Vaccine 40 (2022) 5942–5949

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Side effects during the week after first dose vaccination with four Covid-19 vaccines. Results of the ProVaVac Survey Study with 13,837 people in Spain

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ARTICLE INFO

Article history:
Received 23 February 2022
Received in revised form 12 July 2022
Accepted 15 August 2022
Available online 29 August 2022

Keywords:
Covid-19
Vaccines
Side effects
Survey
Spain

ABSTRACT

Background: In 2021, four vaccines against Covid-19 (BNT162b2, mRNA-1273, ChAdOx1nCoV-19, and JNJ-78436735) were employed in the region of Valencia, Spain. We conducted a survey to identify real-world, self-reported frequency and severity of side effects during the week after vaccination.

Methods: Survey data was obtained from April 19, 2021, to October 6, 2021, at three different moments in time: day one, day three and day seven after vaccination. Answers were linked to individual-level, personal and clinical information. Respondents were stratified by the vaccine they received and reported effects were presented over time and stratified by severity. We compared our results per vaccine with the frequencies stated in each Summary of Product Characteristics (SmPC). We used binomial logistic models to identify associations between respondent characteristics and side effects.

Results: No symptoms were reported by 1,986 respondents (14.35 %), 6,254 informed exclusively mild symptoms (45.20 %), 3,444 up to moderate symptoms (24.89 %), and 2,153 people (15.56 %) notified also severe symptoms. Among the latter, the more frequent were extreme tiredness (7.0 %), and nausea or vomiting (7.1 %). The reported frequency of facial paralysis (0.4 %) was much higher than reflected in SmPCs. Female sex, younger age, previous positive Active Infection Diagnostic Test, chronicity, and vaccination with other than the BNT162b2 vaccine were associated to an increased risk of side effects ($p < 0.001$).

Conclusions: Side effects after vaccination are common in the real-world. However, they are principally mild, and their frequency declines after a few days. Providing patients with dependable, beforehand information about side effects may improve outcomes and reinforce vaccination programs.

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https://doi.org/10.1016/j.vaccine.2022.08.028
0264-410X/

1. Introduction

By the end of 2021, the European Medicines Agency (EMA) had authorized four Covid-19 vaccines for commercialization in the European Union (EU): Comirnaty (BioNTech-Pfizer, BNT162b2), Spikevax (Moderna, mRNA-1273), Vaxzevria (AstraZeneca, ChAdOx1nCoV-19) and the Covid-19 Vaccine Janssen (Janssen-Cilag, JNJ-78436735) [1]. All of them were tested in several clinical trials, meeting the EMA's scientific standards for efficacy, safety and quality, and their real-world safety is continuously monitored and evaluated through the EU EudraVigilance suspected adverse drug reactions database and other data sources that include pharmacoepidemiologic studies and surveys such as the CoVaST in the European Union [1,2] or the V-safe in the United States [2,3].

Local and systemic reactions, usually mild and transient but common after the administration of any vaccine, may have a negative impact on the perception of safety of those vaccinated and undermine vaccination programs. Given the pivotal importance of implementing successful Covid-19 vaccination programs for healthcare systems to overcome the pandemic challenge, many cross-sectional surveys have been carried out worldwide to inform about vaccine side effects [4–23]. Among these, good to high quality studies tend to converge in that side effects are common but rarely severe, and that some individuals may experience more side effects than others.

From a public health perspective, it is important to gain knowledge about the real-world occurrence of side effects after Covid-19 vaccination. Also, providing patients with dependable, beforehand information about the frequency and characteristics of these effects may help to adjust expectations and to reduce the potential anxiety associated with post-vaccine reactogenicity. With these objectives, by April 2021 the Valencia Government set up a region-wide survey within the framework of the ProVaVac Covid-19 vaccination studies program. The aim of the ProVaVac Survey Study was to identify the frequency and severity of side effects during the week after first dose vaccination against Covid-19 in the region of Valencia, and to identify factors associated to an increased risk of side effects.

2. Methods

2.1. Study design

Online, cross-sectional, self-report survey study with a voluntary sample of people over 12 years old that received their first dose vaccination with any of the four EU-authorized Covid-19 vaccines as of October 2021, within the Covid-19 Vaccination Program of the region. This study follows the guidelines of the STROBE Statement for cross-sectional studies [24].

2.2. Setting

The study took place in the region of Valencia, Spain. The Covid-19 vaccination program was carried out for the approximately 5 million inhabitants of the region, regardless of whether they had public health care coverage, by the Valencia Health System (VHS), an extensive network of public hospitals, primary healthcare centers and public health structures, which is part of the Spanish National Health System [25] and is funded and mostly provided by the Valencia Regional Government. The vaccination program began at the end of Dec 2020, starting with nursing home residents and healthcare workers, and following by age-strata from oldest to youngest scheduling appointments via Short Message Service (SMS). At the end of the campaign, 93 % of those over 11 years of age had been vaccinated (91 % fully vaccinated), with figures close to 100 % for those over 65 years of age.

2.3. Sample size

Sample size was not calculated in the design phase of this study, as the survey was conducted as part of an epidemiological surveillance program of the Valencia regional government and its primary purpose was not research. With regard to the accuracy of our estimates based on the number of respondents, for the main objective of the survey – to estimate the frequency of adverse events in the general population-, with a population of about 5 million inhabitants (equivalent to an infinite population), and considering a confidence interval of 99 %, our sample size of 13,837 participants provides estimates with a margin of error of less than 1 % (for instance, for events with a prevalence of 50 %, d = 0.01093) [26,27].

2.4. Data sources

Self-reported data obtained from the ProVaVac Survey were linked to individual-level data of the respondents, extracted from the Valencia Healthcare Integrated Databases (VID). VID is the result of the linkage, by means of a single personal identification number, of a set of publicly owned, population-based healthcare, clinical and administrative electronic databases in the region of Valencia. VID includes sociodemographic and administrative data as well as health and healthcare information, including microbiological results (results of any Covid-19 antigen or PCR test carried out in the region, including private laboratories), as well as the vaccination registry [28].

