Received: 25 May 2021 | Accepted: 4 July 2021

DOI: 10.1111/ijcp.14605

ORIGINAL PAPER

Infectious diseases

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Adverse reactions to Pfizer-BioNTech vaccination of healthcare workers at Malta's state hospital

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Abstract

Background: The long-term control of COVID-19 depends on an effective global vaccination strategy. Protecting healthcare workers (HCWs) from serious infection is critical. Malta, a European country, initiated the vaccination roll-out using Pfizer-BioNTech COVID-19 vaccine targeting HCWs. This study determined vaccination adverse effects (AEs) in this cohort.

Method: An online survey was disseminated to all HCWs via work email (29/3/21 to 9/4/21) to gather AEs regarding pain, redness and swelling at injection site, fever, chills, fatigue, muscle/joint pains, headache, vomiting and diarrhoea severity following each dose (Likert scale). Descriptive, comparative and multiple binary regression analyses were performed.

Results: A response of 30.30% (n = 1480) was achieved with the commonest AEs being pain at injection site (88.92% CI 95%: 87.21-90.42), mostly mild (51%) and moderate (43%). Fatigue was reported by 72.97% (CI 95%: 70.65-75.17), 42% were mild and 41% were moderate. Females reported significantly ($P \leq .05$, respectively) more pain (OR: 1.90), redness (OR: 2.49), swelling at injection site (OR: 1.33), fever (OR: 1.74), chills (OR: 2.32), fatigue (OR: 2.43), muscle (OR: 1.54) and joint pains (OR: 2.01), headache (OR: 2.07) and vomiting (OR: 3.43) when adjusted for age and HCW role. Localised AEs were reported following both vaccine doses unlike systemic AEs that were mostly reported after second doses.

Conclusion: Vaccination benefits outweigh the minor AEs experienced, with females exhibiting a higher susceptibility. The general low vaccination AEs observed within the HCW cohort is encouraging and should help in allaying vaccine hesitancy among the population.

1 | INTRODUCTION

It is generally accepted that the long-term control of COVID-19 will depend on an effective global vaccination strategy.[1] To this end, a vaccination coverage between 55% and 82% of any target population has been recommended.[2] Healthcare workers (HCWs) are an especially important risk group where effective vaccination coverage is essential because of the risk of occupationally related infection.[3] Nevertheless this objective can be potentially derailed by vaccine hesitancy among healthcare professionals.[4] One of the often cited reason for vaccine hesitancy among these groups is concern about the side effects, especially in the light of the rapid development of these vaccines.[5]

Malta is a Mediterranean island state with a population of approximately 450 000. It is served by one large state hospital: Mater Dei Hospital. In line with national priorities, hospital staff were included in the first groups to be vaccinated, starting on 27 December

2020.[6,7] Vaccination was undertaken using the Pfizer-BioNTech COVID-19 vaccine through the manufacturer-recommended two-dose protocol, 3 weeks apart. This study was carried out in order to determine the degree and nature of adverse effects to this cohort of HCWs.

What's known

- Adverse effects following Covid-19 vaccination have been reported by manufacturers.

What's new

- This is an independent study to evaluate the adverse effects reported among the healthcare workers in Malta.
- This is a population-based study that not only explored the adverse effects of Pfizer-BioTech vaccine but also evaluated whether there are contributing factors that increase susceptibility for adverse effects.

2 | METHODS

2.1 | Data

Vaccinees were emailed a personal invitation to complete an anonymised questionnaire in a bespoke Google form after the vaccination drive was concluded. Data collection was performed from 29/03/21 to 09/04/21. The Google form did not record any identifiable variables or the participant's computer IP address, to ensure responders' privacy. Respondents were asked questions on basic demographics (sex and age), role (nurse, doctor, etc) and specific questions pertaining to known adverse effects. These included local reactions at the vaccination site (pain, redness and swelling) and more generalised systematic symptoms (fever, chills, fatigue, muscle/joint pains, headaches, vomiting and diarrhoea). For each of these, respondents were asked to grade severity on a Likert scale of five. They were also queried if the adverse effect was experienced with the first, the second or both doses, and at what day after the vaccine did this peak. Respondents were also asked whether they needed to take days off. The University of Malta Research and Ethical Committee granted clearance to conduct this study (ID: 7304_03122020). Data protection clearance was obtained from the Mater Dei Hospital data protection office.

