ORIGINAL ARTICLE

Incidence and factors associated with early and late adverse reactions after the first dose of Pfizer-BioNTech vaccine among healthcare workers

Incidencia y factores asociados con las reacciones adversas tras la primera dosis de la vacuna Pfizer-BioNTech en trabajadores de la salud

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Abstract

Objective: *To determine the incidence of adverse reactions (AR) after the first dose of Pfizer-BioNTech vaccine, and to identify some factors associated with AR.* **Method:** *A retrospective cohort study was conducted. Data were obtained through an epidemio- logical survey answered online. Multivariate analyses were performed to identify factors associated with early (< 2 h) and late (≥ 2 h) AR.* **Results:** *A total of 2295 health care workers were included; in them, the cumulative incidence of AR was 18.2% (95% confidence interval: 16.6-19.8), where the majority were late (78.2%). The associated factors that increased the risk of early AR were being female (odds ratio [OR]: 2.23, p = 0.002) and belonging to the medical staff (OR: 1.56; p = 0.041). In late AR were being female (OR: 1.94; p < 0.0001); on the other hand, diabetes (OR: 0.46; p = 0.021), asthma (OR: 0.53; p = 0.040) and smoking (OR: 0.44, p = 0.002) were inversely associated factors. Interestingly, history of COVID-19 was not associated with either early or late AR.* **Conclusions:** *The risk of presenting some type of AR due to the Pfizer-BioNTech vaccine in health care workers is < 20%.*

Keywords: *Adverse reactions. BNT162b2 vaccine. COVID-19. Health care workers.*

Resumen

Objetivo: *Determinar la incidencia de reacciones adversas (RA) tras la primera dosis de la vacuna Pfizer-BioNTech e identificar algunos factores asociados con ellas.* **Método:** *Se realizó un estudio de cohorte retrospectiva. Los datos fueron obtenidos median- te una encuesta epidemiológica contestada en línea. Se realizaron análisis multivariados para identificar factores asociados con las RA tempranas (< 2 h) y tardías (≥ 2 h).* **Resultados:** *Se incluyeron 2295 trabajadores de la salud; en ellos, la incidencia acumu- lada de RA fue del 18.2% (intervalo de confianza del 95%: 16.6-19.8%) y la mayoría fueron tardías (78.2%). Las RA tempranas más frecuentes fueron dolor local, cefalea y mareo; en las tardías fueron dolor local, cefalea y fatiga. No se documentaron casos de anafilaxia; sin embargo, en el grupo de RA tempranas y tardías hubo un caso y tres casos, respectivamente, con síntomas sistémicos que afectaron a dos órganos diferentes. Los factores asociados que incrementaron el riesgo de RA tempranas fueron ser mujer (odds ratio [OR]: 2.23; p = 0.002) y pertenecer al personal médico (OR: 1.56; p = 0.041). En las RA tardías fue ser mujer (OR: 1.94; p < 0.0001); por su parte, la diabetes (OR: 0.46; p = 0.021), el asma (OR: 0.53; p = 0.040) y el tabaquismo (OR: 0.44; p = 0.002) fueron factores asociados inversamente.*

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Es interesante que la historia de COVID-19 no se asoció con RA tempranas ni tardías. **Conclusiones:** *El riesgo de presentar algún tipo de RA debido a la vacuna Pfizer-BioNTech en trabajadores de la salud es < 20%.*

Palabras clave: *Reacciones adversas. Vacuna BNT162. COVID-19. Personal de salud.*

Introduction

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it triggers (COVID-19) have caused significant disruptions to our way of life. Additionally, numerous cases and deaths have been reported around the world. As of September 5, 2021, over 220 million cases had been detected worldwide, with the death toll exceeding 4.5 million people for a fatality rate of 2.1%[1]. By that same date, in our country, the number of COVID-19 cases reached nearly 3.5 million, with over 260,000 deaths and an estimated fatality rate of 7.7%[2]. To constrain the pandemic, the emergence and use of COVID-19 vaccines have become increasingly popular worldwide. Among them, messenger RNA vaccines have gained importance due to their high efficacy in reducing symptomatic infections caused by SARS-CoV-2 and low rate of severe adverse events (AE)[3,4].

