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Predictors of moderate-to-severe side-effects following COVID-19 mRNA booster vaccination: a prospective cohort study among primary health care providers in Belgium

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Abstract

Background COVID-19 vaccine effectiveness declines months after vaccination. Therefore, it is likely that during the next few years, people may be repeatedly offered a booster vaccine to enhance humoral immunity levels. A growing number of people are questioning whether the benefits of a booster vaccine outweigh the side-effects.

Objective This study aims (1) to identify the most frequently reported side-effects after different doses of COVID-19 mRNA vaccines, (2) and the longest lasting symptoms; and (3) to predict the likelihood of having moderate-to-severe side-effects after a booster COVID-19 mRNA vaccine given individual- and vaccine-specific characteristics.

Design, setting, and participants Secondary analysis of a prospective cohort study in primary health care providers (PHCPs) in Belgium conducted between December 2020 and December 2021, and in February-March 2023.

Methods In nine subsequent surveys over a period of 2 years vaccine dose-number and side-effects after COVID-19 vaccines were collected. A Generalized Estimation Equations approach on the data of the first and second booster dose was used to investigate the probability of having moderate-to-severe side-effects after mRNA booster vaccination. Predictive performance of a binary classifier was assessed by looking at discrimination (i.e., quantified in terms of the area under the receiver operating characteristic curve). The final prediction model was validated using data with regard to the third booster by assessing misclassification rate, sensitivity and specificity.

Results In total, 11% of the PHCPs had moderate-to-severe side-effects after their booster COVID-19 mRNA vaccine. The most common side-effects of COVID-19 mRNA doses included fatigue, local pain at the injection site, general pains, and headache. These side-effects typically lasted for a median of 1 to 2 days. The final model included five predictors: sex, alcohol consumption, history of moderate-to-severe side-effects after any previous dose, recent COVID-19 infection, and the booster dose-number (first, second). Having experienced moderate-to-severe side-

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effects after any previous dose was the strongest predictor of moderate-to-severe side-effects following an mRNA vaccine booster, with an odds ratio (OR) of 3.64 (95% CI: 2.80–4.75). The OR for female sex was 1.49 (95% CI: 1.21–1.84) implying that females have a higher odds of moderate-to-severe side-effects following booster vaccination. The differences in effect for booster dose-number, alcohol consumption and recent COVID-19 infection was not significant.

Conclusion and relevance COVID-19 mRNA booster vaccination implies a low prevalence of moderate-to-severe side-effects among PHCPs, with a short median duration of symptoms if any. The strongest predictors are a history of moderate-to-severe side-effects after any previous dose and being female. These reassuring findings can help addressing concerns about booster vaccination and encourage their uptake.

Trial Registration NCT04779424 (registration date: 2021-02-22).

Keywords COVID-19, SARS-CoV-2 mRNA booster vaccine, Side-effects

Rationale

Vaccination plays a crucial role in preventing severe COVID-19, the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On December 21, 2020, the European Medicines Agency (EMA) granted the first conditional marketing authorisation for the Comirnaty vaccine, a messenger RNA (mRNA) vaccine developed by BioNTech and Pfizer [1]. In January 2021, a second mRNA vaccine, named Spikevax and developed by Moderna, received a conditional marketing authorisation in the EU [2]. As opposed to adeno-based vaccines, which were produced and licensed later on, the aforementioned vaccines contain mRNA that provides instructions to the body for generating the spike protein characterising SARS-CoV-2. As a consequence, the immune system will recognise the protein as foreign, and consequently produces antibodies and activate T-cells [1].

Initial large phase III placebo controlled randomized clinical trials (RCTs) in humans showed great vaccine efficacy (VE) of the primary vaccination course of two doses for both available mRNA vaccines, 94.1% for Spikevax (95% confidence interval (CI): 89.3–96.8%) and 95% for Comirnaty (95% credible interval: 90.3–97.6%), against symptomatic COVID-19 with onset measured at least seven days after the second dose [3–5]. However, the primary effectiveness of COVID-19 vaccines against infection and symptomatic disease declined by 20 to 30% points six months after vaccination [6]. The CHARMING study in primary health care providers (PHCPs) also showed waning of IgG antibodies in September 2021, i.e., six months or more after full vaccination with the primary vaccination course (i.e., a two-dose vaccination scheme for the aforementioned mRNA vaccines) [7, 8].