2.5. The ProVaVac survey

The ProVaVac survey, an ad-hoc, telematic, self-administered questionnaire, available in Spanish and Valencian (local language), was developed by an expert panel, and a web tool was designed by the Department of Health of the Valencia Government (see Supplementary Material Table S1). Respondents were asked to self-assess the intensity/severity (any, mild, moderate or severe) of a list of six side effects (discomfort in the injection arm / arm pain, headache, muscle pain, fever, tiredness, and cutaneous eruptions) as well as the presence or not of three additional side effects (loss of appetite, nausea or vomiting, and facial paralysis). A free-text field allowed the report of any additional side effect not included in the list. The survey was carried on following the Health Department data protection standards, and participants were asked to introduce their VID identification number and to verify their identity by confirmation SMSs sent to their mobile phones to enter the survey web tool. The survey took place from April 19, 2021, to October 6, 2021, (end of the mass vaccination campaign) and was planned to be repeated at three moments in time (day one, three and seven after vaccination), in order to observe the declination of the symptoms along time and to capture late side effects. Each of the three rounds of the survey only could be answered on the corresponding day (24 h window). In case of failing to respond to a survey on time, respondents were still allowed to answer to the next round.

2.6. Variables and outcomes

Survey data was linked using the single VID id number of each respondent to a set of clinical and socio-demographic individual-level data: type of vaccine used, age, sex, previous Active Infection Diagnostic Test (AIDT) with a positive result, country of origin, income in the previous year (using the thresholds used by the Spanish legal regulations to establish the pharmaceutical copayment brackets), and chronicity, a summary measure of individual

disease burden derived from the Clinical Risk Groups (CRGs) and stratified in 4 categories (0: healthy, 1: minor or single chronic disease, 2: chronic diseases with involvement of more than one organ systems, and 3: chronic dominant disease in three or more organ systems, active neoplasms, and severe conditions).

2.7. Ethics

The "ProVaVac Survey Study" was carried out under the epidemiological surveillance competences of the Valencia Regional Government (Law 10/2014, Dec 29 on Public Health of the region of Valencia), without requiring informed consent or ethics approval by an institutional review board. All participants authorized access to their personal data for the purposes of the study and all personal data were processed in accordance with the European data protection regulations and the Spanish laws on data protection.

2.8. Statistical analysis

First, the respondent population was stratified according to the vaccine received. Second, to compare the characteristics of the four groups, we used the Kruskal-Wallis test for differences in medians between groups and χ^2 tests for proportions. All p values, for both Kruskal-Wallis and χ^2 tests, were adjusted using Holm's method to avoid significance by chance derived by multiple comparisons. Holm's method adjusts the p values as following: let n be the number of tests performed, then the lowest p value is multiplied n times, the second lowest p value is multiplied n-1 times, and so on, until the second highest p value, which is multiplied twice, and, finally, the highest p value, which remains unadjusted [29]. Third, we described the frequency of reported side effects, graded by intensity where applicable and over time (day after, 3 and 7 days after). Fourth, we compared our findings to the frequencies stated in the Summary of Product Characteristics (SmPC) of each vaccine. Since in SmPCs, fever and slight fever side effects are differentiated; we split the responses to the survey with regard to fever into slight fever (reports of mild fever) and fever (responses of moderate and severe fever). Fifth, we used binomial logistic models to identify associations between patient characteristics and side effects. We used the Holm's method to provided adjusted significance estimators [29]. Finally, we conducted a sensitivity analysis using multinomial logistic model and compared these results to those of the binomial regressions. All analyses were performed using R 4.0.5 (R Core Team 2021) statistical software [30].

3. Results

A total of 13,837 individuals who received a first dose of the Covid-19 vaccine filled 29,122 surveys (10,134 in day one after vaccination, 9,201 in day three and 9,787 in day seven). All respondents filled at least one round of the survey. mRNA vaccines were the most prescribed -BNT162b2 (49.4 %) and mRNA-1273 (28.3 %)-, followed by JNJ-78436735 (18.3 %), and ChAdOx1nCoV-19 (4.0 %). Median age of respondents was 49 years old and 52.8 % were female; all groups were non-different ($p < 0.001$) except for ChAdOx1nCoV-19 (median age of 60 years old, 56.5 % male, $p < 0.001$). JNJ-78436735 was mainly prescribed to the 45–64 years old age group (81.9 % of administered JNJ-78436735 doses) whereas ChAdOx1nCoV-19 was devoted almost completely to the 45–64 yr. age group (99.5 % of ChAdOx1nCoV-19 doses). For mRNA vaccines, 87.6 % of BNT162b2 doses and 90.5 % of mRNA-1273 doses were used in patients younger than 65 years old. 8.0 % of the respondents had a positive AIDT result and 54.9 % had no comorbidity, 71.2 % were Spanish and 49.8 % earned less 18000 € (see Table 1).

3.1. Frequency and severity of side effects

Mild arm pain, the most reported side effect, was experienced by more than 50 % of respondents on day one after vaccination but less than 10 % on day seven. All side effects tended to decrease over the week after vaccination except eruption which was stable. No symptoms were reported by 1,986 respondents (14.35 %), 6,254

Table 1
Demographic characteristics of the study population.