In Mexico, same as in other parts of the world, the vaccination strategy against COVID-19 focused primarily on health care workers responsible for assisting COVID-19 patients. The institutional policy at the hospital where this study was conducted was to administer the Pfizer BioNTech vaccine to all health care workers. This vaccine is based on lipid nanoparticles containing messenger RNA that induces the formation of spike proteins of SARS-CoV-2. The vaccine 2-dose regimen provides 95% protection[3]. The vaccination campaign with the Pfizer-BioNTech vaccine started in Mexico back in December 11, 2020. The immunization schedule consists of a first 30 μg dose in 0.3 mL5 administered intramuscularly in the deltoid muscle of the non-dominant arm. The second dose is administered 21 to 42 days after the first one[5]. Since the beginning of the vaccination campaign with the Pfizer-BioNTech vaccine, there were concerns among medical and non-medical personnel on the possibility of severe systemic AE being reported. Safety studies conducted on this vaccine were scarce when it started to be administered massively to the population, raising concerns on its potential for AE. Additionally, clinical trials may not fully identify the true size of AE among the population because they are often conducted in subgroups with specific inclusion criteria, and results might just not be entirely applicable to the rest of the population. With these concerns in mind, the objectives of our study were to determine the rate of early and late AE after the first dose of the Pfizer-BioNTech vaccine, using an online survey sent to the health care workers of a hospital located in Western Mexico. Also, to explore the rate of events consistent with anaphylactic reactions and identify factors associated with AE.

Method

Design

This was a retrospective cohort study conducted of a single group based on the census of health care workers at a second-level teaching hospital from Western Mexico. The study focused on those who voluntarily received the Pfizer-BioNTech vaccine. The recruitment period spanned from January through April 2021. Health care workers aged ≥ 18 years were included in the study. Those with the following conditions were excluded: age ≥ 65 years, uncontrolled diabetes, uncontrolled arterial hypertension, morbid obesity, neoplastic diseases, use of immunosuppressive medications, pregnant women, uncontrolled chronic obstructive pulmonary disease (COPD), or uncontrolled cardiovascular diseases. Health care workers on whom there was no information available or who remained confined at the time of vaccination and, therefore, could not be vaccinated were also excluded.

Follow-up

Follow-up of all study subjects began from the date the Pfizer-BioNTech vaccine started being administered and extended until 30 days after vaccination. During this time, all AE were recorded.

Measuring tool

Data were collected using an epidemiological survey that was answered online to limit physical contact between individuals. The survey included questions on age, sex, history of COVID-19, and comorbidities such as diabetes, systemic arterial hypertension, cardiovascular disease,

COPD, asthma, current smoking status, and history of allergies. In our study, health care workers were categorized as either medical personnel (physicians and nurses) or non-medical personnel.

Variables

Operatively, variables for the study were collected through the online survey based on self-reporting by all participants. Possible factors associated with AE included gender (female), medical personnel status, diabetes, systemic arterial hypertension, asthma, smoking, and history of COVID-19. All these factors were categorized as present (yes) or absent (no) based on the participant's response.

Adverse events

The outcome variables were classified according to the time they occurred during the post-vaccination follow-up: 1) no AE, 2) early AE (< 2 hours), and 3) delayed AE (≥ 2 hours). The discomfort caused by the vaccine was categorized as local (pain, swelling, redness, cellulitis, among others) or systemic (added to the presence of a local reaction, affecting a different organ or system) and depending on the organs or systems damaged. To identify anaphylactic reactions associated with the Pfizer-BioNTech vaccine, the definitions of anaphylaxis proposed by different international organizations were adapted to our study[6-8].

The history of COVID-19 was defined as the presence of symptoms of the disease plus confirmation of SARS-CoV-2 infection with a positive result in a real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2.

