05.
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	9 (12)	2 (7)	Fisher exact test= 0.7241. NS
Neurological (headache, dizziness, mental confusion -brain fog)	7 (9)	1 (4)	Fisher exact test= 0.6769. NS
Psychiatric (Anxiety, insomnia)	8 (10)	0	Fisher exact test= 0.0601. NS
Skin (chilblains, flictenas, rash, petechiae)	2 (3)	0	Fisher exact test= 1. NS
Total symptoms*	77 (100)	27 (100)	---

(): Denotes percentages; NS: Not significant; *Patients could have more than one symptom; the percentages are over the total of symptoms

Discussion

Main Findings of the Study

The main finding of our study is that the symptoms of covid-19 were different in 2021 compared to 2020 (In 2020 vs. 2021, Respiratory (cough, dyspnea, chest pain), Digestive (anorexia, nausea / vomiting,

diarrhea, abdominal pain), Neurological (headache, dizziness, mental confusion - brain fog), Psychiatric (Anxiety, insomnia), and of Skin (chilblains, flictenas, rash, petechiae), predominated in 2020 but without statistical significance; and in 2021 the symptoms General (discomfort, asthenia, myalgia, fever, arthralgia), ENT

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(Anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epistaxis) [the latter with statistical significance), while the population and the environment did not vary (the population was the same in both periods being compared: this population (N=2,000 people) was the list of patients from the same general medicine clinic; thus, the context (the community) was the same in 2020 and in 2021, and on the other hand, the cases of covid-19 not vaccinated during 2020 vs. partially vaccinated covid-19 cases -which is assimilated to unvaccinated- during 2021 did not differ in a statistically significant way, by age, sex, severity of covid-19, or chronic diseases, or presence of social health workers). Consequently, if the results of covid-19 were different, but in the epidemiological triad the host and environment remained unchanged, it must be concluded that these different results of covid-19 are due to changes in the agent, in SARS-CoV-2.

Variation of Covid-19 Symptoms during the Pandemic

The main clinical difference between flu and covid-19 was said to be that the latter had shortness of breath as a differential symptom (35). In the same population of this study, in 2020, we proposed that symptoms suggestive of covid-19 vs. common cold or flu, were cough, fever, dyspnea, general pain, asthenia, nausea-vomiting, pneumonia (36). The first reports from China since late 2019 showed that these patients had symptoms of a lower respiratory tract infection, including cough, fever, and shortness of breath. 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 (37). On the other hand, it has been found that the frequency of the main symptoms in 2020 (cough, fever and loss of smell), was different depending on the country and the presence of underlying health conditions such as asthma and diabetes (17).

In the context of general medicine in Toledo (Spain), in the current study population, it

was found that cases of covid-19 in 2022 were different from those of 2020, affecting older people and showing symptoms of upper respiratory tract infection similar to a common cold (21).

The Not Fully Vaccinated As a Proxy Indicator of Not Vaccinated

A proxy indicator is an indirect measurement or signal that approximates or represents a phenomenon in the absence of a direct measurement or signal (38). In this way, in our study we use the variable "cases of covid-19 in not fully vaccinated people" as a proxy indicator of "not vaccinated people", since the variable "cases of covid-19 in not vaccinated" is hardly observable or very difficult to measure or value. It must be taken into account that in Spain as of April 27, 2021, 23.7% of the population had received at least one dose (39). And as of May 6, 2021, the percentage of vaccination with the complete schedule was 85.4% (29). In the community of Castilla-La Mancha, where this study was carried out, as of November 10, 2021, there were 76% with 2 doses and 79% with one dose (40). 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 (41).

Therefore, it can be estimated that in the population of the general medicine consultation object of the study (N=2,000 people), the percentage of unvaccinated in mid-2021 was 140 people, especially children. In summary, it is not feasible to use, for comparisons with respect to 2020, the figures of covid-19 cases in unvaccinated, since their number is close to zero. That is why the researchers opted for the proxy indicator of not fully vaccinated people. Experts suggested that a single dose of the COVID-19 vaccine from Moderna or Pfizer is not enough to reliably prevent infection (28). In a study in the same population, an vaccine effectiveness (VE) of the incomplete vaccine against transmission among household among contacts > 1% was found (27).

Figures communicated in the different published data regarding the VE of a single dose of COVID-19 vaccine are confusing and

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variable according to the definition of effectiveness (number of people who tested positive for the virus, prevention of symptomatic disease, prevention of severe disease, hospitalization), population, type of vaccine and predominant variant of the virus, but in general they are between 36% and 80% (27). An example has been the story of Colin Horseman, 85, one of the first people in the world to receive the initial dose of a Covid-19 vaccine (Pfizer-BioNTech) in the UK, who died of COVID-19 less than three weeks later; He received that first dose, but he must have received the second dose two days before his death (42).

The SARS-CoV-2 host

The possible variation of the characteristics of the host between 2020 and 2021, 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 (43), and so on, can be the cause of different clinical outcomes or symptoms of covid-19. However, in our study we did not find significant changes in these variables, and on the other hand, the study population and community were the same, so this confounding factor regarding the cause of the different covid-19 symptoms between 2020 and 2021 can be ruled out. .

Of course, in the general population, the cases of covid-19 in 2021 differed from those in 2020 in their vaccination status. Vaccines have been shown to be effective in reducing the severity of SARS-CoV-2 infection (44, 45), and thus the variable "being fully vaccinated" undoubtedly affects the symptoms presented; for this reason, data are used only from patients with incomplete vaccination (a single dose), which, as mentioned before, may represent unvaccinated patients.

The importance of the causal agent in the variation of the epidemiological triad in the evolution of the covid-19 pandemic

The global emergence of many variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compromises the protective antiviral immunity induced after infection or vaccination. 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 main antigenic target of all SARS-CoV-2 vaccines currently in use. 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 (46).

Since the start of the pandemic, the coronavirus that causes COVID-19 has been mutating. Its genetic code was slowly changing as it spread from person to person around the world. Most of the changes or mutations that the original SARS-CoV-2 went through have little or no effect on the properties of the virus. However, changes may influence some of them, such as their ease of spread, the severity of associated disease, or the effectiveness of vaccines, treatment drugs, diagnostics, or other public health measures, and Social (47).

When the Omicron variant of SARS-CoV-2 began to spread rapidly and outcompete other variants in late 2021, it quickly became clear that the variant was quite different from previous ones. Unlike Delta, which emerged in December 2020, Omicron didn't seem to be that dangerous. Yet the count of new cases broke records day after day, largely because a series of mutations in the virus' spike protein make vaccines much less effective at stopping infection than earlier variants. It is quite clear that Omicron causes less severe disease than the Delta variant (13). Experts are unclear if comparing these differences in SARS-Co-2 reveals a general trajectory in the evolution of new variants. And whether or not a trend toward decreased virulence emerges, they think it's possible that the next variant of SARS-CoV-2 that emerges will be more severe (13).

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.

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3. 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 context of general medicine in Toledo (Spain), the clinical presentation of covid-19 cases in 2020 was different than in 2021, and this difference does not seem to be due to the characteristics of the hosts or the context (which did not vary in the compared studies), but to variables dependent on the virus. Consequently, applying this result to the current moment in the course of the covid-19 epidemic, one would have to think that it is only an "interpandemic" period and any opportunity that the virus has to mutate will take advantage of it. Therefore, the least advisable thing to do would be to slow down the rate of vaccination and abandon other public health measures. If these preventive regulations are completely eliminated, there will be more opportunities for SARS-Co-2 to mutate, change and cause a more serious health situation, with a rebound in cases.

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