	BNT162b2	mRNA-1273	ChAdOx1n CoV-19	JNJ-78436735	Adjusted p value *	Overall
Female (%	3675 (53·8%)	2069 (52·8%)	239 (43·5%)	1326 (52·2%)	0·0015†	7309 (52·8%)
Age median (IQR), yr.	48 (36–55)	41 (36–55)	60 (60–61)	50 (47–53)	< 0·0001†	49 (39–55)
Age distribution, yr (%)						
<45	2646 (38·7%)	2340 (59·7%)	0 (0·0%)	439 (17·3%)	< 0·0001†	5425 (39·2%)
45–64	3342 (48·9%)	1205 (30·8%)	546 (99·5%)	2079 (81·9%)		7172 (51·8%)
≥65	843 (12·3%)	373 (9·5%)	3 (0·5%)	21 (0·8%)		1240 (9·0%)
Positive Covid Test	567 (8·3%)	439 (11·2%)	31 (5·6%)	76 (3·0%)	< 0·0001†	1113 (8·0%)
Country of origin (%)						
Spain	4845 (70·9%)	2665 (68·0%)	434 (79·1%)	1906 (75·1%)	< 0·0001†	9850 (71·2%)
Europe	221 (3·2%)	98 (2·5%)	21 (3·8%)	52 (2·0%)		392 (2·8%)
Other countries	240 (3·5%)	198 (5·1%)	10 (1·8%)	85 (3·3%)		533 (3·9%)
Unknown	1525 (22·3%)	957 (24·4%)	84 (15·3%)	496 (19·5%)		3062 (22·1%)
Income, €/yr. ‡ (%)						
<18,000	3611 (52·9%)	1888 (48·2%)	266 (48·5%)	1125 (44·3%)	< 0·0001†	6890 (49·8%)
18,000–100,000	2666 (39·0%)	1656 (42·3%)	204 (37·2%)	1210 (47·7%)		5736 (41·5%)
>100,000	61 (0·9%)	48 (1·2%)	5 (0·9%)	32 (1·3%)		146 (1·1%)
Unknown	493 (7·2%)	326 (8·3%)	74 (13·5%)	172 (6·8%)		1065 (7·7%)
Chronicity § (%)						
0 Healthy	3693 (54·1%)	2272 (58·0%)	210 (38·3%)	1424 (56·1%)	< 0·0001†	7599 (54·9%)
1 Minor/Unique	2731 (40·0%)	1440 (36·8%)	267 (48·6%)	991 (39·0%)		5429 (39·2%)
2 Moderate/Severe	350 (5·1%)	183 (4·7%)	62 (11·3%)	108 (4·3%)		703 (5·1%)
3 Very High Risk	57 (0·8%)	23 (0·6%)	10 (1·8%)	16 (0·6%)		106 (0·8%)
Total n (%)	6831 (49·4%)	3918 (28·3%)	549 (4·0%)	2539 (18·3%)		13,837 (100·0%)

All percentages are presented as column-wise calculations except for the Overall row, where row-wise is performed.* p values using Kruskal-Wallis and $\chi 2$ tests, accounting for medians and proportions differences, respectively, were adjusted using Holm's method. † Significant difference between groups at $\alpha = 0.01$. ‡Unknown: mainly civil servants, subject to different co-payment system not associated with the income of the previous year. § Chronicity value from the Population Health Stratification System.