Analysis

Data analysis was performed using IBM SPSS Statistics Version 23.0. The rate of AE following vaccination was expressed as cumulative incidence (number of new events among subjects at risk or vaccinated). The confidence interval was obtained using Wald or Wilson Score Interval as necessary. Categorical variables were expressed as frequency and percentage, and quantitative ones as mean and standard deviation. The chi-square test or Fisher's exact test were used to compare percentages between groups as necessary. The ANOVA formula with Sheffé correction was used to compare means in two or more groups. Finally, to identify variables associated with early or late AE (dependent variables), different multivariate logistic regression models were used, one for each category. The independent variables entered into the models were gender (female or male), medical personnel (yes or no), diabetes (yes or no), systemic arterial hypertension (yes or no), asthma (yes or no), smoking (yes or no), and COVID-19 (yes or no). P values < 0.05 were considered statistically significant.

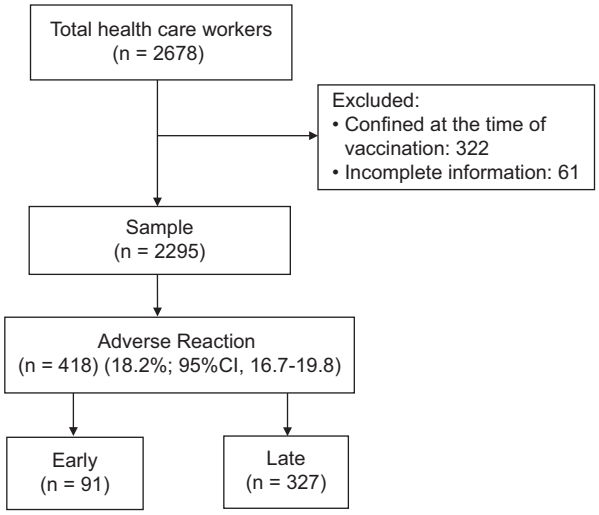

Figure 1. *Flowchart of health care workers with AE to the Pfizer-BioNTech vaccine.*

Ethics

The research was approved by the Ethics Committee of Nuevo Hospital Civil de Guadalajara, Jalisco, Mexico while the epidemiological survey responded by each participant was considered as willingness to participate in the study.

Results

From an overall population of 2678 health care workers, 322 were excluded as they remained confined at the time of vaccination, plus 61 due to incomplete information. The final sample included a total of 2295 health care workers (86% of the overall population) who had received the first dose of the Pfizer-BioNTech vaccine (Fig. 1).

Table 1 shows the characteristics of the population studied. A total of 63.1% of the total were women, and the mean age was 38.1 ± 11.3 years. Overall, 418 out of 2295 health care workers experienced some type of AE (cumulative incidence, 18.2%; 95% confidence interval [CI]: 16.6-19.8), with the majority being late AE

Table 1. Characteristics of healthcare workers based on the type of AE to the Pfizer-BioNTech vaccine

	Total (n = 2295)	No (n = 1877)	Adverse event		p
			Early (n = 91)	Late (n = 327)	
Age, years, mean ± SD	38.1 ± 11.3	39.2 ± 11.0	37.3 ± 12.0	38.9 ± 11.4	0.258
Sex, woman, n (%)	1449 (63.1)	1133 (60.4)	70 (76.9)	246 (75.2)	< 0.0001
Healh care worker, n (%)					
Medical personnel	1550 (67.5)	1269 (67.6)	53 (58.2)	228 (69.7)	0.116
Non-medical personnel	745 (32.5)	608 (32.4)	38 (41.8)	99 (30.3)	
Comorbidity, n (%)					
Diabetes	135 (5.9)	123 (6.6)	2 (2.2)	10 (3.1)	0.014
Systemic arterial hypertension	170 (7.4)	149 (7.9)	2 (2.2)	19 (5.8)	0.061
Cardiovascular disease	46 (2.0)	42 (2.2)	1 (1.1)	3 (0.9)	0.239
COPD	16 (0.7)	13 (0.7)	1 (1.1)	2 (0.6)	0.884
Asthma	138 (6.0)	120 (6.4)	6 (6.6)	12 (3.7)	0.156
Current smoker, n (%)	247 (10.8)	225 (12.0)	5 (5.5)	17 (5.2)	< 0.0001
COVID-19, n (%)	529 (23.1)	435 (23.2)	20 (22.0)	74 (22.6)	0.947

COPD: chronic obstructive pulmonary disease; SD: standard deviation.
Proportions compared using a Chi-square test for 2 degrees of freedom.
Means compared using the ANOVA test.

