JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Epidemiology of reinfections by SARS-CoV-2 variants during the third and fourth waves of the COVID-19 pandemic

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) pandemic is a global health concern and has persisted through the emergence of variants that have caused subsequent waves of COVID-19 due to the high dispersion and contagiousness of the virus. The aim of this work was to analyze the epidemiology of the cases of reinfection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants during the third and fourth wave of the COVID-19 pandemic at the Hospital Juárez de México (HJM).

Methodology: A prospective study of the cases of SARS-CoV-2 reinfection, variants detected, symptoms, and associated comorbidities was carried out on 1,347 patients who attended the HJM from September 2021 to July 2022.

Results: 760 (56.4%) and 587 (43.6%) patients were negative and positive for SARS-CoV-2, respectively. The Omicron variant was the most frequent and the most common symptoms were: cough (80%), headache (61.32%), fever (51.6%), and dyspnea (40%). A higher proportion of females were vaccinated, ranging from one dose to the complete schedule. The factors that were associated with a greater risk of death from complications of SARS-CoV-2 reinfection were male gender, diabetes mellitus, and arterial hypertension.

Conclusions: Females were the most susceptible to an Omicron reinfection event, even though they were vaccinated. However, the risk of death was higher when the patient was male; being male was a potential risk factor for death from COVID-19 and comorbidities.

Key words: SARS-CoV-2; variants; COVID-19; pandemic waves.

J Infect Dev Ctries 2024; 18(9.1):S126-S134. doi:10.3855/jidc.19753

(Received 22 December 2023 – Accepted 04 April 2024)

Introduction

The coronavirus disease 2019 (COVID-19) has persisted through the emergence of variants that have caused worldwide concern due to their high dispersion and infectiousness. For example, the Omicron (o) variant was first detected in Botswana, South Africa, in November 2021 by genomic surveillance teams [1]. Three weeks later, this variant was detected in 87 countries worldwide. Due to the high number of mutations (more than 30) in the spicule glycoprotein coding gene, the Omicron variant could evade the host innate immune response and the humoral response generated by vaccination. Epidemiological and laboratory analyses confirmed that this variant has the ability for "immunological escape", greater affinity for the angiotensin type 2 receptor (ACE2), and modifications that are involved in accelerating the entry of the virus into the host cell [2]. Since the variant was able to evade immune response, it spread rapidly among the vaccinated population, even when they had been administered the complete vaccination schedule [3]. This super propagation of the variant, just after a single contact, has been reported among healthcare workers who had received the three-vaccine schedule [4]. Given the appearance of this and other variants, and changes in the symptomatology of the infection in vaccinated and non-vaccinated populations, most diagnostic centers implemented the protocol for regular identification of the wild virus and its variants in the infected population, in order to understand the emergence and dynamics of new variants and their characteristic symptoms [5].

At the beginning of the pandemic, the most common COVID-19 symptoms were fever, cough, odynophagia, myalgia, and headache. Rare symptoms such as abdominal pain, vomiting, polypnea, conjunctivitis, skin rash, and anosmia were also reported, and made differential diagnosis more complex. However, with the emergence of the Omicron variant, COVID-19 was mainly associated with symptoms of the upper respiratory tract such as rhinorrhea [6,7]. Since scientific evidence showed that vaccines did not offer full protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, mainly in susceptible individuals, vaccine boosters were implemented worldwide [8-9]. Additional strategies such as the therapeutic use of COVID-19 specific drugs as well as the use of convalescent plasma continued to be treatments that were used as measures to control the spread of the virus; and the Omicron variant received the most attention [10-12]. After the COVID-19 safety measures for protection of the respiratory tract and maintaining safe distance were relaxed, it was necessary to continue with the epidemiological surveillance on the emergence of the variants and associated symptomatology in the population to know the dynamics of the virus, including its evolution in the form of variants and their dissemination. The aim of this work was to demonstrate the epidemiological picture of SARS-CoV-2 reinfections during the third and fourth waves of the COVID-19 pandemic in Hospital Juárez de México (HJM) through a prospective study of reinfection cases, detected variants, and associated symptomatology. Implications on the risks associated with biological factors in the population susceptible to reinfection by SARS-CoV-2 in HJM were also analyzed.