Based on humoral immunity levels in those PHCPs, the administration of a first booster vaccine was recommended in Belgium for PHCPs in November 2021. Vaccine effectiveness after the Comirnaty booster was 89.6% (95% CI: 88.6–90.4) and 95.3% (95% CI: 91.8–97.3) after the Spikevax booster. Four to five months after this first booster administration, vaccine effectiveness decreased to 46% (95% CI: 44–49%) against emergency department or urgent care visits [9]. Therefore, it is possible that PHCPs could be repeatedly offered a booster vaccine in the coming years to enhance their humoral immunity levels [10]. With the initiation of global COVID-19 booster vaccination campaigns, a growing number of people, including PHCPs, are questioning whether the benefits of a booster vaccine outweigh the side-effects [11].

In Belgium, the first booster campaign, conducted between September 2021 and February 2022, invited the entire adult population [12]. The second booster campaign, which started in September 2022, targeted individuals aged 50 and older, nursing home residents, and healthcare workers [13]. The total uptake of the first booster in individuals aged 18 and above was 72.65%, while the uptake of the second booster in individuals aged 50 and above was only 60.65% [14].

PHCPs play a pivotal role in improving vaccination rates for several reasons. In our study population, 14% of PHCPs expressed hesitancy toward taking the next booster, a trend also observed in other research [15–17]. This hesitancy is concerning, given the regular contact of PHCPs with vulnerable individuals and their influential role in vaccine promotion. A survey-based study revealed that 15% of unvaccinated individuals were more inclined to get vaccinated when recommended by their primary physician [18]. Concerns about safety are a major factor contributing to vaccine hesitancy [19].

The most prominent reported side-effects in the aforementioned trials included short-term, mild-to-moderate pain at the injection site, fatigue, headache, and muscle pains [3, 4]. Serious adverse events are infrequent in both trials, with a comparable occurrence among participants in both the vaccine and placebo groups. In the Comirnaty trial, adverse events were observed in 27% of the participants after the first two doses, and 21% after the third [4, 5]. In the Spikevax trial, adverse events were seen in 54.9% of the participants after the first dose, 79.4% after the second dose, and 21% after the first booster [20]. It

is noteworthy that in both vaccination schedules, side-effects are more prominent after administration of the second vaccination dose, and lower after the first booster dose [3, 5, 20].

Published and ongoing research have primarily focused on the safety of the initial regimen of two vaccines, and single booster doses [[3–5], [20–23]. As a result, there is a lack of data on side-effects following different doses within the same participants. National surveillance systems capture post-vaccination side-effects, like the voluntary smartphone-based system in the United States [24]. However, this system only records information for those reporting side-effects, making it difficult to estimate the likelihood of side-effects for any given individual receiving a COVID-19 mRNA vaccine.

The present paper aims at (1) identifying the most frequently reported side-effects after the different doses of COVID-19 mRNA vaccines, (2) and the longest lasting symptoms reported as side-effects following various administrations of COVID-19 mRNA vaccines; (3) predicting the likelihood of having self-perceived moderate-to-severe side-effects after a booster COVID-19 mRNA vaccine given individuals' characteristics (i.e. age, sex, comorbidities, smoking, alcohol consumption, recent COVID-19 infection) and vaccines' characteristics (i.e. interval-length between previous vaccination, number of previous doses of COVID-19 vaccines, history of side-effects after any of the previous COVID-19 vaccine doses).