(78.2%) and the rest, early AE (21.8%). The early AE group mainly included local pain, headache, and dizziness, while the late AE group included local pain, headache, and fatigue. The early AE group had significantly more dizziness and xerostomia compared to the late AE group ($p < 0.05$). On the other hand, the late AE group had significantly more fever, headache, fatigue, local pain, diarrhea, pharyngeal pain, and myalgia compared to the early AE group ($p < 0.05$) (Table 2). Out of the 17 subjects with hives, 5 had early presentation (29.4%) compared to 12 late presentations. The ratio of AE with systemic manifestations was 4 out of 2295 participants (0.17%; 95%CI 0.07-0.45), 1 occurring in the early AE group characterized by hives, body itching, and rhinorrhea (0.04%), and 3 in the late AE group (0.13%) with the same symptoms. In the latter group, a case of wheezing and dyspnea was reported in a 43-year-old woman with a history of smoking.

The factors associated with early AE were being a woman and a member of the medical personnel. Regarding late AE, being a woman increased the chances of early AE by 94%, while having diabetes, asthma, or being a current smoking were inversely associated factors. We should mention that, interestingly enough, the history of COVID-19 was not associated with the presence of early or late AE (Table 3).

Discussion

This study has multiple important findings. First, it shows that little over one fifth of all health care workers experienced some type of AE after receiving the first dose of the Pfizer-BioNTech vaccine. Local pain and headache were the most common clinical signs reported in both the early and late AE groups. Second, as far as we know, this study is the first one ever conducted to report AE related factors associated with the Pfizer-BioNTech vaccine based on when these reactions appeared. Among other things, we saw that women had more chances of experiencing both early and late AE compared to men. Also, the personal history of asthma did not increase the risk of late AE. Third, the history of COVID-19 was also not associated with vaccine-related AE. Finally, the study found that allergic reactions were rare, and specific anaphylactic reactions could not be fully identified.

In the first landmark study ever conducted to assess the efficacy and safety profile of the Pfizer-BioNTech vaccine of over 43,000 subjects, the overall rate of any AE was 27% despite the vaccine 95% efficacy profile. This contrasted significantly with the placebo group, where the rate of any AE was 12%[3]. Similarly, a different study found similar findings, with a 25.4% rate of AE[9]. However, other studies have also shown different results; for example, in Poland, the rate of AE was 94%[10], in Malta, 73% in men and 82% in women[11]; while in Iraq, it was 67%[12]. Probably, the perception of symptoms among participants is a relevant factor in the different AE frequencies reported among the studies. Another explanation could be the manner and timing of data collection. In our case, since the population analyzed were health

Table 2. Comparison of signs and symptoms based on the type of AE to the Pfizer-BioNTech vaccine