Methodology

Ethical considerations

The Institutional Research, Ethics, and Biosafety Committee of HJM approved the protocol under the registration number HJM 001/20-I in accordance with the Regulations of the General Law of Health on Health Research (https://www.diputados.gob.mx/LeyesBiblio/regley/Reg_LGS_MIS.pdf) [13].

Study population and selection strategy

A descriptive cross-sectional study was conducted with a total population of 1,347 patients who attended the HJM from September 2021 to July 2022 (third and fourth wave of the COVID-19 pandemic) with symptoms due to SARS-CoV-2 reinfection. The confirmatory diagnosis was performed in two stages. Initially, SARS-CoV-2 virus detection was performed through viral RNA amplification using the "Detection Kit for 2019 Novel Coronavirus (2019-nCoV) RNA (PCR-Fluorescence Probing)" system (Daan Gene Co., Ltd, Sun Yat-Sen University, Guangdong, China). Patients who tested positive for SARS-CoV-2 by RNA amplification method were included in the second round of tests to identify the virus variant. A second RNA amplification was performed for the detection of the virus variants by using the "Master Mut" kit (Genes2Life, Irapuato Guanajuato, Mexico), which is a quantitative polymerase chain reaction (qPCR) system that allows the detection of the variants: Alpha (α), Beta (β), Gamma (γ), Delta (δ), Epsilon (ε)/Kappa (κ), Eta (η), Iota (ι), Lambda (λ), Mu (μ), Zeta (ζ), Omicron (ο) (lineages BA.1 and BA.2), VUM B.1.1.318, VUM C.1.2, VUM B.1.640.1, VUM B.1.640.2 (IHU), and B.1.1519 (Mex). The Instituto de Diagnóstico y Referencia Epidemiológicos (InDRE-Mexico) provided positive controls for the *E*, *RdRp*, and *RNAse P* genes for the first phase of reverse transcriptase polymerase chain reactions (RT-PCR).

Operational definition of SARS-CoV-2 reinfection in the study population

The "operational definition of reinfection" that was proposed by the World Health Organization (WHO) [14] and Yahav *et al.,* [15] was used to identify cases of SARS-CoV-2 reinfection. Reinfection was defined as clinical recurrence of symptoms compatible with COVID-19 disease; in addition to a positive COVID-19 specific RT-PCR test; more than 90 days after the onset of the primary infection and supported by close-contact exposure. In the presence of epidemiological risk factors by exposure, reinfection should be considered during the first 90 days. Finally, SARS-CoV-2 RT-PCR was used to test the primary and secondary samples to identify the variants in them [14,15].

Demographic data, comorbidities, and symptomatology in the study population

Demographic data such as month of admission to medical care, COVID-19 patient classification by age group (pediatric, young adult, adult, and elderly), gender, SARS-CoV-2 variant by gender, symptomatology by SARS-CoV-2 variant detected, comorbidities (diabetes mellitus, hypertension, chronic obstructive pulmonary disease [COPD]), smoking, vaccination history, type of vaccine administered, and COVID-19 patient classification by severity (moderate, severe, and critical) were recorded. The criteria

Table 1. Distribution, by age groups, of the SARS-CoV-2 positive patient population at Hospital Juárez de México.

COVID-19 patient classification	Gender (*n*/%)		Test	
	Male	Female	One sample *t* and Wilcoxon	Chi-squared
Pediatrics [a]	15/5.6	8/2.8	0.1881	0.0041*
Young Adults [b]	79/29.7	132/41.1	0.1567	
Adults [c]	121/45.5	141/44	0.0485*	
Elderly [d]	51/19.2	40/12.5	0.0766	
Total	266/100	321/100		

*Significant difference; [a] 0-18 years old; [b] 19-35 years old; [c] 36-64 years old; [d] >65 years of age. COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

described by Feng *et al*. [16] were used to classify patients according to the severity of the disease, as follows: moderate COVID-19: fever, cough, and other symptoms were present with pneumonia on chest; severe COVID-19: respiratory distress, respiratory rate > 30/min., oxygen saturation in room air at rest < 93%, partial pressure of oxygen in arterial blood/FiO_2 < 300 mm Hg; critical COVID-19: respiratory failure, requirement of mechanical ventilation, shock, organ dysfunction, requirement of intensive care unit (ICU) monitoring and treatment.

