fortune Journals

Research Article

ARCHIVES OF MICROBIOLOGY & IMMUNOLOGY

ISSN: 2572-9365

Impact of SARS-CoV-2 Infection in Healthcare Workers and Nursing Students: Incidence, Adherence to Vaccination and Effects of Vaccines

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Abstract

Objective: To evaluate the incidence of COVID-19 in two groups, health personnel and nursing students, their adherence to vaccination and the effects of the vaccines 6 months after complete vaccination.

Methods: Observational study in healthcare workers in Spain during 2021. It was conducted with a sample of 179 healthcare workers and 120 nursing students. A self-administered questionnaire and a venous blood sample collected 6 months after the vaccination were used. A descriptive bivariate analysis was performed with parametric or nonparametric tests.

Results: Of the professionals, 83.1% had occupational exposure to COVID-19, with 19.3% contracting the disease, while 42.5% of the students had contact with the disease, with 13.6% contracting it. Mild clinical symptoms predominated. After vaccination, the incidence of COVID-19 was 2.8% in the professionals and 2.5% in the students. A total of 96.7% of the professionals and 100% of the students had been vaccinated. The immune response was positive in both cases, with mean IgG values of 3017.4 AU/ml for health professionals and 2484.6 for students, with higher levels in those with a history of infection.

Conclusions: The immune response showed reactivity in 100% of the cases. Compliance with vaccination was very high in both groups.

Keywords: COVID-19 incidence; adaptative immunity; COVID-19 vaccine; healthcare workers; Vaccine Efficacy; vaccination adherence; adverse effects

Introduction

Three years after its declaration by the World Health Organisation, the COVID-19 pandemic is no longer an international emergency [1]. Although the pandemic has not finished, the end is in sight and the balance shows a major impact on morbidity and mortality. Globally, as of 21 June 2023, the WHO had been notified of 768,187,096 confirmed cases of COVID-19, including 6,945,714 deaths. As of 18 June 2023, 13,398,054,518 doses of vaccine had been administered [2]. In Europe, more than 2 million people have died as a result of COVID-19 and more than 273 million cases have been confirmed [3]. In Spain, as of 30 June 2023, 13,914,811 confirmed cases had been reported, accounting for 121,760 deaths [4]. The price paid by healthcare workers around the world during the emergency has been high. Globally, some 115,500 workers died from COVID-19 in the first 18 months of the pandemic, according to data published by the United Nations (UN) and the WHO [5]. In the early stages, health workers were at high risk

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Citation: Delicado-Useros Victoria, Navarro-Rodenas Esther, Ortega-Martínez Carmen, Pérez-Domenech Teresa, García-Alcaraz Francisco, Pérez-Serra Juan Daniel and Sánchez-Onrubia Indalecio Miguel. Impact of SARS-CoV-2 Infection in Healthcare Workers and Nursing Students: Incidence, Adherence to Vaccination and Effects of Vaccines . Archives of icrobiology and Immunology. 7 (2023): 428-442.

Received: November 12, 2023
Accepted: November 22, 2023
Published: December 13, 2023

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DOI:10.26502/ami.936500138

due to prolonged exposure to large numbers of infected and asymptomatic individuals and lack of adequate personal protection resulting from a shortage of personal protective equipment (PPE), among other factors.

The review by Wauters (2022) evidenced deterioration in the quality of life of health workers and detected stigmatisation, stress, anxiety and fatigue, particularly following the first waves of the pandemic. Throughout the COVID-19 pandemic, risk factors impacting wellbeing, such as stress, lack of support and social rejection, have been identified. The presence of errors, oversights and deficiencies in the management of work environments, lack of competences and an initial shortage of PPE might have affected the level of health professional's identification with the organisation and their job performance, in an environment with a high risk of infection and transmissibility [7]. The COVID-19 pandemic has also been associated with burnout among nurses, a large number of whom have abandoned the profession or have a clear intention to do so, as highlighted in a recent review reporting the negative impact of the pandemic on nurses' psychological wellbeing [8]. There is little doubt that the measure with the most positive impact on the serious effects of SARS-CoV-2 on morbidity and mortality is the availability of effective vaccines and widespread vaccination coverage in many countries around the world. The efficacy of vaccines in preventing COVID mortality and reducing severe cases leading to hospitalisation has been robustly evidenced. However, what has not been as effectively measured is the impact of vaccination on the prevention of transmission [9].

At the start of 2023, Tedros Adhanom Ghebreyesus, Director-General of the WHO informed the International Emergencies Committee that, globally, 89% of health workers and 81% of older adults (>60 years) had completed primary vaccination coverage. Concerns remained, nevertheless, about the continued risk of COVID-19, with the number of deaths compared to other respiratory infectious diseases still being high. Additionally, questions were raised about the insufficient uptake of vaccination in low- and middle-income countries, as well as in the most at-risk groups globally, and uncertainty associated with emerging variants [10]. In Spain, more than 40.7 million people (85.8% of the population) are fully vaccinated and 55.9% have received booster doses. More than 92% of people aged over 12 years have been fully vaccinated [11]. Spain had one of the largest percentages of infected healthcare employees, which justified the prioritisation of immunisation in this population, with their being one of the first groups to be vaccinated [12]. Studies on healthcare workers pioneered the evaluation of both occupational risk for COVID-19 and the monitoring of the immune and clinical response to the vaccines thus far administered.

Nursing students were also especially affected by the pandemic. Initially, their practical clinical training was interrupted, and they continued their studies under the academic limitations imposed by lockdowns [13]. Meanwhile, hired as community aid workers, some were in the front line of the healthcare system, caring for the general population in services with COVID-19 patients as well as in primary care, emergency services, hospital wards, care homes, etc. When needed, health science students were a vital resource for Spain's health system and for society. It is necessary for those in charge of education and health to increase their efforts by implementing the improvements needed in training and safety measures, considering both the health of the population and these future health professionals, who will be crucial in future pandemics. This study was designed in February and March 2021, when vaccination in the priority populations (including health workers and health science students) had just begun and there was considerable uncertainty about vaccine efficacy and duration of immunity. The research team was highly motivated about the impact of the pandemic on these groups. Therefore, we felt it was important to provide an assessment of the impact of COVID-19 and the response to vaccines in our setting, in known populations that were accessible to us.