	Rate of AE in 2295 participants	AE		p
		Early (n = 91)	Late (n = 327)	
Local symptoms, n (%)				
Local pain	374 (16.3)	68 (74.7)	306 (93.6)	< 0.0001
Local edema	81 (3.5)	18 (19.8)	63 (19.3)	0.913
Local erythema	15 (0.7)	2 (2.2)	13 (4.0)	0.540
Systemic signs, n (%)				
Musculoskeletal	260 (11.3)	35 (38.5)	225 (68.8)	< 0.0001
Fatigue	218 (9.5)	28 (30.8)	190 (58.1)	< 0.0001
Myalgias	190 (8.3)	23 (25.3)	167 (51.1)	< 0.0001
Adynamia	47 (2.0)	6 (6.6)	41 (12.5)	0.112
Arthralgias	23 (1.0)	3 (3.3)	20 (6.1)	0.436
GI	185 (8.1)	52 (57.1)	133 (40.7)	0.005
Dizziness	119 (5.2)	37 (40.7)	82 (25.1)	0.004
Nausea	80 (3.5)	22 (24.2)	58 (17.7)	0.167
Diarrhea	50 (2.2)	4 (4.4)	46 (14.1)	0.010
Abdominal pain	32 (1.4)	4 (4.4)	28 (8.6)	0.264
Vomiting	17 (0.7)	3 (3.3)	14 (4.3)	0.999
Xerostomia	6 (0.3)	5 (5.5)	1 (0.3)	0.002
Respiratory	156 (6.8)	26 (28.6)	130 (39.8)	0.051
Rhinorrhea	91 (4.0)	13 (14.3)	78 (23.9)	0.050
Pharyngeal pain	88 (3.8)	12 (13.2)	76 (23.2)	0.037
Cough	61 (2.7)	10 (11.0)	51 (15.6)	0.271
Dyspnea	22 (1.0)	9 (9.9)	13 (4.0)	0.034
Wheezing	1 (0)	0 (0)	1 (0.3)	0.999
Cutaneous	137 (6.0)	26 (28.6)	111 (33.9)	0.334
Chills	118 (5.1)	21 (23.1)	97 (29.7)	0.217
Body itching	18 (0.8)	5 (5.5)	13 (4.0)	0.528
Hives	17 (0.7)	5 (5.5)	12 (3.7)	0.436
Cellulitis	2 (0.1)	0 (0)	2 (0.6)	0.999
Cardiovascular	28 (1.2)	13 (14.3)	15 (4.6)	0.001
Tachycardia	18 (0.8)	8 (8.8)	10 (3.1)	0.017
Hypertension	14 (0.6)	8 (8.8)	6 (1.8)	0.001
Other	310 (13.5)	56 (61.5)	254 (77.7)	0.002
Headache	294 (3.9)	56 (61.5)	238 (72.8)	0.038
Fever	90 (3.9)	7 (7.7)	83 (25.4)	< 0.0001

P-values were obtained using the Chi-square test or Fisher's exact test, as necessary (early AE or late AE).

care workers, some discomforts may not have been given proper importance, and consequently, when filling out the online survey, they may have been misrepresented. On the other hand, since the vaccine was applied to the deltoid region of the arm, the most common AE were local, among them, pain was the most significant one. In our study population, this discomfort was more frequently observed in a delayed manner. Other local discomforts, although not as common, were erythema and edema. Similar findings have been reported in previous studies[3,9-12]. Regarding systemic AE, in our study, the most common ones were fatigue and muscular pain, which is consistent with previous studies[9,11-13].

Notably, no cases of anaphylaxis were documented among health care workers in this study. However, in the group of both early and late AE, 1 and 3 cases were reported, respectively, with systemic symptoms affecting 2 different organs. According to the classification system for systemic allergic reactions proposed by the World Allergy Organization, these cases would qualify as grade 2 AE[6]. Using the definition of anaphylaxis established by the Brighton Collaboration, these same subjects would fall under level 2 of diagnostic certainty for anaphylaxis[7]. Finally, based on the severity scale of anaphylaxis proposed by the German Working Group of Anaphylaxis Training and Education, these subjects had grade II AE[8]. In conclusion, individuals

Table 3. Multivariate analysis of factors associated with AE to the Pfizer-BioNTech vaccine