Data analysis

Descriptive statistics were used for the statistical analysis. The clinical picture of the disease was classified into moderate, severe, and critical, according to the SARS-CoV-2 variant detected. Odds ratio (OR) was calculated with 95% confidence intervals (95% CI). A $p \leq 0.05$ was used to evaluate statistically significant differences and determine the risk of death according to the characteristics of the population. Microsoft Office version 365, Epi Info™ version 7.2.5 and Stata™ version 25.0 were used for the analyses [17,18]. The epidemiological information presented showed a non-parametric behavior; therefore, the following statistical tests were used to identify significant ($p < 0.05$) differences between populations: one sample *t* and Wilcoxon, Chi-squared, Fisher´s exact and Friedman tests. Finally, the association between detected SARS-CoV-2 variants and the course of the third and fourth waves of the COVID-19 pandemic was analyzed by using the ShinyCircos software (https://github.com/venyao/shinyCircos) as described by Yu *et al*. [19].

Results

Age and gender of the COVID-19 study population

A population of 1,347 patients attending HJM during the third and fourth waves of the COVID-19 pandemic with clinical features of SARS-CoV-2 virus reinfection were included in this study. PCR results showed that 760 (56.4%) and 587 (43.6%) patients were negative and positive in the first stage of detection of SARS-CoV-2, respectively, with a predominance of reinfection cases in the female population (321/54.7%). In the case of the male patient population, 266 (45.3%) positive cases were observed. According to WHO age group classification, the age group most affected by reinfection was adults (average age of 41 years) with a *p* value of 0.0485 and 0.0041 for one sample *t*, Wilcoxon and Chi-squared tests, respectively. Nevertheless, 23 cases of infection were recorded in pediatric patients and one case in the elderly group (99 years old). Table 1 shows the distribution of the HJM population (by age group) that was positive to the initial PCR test for SARS-CoV-2 and the corresponding *p* value.

Detection of wild-type SARS-CoV-2 and its variants by gender in the study population

Detection of SARS-CoV-2 and its variants revealed a diversity of six types of variants along with the wild-type strain. The variants along with their frequencies were: Omicron (*n* = 474/80.7%), wild strain (*n* = 57/9.7%), Delta (*n* = 42/7.2%), Omicron lineage BA.2

Table 2. Distribution of detected SARS-CoV-2 variants by gender of patients with COVID-19.

SARS-CoV-2 and/or variant detected	Gender (*n* /%)	
	Male	Female
Omicron (o)	212/79.7	262/81.6
Wild type strain	31/11.7	26/8.1
Delta (δ)	17/6.4	25/7.8
Omicron Lineage BA.2	5/1.9	6/1.9
Zeta (ζ)	0/0	2/0.6
Eta (η) B.1.1.519 MEX	1/0.3	0/0
Total	266/100	321/100

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Table 3. Frequency distribution of symptoms in the COVID-19 patients categorized by SARS-CoV-2 variant.