Methods

Study design

In this study, we adhered to the "Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis" (TRIPOD) guideline for the development and reporting of the prediction model (Online Supplementary Table S1) [25]. The parent study is a prospective cohort study assessing the seroprevalence of SARS-CoV-2 in PHCPs in Belgium [7]. During a one-year follow up including eight measurements as part of the CHARMING study, information about the primary vaccination course (one or two doses) and the first booster dose were collected (December 2020 – December 2021) [7, 8]. In February–March 2023, one year after the eight testing timepoints (T1-T8), a ninth (T9) survey was sent to collect information about vaccination status, side-effects related to each vaccine received, recent COVID-19 infection and severity of symptoms, in the past year (Fig. 1).

This secondary analysis of the CHARMING study includes an additional survey conducted in February 2023 [7, 8]. Originally, participants measured SARS-CoV-2 antibodies at seven time points from December 2020 to December 2021, along with providing data on their vaccinations and side-effects. In February 2023, an additional survey was administered to the same participants to gather information on the booster doses they received in the past year and any associated side-effects.

Participants

Any general practitioner (GP) working in primary care in Belgium (including those in training) and any PHCP from the same practice who physically manages (examines, tests, treats) patients were eligible for the parent study. They were invited to register online for the study and were asked to invite the other PHCPs (e.g., nurses, dieticians, dentists, practice assistants, etc.) in their practice to do the same. Online registration was available between 15 November 2020 and 15 January 2021. Information about the study was disseminated via professional organizations (Domus Medica and Collège de Médecine Générale), university networks and through professional media channels. This convenience sample was checked for geographical representativeness by comparing the distribution of active GPs by Belgian region and by province 2020 (source: www.ima-aim.be) with the observed distribution of GPs. All participants were enrolled at T1 or T2 and were invited to participate in all subsequent measurement time points (T3-T8). At their initial testing, all participants were invited to participate in additional research, and those who agreed to be contacted again were subsequently contacted for the T9 survey.

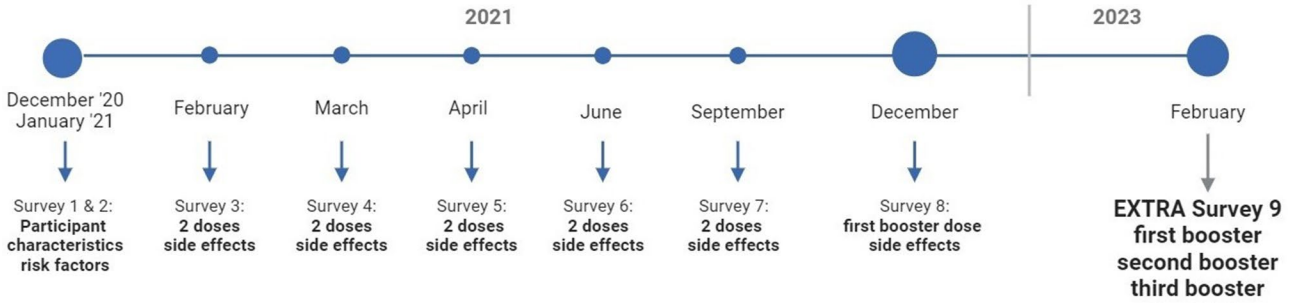

Fig. 1 Study design

Data collection

Data was collected in a secured online data capturing tool, LimeSurvey, hosted by Sciensano (LimeSurvey version 3.22, LimeSurvey GmbH, Hamburg, Germany). Participant characteristics, such as sex, age, comorbidities, smoking and alcohol consumption were collected once at their first testing timepoint (T1 or T2, December 2020 - January 2021). At each testing timepoint participants were questioned about the period since the last testing timepoint. Participants were asked about the date and type of their last vaccination, the self-perceived severity of side-effects *(Question: Did you experience side-effects after receiving the … dose?", response options none/negligible/mild/moderate/severe)*. Presence of specific symptoms (pain at the injection site, fever, general pains, headache, fatigue, nausea, allergy, dyspnea, and cough), and number of days of these specific symptoms were only asked for when they indicated moderate or severe side-effects (see Supplementary Materials: Survey testing timepoint T9). Local pain at the injection site and nausea were not asked at the nineth testing timepoint (T9) and therefore not available for the second and third booster. On the other hand, information on presence of cough and dyspnea was only collected at T9 and is therefore not available for any of the other vaccine doses.