Aims

General aim is to evaluate the incidence of COVID-19 in two groups, health per-sonnel and nursing students, their adherence to vaccination and the effects of the vaccines 6 months after complete vaccination.

Specific objectives are:

To describe the incidence of COVID-19 disease in the year prior to vaccination, clinical characteristics and occupational exposure to the pandemic in healthcare workers and nursing students.

To assess the impact of vaccination on the evolution of the cases of SARS-CoV-2 infection.

To determine adherence to vaccination against SARS CoV-2 and the motives reported.

To identify the immune response of SARS-CoV-2 vaccines at 6 months after full vaccination.

To describe adverse reactions to the vaccines in the population under study.

Methods

Design: Based on a follow-up observational design, this paper presents a cross-sectional information obtained from a first observation in the study population in the second half of 2021, 6 months after completion of the SARS-CoV-2 vaccination schedule. This study addresses the question of incidence of COVID-19, acquired immunity, vaccination ad-

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DOI:10.26502/ami.936500138

herence and the impact of SARS CoV-2 vaccines in healthcare workers in 2020 and 2021. **Population and sample:** Workers from the health service area of Almansa (Albacete) (n1) and nursing students from the Faculty of Albacete (n2), with an initial population of 620 individuals for n1 and 230 for n2, (2nd-, 3rd- and 4th-year students). The sample size was calculated for a confidence level of 95% and an estimated error of ±0.03 and an estimated proportion of 95%. To this number, we added 10%, estimating possible losses. The resulting sample size was 179 persons for the employees of the Integrated Care Management (ICM) of Almansa (healthcare workers - HCWs) and 120 for the nursing students (NS). Simple random sampling was performed, drawing on the corporate mailing lists provided by the ICM of Almansa, and the persons selected were invited to participate in the study, using an informed consent form. Those that accepted were included in the sample. Those failing to answer or declining to participate were replaced by others from the same population. The final sample of persons recruited and that participated in the study comprised 150 individuals, in the case of the ICM of Almansa (83.8% of the initial sample) and 81 nursing students (67% of the initial sample, selected in this case in a convenience sample). In the student population, we only requested the participation of those that had had contact with patients, thus limiting the sample to the 2nd-, 3rd- and 4th year undergraduates, since the 1st-year students receive no practical training in clinical centres.

Sources of information: a self-report questionnaire and a venous blood sample collected six months after full vaccination. Variables: sociodemographic, clinical, epidemiological and employment/academic data; vaccination against SARS-CoV-2, (type of vaccine, motives and adverse effects); incidence of COVID-19 (self-reported on PCR tests), adherence to vaccination; and IgG levels against SARS-CoV2 at six months. The questionnaire was designed by the research team, using WHO-validated classification criteria. It was subjected to the review of experts and an initial pilot test was implemented to ensure that the items were easily understandable. The English version of the questionnaire is available to interested persons upon request to the authors. Determination of anti-SARS-CoV2 serum IgG levels: the Alinity SARS-CoV-2 IgG II Quant assay (Abbott®) was carried out for all the samples. This test is based on chemiluminescent microparticle analysis (CMIA), which quantitatively and qualitatively determines IgG antibodies against the receptor binding domain (RBD) located in spike protein subunit 1 (S1) of SARS-CoV-2. The laboratory distributing the test has reported that sensitivity is 100% and specificity 99.9%. The unit of measurement is AU/ml (arbitrary units per millilitre). A positive Ac response was considered when the IgG level is ≥50 AU/ml (16) (17).

Data analysis: The data collected were processed and analysed using SPSS® IBM 24.0, which was also used to run the statistical analysis. A descriptive univariate analysis was performed using measures of central tendency and dispersion: arithmetic means, standard deviations (SD), minimum and maximum, for continuous variables, and absolute frequencies and proportions for categorical variables. We calculated 95% confidence intervals. Bivariate analysis was conducted using the corresponding tests for the comparison of proportions and means: Chi-squared, t-Student, ANOVA and with the non-parametric Kruskal-Wallis and Mann-Whitney tests. The relationships between the quantitative variables were examined using Spearman's correlation. In all cases, bilateral comparisons were used with a significance level of $p<0.05$.

Ethical considerations

The project was approved by the Ethics and Clinical Research Committee of the corresponding health area (21/05/2021), and the Castilla-La Mancha Health Service (SESCAM) gave its permission for the study to be implemented. All the participants were informed that personal data would remain confidential and gave their signed consent. The samples were anonymised. The researchers declared that they had no conflicts of interest.

Results

Socio-occupational and epidemiological characteristics of exposure to SARS-CoV-2

Table 1 details the **sociodemographic characteristics** of the study population: mean age and distribution by age group, sex, level of education, occupation and area of work. In the two populations studied, there is a notably high proportion of women (76% of health workers and 90% of nursing students). Among the healthcare employees (n1), the predominant age group is 40-49 years, the majority have university studies and the most represented professional category is that of nurse. In population n1, the mean age is 46.45 years; 85.1% work at the hospital; and by position, 34% are nurses, 28% are practical nurses and 13.6% are doctors. The length of service is high (mean: 17.9 years). Among the nursing students (n2), the proportion of women is high (90.1%), and the population is young (mean age: 21.8), with only 4% aged 30 years or older. The distribution of participants across the different year groups was unequal, with a higher proportion (54.3%) of 3rd-year students compared to 19.8% of participants from the 2nd year and 25.9% from the 4th .

As regards occupational exposure to SARS-CoV-2 infection, 83.1% of healthcare workers had occupational contact with actively infected individuals. Changes in position resulting from the organisation of services due to the pandemic affected few participants (the positions of 21.9% were changed in 2020) albeit intensively: 23 persons (15.2%) worked in two positions in the last year; 9 participants (6%) had

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DOI:10.26502/ami.936500138

three positions and, in one case (0.7%), a participant worked in four different positions. Table S1 (Supplementary Material) provides information on job characteristics and SARS-CoV-2 exposure of this group. Table S1 (supplementary material) shows the information on these participants' occupational characteristics and exposure to SARS-CoV-2.