Dependent variable: early adverse event			
	aOR	**95%CI**	**p**
Woman	2.23	1.35-3.67	0.002
Medical personnel	1.56	1.02-2.41	0.041
Diabetes	-	-	0.183
Systemic arterial hypertension	0.26	0.06-1.06	0.060
Asthma	-	-	0.988
Smoking	-	-	0.089
COVID-19	-	-	0.714
Dependent variable: late AE			
	aOR	**95%CI**	**p**
Woman	1.94	1.48-2.54	< 0.0001
Medical personnel	-	-	0.70
Diabetes	0.46	0.24-0.89	0.021
Systemic arterial hypertension	-	-	0.629
Asthma	0.53	0.29-0.97	0.040
Smoking	0.44	0.26-0.74	0.002
COVID-19	-	-	0.132

aOR: adjusted odds ratio; 95%CI: 95% confidence interval. Adjusted ORs were obtained through binary logistic regression. Covariates were introduced dichotomously using the forward method: conditional. ORs are not calculated for variables that were removed from the model due to the lack of a significant association.

receiving the Pfizer-BioNTech vaccine who experience hives as a primary symptom, either early or late, should be closely monitored to make sure that their symptoms do not progress into overt anaphylaxis.

The results of this study show an association between AE and certain factors such as sex and a personal history of asthma, among others. Regarding sex and the rate of AE, Menni et al[9]. also showed that the number of local and systemic AE is higher in women compared to men, both with the Pfizer-BioNTech and the ChAdOx1 nCoV-19 vaccines. Similar results have been documented across the world[11,12,14,15]. Probably, differences in innate and acquired immune responses between women and men, higher inflammatory responses in women or information biases could be contributing factors to the higher rate of AE reported in women[16,17].

One relevant finding in this study is the inverse association between asthma and the presence of AE, specifically late AE. Several meta-analyses conducted during the pandemic showed that asthma is related to a lower severity of COVID-19[18,19]. The proposed mechanisms to explain this lack of association could be related to a predominance of the Th2 type inflammatory response over the Th1 type[20], which is primarily responsible for COVID-19 symptoms. Finally, former studies have shown that having a history of COVID-19 is associated with a higher rate of AE following the use of vaccines against this virus[9,12,21]. The arguments that have been put forward to explain this association are related to an improved immune response following the use of the vaccine[22,23]. However, in this study, neither early nor late AE were associated with a history of previous COVID-19.

Another noteworthy finding is the inverse relationship found between diabetes, smoking, and AE. It is possible that some individuals with diabetes may not have initially gone to vaccination centers, which could explain why the rate of diabetes found in the study was relatively lower than the national rate. This could have artificially resulted in a higher rate of AE in people without diabetes. Regarding smoking, one possible explanation could be how health care workers perceive and report their smoking habits. The rate of this addiction might be higher in this population than reported. In both situations, it is suggested to approach these associations with caution and wait for further epidemiological studies to confirm the findings.

Limitations

The study has several limitations. The epidemiological survey did not inquire about the intensity of AE, the duration of discomfort or the need for treatment to control them. Additionally, although the participation rate of health care workers in responding to the survey after the first dose of the vaccine was very good, it decreased notably after the second dose. Therefore, the study is limited regarding whether the rate of AE was higher or lower in relation to the first dose. We have the perception that, once the fears that existed in the survey participants due to the information circulating regarding the side effects of a new vaccine were overcome, the participation to complete the survey decreased significantly. As a result, the follow-up of late AE was limited until the time of the second dose of the vaccine was reached. Furthermore, individuals with a personal history of anaphylaxis may not have gone to vaccination centers as scheduled, which may have influenced the lack of observation of this type of discomfort. As mentioned

earlier, we should consider that the type of population studied (health care workers) may have perceived and reported on the occurrence of vaccine-associated AE differently, as well as some of the factors investigated (asthma, diabetes, or smoking). Therefore, caution should be exercised when extrapolating the results to the general population.

Conclusions

The risk of experiencing any type of AE to the Pfizer-BioNTech vaccine in health care workers was < 20%, which is similar to what has been reported in previous clinical trials. Early and late AE were more frequent in women than in men. Notably, asthma, diabetes, and smoking showed an inverse association with late AE, a finding that requires further epidemiological studies for confirmation purposes. Finally, the risk of AE with systemic sign was very low (< 1%). Also, no cases of anaphylaxis were ever documented in this study.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this study.

Patients' data protection. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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