Data management and statistical analysis

Data management

We generated new variables at each timepoint. Participants were classified as having comorbidities if they responded "yes" to the question, "Do you have one or more chronic diseases?". Participants were considered to have had moderate-to-severe side-effects if they reported moderate or severe side-effects after a specific dose. Having a history of side-effects at subsequent testing timepoints was assigned if they reported moderate-to-severe side-effects at any prior timepoint. Additionally, we labelled recent COVID-19 infection as 'Yes' when the time interval between the reported COVID-19 diagnosis and the administered dose was less than six months. Participants who answered "I do not know" about the severity of side-effects were categorized as not experiencing moderate-to-severe side-effects. They reported the number of the dose they received at the timepoint of data collection. To calculate the interval length between two consecutive doses, we considered the time elapsed between the previously reported dose and the current one.

When no information was available for a specific dose, this information was considered missing. The extent of missing participant-specific covariate information (i.e., for sex, age, comorbidities, smoking, alcohol consumption, interval-length, dose, recent COVID-19 infection) was quantified per variable. A study of the missingness pattern involved an investigation of the association between observed covariate information and the probability of missingness of covariates and outcome [26]. Multiple imputation with Chained Equations (MICE), providing valid inference under missing at random, was considered using the MICE package in R (version 3.15.0). More specifically, multiple imputed datasets were generated with the final number of imputations (i.e., $M=5$) used based on the stability of the model coefficients when adding an extra imputed dataset.

After multiple imputation, the imputed datasets were divided into training datasets, which comprised the first and second booster dose information, and validation datasets which comprised information about the third booster. In the validation datasets only the PHCPs who reported a third booster were selected. Imputation-specific results were pooled relying on Rubin's rules for quantities on the original or log-transformed scale to comply with the underlying assumption of asymptotic normality of the statistic under study [27].

Statistical analysis

To describe characteristics of the participants we used proportions and absolute frequencies for categorical variables, and medians and inter-quartile ranges (IQR: Q1–Q3) for continuous variables. The most frequently reported symptoms after the different doses of COVID-19 mRNA vaccines among people reporting moderate-to-severe side-effects are presented as proportions. The duration of those side-effects (in number of days) is graphically depicted as a boxplot.

A generalized estimating equations (GEE) approach for the binary outcome (i.e., presence or absence of moderate-to-severe side-effects) was considered for the training data. We used this approach to predict the probability of moderate-to-severe side-effects after mRNA COVID-19 booster doses given a set of determinants. This method accounts for association in participant-specific outcome values at different timepoints [28].

To identify predictors of moderate-to-severe side-effects following mRNA COVID-19 booster vaccines, we initially assessed multicollinearity using generalized variance inflation factors [29]. We then examined each potential predictor individually, using Wald-tests in each imputed dataset to test for significance. Variables with p-values <0.15 in the majority of the imputed datasets were included in the multivariable analysis [30]. The selection of a working correlation structure for the GEE approach and a backward variable selection procedure to arrive at the final model were based on the quasi-log-likelihood under the independence model information criterion (QIC) [31, 32]. In the multivariable model we used two-sided testing at a 5% significance level.

Table 1 Characteristics of all participating primary health care providers (PHCPs)

	All PHCPs* (n = 3376)
Sex, n (%)	
Female, n (%)	2267 (67)
Male, n (%)	1107 (33)
Missing	2
Age, median (IQR)	39 (30–53)
Missing	57 (2)
Comorbidities n (%)	
Yes	606 (18)
No	2692 (80)
Missing	76 (2)
Profession, n (%)	
General practitioner (GP)	2856 (78)
Other	520 (22)
Missing	0
Smoking, n (%)	
Ex-smoker	335 (10)
Never smoked	2850 (84)
Smoker	113 (3)
Missing	76 (2)
Alcohol consumption (glasses/ week), n (%)	
None	870 (26)
1 to 5	1779 (53)
6 to 10	452 (13)
10 to 15	148 (4)
16 to 20	33 (1)
> 20	18 (1)
Missing	76 (2)

* All PHCPs who filled in at least one survey

IQR: first quartile – third quartile

The presence of effect modification was studied through inclusion of pairwise interaction terms in models with two independent variables. Such interactions were retained in the multivariable analysis when Wald-based p-values were smaller than 0.15 in the majority of the imputations.