Of the students, 42.5% were exposed to actively infected persons, a much lower proportion compared to that of the healthcare workers. Of the participants, 18.5% of (n1) and 6.1% of (n2) presented one of the risk factors for complicated COVID-19 These conditions have been recognised as important factors associated with poor disease outcome (18). More detailed data on these conditions in each group can be found in Table 1. Over time, terms were coined for those presenting such factors, including vulnerable person and/or vulnerable worker or vulnerable groups [19].

Incidence and clinical picture of COVID-19 pre- and post-vaccination

Tables 1 and 2 provide information on the rate of incidence of infection for the two populations under study. The source of infection is unknown in most cases, although 34% of those infected reported occupational origin. We found that 19.3% of the **health professionals** (n1) had COVID-19 in the year prior to vaccination. Among those affected by COVID, mild clinical symptoms predominated, with more than 50% reporting symptoms such as headache, cough, fever, weakness and tiredness, loss of smell/taste and muscle pain. The clinical picture was moderate in 7% of cases and, in two cases (3.5%), hospitalisation was required. No cases were admitted to intensive care. Four cases were identified as long Covid. Occupational infection was reported in 41.2% of the cases, although for most of this group the source was unknown (55.9%). After vaccination, the frequency of breakthrough COVID infection was 2.8% in the 6 months between full vaccination and data collection. Of the **nursing students** (n2), 13.6% contracted COVID-19 in the year prior to vaccination. Among those affected by COVID-19, mild clinical symptoms predominated; more than 50% had symptoms such as weakness or tiredness and loss of smell/taste; more than 40% reported headaches and muscle pain; one third of the cases had cough and fever, while 25% had diarrhoea and 8.3% had odynophagia. There were no cases with moderate or severe symptoms (dyspnoea). None of the participants were admitted to hospital and none reported suffering long Covid. Occupational infection was identified

Table 1: Participants' socio-demographic characteristics and exposure

Age (years):	**n1: Healthcare Workers:** Mean: 4.,45; (SD= 9.95); Minimum value= 23.9 years; Maximum value= 65.8; Range=41.74; 95% CI Mean= [44.80; 48.11] **n2: Nursing Students:** Mean: 21.85; (SD= 4.65); Minimum value= 18.88; Maximum value= 46.62; Range=27.73; 95% CI Mean = [20.82; 22.87]				
Age (groups)	**n1 (%) Healthcare workers**	**n2 (%) Nursing students**	**Risk factors for complicated COVID-19**		
				n1(%)	**n2 (%)**
18-29	8 (5,7)	78 (96,3)	HTA and/or heart disease	17 (11,7)	1 (1,2)
30-39	25 (17.7)	1 (1.2)	Diabetes (T1 or T2)	6 (4.2)	1 (1.2)
40-49	60 (42.6)	2 (2.5)	Chronic pulmonary disease	3 (2.1)	3 (3.7)
50-59	31 (22.0)	-	Chronic kidney disease	1 (0.7)	-
≥ 60	17 (12.1)	-	Chronic liver disease	-	-
Sex	**n1 (%)**	**n2 (%)**	Active cancer disease	1 (0.7)	-
Female	114 (76)	73 (90.1)	Immunodeficiency	2 (1.4)	-
Male	36 (24)	8 (9.9)	Obesity at BMI>40	-	-
Total	**150 (100)**	**81 (100)**	Pregnancy	1 (0.7)	-
Occupational exposure to SARS-CoV-2			**SARS-CoV2 infection**		
	n1 (%)	**n2 (%)**		**n1 (%)**	**n2 (%)**
Yes	113 (83.1)	31 (42.5)	Pre-vaccination	29 (19.3)	11 (13.6)
No	23 (16.9)	42 (57.5)	Post-vaccination	7 (4.7)	2 (2.5)

Occupational origin of SARS-CoV-2 infection: Infection related to activity at work (n1): 41,2% or clinical practice (n2): 15,4%

Own preparation: Data on the study population from the ICM of Almansa (Albacete) n1 and the Albacete Faculty of Nursing n2, 2021. Non-responses have not been reflected although the percentages were calculated for valid data

Citation: Delicado-Useros Victoria, Navarro-Rodenas Esther, Ortega-Martínez Carmen, Pérez-Domenech Teresa, García-Alcaraz Francisco, Pérez-Serra Juan Daniel and Sánchez-Onrubia Indalecio Miguel. Impact of SARS-CoV-2 Infection in Healthcare Workers and Nursing Students: Incidence, Adherence to Vaccination and Effects of Vaccines . Archives of Microbiology and Immunology. 7 (2023): 428-442.

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DOI:10.26502/ami.936500138

in 15.4% of cases, although, in this group, the source of infection was predominantly non-occupational (46%). Post-vaccination, the frequency of disease was 2.5% (6 months after full vaccination). The occupational or non-occupational source of COVID-19 infection differed significantly between the healthcare workers (n1) and nursing students (n2), with a large proportion of cases of occupational origin among the healthcare professionals (corrected Chi-squared= 8,5; p<0,001).

Table 2 shows the most frequent **clinical symptoms**. Mild symptoms are predominant in both groups. Generally, the nursing students (n2) were more mildly affected, with no hospital admissions, no severe symptoms and no cases of long COVID.

Concerning the **diagnostic tests** that had confirmed the diagnosis of COVID-19, PCRs were performed in most cases. A PCR+ test was performed on 19 healthcare workers (55.8%) and 8 on students (61.5%) and an Ag+ test was performed on 7 healthcare workers (20.6%) and 2 students (15.4%). In the remaining cases, the diagnosis of infection was based on clinical suspicion. It should be taken into account that, at the time of data collection (second semester of 2021), the availability of active infection tests was somewhat limited.