TABLE 1 Demographic characteristics of the study population

		Male (n = 493)	Female (n = 987)	Chi square
Role	Allied health	20.89%	25.43%	<0.001
	Doctor	27.59%	16.21%	
	Midwife	0.00%	5.88%	
	Nurse	26.77%	39.11%	
	Admin	24.75%	13.37%	
Age groups	18-24 years	5.48%	11.85%	<0.001
	25-34 years	29.41%	33.33%	
	35-44 years	20.89%	19.05%	
	45-54 years	22.52%	21.99%	
	55-64 years	21.30%	13.17%	
	65+ years	0.41%	0.61%	

2.2 | Data analyses

Statistical analyses were performed using IBM SPSS (IBM Corp. Release 2012 Version 21). Descriptive analyses are presented through frequencies. Comparative analyses were conducted through Chi Square test. Multivariable binary logistic regressions were performed with the different adverse effects as the dependent variables and sex, age and role as the independent variables. A *P*-value of ≤.05 was considered as significant.

3 | RESULTS

The questionnaire was sent to 4885 vaccinees. A total of 1480 responded (30.30% response rate), with a female predominance (66.69% CI 95%: 64.25-69.04). The characteristics of the participants are shown in Table 1. The commonest reported adverse effects were "pain at injection site" followed by "fatigue." Females reported a higher incidence of adverse effects when compared with males (Table 2). Those experiencing adverse effects mostly recalled the severity of these effects to be "mild" to "moderate." Only a small proportion of participants recalled having "severe" or "very severe" adverse effects. However, "severe fatigue" was reported by a higher proportion of males and females when compared with the other effects.

The majority of the adverse effects was reported by the younger cohorts (<45 years of age) irrelevant of their sex (Table 3). As a general trend, localised adverse effects were mostly reported following both doses of the vaccine, while systemic adverse effects mostly were experienced after the second dose (Table 3). Indeed, although the majority of the participants did not take any days off work following vaccination (71.89% CI 95%: 69.55-74.12), those that took days off predominantly did so following the second dose of the vaccine (83.25% CI 95%: 79.26-86.60; $P \leq .001$) and were more commonly females (78.07% CI 95%: 73.84-81.79; $P \leq .001$). All adverse effects were reported to have peaked following the first or the second day of the vaccine dose.

Multivariate logistic regression analyses linked females to a higher likelihood of adverse effects when compared with males, for localised pain at injection site (OR: 1.91 CI 95%: 1.34-2.72; $P \leq .01$), redness at injection site (OR: 2.49 CI 95%: 1.66-3.73; $P \leq .01$),

TABLE 2 Comparison of adverse effects severity among the study population and stratified by sex

	Adverse effects	Male (n = 493)	Female (n = 987)	Chi square
Pain at injection site	None	17.04%	8.11%	<0.001
	Mild	54.77%	40.43%	
	Moderate	25.56%	43.97%	
	Severe	2.64%	7.50%	
	Very severe	0.00%	0.00%	
Redness at injection site	None	93.10%	85.01%	<0.001
	Mild (2 to 5 cm in diameter)	5.68%	12.87%	
	Moderate (5 to 10 cm in diameter)	1.22%	1.72%	
	Severe (>10 cm in diameter)	0.00%	0.41%	
	Very severe (necrosis or exfoliation)	0.00%	0.00%	
Swelling at injection site	None	90.26%	83.79%	0.006
	Mild (2 to 5 cm in diameter)	8.11%	14.08%	
	Moderate (5 to 10 cm in diameter)	1.62%	1.93%	
	Severe (>10 cm in diameter)	0.00%	0.20%	
	Very severe (necrosis or exfoliation)	0.00%	0.00%	
Fever	None	73.23%	59.78%	<0.001
	Mild (38.0-38.4)	18.46%	25.94%	
	Moderate (38.4-38.9)	6.29%	11.25%	
	Severe (38.9-40)	2.03%	2.74%	
	Very severe (>40)	0.00%	0.30%	
Chills	None	67.14%	45.19%	<0.001
	Mild	17.85%	23.61%	
	Moderate	10.34%	21.78%	
	Severe	4.67%	9.32%	
	Very severe	0.00%	0.10%	
Fatigue	None	40.37%	20.36%	<0.001
	Mild	30.02%	30.60%	
	Moderate	22.52%	33.74%	
	Severe	7.10%	15.30%	
	Very severe	0.00%	0.00%	
Muscle pain	None	50.91%	39.31%	<0.001
	Mild	30.83%	27.05%	
	Moderate	14.81%	22.59%	
	Severe	3.25%	10.84%	
	Very severe	0.20%	0.20%	
Joint pain	None	78.09%	60.49%	<0.001
	Mild	13.18%	17.83%	
	Moderate	6.69%	14.29%	
	Severe	2.03%	7.09%	
	Very severe	0.00%	0.30%	