Symptom	SARS-CoV-2 and variants (n/%)						
	wild strain	Omicron (ο)	Delta (δ)	Omicron BA.2 Lineage	Zeta (ζ)	B.1.1.519 MEX	Total
Fever	36/63.2	233/49.2	24/57.1	7/63.6	2/100	1/100	303/51.6
Cough	43/75.4	386/81.4	35/83.3	8/72.7	1/50	1/100	474/80.7
Headache	24/42.1	305/64.3	25/59.5	4/36.4	1/50	1/100	360/61.3
Dyspnea	41/71.9	161/34	28/66.7	2/18.2	2/100	1/100	235/40
Irritability	4/7	91/19.2	3/7.1	0/0	0/0	1/100	99/15.2
Diarrhea	7/12.3	72/15.2	7/16.7	3/27.3	0/0	0/0	89/15.2
Chest pain	2/3.5	88/18.6	2/4.8	2/18.2	0/0	0/0	94/16
Chills	6/10.5	176/37.1	1/2.4	2/18.2	0/0	1/100	186/31.7
Odynophagia	11/19.3	188/39.7	7/16.7	2/18.2	1/50	0/0	209/35.6
Arthralgia	25/43.9	186/39.2	13/31	4/36.4	1/50	0/0	229/4
Myalgia	11/19.3	188/39.7	7/16.7	2/18.2	1/50	0/0	209/35.6
Rhinorrhea	7/12.3	72/15.2	7/16.7	3/27.3	0/0	0/0	89/15.2
General discomfort	23/40.4	182/38.4	23/54.8	4/36.4	2/100	1/100	235/40
Polypnea	5/8.8	27/5.7	5/11.9	0/0	1/50	0/0	38/6.5
Threw up	2/3.5	21/4.4	4/9.5	0/0	1/50	0/0	28/4.8
Abdominal pain	3/5.3	28/5.9	4/9.5	0/0	1/50	0/0	36/6.1
Conjunctivitis	1/1.8	7/33	2/4.8	0/0	1/50	0/0	37/6.3
Cyanosis	2/3.5	10/2.1	1/2.4	0/0	1/50	0/0	14/2.4
Anosmia	0/0	15/3.2	4/9.5	0/0	1/50	1/100	21/3.6
Dysgeusia	0/0	9/1.9	4/9.5	0/0	1/50	0/0	14/2.4

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

(n = 11/1.9%), Zeta (n = 2/0.3%), and only one case of a Mexican strain B.1.1.519 MEX (n = 1/0.2%). An analysis of the distribution of SARS-CoV-2 and its variants by gender showed that females had the highest rate of reinfection with the Omicron variant (n = 262/81.62%), while there were 212 (79.70%) cases with the Omicron variant among males. Contingency table analysis identified that there was a significant difference between susceptibility to the six variants among the different age groups ($p < 0.001$). On the other hand, no significant differences were observed in the distribution of variants by gender in the study population ($p = 0.05$). Table 2 presents a summary of the distribution of the SARS-CoV-2 variants detected (including the wild-type strain) by gender of COVID-19 patients seen at HJM.

Symptomatology in the study population by SARS-CoV-2 variants

A frequency analysis of the symptomatology of COVID-19 patients categorized by SARS-CoV-2 variants (including the wild-type strain) was performed. The results showed that the predominant symptoms were cough with 474 (80%) cases, headache 360 (61.32%) cases, fever 303 (51.61%) cases, dyspnea 235 (40.03%) cases, general discomfort 235 (40.03%) cases, and arthralgia 229 (39.01%) cases. Contingency analysis showed a relationship between dyspnea, chills, cyanosis, dysgeusia, and anosmia with the six detected variants ($p < 0.001$). On the other hand, significances of 0.01 to 0.04 were identified for headache, irritability, chest pain, odynophagia, rhinorrhea, and vomiting. Finally, no significant relationship was identified for the other symptoms (p = 0.068 to 0.827). Table 3 summarizes the distribution of symptoms in COVID-19 patients categorized by SARS-CoV-2 variant (including the wild-type strain) at HJM.

Risk of death, associated comorbidities, and symptoms

Analysis of the risk of death in the COVID-19 population revealed that males were at 1.8 times higher risk of dying from complications of SARS-CoV-2 reinfection than the females ($p = 0.0240$, by Fisher test). Chronic degenerative diseases such as diabetes mellitus and arterial hypertension, showed 2.59 ($p = 0.0024$) and 3.4 ($p < 0.0001$) times higher risk of death, respectively. Furthermore, the risk analysis considering symptoms showed that dyspnea was associated with 23 times the risk of death, and when combined with moderate clinical symptoms, there was 18 times the risk of death. Regarding vaccination data, we identified rates of 396 (67.46%) and 191 (32.53%) of vaccinated and unvaccinated patients respectively, which represents five times higher risk of death for the unvaccinated (p = 0.001). Regarding the death rates due to the severity of infection, the results showed that the severe symptoms were a predominant condition (n = 45/60.8%), followed by moderate (n = 25/33.8%), and mild (n = 4/5.4%). The Chi square contingency analysis between the severity of the disease and the SARS-CoV-2 variant detected revealed that all variants were related to mild ($p < 0.001$) and severe ($p = 0.003$) conditions. However,

Table 4. Risk analysis (odds ratio, OR) to SARS-CoV-2 reinfection in COVID-19 patients at Hospital Juárez de México.