Table 2: Types and clinical picture of the COVID-19 cases in healthcare workers and students

Clinical characteristics of COVVID-19 cases:	**n1 (%) Healthcare workers (34)**	**n2 (%) Nursing students (13)**
Asymptomatic	1 (2.9)	3 (23)
Mild	29 (85.3)	10 (77)
Moderate/Serious	4 (11.8)	-
Most common symptoms Mild: (Multi-response)	**n1 (%)**	**n2 (%)**
Fever	18(52.9)	4(33.3)
Cough	17(50.0)	4(33.3)
Loss of smell/taste	17(50.0)	6(50.0)
Odynophgia	2(5.9)	1(8.3)
Weakness/Tiredness	21(61.8)	7(58.3)
Headaches	22(64.7)	5(41.7)
Diarrhoea/Vomiting	6(17.6)	3(25.0)
Muscle pain	21(61.8)	5(41.7)
Moderate/Serious: (Multi-response)		
Worsening of mild clinical symptoms	1(2.9)	-
Dyspnoea	3(8.8)	-
Chest pain	3(8.8)	-
Others	6(17.6)	-
Hospitalisation	2(6.1)	-
Admission to ICU		-
Long COVID:	4 (11.8)	-

Own preparation. Data on the study population from the ICM of Almansa (Albacete) n1 and the Albacete Faculty of Nursing n2, 2021 and 2022. Non-responses have not been reflected although the percentages were calculated for valid data .

Adherence to SARS CoV-2 vaccination and adverse reactions according to dose and type of vaccine

A total of 96.7% of the healthcare workers (n1) had been vaccinated with a full course of Pfizer/BioNTech vaccine at the time of data collection. This demonstrates high adherence to the vaccination schedule in both healthcare and non-healthcare staff, although 2.7% had not been vaccinated at this time (start of study). However, as participants were followed up in subsequent months, delayed vaccination was noted, with three of the four unvaccinated having started the vaccination process by the end of 2021. In the case of the students (n2), 100% were fully vaccinated. They had been given three different types of vaccine; most were vaccinated with Pfizer/BioNTech, followed by Astra-Zeneca and, to a lesser extent, Moderna. Table 3 shows the distribution of the types of vaccines administered, the reasons for vaccination in both groups and their behaviour with respect to previous vaccinations (flu vaccination in the 2021-22 campaign and previous years).

Both groups report working in health care (or similar) as the main **reason for vaccination**, which is compatible with social responsibility, the benefits of immunity and confidence in vaccines. Moreover, the three participants that had not initially been vaccinated in the healthcare worker group gave different reasons: two were health-related (a problem of low immunity and an ongoing pregnancy) and a third expressing mistrust of the SARS-CoV-2 vaccine. Regarding the **adverse effects** of the vaccines, it is worth noting the high frequency of local symptoms (pain at the injection site and pain in extremities) and a lower incidence of other symptoms, both local and general, among those vaccinated with BioNTech/Pfizer. In the case of those given the Oxford AstraZeneca vaccine, adverse effects are much more frequent, both local and general symptoms, with incidences of more than 80%, and with a higher rate after the first dose of the vaccine. The effects after the second dose of the vaccine are less frequent (and less intense) in the case of those vaccinated with AstraZeneca, while, in contrast, more general symptoms are reported and the rate of local symptoms is maintained among those vaccinated with BioNTech/Pfizer. The differences in many of the side effects of each of these vaccines are statistically significant. Table S2 (Supplementary Material) shows the data on the **adverse effects** of vaccination for the two doses in each of the groups. It is worth noting that all the healthcare workers in Almansa were vaccinated with BioNTech/Pfizer, while the students received both this vaccine and Oxford AstraZeneca and, in some cases, the Moderna vaccine.

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DOI:10.26502/ami.936500138

Table 3: Adherence to SARS-CoV-2 vaccination, related factors and vaccine side effects assessed 6 months after the full course.

Total individuals (n)	**Healthcare workers n1 (%)**	**Nursing Students n2 (%)**
	146	81
Fully vaccinated	143 (97.9)	81 (100)
Reasons for vaccination:	**Multi-response n1 (%)**	**Multi-response n2 (%)**
Social responsibility	54 (43.9)	27 (33.8)
Benefits of immunity	45 (36.9)	21 (26.3)
Confidence in vaccine effectiveness	30 (24.8)	14 (17.5)
Working in health care	101 (84.4)	71 (89.9)
Other reasons	1	-
Previous vaccinations (flu):	**n1 (%)**	**n2 (%)**
Flu campaign 2021-22 (Yes)	89 (62.5)	44 (55)
Previous flu campaigns (Yes)	74 (52.1)	22 (27.5)
Type of vaccine:	**n1 (%)**	**n2 (%)**
BioNTech/Pfizer	143 (100)	42 (51.9)
Astra Zeneca	-	37 (45.7)
Moderna	-	2 (2.5)
Exposure to factors related to immunity:	**n1 (%)**	**n2 (%)**
Active smokers	25 (17.6)	7 (8.6)
Weekly alcohol consumption	18(13.2)	6 (7.4)
Adverse reactions 1ª dose	**Vacuna BioNTech/Pfizer n (%)**	**Vacuna Oxf/Astra-Zeneca n (%)**
Insomnia (*)	-	7 (18.9)
Dizziness (*)	4 (2.2)	14 (37.8)
Swelling at injection site	20 (10.9)	7 (19.4)
Shivers (*)	11 (6.0)	32 (86.5)
Fatigue (*)	8 (4.4)	22 (62.9)
Nausea/vomiting (*)	2 (1.1)	13 (35.1)
Diarrhoea (*)	2(1.1)	5 (13.5)
Decreased appetite (*)	2 (1.1)	9 (24.3)
Pain at injection site (*)	92 (50.3)	31 (83.8)
Fiver (*)	10 (5.5)	31 (83.8)
General discomfort (*)	25 (13.7)	31 (83.8)
Myalgia (*)	10 (5.5)	19 (51.4)
Arthralgia (*)	10 (5.5)	19 (51.4)
Pain in the extremities (*)	64 (35.0)	26 (70.3)
Drowsiness (*)	14 (7.7)	29 (78.4)
Adverse reactions 2nd dose	**Vacuna BioNTech/Pfizer n (%)**	**Vacuna Oxf/Astra-Zeneca n (%)**
Dizziness	12 (6.6)	4 (10.8)

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Nausea/vomiting	5 (2.7)	4 (10.8)
Swelling at injection site	24 (13.1)	2 (5.4)
Shivers	38 (20.8)	6(16.7)
Fatigue	24 (13.1)	6 (16.7)
Pain at injection site	88 (48.1)	19 (51.4)
Fever	41 (22.4)	11 (29.7)
General discomfort	72 (39.3)	16 (43.2)
Myalgia	33 (18.0)	7 (18.9)
Arthralgia	22 (12.0)	7 (18.9)
Pain in the extremities	65 (35.5)	19 (51.4)
Drowsiness	35 (19.1)	11 (29.7)

Adverse effects: *Those reported in at least 10% of cases in either group are cited. Significant differences were found in the adverse effects of the first dose of BioNTech/Pfizer and Oxf/Astra-Zeneca vaccines. Comparison of proportions was conducted using the Chi-square test (*) p-value <0.001. Differences between side effects in the second dose of BioNTech/Pfizer and Oxf/Astra-Zeneca vaccines were not statistically significant.*

Source: own preparation. Population from the ICM of Almansa (Albacete) and the Albacete Faculty of Nursing (2021). Non-responses have not been reflected but the percentages were calculated for valid data.