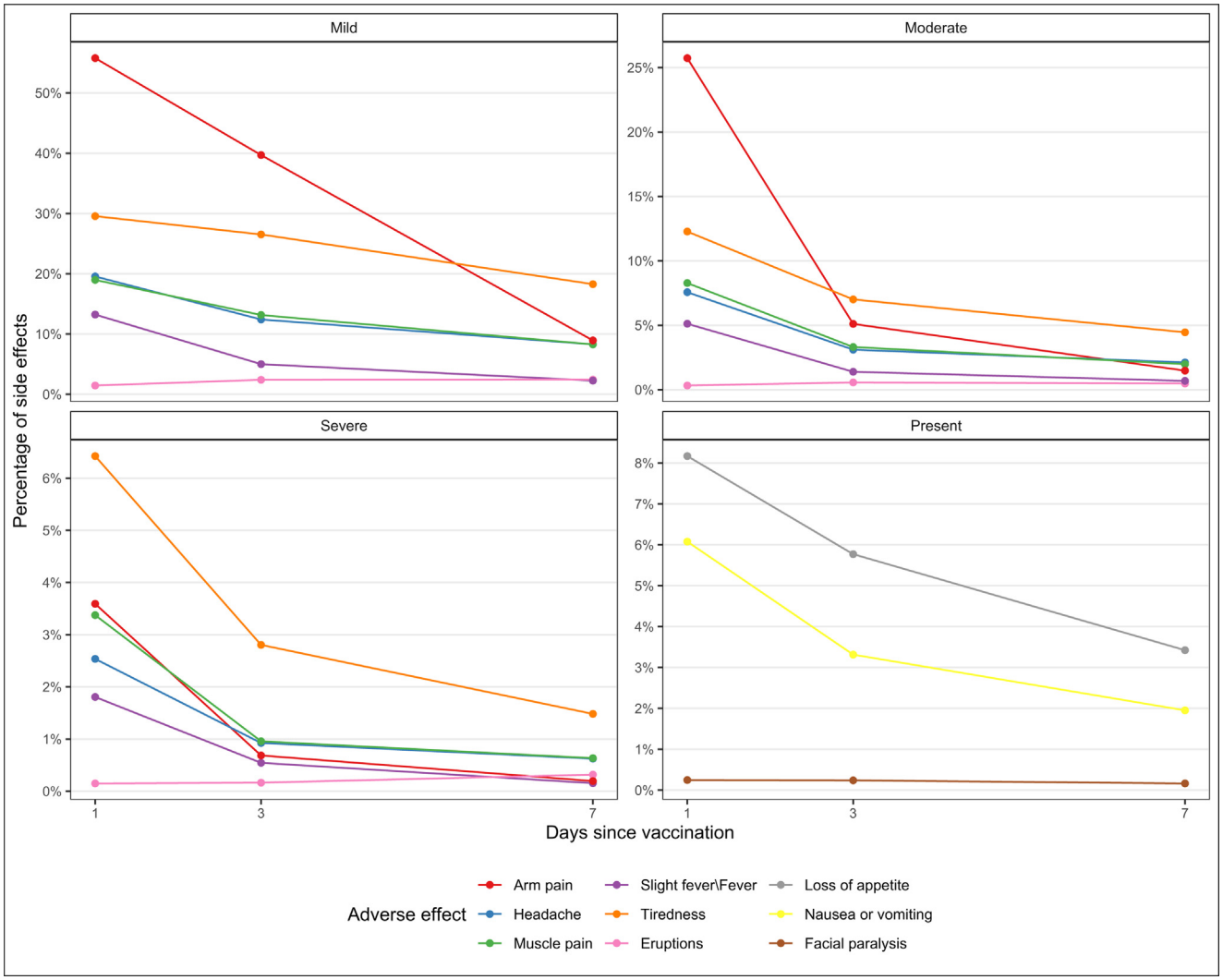

Fig. 1. Self-reported side effects after Covid-19 vaccination. Denominators are 10,134, 9,201, and 9,787 for days one, three and seven after vaccination, respectively.

informed exclusively mild symptoms (45.20 %), 3,444 up to moderate symptoms (24.89 %), and 2,153 people (15.56 %) notified also severe symptoms (see Fig. 1). Moderate and severe arm pain were reported by 23.7 % and 36.7 % of patients vaccinated with BNT162b2 and mRNA-1273, respectively, versus 11.3 % and 11.8 % with ChAdOx1nCoV-19 and JNJ-78436735, respectively ($p < 0.001$). Moderate to severe muscle pain and tiredness were less noted for mRNA vaccines (20.80 % and 29.5 % for ChAdOx1nCoV-19, 24.2 % and 33.7 % for JNJ-78436735, versus 6.9 % and 13.5 % for BNT162b2, and 11.3 % and 20.3 % for mRNA-1273; $p < 0.001$). Severe symptoms reporting was below 5 % for all side effects except for tiredness (7.0 %), and nausea or vomiting (7.1 %). Facial paralysis was informed by 0.4 % of respondents (see Table 2). Twenty-two additional side effects were recounted as free text, the more frequent being dizziness, reported by 469 patients (3.39 %) and somnolence (282 patients, 2.04 %; see Supplementary Material Table S2).

3.2. Comparison to SmPC risk data

Arm pain, headache, muscle pain, fever or low-grade fever, and tiredness are classified as "very frequent" (<10/100) in the SmPC of the four vaccines, which is overall consistent with our results (with the exception of feverish feeling, which was "frequent", <1/100, for mRNA vaccines). Eruption, which is classified as "rare" (<1/10,000) for ChAdOx1nCoV-19 and JNJ-78436735, was "frequent" for all vaccines in our survey. Nausea or vomiting is classified as "frequent" for BNT162b2 and "very frequent" for the rest of the vaccines, whereas our findings found "frequent" occurrence for all vaccines. Lateral facial paralysis appeared in the four groups and was "uncommon" (<1/1,000) in our setting, whereas it is reported as a "rare" event in SmPCs of mRNA vaccines and is not reported in adenovirus-based vaccines. Loss of appetite is tagged as "uncommon" in the case of ChAdOx1nCoV-19 vaccine but showed to be "very frequent" (see Fig. 2).

3.3. Associated patient factors

In binomial logistic regression models, female sex and vaccination with mRNA-1276 were associated to a higher risk of all side effects under analysis ($p < 0.001$; facial paralysis results are not included as no significant OR was found for any variable). Being younger than 65 years old was associated to an increased risk of all side effects but eruption ($p < 0.001$). Risk of side effects also increased in patients with positive AIDT or people vaccinated with other than BNT162b2 in six categories ($p < 0.001$) and chronicity increased risk in four categories over eight ($p < 0.001$, see Supplementary Material Table S3). For intensity-graded side effects (arm

Table 2
Vaccines side effects of the study population.