Characteristics of COVID-19 patient	Odds ratio (OR)	IC INF	IC SUP	*Q*
Male gender	1.8	1,10	2.95	0.02
Diabetes mellitus	2.59	1.45	4.60	0.002
Hypertension	3.4	1.98	5.84	0
Fever	1.99	1.19	3.32	0.008
Dyspnoea	23.82	10,13	56.02	0
Smoking	2.85	1.15	7.09	0.02
COPD	4.03	1.31	12.38	0.02
Unvaccinated patient	4.79	2.86	8.02	0.001
Moderate COVID-19	0.10	0.03	0.28	0.001
Severe COVID-19	18.27	10.35	32.22	0.001
Critical COVID-19	0.058	0.02	0.16	0.001

COPD: Chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

the relationship between the clinical pictures described above, with the variants could have statistical bias due to the discrepancies in the COVID-19 patient population. Table 4 shows the results of the odds ratio (OR) analysis for death due to SARS-CoV-2 reinfection in COVID-19 patients at HJM.

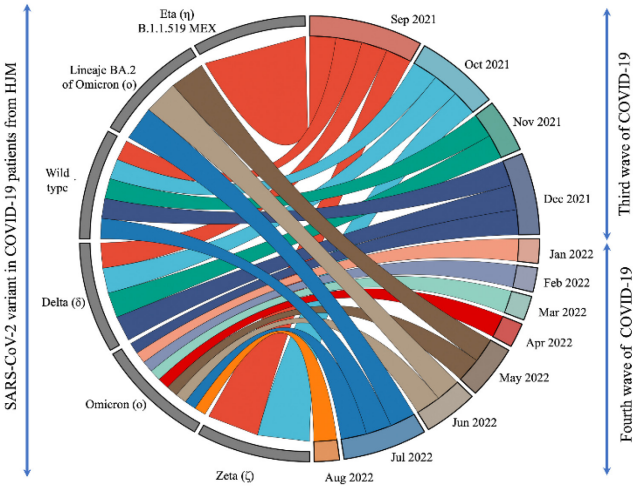
Vaccination schedules of the population with SARS-CoV-2 reinfection

The epidemiological study revealed that of the 587 patients with SARS-CoV-2 reinfection, 396 (67.5%) patients received the vaccine and 191 (32.5%) patients were not vaccinated. Of the non-vaccinated population, 95 (49.7%) and 96 (50.3%) patients were female and male, respectively. In contrast, for the vaccinated population (regardless of the number of doses), 226 (57%) and 170 (43%) patients were female and male, respectively. Therefore, it was determined that the female gender (226/70.4%) was the population that received at least one vaccination dose, compared to the male gender (170/64%). The analysis of the vaccination schedules in the population showed that, of the 587 patients, 396 (67.46%) had at least one vaccination dose and 191 (32.53%) patients had no evidence of any vaccination. Of the population with evidence of vaccination, 94.4% had a second dose and only 12.3% had the complete vaccination schedule (three doses). Regarding the vaccines used, BNT162b2 (*Pfizer-BioNTech*, Michigan, USA) was the one most frequently administered at the beginning and end of the vaccination schedule, followed by AstraZeneca (Oxford University, England, UK), Gamaleya (Sputnik V, Moscow, Russia) and Sinovac (Sinovac Biotech Ltd, Beijing, China) (Table 5). We observed higher mortality among unvaccinated patients. Of the 587 patients positive for COVID-19, 74 (12.60%) deaths were recorded, of which 51 (68.91%) were unvaccinated and 23 (31.08%) had a history of vaccination. For the latter group, the vaccination record was as follows: AstraZeneca (7/30.43%), Gamaleya (4/17.39%), Jansen (Johnson & Johnson, Maryland, USA) (1/4.34%), BNT162b2 (6/26.08%), and Sinovac (5/21.73%). It was determined that the risk of dying from the wild strain variant was almost 3 times higher (p = 0.0013) than from Omicron (p = 0.0701), which could be related to the lack of vaccination coverage (full vaccination schedule).