Immune response of the groups according to dose and related factors.

Table 4 shows the descriptive values of the IgG levels in each group at 6 months after full vaccination. It should be noted that, in all cases, the immune response was positive (100% seropositivity) and mean IgG values of 3017.4 AU/ml were recorded in (n1) and 2484.6 in (n2). Comparison of the log of these mean IgG values with the t-Student test indicates shows the differences are not statistically significant.

We examined possible variations in IgG levels associated with personal characteristics, such as age and gender, without finding differences that could be considered random, as shown in Table 4, in both the healthcare worker and student populations. The participants were asked about habits related to immunity, such as smoking and alcohol consumption. We found differences between the two populations, which were statistically significant in the case of smoking, with a lower proportion of smokers among the nursing students (n2), where 8.6% were active smokers, than among the healthcare professionals (n1), where 16,7 % smoked. As can be seen in Table 4, IgG levels in the n1 population differ according to smoker status, with significantly lower levels in active smokers than in non-smokers or ex-smokers. This smoking-related variation in IgG is not confirmed in the sample of nursing students. There are also differences in the responses between the two groups in the case of alcohol consumption: weekly alcohol consumption was reported by 13.1% of the healthcare workers (n1) and 7.4% of the students (n2). However, these differences are not statistically significant and are not associated with the mean IgG levels. Another of the study variables found to be associated with significant variations in IgG is the history of COVID-19 infection prior to vaccination, the so-called hybrid immunity. The data in Table 4 show significantly higher mean IgG levels in infected healthcare workers (7520.05 AU/ml) than in their uninfected counterparts (1567.62 AU/ml) (p= 0.000). These significant differences (p= 0.01), albeit not so notable, are also found in the mean IgG values of the students (infected 3802.72 AU/ml; non-infected 2326.04 AU/ml).

Discussion

Populations in studies on healthcare workers consist largely of females, with a high proportion of young adults, which is consistent with our results. For example, a hospital study in Spain [20] found 85.3% women and a mean age of 41 years. Meanwhile, a European study with HCWs from more than 40 countries [21] reported a population with 66% women and a mean age of 42 (±11) years. The COVID-19 pandemic has had a higher incidence in healthcare workers than in the general population. This was revealed in the three-wave ENE-COVID study conducted in Spain in 2020, which estimated an overall prevalence in infected persons of 9.9% and of 16.8% in healthcare workers, a figure close to that found in our work in both groups [22]. Data from a systematic meta-analysis of seroepidemiological studies from 2020 show that seroprevalence was low in the general population (mean 4.5% and IQR 2.4-8.4%), although it varied widely across specific populations and different regions of the world [23]. The work performance and overall health of healthcare workers have been greatly impacted by the pandemic. Working in pandemic conditions exposes health workers to the risk of infection and psychological stress. A European study on HCWs from more than 40 countries revealed a fear of infection at the onset of

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DOI:10.26502/ami.936500138

Table 4: Immunity, associated factors and IgG levels in vaccinated population at 6 months. Descriptive statistics and variations.

	Healthcare workers (n1) Ig G 6 months	**Nursing students (n2) Ig G 6 months**
Total individuals (n)	141	79
Mean IgG (95% CI)	3017.4 (2124.48-3910.31)	2484.62 (1590.13-3379.10)
SD	5362.91	3993.45
Minimum	62.6	87.7
Maximum	36644.7	24912.4
Median	1132.6	1266
Interquartile range (IQR)	2020.7	1900
Comparison of IgG log means at 6 months between the two groups: t- Student=0,537 p =0,592		
Sex (mean)	**Healthcare workers (n1) Ig G 6 months**	**Nursing students (n2) Ig G 6 months**
Women	(106) 2782.91	(71) 2546.62
Men	(35) 3727.57	(8) 1934.38
Statistic and p-value	t-Student *=1.117; p=0.266	U-Mann Whitney=272; p=0.845
Age groups	**Healthcare workers (n1) Ig G 6 months**	**Nursing students (n2) Ig G 6 months**
< 35 years	3131.5	Not applicable
35-49 years	2642.8	
≥ 50 years	3663.1	
Statistic and p-value	K-Wallis= 3,847; p = 0.08 (NS)	
Smoking	**Healthcare workers (n1) N (%) and Ig G 6 meses**	**Nursing students (n2) N (%) and Ig G 6 months**
Non-smokers	75(50%) 3912.23	69(85%) 2632.54
Smokers	25(16.7%) 1267.7	7(8.6%) 1113.42
Ex-smokers	42(28.0%) 2701.7	5(6.2%) 2422.10
Statistic and p-value	K-Wallis= 9,916; p= 0.01	K-Wallis=2,256; p=0.324 NS
Occupation exposure to COVID-19	**Healthcare workers (n1) Ig G 6 meses**	**Nursing students (n2) Ig G 6 months**
Yes	(107) 2112.61	(30) 2086.91
No	(22) 7232.53	(41) 2467.81
Statistic and p-value	U de Mann Whitney = 937; P=0.133	U de Mann Whitney = 599,0 p=0.898
COVID-19 history (prior to vaccination)	**Healthcare workers (n1) Ig G 6 meses**	**Nursing students (n2) Ig G 6 months**
Yes	(33) 7520.05	(9) 3802.72
No	(101)1567.62	(65) 2326.04
Statistic and p-value	U de Mann Whitney = 676.0 p = 0.000	U de Mann Whitney= 139 p=0.011

IgG values expressed in AU/ml. All comparisons of IgG means have been performed with non-parametric tests.