	BNT162b2	mRNA-1273	ChAdOx1n CoV-19	JNJ-78436735	Adjusted p value *	Overall
Arm pain (%)						
Any	5131 (75·1%)	3283 (83·8%)	346 (63·0%)	1706 (67·2%)	< 0·0001†	10,466 (75·6%)
Mild	3515 (51·5%)	1844 (47·1%)	284 (51·7%)	1404 (55·3%)		7047 (50·9%)
Moderate	1455 (21·3%)	1196 (30·5%)	56 (10·2%)	278 (10·9%)		2985 (21·6%)
Severe	161 (2·4%)	243 (6·2%)	6 (1·1%)	24 (0·9%)		434 (3·1%)
Headache (%)						
Any	1752 (25·6%)	1253 (32·0%)	241 (43·9%)	1190 (46·9%)	< 0·0001†	4436 (32·1%)
Mild	1247 (18·3%)	826 (21·1%)	158 (28·8%)	719 (28·3%)		2950 (21·3%)
Moderate	402 (5·9%)	319 (8·1%)	63 (11·5%)	322 (12·7%)		1106 (8·0%)
Severe	103 (1·5%)	108 (2·8%)	20 (3·6%)	149 (5·9%)		380 (2·7%)
Muscle pain (%)						
Any	1766 (25·9%)	1223 (31·2%)	275 (50·1%)	1239 (48·8%)	< 0·0001†	4503 (32·5%)
Mild	1291 (18·9%)	778 (19·9%)	161 (29·3%)	625 (24·6%)		2855 (20·6%)
Moderate	376 (5·5%)	318 (8·1%)	79 (14·4%)	409 (16·1%)		1182 (8·5%)
Severe	99 (1·4%)	127 (3·2%)	35 (6·4%)	205 (8·1%)		466 (3·4%)
Fever (%)						
Any	754 (11·0%)	780 (19·9%)	175 (31·9%)	960 (37·8%)	< 0·0001†	2669 (19·3%)
Mild	603 (8·8%)	494 (12·6%)	109 (19·9%)	544 (21·4%)		1750 (12·6%)
Moderate	124 (1·8%)	200 (5·1%)	47 (8·6%)	305 (12·0%)		676 (4·9%)
Severe	27 (0·4%)	86 (2·2%)	19 (3·5%)	111 (4·4%)		243 (1·8%)
Tiredness (%)						
Any	3094 (45·3%)	2120 (54·1%)	354 (64·5%)	1743 (68·6%)	< 0·0001†	7311 (52·8%)
Mild	2105 (30·8%)	1283 (32·7%)	192 (35·0%)	887 (34·9%)		4467 (32·3%)
Moderate	721 (10·6%)	542 (13·8%)	116 (21·1%)	501 (19·7%)		1880 (13·6%)
Severe	268 (3·9%)	295 (7·5%)	46 (8·4%)	355 (14·0%)		964 (7·0%)
Cutaneous eruptions (%)						
Any	279 (4·1%)	236 (6·0%)	26 (4·7%)	133 (5·2%)	0·0002†	674 (4·9%)
Mild	222 (3·2%)	156 (4·0%)	23 (4·2%)	97 (3·8%)		498 (3·6%)
Moderate	41 (0·6%)	54 (1·4%)	1 (0·2%)	21 (0·8%)		117 (0·8%)
Severe	16 (0·2%)	26 (0·7%)	2 (0·4%)	15 (0·6%)		59 (0·4%)
Loss of appetite (%)						
	474 (6·9%)	434 (11·1%)	82 (14·9%)	388 (15·3%)	< 0·0001†	1378 (10·0%)
Nausea/vomiting (%)						
	362 (5·3%)	332 (8·5%)	51 (9·3%)	240 (9·5%)	< 0·0001†	985 (7·1%)
Facial paralysis (%)						
	25 (0·4%)	18 (0·5%)	4 (0·7%)	10 (0·4%)	1·0000	57 (0·4%)

All percentages are presented as column-wise calculations. * p values from $\chi 2$ tests, for accounting proportions differences, have been adjusted using Holm's method. † Significant difference among groups at $\alpha = 0.01$.

pain, headache, muscle pain, fever, tiredness, and eruption), results of multinomial logistic regressions were, overall, comparable to those found in binomial analyses (see Supplementary Material, Table S4 and Figures S5 to S10) Fig. 3.

4. Discussion

In this population-based, three-round survey to identify the self-reported frequency and severity of side effects during the week after Covid-19 vaccination, we showed that side effects are common, but generally mild, and tend to disappear in a few days. Overall, potential side-effects risks described in SmPCs are consistent with our result with some exceptions, such as cutaneous eruption or loss of appetite which appear to be more frequent in our setting. More important, however, may be the rate of facial paralysis, with values greater than 1/1000, when it is only considered as a rare event in SmPCs, and only in mRna vaccines factsheets. This difference between clinical trial data and observational evidence on incidence of facial paralysis has been observed previously and merits attention [31].

We also found that some patients characteristics, notably younger age, female sex, and previous Covid-19 infection appear to be associated with increased risk of experiencing side effects. Our results are consistent to those of similar studies carried out in different settings, of varying quality and representativeness (although some are of high quality and included a vast number of respondents), where younger, female, and previously infected patients systematically report experiencing more side effects [4–16]. Other studies have not found associations between patient characteristics and side effects, but those come from less comparable settings or do not seem powered enough to draw reliable conclusions [17–23].

This study has some strengths. To our knowledge, this is the first work to address self-reported side effects of four widely used Covid-19 vaccines worldwide, and to provide results for the whole population, per vaccine, and in three moments of time during the first week after first dose vaccination in southern Europe. Also, we highlighted the differences between observed local risks and those stated in the SmPCs. In this way, our findings may be useful to optimize the accuracy of patient's information strategies in our setting. Finally, we aimed to include a large number of patients in the three rounds of the survey, allowing for the obtention of robust estimators and minimizing risk of bias.

It has also some limitations. First, our population is not representative of the general population of the region, therefore extrapolation of results should be made with caution. As older populations and essential workers were the first groups to be vaccinated in the country, by the time of the start of the survey most of the population over 70 years old was already vaccinated in our setting, resulting in a relatively young population of respondents in the ProVaVac survey. Second, other biases may be affecting our results, derived from the relatively limited number of respondents (when compared to the total number of people vaccinated for a first dose, which is, to date, roughly 90 % of the population), the digital breach (differences in access to communication technologies due to sociodemographic factors), or other artifacts, such as the difference in the percentage of use of vaccines by different