Discrimination was assessed by the area under the receiver operating characteristic curve (AUC) (0.5 indicates no discrimination −1.0 indicates perfect discrimination) on all imputed datasets. AUCs were combined using Rubin's rules. The Youden index was used to identify the threshold that maximizes the both sensitivity and specificity. In addition, we reported the pooled misclassification rate, sensitivity and specificity of the prediction model.

The prespecified threshold was used to validate the prediction model on the test data. The accuracy of the prediction model was evaluated using a 2×2 contingency table, and corresponding misclassification rate, sensitivity, and specificity.

Table 2 Distribution of side-effects for the different doses of mRNA vaccines

	Primary vaccination		Booster doses		
Side-effects n (%)	**Dose 1** ***n*** **= 2755**	**Dose 2** ***n*** **= 2711**	**Dose 3** ***n*** **= 2309**	**Dose 4** ***n*** **= 1304**	**Dose 5** ***n*** **= 122**
No	845 (31)	640 (24)	611 (26)	607 (47)	64 (53)
Negligible	1300 (47)	880 (32)	834 (36)	377 (29)	34 (28)
Mild	444 (16)	682 (25)	583 (25)	193 (15)	20 (16)
Moderate	154 (6)	472 (17)	258 (11)	108 (8)	3 (2)
Severe	12 (0)	37 (14)	23 (0)	13 (1)	1 (1)
I do not know*	NA	NA	NA	6	0
Missing	NA	NA	NA	NA	NA

* 'I do not know' was only provided as an answer option at T9 and therefore not applicable for dose 1, 2 and 3

Finally, a sensitivity analysis was performed on the complete data only to assess the robustness of our findings.

Software

All statistical analyses were performed with R, version 4.2.3.

Results

Overall, 3376 participants completed at least one survey (T1-T9), with the majority being female (67%) and GP (84%), and having a median age of 39 (IQR: 30–53) years (Table 1). Since only 549 out of the 7.2 million administered booster doses in Belgium were different from mRNA vaccines, unknown booster brands were considered to be mRNA as well [33]. A total of 3096 participants reported information on side-effects after one or more mRNA COVID-19 vaccines, of which 2309 participants reported this after a first mRNA booster dose (dose 3), 1304 after a second (dose 4), and only 122 after a third dose (i.e., dose 5) (see Table 2).

Fatigue, local pain at the injection site, general pains and headache are the most frequently reported symptoms across all mRNA COVID-19 vaccine doses among participants who reported moderate-to-severe side-effects (Fig. 2). Fatigue was reported in 84%, 92%, 89%, 78%, and 100% of participants reporting moderate-to-severe side-effects after the first, second, third, fourth, and fifth dose, respectively (Table 3). Local pain at the injection site in 95%, 88%, and 76% of the participants after the first three doses. General pains were observed in 73%, 78%, 78%, 81%, and 100%, respectively of the participants with moderate-to-severe side-effects, and headache in 75%, 77%, 79%, 65%, and 75%, respectively. Observed symptom prevalence after the fifth vaccine dose are only based on 4 participants with moderate-to-severe side-effects out of a total of 122 individuals.