The comparison statistic and p-value are shown.

(*) This comparison was conducted using the IgG log mean.

Source: own preparation. Population from the ICM of Almansa and the Albacete Faculty of Nursing (2021). Non-responses have not been reflected although the percentages were calculated for valid data.

Citation: Delicado-Useros Victoria, Navarro-Rodenas Esther, Ortega-Martínez Carmen, Pérez-Domenech Teresa, García-Alcaraz Francisco, Pérez-Serra Juan Daniel and Sánchez-Onrubia Indalecio Miguel. Impact of SARS-CoV-2 Infection in Healthcare Workers and Nursing Students: Incidence, Adherence to Vaccination and Effects of Vaccines . Archives of Microbiology and Immunology. 7 (2023): 428-442.

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the pandemic: HCWs reported a high level of concern about the risk of COVID-19 infection for themselves (71%) and their family (82%) as a result of their work. A total of 40% of HCWs felt that becoming infected with COVID-19 was beyond their control (21).

In the Spanish salaried population, the impact of temporary incapacity (TI) due to COVID after the early months of the pandemic was evident, and the incidence was multiplied in healthcare and social-health workers compared to the general population (3.6% in the total population, compared to 17.0% in senior carers, 10.5% in nurses and 6.6% in medical staff). The Work and Health Conditions Study, which surveyed more than 20,000 workers in Spain and was published in June 2020 (24), collected data on individuals that had gone to work during the state of emergency with symptoms compatible with COVID-19, finding 13.1% in the study as a whole and much higher proportions in healthcare and social-healthcare occupations (25% in practical nurses, 23% in nurses and senior carers [24]. Our study collected data on the changes in healthcare workers' positions in the early months of the pandemic, which affected one in five professionals. Seroprevalence studies have shown higher values in specific populations and, in particular, the risk for healthcare workers in contact with infected persons is estimated to have been 2.1 times higher compared to their counterparts with no known contact [23]. Studies in specific populations, such as German critical care and emergency doctors, evidence that contact with infected patients increased the risk of infection (overall positive rate of 3.5%), and a large proportion of these (39%) were unaware of their infection [25]. However, the overall rate in German doctors was low compared to other countries, arguably because the German health system was not overwhelmed by the first wave of the pandemic, as occurred in other countries, including Spain. Seroprevalence in healthcare workers was high during the first wave of the pandemic, with two studies conducted in the UK reporting rates of 20% [26] and 27% [27], which are close to our findings, while another work reports a figure as high as 29% [28]. The international study on healthcare workers from 37 countries found that one fifth had previously been infected with COVID-19 [29]. In a study conducted in paediatric and maternity hospital services in Spain, the proportion of healthcare professionals infected with SARS-CoV-2 during the first wave of the pandemic was 20.9% [20], confirming healthcare workers' increased risk of SARS-CoV-2 infection, even in services where the risk of exposure to COVID-19 patients is considered medium. Nonetheless, the data are highly disparate. A systematic review and meta-analysis estimated a weighted mean seroprevalence among healthcare workers before vaccination of 8% (95% CI 6-10%), with variations in this prevalence associated with several circumstances, often external to their professional performance [30]. The study reported that working on the front line was not consistent with higher seroprevalence. Most infected healthcare workers did not present complications, with mild cases predominant in various studies. Less severe symptoms, such as headaches, loss of smell, fever and cough were cited as affecting 40-60% of infected individuals. In one study, the proportion of severe cases requiring hospitalisation was 8% (20) a result that is similar to our findings, albeit slightly higher. Following full vaccination, the incidence of COVID-19 decreased notably [31]. So-called breakthrough infections were rare, mostly mild and asymptomatic cases, with a rate of 2.6% reported among workers at an Israeli hospital (32), which is consistent with our findings. Additionally, the same study reports cases of persistent symptoms (more than 6 weeks) in 19% of those infected post-vaccination [32], a somewhat higher percentage compared to our study.

The report published by the Spanish Association of Public Health and Healthcare Administration describes the impact of the pandemic on primary care (PC), reporting a highly disturbing situation of saturated and exhausted staff, as the large number of patients to be attended was exacerbated by the lack of resources that had accumulated in previous years. A new approach to care orientation was generated, neglecting the capacity of PC to resolve chronic and acute health problems, interrupting health programmes and prioritising tele-care as the predominant model. Continued pressure on care laid bare the crisis in PC, highlighting a high level of dissatisfaction among professionals and users. No solutions have been found, in terms of either investment (human and financial resources) or organisational changes [33]. The various groups of healthcare personnel have shown a high adherence to the pandemic prevention measures, constituting a positive reference for the general population. The capacity to vaccinate large numbers of the population in a short time, with safe and effective vaccines, has proven to be the most powerful tool, bolstering the role of nurses in prevention. Healthcare workers have emerged as the most trusted and influential advisors on vaccination decisions, and, hence, the success of the COVID-19 vaccination programme is primarily influenced by these professionals. As the provision of COVID-19 vaccines generated some controversial reluctance, albeit among a minority, we considered it important to assess adherence to COVID-19 vaccination in healthcare workers, understood as consent or refusal to receive the vaccine. Additionally, we thought it important to examine the reasons that led them to decide to be vaccinated (or to have doubts and avoid vaccination, if applicable). In our study, we found high adherence to the vaccination programme, although 2% of our participants delayed the first dose. A large survey of HCWs in more than 37 countries, conducted at the beginning of the SARS-CoV-2 vaccination process, found that the majority (93%) had been vaccinated

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DOI:10.26502/ami.936500138

against COVID-19 or were willing to do so, especially those working on the frontline. In contrast, 6.6% were hesitant and the respondents' main concern was safety or possible side-effects (29). Being a healthcare worker (or similar) is reported as the main motivation in our population groups (more than 85%) and, to a lesser extent (< 50%), participants indicate reasons such as social responsibility, expected benefits and confidence in the vaccines.