(Continues)

TABLE 2 (Continued)

	Adverse effects	Male (n = 493)	Female (n = 987)	Chi square
Headache	None	69.37%	48.94%	<0.001
	Mild	21.50%	23.91%	
	Moderate	7.10%	19.55%	
	Severe	1.83%	7.60%	
	Very severe	0.20%	0.00%	
Vomiting	None	99.19%	96.96%	0.054
	Mild	0.61%	1.72%	
	Moderate	0.20%	0.91%	
	Severe	0.00%	0.41%	
	Very severe	0.00%	0.00%	
Diarrhoea	None	96.15%	93.72%	0.324
	Mild	2.64%	4.15%	
	Moderate	0.61%	1.42%	
	Severe	0.61%	0.61%	
	Very severe	0.00%	0.10%	

TABLE 3 Reported adverse effects by age stratification and dose administration among the study population

		Age		
Adverse effect	Total N	18-44 years (%)	45+ years (%)	Chi square
Pain at injection site	1316	840 (63.83)	476 (36.17)	<0.001
Redness at injection site	182	97 (53.30)	85 (46.70)	0.016
Swelling at injection site	208	138 (66.35)	70 (33.65)	0.115
Fever	529	369 (69.75)	160 (30.25)	<0.001
Chills	703	491(69.84)	212 (30.16)	<0.001
Fatigue	1080	715 (66.20)	365 (33.80)	<0.001
Muscle pain	841	563 (66.94)	278 (33.06)	<0.001
Joint pain	498	325 (65.26)	173 (34.74)	0.031
Headache	655	440 (67.18)	215 (32.82)	<0.001
Vomiting	34	26 (76.47)	8 (23.53)	0.068
Diarrhoea	81	44 (54.32)	37 (45.68)	0.177

		Dose			
Adverse effect	Total N	First dose (%)	Second dose (%)	First and second doses (%)	Chi square
Pain at injection site	1294	430 (33.23)	219 (16.92)	645 (49.85)	<0.001
Redness at injection site	177	73 (41.24)	49 (27.68)	55 (31.07)	<0.001
Swelling at injection site	118	41 (34.75)	34 (28.81)	43 (36.44)	<0.001
Fever	524	52 (9.92)	419 (79.96)	53 (10.11)	<0.001
Chills	696	78 (11.21)	547 (78.59)	71 (10.20)	<0.001
Fatigue	1060	188 (17.74)	641 (60.47)	231 (21.79)	<0.001
Muscle pain	712	106 (14.89)	434 (60.96)	172 (24.16)	<0.001
Joint pain	491	77 (15.68)	360 (73.32)	54 (11.00)	<0.001
Headache	639	115 (18.00)	384 (60.09)	140 (21.91)	<0.001
Vomiting	31	6 (19.35)	21 (67.74)	4 (12.90)	0.07
Diarrhoea	80	14 (17.50)	55 (68.75)	11 (13.75)	<0.001

swelling at injection site (OR: 1.89 CI 95%: 1.33-2.69; $P \leq .01$), fever (OR: 1.74 CI 95%: 1.36-2.23; $P \leq .01$), chills (OR: 2.32 CI 95%: 1.83-2.94; $P \leq .01$), fatigue (OR: 2.43 CI 95%: 1.89-3.122; $P \leq .01$), muscle pain (OR: 1.54 CI 95%: 1.23-1.94; $P \leq .01$), joint pains (OR: 2.01 CI 95%: 1.61-2.69; $P \leq .01$), headaches (OR: 2.07 CI 95%: 1.63-2.63; $P \leq .01$) and vomiting (OR: 3.43 CI 95%: 1.18-9.84; $P = .02$) when adjusted for age and HCW role.