In individuals who reported moderate-to-severe side-effects, the most persistent symptoms after the first three

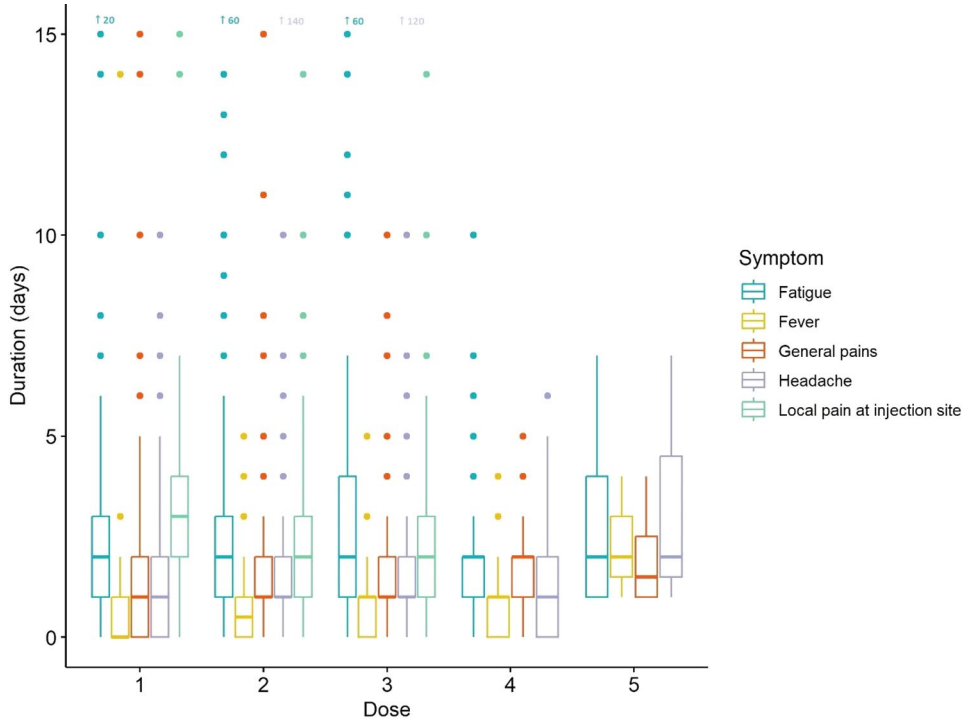

Fig. 2 Boxplot of duration (expressed in days) of moderate-to-severe symptoms for the different doses of COVID-19 mRNA vaccines

Table 3 Number of participants with moderate-to-severe symptoms after different doses of COVID-19 mRNA vaccines

	Primary vaccination		Booster doses		
Total participants	**Dose 1 n = 2755**	**Dose 2 n = 2711**	**Dose 3 n = 2309**	**Dose 4 n = 1304**	**Dose 5 n = 122**
Moderate-to-severe side-effects n (%)*	166 (6)	509 (19)	281 (12)	121 (9)	4 (3)
Pain at injection site**	158 (95)	451 (88)	213 (76)	NA	NA
Fatigue	139 (84)	466 (92)	251 (89)	94 (78)	4 (100)
General Pains	122 (73)	399 (78)	218 (78)	98 (81)	4 (100)
Fever	70 (42)	253 (50)	178 (63)	71(59)	3 (75)
Headache	124 (75)	390 (77)	221 (79)	79 (65)	3 (75)
Nausea	39 (23)	131 (26)	77 (27)	NA	NA
Allergies	4 (2)	10 (2)	3 (11)	NA	NA
Dyspnee	NA	NA	NA	9 (7)	0
Cough	NA	NA	NA	8 (6)	0

* percentage of participants with moderate-to-severe side-effects following the specific dose

** percentage of participants who reported this symptom among participants who indicated their symptoms to be moderate-to-severe

doses were fatigue and pain at the injection site (Fig. 2). The median duration of fatigue was similar across the five subsequent doses, lasting for 2 days. The median number of days of pain at the injection site was also similar, lasting three days after the first, and two days after the second and third dose. This symptom was not asked for after the fourth and fifth dose.

Only moderate-to-severe symptoms with a median duration of more than one day are presented in the boxplot. to ensure an accurate visualization of the data. Duration of moderate-to-severe side-effects after the fifth dose are only based on the report of 4 individuals. Values of single outliers characterized by extreme values are indicated with an arrow.

Missing data

The percentage of missing values ranged from no missing information for sex, to 2% for other participant characteristics (Table 1), up to 65% for the interval-length between dose 3 and 4.