Epidemiological association between SARS-CoV-2 variants and pandemic waves

Epidemiological analysis on the detection of SARS-CoV-2 variants during the third and fourth waves of the COVID-19 pandemic revealed that September 2021 was the month when the highest number of SARS-CoV-2 variants were detected in the study population (Eta, Delta, Zeta, and the wild-type strain), followed by October (wild-type strain, Delta and Zeta), December (wild-type strain, Delta, and Omicron) and July (wild-

Figure 1. Global epidemiological behavior of the SARS-CoV-2 variants detected during the third and fourth waves in the population treated at the Hospital Juárez de México.



COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Table 5. Vaccination schedules of the study population and the occurrence of reinfection by SARS-CoV-2.

Vaccine type	Vaccine dose (n/%)		
	First	Second	Third
AstraZeneca	72/18.18	65/17.38	7/14.29
Cancino	5/1.26	0/0	5/10.20
Gamaleya	31/7.83	28/7.49	5/10.20
Jansen (Jhonson & Jhonson)	4/1.01	0/0	0/0
Moderna	3/0.76	3/0.80	1/2.04
Pfizer Biontech	264/66.67	263/70.32	34/69.39
Sinopharma	2/0.51	2/0.53	0/0
Sinovac	15/3.79	13/3.48	2/4.08
Total	396/100	374/100	49/100

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

type strain, lineage BA.2, and Omicron lineage) of 2022. In contrast, during the first four months of 2022 (fourth pandemic wave), the Omicron strain was exclusively detected. Figure 1 shows the overall epidemiological behavior of the SARS-CoV-2 variants detected (including the wild-type strain) during the third and fourth waves in the population treated at HJM. Finally, comparison of the mortality and infectivity rates of the variants in the patients showed that the Omicron and Delta variants were the most infective and deadly respectively ($p = 0.0201$).

Discussion

The emergence of SARS-CoV-2 genetic variants is an important factor influencing resilience of the COVID-19 pandemic. The Omicron variant has been a determining factor in reinfection events in vaccinated populations due to its high level of contagiousness within a short period of time. Therefore, epidemiological surveillance in the detection of this and other variants is necessary to know the dynamics in the entry and exit of these viruses in the population during the course of the pandemic, mainly in the vaccinated population.

In the present study, we observed that females were more vulnerable (in comparison with the males) to reinfection by SARS-CoV-2 and its variants, even when they had received at least one vaccination dose. Similar findings were reported by Mensah *et al.* who noted contrasting reinfection rates of 53% and 67% for males and females, respectively [20]. This work also showed that men were 42% less likely to experience reinfection compared to women [20]. In another study that analyzed the risk of reinfection during the pandemic waves due to the Omicron variant in the United Kingdom, it was concluded that females in adulthood exceeded the reinfection rates compared to males with rates of 58% vs. 42%, 64.8% vs 35.2%, and 73.5% vs 26.5%, for the second, third and fourth reinfection events, respectively [21]. The biological basis for this susceptibility to reinfection linked to the female gender, may lie in the expression patterns of proteins that participate in the binding and entry of the virus, and the divergence of the immune and endocrine systems [22]. On the other hand, the Omicron variant was the most prevalent (detected in both genders), followed by the wild-type strain, and the Delta variant. This type of behavior in the dynamics of variant detection has been observed in other countries, such as United Kingdom and Brazil [20,23]. However, in this investigation the association between the infectivity of the detected variants and the age groups was not analyzed. In our study, an association was identified between the age groups and the infectivity of the six variants ($p < 0.001$). Similarly, Ekroth *et al*., through contingency analysis, demonstrated that the Omicron variant (2.7%) also showed greater infectivity in the pediatric population, compared to the Delta variant (0.8%) [24].