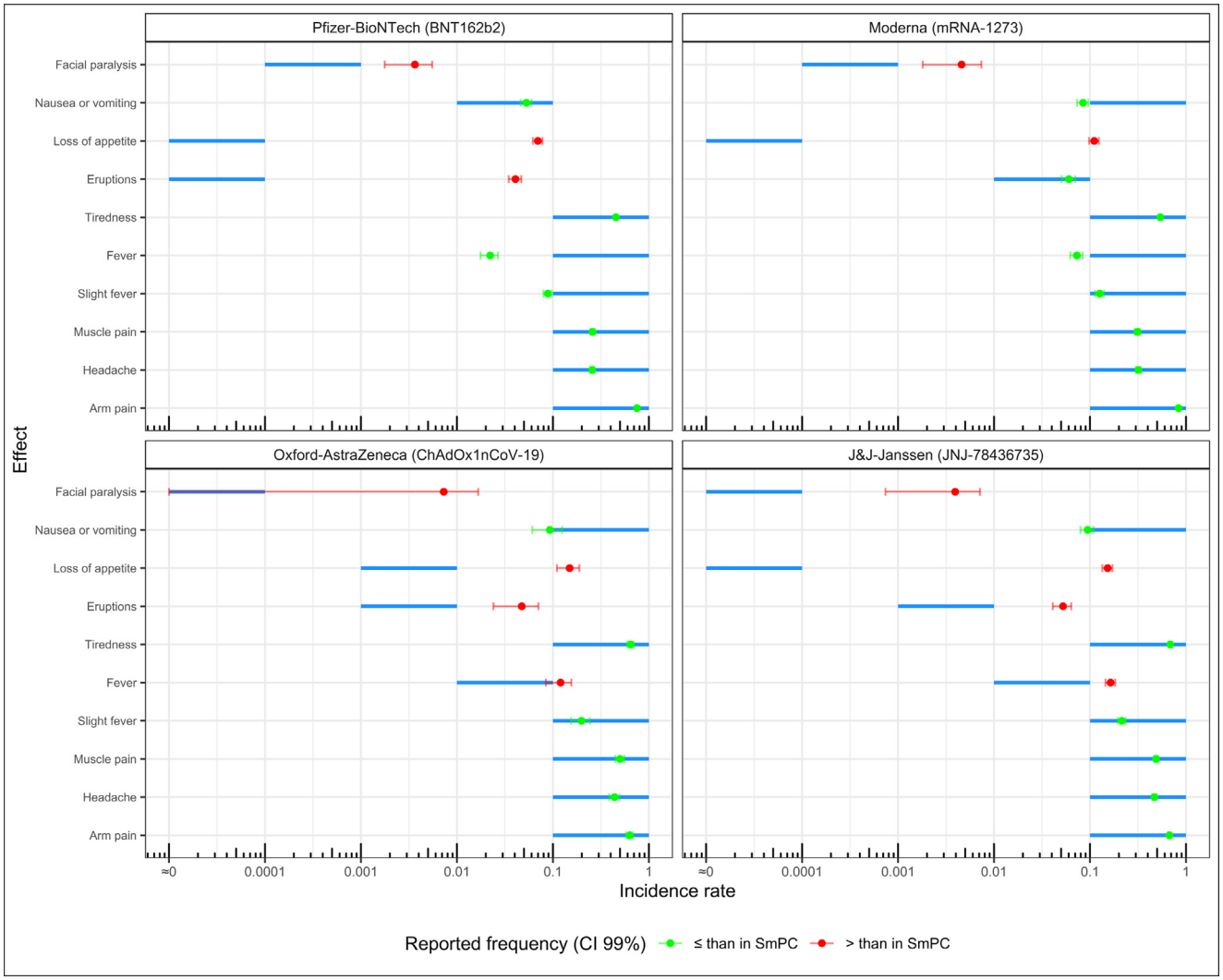

Fig. 2. Comparison between the risks in the Summary of Product Characteristics factsheets and the observed risks in ProVaVac.

age groups, resulting from national policy guidance allocating specific vaccines to specific age groups, or the different rate of positivity between age ranges, with younger people being more exposed to Covid-19 infection, and therefore more exposed to side effects after vaccination than older populations. Third, data from self-reported questionnaires are subject to potential lack of validity and reliability and may be affected by biases such as self-reporting bias, or social desirability bias, where respondents report higher or lower levels of side-effects based on subjective factors [32]. Recall and selective recall biases, usually present too in self-report studies, were minimized by allowing participants only 24 h to complete the survey. Fourth, not all the patients fulfilled the three rounds of the survey, resulting in incomplete longitudinal data. However, we had a large number of patients in each round and provided robust findings at day one, three and seven after vaccination.

Side effects after Covid-19 vaccination are frequent in our setting. Even if the symptoms are generally mild and transient, we found some noteworthy differences in the occurrence of some symptoms to of those reported in clinical trials. In combination with the identification of factors associated with a higher frequency of side effects, our findings may contribute to a better understanding of the impact of vaccination side effects in our population and to refining patient communication strategies, in order to improve patient outcomes and to ultimately reinforce vaccination programs.

Author contribution

Conceptualization: FS, IH, AG, SP, GS. Data curation: FH, IH. Formal analysis: FI, IH, SP. Funding acquisition: SP, DN. Investigation: all authors. Methodology: SP. Project administration: FS, IH, AG, SP. Software: LC. Supervision: SP, GS, AG, DN. Validation: all authors. Writing - original draft: AG. Writing - review and editing: all authors.

Funding

Project funded by Consellería de Sanitat Universal i Salut Pública (Generalitat Valenciana, Spain) and the EU Operational Program of the European Regional Development Fund (ERDF) for the Valencian Community 2014-2020, within the framework of the REACT-EU programme, as the Union's response to the COVID-19 pandemic.