In recent years, vaccination for flu has been linked to that for COVID-19, with the aim being to protect the most vulnerable population and alleviate the strain on the health system. We consider that adherence to these vaccines might be related, although the perceived risk is different for each disease. Our data reveal low adherence to flu vaccination in pre-pandemic years, being higher in healthcare workers than in nursing students, and an increase in 2021-2022 compared to previous campaigns. Other studies report similar results, with variations depending on whether the study concerns the general population (lower adherence) or healthcare workers. For example, in 2020, in the autonomous region of Castilla and León, 33.40% of the population was vaccinated against flu, while only 22.3% had been vaccinated in the year before [34].

Our findings are important for the implementation of vaccination strategies for COVID-19 booster doses. The debate on how to enhance vaccine adherence includes determining the reasons for mistrust and whether the information available to the target population is sufficient or could be expanded and doubts resolved. The international study on HCWs launched from the UK [29] clearly shows that unfounded beliefs, distrust and denialism are also present in the small proportion of health workers that were vaccine-hesitant or preferred to wait to see the effect of vaccines in the population. In contrast, the majority of those adherent to vaccines were concerned that vaccines should be available to the world's entire population, being convinced they were the best measure against the pandemic. Among the main reasons for not being vaccinated, 5% cited concerns about safety or potential side effects of vaccines. Although few studies have reported adverse effects of the vaccines, the main findings are substantially consistent: non-serious adverse events, such as pain at the injection site, fever and fatigue, were reported with certain frequency, and no serious adverse events have been evidenced [35], not even those cited as most frequent, such as traumatic venous and arterial traumatic events, facial paralysis, myocarditis and pericarditis, as indicated in the 2023 review by Sadehalvad [36]. The prevalence of complications was higher after the first dose than after the second one [37], coinciding with our findings .

The immune response after the second dose of the vaccine (full course) has been studied, with multiple publications detailing the results according to the type of vaccine and at different times after follow-up. Our findings refer to the IgG level 6 months after full vaccination and are broadly consistent with the findings of works using similar approaches (by vaccine type, population and time of measurement). In studies with a follow-up of several months, a drop in IgG levels was observed between the first month and subsequent measurements (at 4 and 6 months after full vaccination, although almost 100% of the participants showed a reactive antibody response [38] (2) [39]. With regard to variations in IgG levels, there is substantial agreement on a history of previous SARS-CoV-2 infection being a factor that increases immune response, what is known as hybrid immunity [39, 2, 40], as evidenced by our results. This increased robustness of the hybrid immune response led to the proposal of delaying the second vaccination dose in infected individuals in order to make more efficient use of vaccines [39]. Across all the studies evaluating factors associated with variations in IgG levels, some agree with our findings, such as non-smokers having higher antibody titres than smokers [41]. In contrast, some works have reported differences related to age and sex - lower antibody levels in those over 65 years of age and higher levels in women - which were not corroborated in our data, as well as lower IgG values in participants with immunosuppression [42, 38, 41]. It has been suggested that daily alcohol consumption may hinder or limit the level of antibodies post-vaccination. Tamura reports a 15% lower IgG level in daily drinkers compared to non-drinkers [43]. Our study found no association between alcohol consumption and antibody levels, although the most frequent consumption reported in our study population was weekly or occasional. Our study is a further contribution to the body of literature assessing the efficacy of vaccines, where similar conclusions are drawn, demonstrating the high efficacy of the COVID-19 vaccine in Spanish healthcare workers [31]. This work is part of a prospective observational study on the evolution of acquired immunity after vaccination against SARS-CoV-2 in healthcare workers, the partial findings of which have already been published, evidencing antibody levels that remain positive 6 and 9 months after vaccination [44].

Limitations

The sample of students could not be completed by means of simple random sampling, and we were hence obliged to resort to a convenience sample from the study population that had shown interest in participating. Consequently, the sampling was not equiprobabilistic. Additionally, we did not achieve the sample size calculated for this group, and the inference of the results is thus limited. We must also note the limitations of this type of observational study, in which part of the data is self-reported, involving the possibility of information or memory biases in the reporting of symptoms, adverse effects or dates of positive tests. In this sense, a possible information bias could have occurred in the assessment of the incidence

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of COVID-19 as no screening tests were carried out in the health care workers or students as a whole, and therefore, asymptomatic or mildly clinical cases that were not detected by PCR or Ag-test could have been missed.

Conclusion

The occupational exposure of our participants to persons with active SARS-CoV-2 infection was high, being 83% in the healthcare workers and 42% in the nursing students. Both groups presented a higher incidence of COVID-19 in the year prior to vaccination than that estimated for the general Spanish population (19.3% in HCWs and 13.6% in NS). The source of infection was not always known but was attributed to a different origin in the two groups studied: occupational origin was attributed in a high proportion of cases among the healthcare workers (41%), while among the nursing students, non-occupational origin was predominant (46%). In both groups, the clinical cases were primarily mild (77% in NS and 85% in HCWs). However, no moderate or severe clinical cases were found among the nursing students, nor cases of long COVID, which was reported by 11% of the healthcare workers affected. Post-vaccination, the incidence of COVID-19 decreased notably in both groups in the first 6 months. Adherence to the vaccine was high in both groups, with 100% of the nursing students and 97.5% of healthcare workers being vaccinated. Working in health care (or similar) is cited as the main reason for vaccination in both population groups, with social responsibility, expected benefits and confidence in vaccines being less frequently identified. The immune response 6 months after the full course of vaccination shows a reactive antibody response in 100% of the cases, with mean IgG values of 3017 AU/ml in the HCWs and 2484 AU/ml in the NS, indicating protection levels against SARS-CoV-2. The efficacy of the vaccines is also demonstrated by the decrease in post-vaccination infections and the clinical mildness of the cases. Factors impacting the immune response that have been reported in this and other studies are previous SARS-CoV-2 infection, which enhances the immune response (hybrid immunity), and smoking, which lowers the immune response in active smokers compared to the non-smoking population. The adverse reactions to the vaccines were frequent but transient (disappearing within 24h), mild and mostly local, with some differences found depending on the vaccine administered (more with AstraZeneca than with BioNTech/Pfizer) and the vaccine dose (more in the first dose than in the second). No severe adverse reaction was reported.