4 | DISCUSSION

By the time this study was conducted (April 2021), all HCWs were invited to take the vaccine, with approximately 90% acceptance rate. This demonstrates a low vaccination hesitancy among this group even if the occurrence of adverse reactions following Pfizer-BioNTech COVID-19 vaccine administration was reported by the Food and Drug Administration in early December 2020.[8]

Adverse effects were subdivided into localised or systemic adverse reactions while various degrees of severity were noted.[8] On comparing adverse effects reported by the manufacturer to those reported by this study's participants, similar trends and severities were noted.[9] Our results also coincide with other independent studies conducted among HCWs.[10,11] Indeed, similar to this study, the commonest reported adverse effect was mild-to-moderate pain at the injection site and mostly among the younger cohorts.[9] According to the manufacturer and other independent studies, fatigue and headaches were the second and third most common adverse effects, mostly following the second dose and again among the young cohorts.[9-11] In this study, we observed a slight variation to these reports. Whilst fatigue was the second commonest adverse effect among our cohort, muscle pains and chills were reported as more frequent adverse effects than headaches. However, on comparing the frequency of headaches, similar proportions were noted (this study: 44.26%; manufacturer: 40.06%; Riad et al: 45.6%; Kadali et al: 45.48%).[9-11] Another variation noted was the frequency of "severe fatigue" as an adverse effect. Our study cohort reported a much higher frequency (12.57%) of "severe fatigue" than that reported by the manufacturer (3.8%).[9] A unique finding in this study was the link between females and their susceptibility to all adverse effects (except diarrhea, potentially because of small numbers). This was not reported by the manufacturer, although a study conducted in Saudi Arabia established a comparative difference in frequency of adverse effects between females and males.[12] Sex differences in disease severity and susceptibility have been previously reported for autoimmune diseases, cancers and infectious diseases among other.[13,14] Indeed, females have higher morbidity and mortality susceptibility for influenza and HIV.[15] This has been reported to be a consequence of differences in endocrine and sex hormones that contribute to different immune responses between males and females, with an effect on disease susceptibility and vaccination outcome.[16] It has also been observed that females tend to mount greater vaccine immune responses than males.[16,17] Sex differences have also been noted to influence pharmacokinetics and pharmacodynamics, with females more susceptible to adverse effects. These effects have been linked to females' higher body fat content when compared with males, affecting the volume of distribution and clearance of drugs.[18,19] This may be another plausible explanation to this study's results. Another potential reason is different behavioural attitudes between females and males. In fact, it has been reported that females tend to report adverse effects more than males.[20]

4.1 | Study limitation and strengths

This was an observational survey that was distributed through electronic mail. Any HCW who did not access this platform or changed their address could not participate. Since participation in the survey was on voluntary basis and none of the survey questionnaires were mandatory, only motivated participants would have been inclined to fill in the entire survey. This may have resulted in some questions being skipped with lower response rates. The survey's responders are more likely to have experienced significant symptoms and felt obliged to participate and share their side effects, resulting in selection bias. Therefore, there is a possibility that the survey's results are not entirely representative of the whole HCW body. Additionally, self-reported bias and recall could have occurred, which might have compromised clinical evaluation and standardisation. However, since the participants were HCWs with a high level of health literacy and scientific motivation, it is expected that accurate adverse reactions were reported.

5 | CONCLUSION

Short-term adverse reactions of the Pfizer-BioNTech COVID-19 vaccine have now been established, with a proclivity for the female population and the younger ages. However, on weighing the benefits of vaccination against the risks of acquiring severe Covid-19 infection or development of what appears to be mostly mild to moderate short adverse effects following vaccination, the benefits greatly outweigh these risks. The general low vaccination adverse effects observed within the HCWs cohort is encouraging and should help in allaying vaccine hesitancy among the population. It is recommended that a follow-up study at 3-, 6- and 12-months intervals is carried out to note down longer term COVID-19 and vaccine adverse effects.

DISCLOSURE

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Cuschieri S, Borg M, Agius S, Souness J, Brincat A, Grech V. Adverse reactions to Pfizer-BioNTech vaccination of healthcare workers at Malta's state hospital. *Int J Clin Pract*. 2021;75:e14605. https://doi.org/10.1111/ijcp.14605