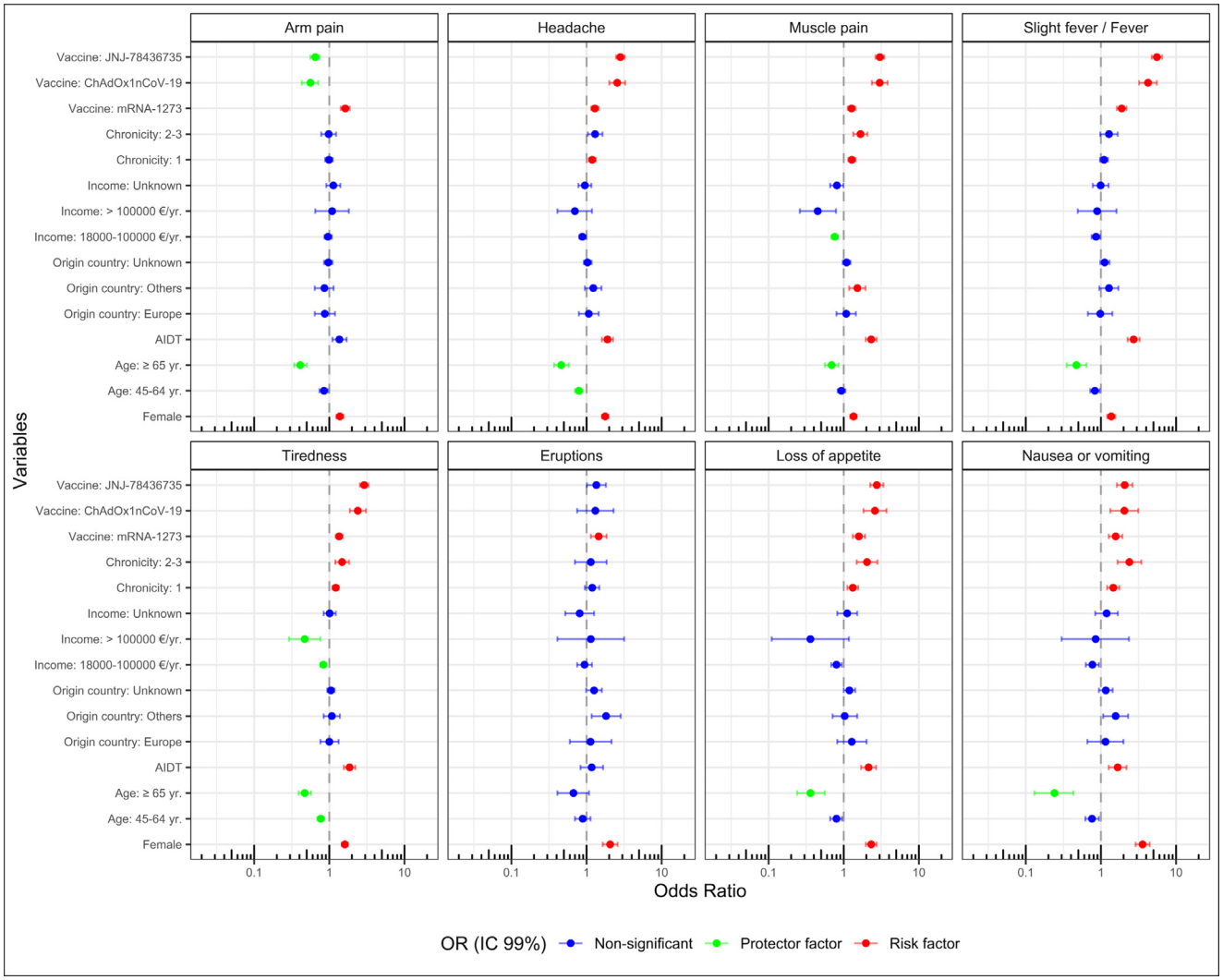

Fig. 3. Results of the binomial regression models. Forest plots showing the OR of respondent characteristic for each side effect. Reference values: Age = < 45 yr., Origin country = Spain, Income < 18000, Chronicity = 0, Vaccine = BNT162b2.

Access to data

Legal restrictions on sharing the data set apply as regulated by the Valencia regional government by means of legal resolution by the Valencia Health Agency [2009/13312] which forbids the cession of data to third parties (accessible at: https://www.san.gva.es/documents/152919/157920/resolucionsolicituddatos.pdf)Upon request, authors can allow access to the databases in order to verify the accuracy of the analysis or the reproducibility of the study. Requests to access the datasets should be directed to Management Office of the Data Commission in the Valencia Health Agency (email: solicitud_datos@gva.es; telephone numbers: +34 961-928207; +34 961-928198).

Data availability

The datasets presented in this article are not readily available because legal restrictions on sharing the data set apply as regulated by the Valencia regional government by means of legal resolution by the Valencia Health Agency [2009/13312] which forbids the dissemination of data to third parties (accessible at: http://www.san.gva.es/documents/152919/157920/resolucionsolicituddatos.pdf). Upon request, authors can allow access to the databases in order to verify the accuracy of the analysis or the reproducibility of the study. Requests to access the datasets should be directed to Management Office of the Data Commission in the Valencia Health Agency (email: solicitud_datos@gva.es; telephone numbers: +34 961-928207; +34 961-928198) Requests to access the datasets should be directed to "solicitud_datos@gva.es".

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.08.028.

References

[1] European Medicines Agency. Covid-19 vaccines: authorized. Available in: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-Covid-19/treatments-vaccines/vaccines-Covid-