Acknowledgements

All the research team would like to thank the management of the ICM Almansa; without their help, it would not have been possible to conduct this study. This work has received funding from the Provincial Council of Albacete, the Faculty of Nursing of Albacete (UCLM), UCLM research grant to the GICES group and the Integrated Care Management of Almansa. We would also like to thank : The laboratory service at the Hospital of Almansa and the microbiology service at Albacete University Hospital. All the participants for their selfless collaboration.

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Citation: Delicado-Useros Victoria, Navarro-Rodenas Esther, Ortega-Martínez Carmen, Pérez-Domenech Teresa, García-Alcaraz Francisco, Pérez-Serra Juan Daniel and Sánchez-Onrubia Indalecio Miguel. Impact of SARS-CoV-2 Infection in Healthcare Workers and Nursing Students: Incidence, Adherence to Vaccination and Effects of Vaccines . Archives of Microbiology and Immunology. 7 (2023): 428-442.

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Citation: Delicado-Useros Victoria, Navarro-Rodenas Esther, Ortega-Martínez Carmen, Pérez-Domenech Teresa, García-Alcaraz Francisco, Pérez-Serra Juan Daniel and Sánchez-Onrubia Indalecio Miguel. Impact of SARS-CoV-2 Infection in Healthcare Workers and Nursing Students: Incidence, Adherence to Vaccination and Effects of Vaccines . Archives of Microbiology and Immunology. 7 (2023): 428-442.

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DOI:10.26502/ami.936500138

SUPPLEMENTARY FILES

Table S1: Professional Characteristics and Occupational Exposure to Sars-Cov-2 tn Health Professionals

Professional experience (year): Mean (SD)= 17.87 (8.99); 95% CI %= 16.30-19.43 Minimum value= 1; Maximum value=47 years; Median: 17; Range=46; Mode (MD)= 15			
Departments /Workplaces	**n1 (%)**	**Departments/Workplaces in the last year**	
Special services*	52 (37.4)	**n1 (%)**	
Wards**	13 (9.5)	One	106 (70.2)
Central services	10 (7.3)	Two	23 (15.2)
Outpatients	30 (22.1)	Three	9 (6)
Management and administration	13 (9.6)	four	1 (0.7)
Primary care centers	13 (8.9)		
Care homes	5 (3.7)		
Length of service in position: Mean (SD) = 5.53 (5.21); Minimum value= 1 month; Maximum value= 18 years; Range=18 years; Median (Mn)= 3.12; Mode (MD)= 1 year			
Occupational exposure to COVID-19	**n (%)**	**Year qualified:** Ranges between 1978 & 2019 Range =41 years Mean= 2000 Median= 2001 Mode= 2001	
Yes	113 (74.8)		
No	23 (15.2)		

Legend: * Includes: Emergency, Critical Care and Surgery ** Includes Internal Medicine, Surgery and Obstetrics – Pediatrics
Lost values not included. Percentages are calculated over valid data. Data on the study population (n1) from ICS Almansa (Albacete) 2022.

Tabla S2: Adverse Reactions to Sars-Cov-2 Vaccines in Two Populations: Health Workers (n1) and Nursing Students (n2)

Organ and system involvement:	**1st dose**		**2nd dose**	
- Adverse reaction	**n1 (%)**	**n2 (%)**	**n1 (%)**	**n2 (%)**
Disorders of the blood and lymphatic system: - - Lymphadenopathy	5 (3,5)	-	6 (4,3)	-
Immune system disorders:				
- Anaphylaxis	-	1 (1,2)	-	-
- Hypersensitivity	-	2 (3,5)	-	-
Psychiatric disorders:				
- Insomnia	-	7 (8,6)	2 (1,4)	-
Nervous system disorders:				
- Dizziness	2 (1,4)	16 (18,9)	7 (5)	9 (11,1)
- Facial paralysis	- 9 (6,4)	-	-	-
- Drowsiness/ Tiredness	1 (0,7)	34 (42,5)	25 (17,7)	21 (25,9)
- Paresthesias		1 (1,2)	1 (0,7)	-
Gastrointestinal disorders:				
- Nausea	1 (0,7)	14 (17,3)	4 (2,8)	5 (6,2)
- Diarrhoea / Vomiting	1 (0,7)	6 (7,4)	4 (2,8)	5 (2,9)
Musculoskeletal and connective tissue disorders:				
- Limb pain	43 (30,5)	47 (58)	42 (29,8)	42 (51,9) (*)
- Arthralgia	9 (6,4)	20 (24,7)	18 (12,8)	12 (13,6)
- Myalgia	8 (5,7)	21 (25,9)	22 (15,6)	18 (22,2)
General disorders and local disturbances at the injection site:				
- General malaise	18 (12,8)	38 (46,9)	48 (34,0)	40 (49,4) (**)
- Fever / Febrile Fever	8 (5,7)	33 (40,7)	22 (15,6)	30 (37,0) (*)
- Local pain (injection site)	62 (44)	61 (75,3)	58 (41,1)	49 (60,5) (**)
- Fatigue	6 (4,3)	23 (30,4)	13 (9,2)	17 (21,0) (**)

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- Chills	10 (7,1)	33 (40,7)	25 (17,7)	19 (23,8)
- Local swelling	16 (11,3)	11 (13,8)	20 (14,2)	6 (7,4)
- Local redness	6 (5,3)	5 (6,2)	10 (7,1)	3 (3,7)
- Itching at injection site	1 (0,7)	1 (1,2)	2 (1,4)	-
Skin and subcutaneous tissue disorders:				
- Hyperhidrosis	-	1, (1,2)	-	-
- Generalised exanthema	-	-	-	-
- Generalised itching	-	-	-	-
Metabolic and nutritional disorders:				
- Decreased appetite	-	11 (13,6)	3 (2,1)	5 (6,3)
Other (specify):				
- Menstrual disorders	1 (0,7)	1 (1,2)	- 1 (0,7)	1 (1,2)
- Elevation of blood pressure	1 (0,7)	-	2 (1,4)	- 1(1,2)
- Headache				

Source: Self-administered questionnaire. Population n1 (141) and n2 (81). Calculated as % of valid data.

Classification of adverse effects according to the Ministry of Health Strategy 2021.

Legends: Significant differences in Chi-square test (*) $p<0.001$; (**) $p<0.05$.