Although it could not be determined whether any SARS-CoV-2 variant could influence the symptoms recorded, symptoms such as fever, cough, headache, dyspnea, irritability, diarrhea, chest pain, chills, odynophagia, arthralgia, myalgia, rhinorrhea, and general discomfort, were the most prevalent in the population infected with the Omicron variant. However, through the contingency analysis, an association was determined between all variants and dyspnea, chills, cyanosis, dysgeusia and anosmia ($p < 0.001$). Other symptoms included fever, cough, headache, and diarrhea, along with others which were not analyzed in the present study, have been significantly related to infection by the Omicron variants ($p < 0.001$) [24]. In a previous study, symptom analysis of 157,861 patients confirmed infection by the Omicron variant, where the most common symptom was having a cough (62.7%), followed by sore throat (60.7%), runny nose (44.3%) and fever (38.8%). Coincidentally, these symptoms were consistently present in the population treated at HJM. Another finding that coincided with those shown in the present

study was that the identification of Omicron was associated with a higher prevalence of systemic symptoms than the Omicron BA.2 variant in vaccinated and unvaccinated individuals [25].

In our work, the frequency of symptoms due to variant BA.2 was lower compared to Omicron BA.5. It is necessary to take into consideration that this observation may or may not be true, since the number of patients infected with variant BA.5 was significantly higher than variant BA.2. Recent studies have explored the severity of the disease and its relationship with SARS-CoV-2 variants. The results have indicated that the Omicron variant, is the most infectious, and could lead to the appearance of critical pictures; however, these studies demonstrated that patients infected with Omicron present a statistically lower risk of death (due to moderate to severe symptoms) than those infected with other variants [26]. Likewise, in this work all variants (including Omicron) were related to mild and severe symptoms, along with low mortality rates. This is in contrast to the Delta variant which has been related in other works (including ours) with higher mortality compared to other variants [27]. The analysis of risk of death by gender, comorbidities, and associated symptoms in the population analyzed clearly showed that comorbidities, the patient's general critical state, and gender (male) are factors that increase the probability of a fatal outcome.

Extensive scientific literature reports the relationship between the severity of COVID-19 and associated comorbidities in patients, with the male gender as an important factor [28]. Genetic and hormonal bases support the hypothesis of disease severity in males [29,30]. Even though in our work the vaccinated female population was the most susceptible to a reinfection event compared to the vaccinated male population, the risk of death was higher when the patient was male (Table 4). Evidence indicates that males present a potential risk factor for death from COVID-19 as well as the development of more severe disease. A study by Scully *et al.,* showed that the risk of death in males was similar to that presented in our study and they reported there was a 1.7 times higher risk of death in males than females [31]. Vaccine findings in the population analyzed clearly showed that even though most of the patients who attended the medical facility for reinfection events were vaccinated (at least one dose), they still developed a new symptomatic picture (Table 3). So far, vaccines have proven to be effective in preventing severe disease, mainly in susceptible patients [32]. Scientific evidence shows that effectiveness of vaccines against the delta variant and other variants for the development of severe disease and death was more than 90% [33]. However, with the emergence of the Omicron variant, which showed a high number of mutations in the spike proteins, there was speculation of possible evasion of the immune response induced by vaccines such as BNT162b2 or AstraZeneca, and indeed, data showed that two doses of the aforementioned vaccines offered limited protection against the Omicron variant [34].

Undoubtedly, vigilance in variant detection has been fundamental in the containment of the COVID-19 pandemic, mainly in the most vulnerable population such as the elderly, since it has been reported that patients older than 70 years with COVID-19 have had a high case fatality rate [35].

Conclusions

Although reinfections with the Omicron variant appeared to be less severe, their high contagiousness prevented effective containment of the pandemic. The above study highlights that since SARS-CoV-2 virus has a high mutation rate, there is a high likelihood that other variants will emerge in the future that may evade vaccine-induced immunity more efficiently than the Omicron variant and cause reinfections, as with common human coronaviruses and influenza. Although the Omicron variant fortunately appeared to be less severe, the risk of the emergence of more variants that may lead to a more severe disease form remains. Vaccines, together with respiratory protection measures, remain the best option, especially for the most vulnerable.

Acknowledgements

AENR and MCRH received grant-aided support from "Consejo Nacional de Humanidades Ciencias y Tecnologías" (CONAHCyT, México); CCCM, GVA, and JMBL received support from the "Sistema Nacional de Investigadores (SNI)" from CONAHCyT, Mexico; CCCM received support from Secretaría de Investigación y Posgrado and Comisión y Fomento de Actividades Académicas (COFAA) from Instituto Politécnico Nacional (IPN).

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Conflict of interests: No conflict of interests is declared.