19/Covid-19-vaccines-authorised#authorised-Covid-19-vaccines-section [accessed: October 18, 2021].
[2] Riad A, Schünemann H, Attia S, Peričić TP, Žuljević MF, Jürisson M, et al. Covid-19 Vaccines Safety Tracking (CoVaST): Protocol of a Multi-Center Prospective Cohort Study for Active Surveillance of Covid-19 Vaccines' Side Effects. Int J Environ Res Public Health 2021;18(15):7859.
[3] Centers for Disease Control and Prevention. V-safe protocol: version 3; 2021. Available in: https://www.cdc.gov/vaccinesafety/pdf/V-safe-Protocol-508.pdf [accessed: Sept 4, 2021].
[4] Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the Covid Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis 2021;21(7):939–49.
[5] Beatty AL, Peyser ND, Butcher XE, et al. Analysis of COVID-19 Vaccine Type and Adverse Effects Following Vaccination. JAMANetw Open 2021;4(12):. https://doi.org/10.1001/jamanetworkopen.2021.40364e2140364.
[6] Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA 2021;326(14):1390–9. https://doi.org/10.1001/jama.2021.15072.
[7] Kim T, Park SY, Yu S, Park JW, Lee E, Jeon MH, et al. Impacts of Side Effects to BNT162b2 and the First Dose of ChAdOx1 Anti-SARS-CoV-2 Vaccination on Work Productivity, the Need for Medical Attention, and Vaccine Acceptance: A Multicenter Survey on Healthcare Workers in Referral Teaching Hospitals in the Republic of Korea. Vaccines (Basel) 2021;9(6):648.
[8] Lee YW, Lim SY, Lee JH, Lim JS, Kim M, Kwon S, et al. Adverse Reactions of the Second Dose of the BNT162b2 mRNA Covid-19 Vaccine in Healthcare Workers in Korea. J Korean Med Sci 2021;36(21):e153.
[9] Bae S, Lee YW, Lim SY, Lee JH, Lim JS, Lee S, et al. Adverse Reactions Following the First Dose of ChAdOx1 nCoV-19 Vaccine and BNT162b2 Vaccine for Healthcare Workers in South Korea. J Korean Med Sci 2021;36(17):e115.
[10] Shay DK, Gee J, Su JR, Myers TR, Marquez P, Liu R, et al. Safety Monitoring of the Janssen (Johnson & Johnson) Covid-19 Vaccine - United States, March-April 2021. MMWR Morb Mortal Wkly Rep 2021;70(18):680–4.
[11] Kadali RAK, Janagama R, Peruru S, Malayala SV. Side effects of BNT162b2 mRNA Covid-19 vaccine: A randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers. Int J Infect Dis 2021;106:376–81.
[12] Izumo T, Kuse N, Awano N, Tone M, Sakamoto K, Takada K, et al. Side effects and antibody titer transition of the BNT162b2 messenger ribonucleic acid coronavirus disease 2019 vaccine in Japan. Respir Investig 2021;59(5):635–42.
[13] Jęśkowiak I, Wiatrak B, Grosman-Dziewiszek P, Szeląg A. The Incidence and Severity of Post-Vaccination Reactions after Vaccination against Covid-19. Vaccines (Basel) 2021;9(5):502.
[14] Klugar M, Riad A, Mekhemar M, Conrad J, Buchbender M, Howaldt H-P, et al. Side Effects of mRNA-Based and Viral Vector-Based COVID-19 Vaccines among German Healthcare Workers. Biology 2021;10(8):752. https://doi.org/10.3390/biology10080752.
[15] Dziedzic A, Riad A, Attia S, Klugar M, Tanasiewicz M. Self-Reported Adverse Events of COVID-19 Vaccines in Polish Healthcare Workers and Medical Students. Cross-Sectional Study and Pooled Analysis of CoVaST Project Results in Central Europe. J Clin Med. 2021;10(22):5338. Published 2021 Nov 16. doi: 10.3390/jcm10225338.
[16] Riad A, Pokorná A, Attia S, Klugarová J, Koščík M, Klugar M. Prevalence of COVID-19 Vaccine Side Effects among Healthcare Workers in the Czech Republic. J Clin Med 2021;10(7):1428. https://doi.org/10.3390/jcm10071428.
[17] Andrzejczak-Grządko S, Czudy Z, Donderska M. Side effects after Covid-19 vaccinations among residents of Poland. Eur Rev Med Pharmacol Sci 2021;25 (12):4418–21.
[18] Riad A, Pokorná A, Mekhemar M, Conrad J, Klugarová J, Koščík M, et al. Safety of ChAdOx1 nCoV-19 Vaccine: Independent Evidence from Two EU States. Vaccines (Basel) 2021;9(6):673.
[19] Al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, et al. Safety of Covid-19 vaccines. J Med Virol 2021;93(12):6588–94.
[20] Hatmal MM, Al-Hatamleh MAI, Olaimat AN, Hatmal M, Alhaj-Qasem DM, Olaimat TM, et al. Side Effects and Perceptions Following Covid-19 Vaccination in Jordan: A Randomized, Cross-Sectional Study Implementing Machine Learning for Predicting Severity of Side Effects. Vaccines (Basel) 2021;9(6):556.
[21] Mathioudakis AG, Ghrew M, Ustianowski A, Ahmad S, Borrow R, Papavasileiou LP, et al. Self-Reported Real-World Safety and Reactogenicity of Covid-19 Vaccines: A Vaccine Recipient Survey. Life (Basel) 2021;11(3):249.
[22] El-Shitany NA, Harakeh S, Badr-Eldin SM, Bagher AM, Eid B, Almukadi H, et al. Minor to Moderate Side Effects of Pfizer-BioNTech Covid-19 Vaccine Among Saudi Residents: A Retrospective Cross-Sectional Study. Int J Gen Med 2021;14:1389–401.
[23] Saeed BQ, Al-Shahrabi R, Alhaj SS, Alkokhardi ZM, Adrees AO. Side effects and perceptions following Sinopharm Covid-19 vaccination. Int J Infect Dis 2021;111:219–26.
[24] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61(4):344–9. PMID: 18313558.
[25] Martin-Moreno JM, Alonso P, Claveria A, Gorgojo L, Peiró S. Spain: a decentralised health system in constant flux. BMJ 2009;338:b1170.
[26] Cochran WG. Sampling Techniques. 2nd ed. New York: John Wiley and Sons Inc; 1963.
[27] Israel GD PEOD-6. In: Determining Sample Size. Institute of Food and Agricultural Sciences (IFAS), University of Florida; 2013. p. 1–5.
[28] García-Sempere A, Orrico-Sánchez A, Muñoz-Quiles C, Hurtado I, Peiró S, Sanfélix-Gimeno G, et al. Data Resource Profile: The Valencia Health System Integrated Database (VID). Int J Epidemiol 2020;49(3):740–741e.
[29] Holm S. A Simple Sequentially Rejective Multiple Test Procedure. Scand J Stat 1979;6:65–70.
[30] Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; 2021. https://www.r-project.org/.
[31] Cirillo N, Doan R. Bell's palsy and SARS-CoV-2 vaccines—an unfolding story. Lancet Infect Dis 2021;21:1210–1.
[32] Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. J Multidiscip Healthc 2016;9:211–7. https://doi.org/10.2147/JMDH.S104807. Published 2016 May 4.