Determinants of moderate-to-severe side-effects after a booster COVID-19 mRNA vaccine

Participants reported moderate-to-severe side-effects for 11% (406 out of 3735) of the booster doses. Univariable analyses show an association between the outcome and female sex, alcohol consumption, a recent COVID-19 infection, a history of side-effects after any of the previous COVID-19 vaccines, and booster dose in the majority of the imputed datasets (≥3) (see Table S2). No significant interaction terms were identified.

After model building, the final model for predicting the presence of moderate-to-severe side-effects after a booster COVID-19 mRNA vaccine included five independent predictors: sex, alcohol consumption, recent COVID-19 infection, history of side-effects after any of

the previous COVID-19 vaccines, and booster dose-number. Among these predictors, the strongest predictor of moderate-to-severe side-effects was a history of side-effects after any previous dose, with an estimated adjusted odds ratio of 3.64 (95% CI: 2.80–4.75). Adjusting for alcohol consumption, booster dose, and history of side-effects, women showed a 1.49 times higher odds of experiencing side-effects compared to men (95% CI: 1.21–1.84). The adjusted odds ratio for experiencing moderate-to-severe side-effects did not decrease significantly with the next booster dose. For the increase of one dose, the adjusted odds ratio was 0.80 (95% CI: 0.63–1.02). No significant effect was observed between different categories of alcohol consumption (see Table 4) nor for a recent COVID-19 infection (aOR 0.81, 95%CI: 0.47–1.39).

As the effect of the number of booster doses will cease, we included a final model without booster dose in the supplementary materials (Table S3).

Table 4 (Adjusted) odds ratios of having moderate-to-severe side-effects after a COVID-19 booster vaccination using Rubin's rules on the estimates of M = 5 imputed datasets

Predictors	Final model	
	aOR (95% CI)*	**p-value**
Participant		
Sex		
Male	Ref	
Female	1.49 (1.21–1.84)	**< 0.001**
Alcohol consumption (glasses/week)		
No alcohol	Ref	
1–5	1.17 (0.88–1.54)	0.302
6–10	0.74 (0.41–1.33)	0.345
10–15	1.037 (0.52–2.06)	0.918
≥ 16	1.41 (0.56–3.52)	0.469
Recent COVID-19*		
No	Ref	
Yes	0.81 (0.47–1.39)	0.469
Vaccine		
Booster dose + 1	0.80 (0.63–1.02)	0.103
History of side-effects after any previous dose		
No	Ref	
Yes	3.64 (2.80–4.75)	**< 0.001**

We used a Generalized Estimating Equations (GEE) approach for the selection of determinants in the multivariable model. First, determinants were considered for inclusion if they demonstrated statistical significance on the univariable Wald-test ($p < 0.15$) in the majority of the imputed datasets (≥ 3) (see Table S3). The final model was selected based on the optimization of the quasi-log-likelihood under the Independence Model Information Criterion (QIC). Two-sided testing was used in the final model at a 5% significance level, p-values less than 0.05 are highlighted in bold

* adjusted odds ratios (aOR) and 95% confidence intervals

** a reported COVID-19 infection in the six months before their reported booster COVID-19 vaccine

Model performance and validation

The model fit (calibration) to the imputed datasets demonstrated a moderate ability to separate individuals with and without moderate-to-severe side-effects after booster vaccination, with an AUC value of 0.71 (95% CI: 0.70–0.72). The Youden index threshold of our model is 0.119 with a sensitivity of 57% and a specificity of 76%. The performance of each of the imputed datasets separately is included in the online supplementary material (Figure S1).

External validation of our prediction model in the imputed datasets containing participants who reported a third booster dose, showed a pooled misclassification rate of 14% with a sensitivity of 65% and a specificity of 87%. The majority (92%) of the misclassified participants did have moderate-to-severe side-effects while our prediction model could not identify them as being at risk for moderate-to-severe side-effects.

Sensitivity analysis

In the complete case analysis, sex, history of side-effects after any of the previous doses, and alcohol consumption are associated with moderate-to-severe side-effects after COVID-19 booster vaccines (Online Supplementary Table S4). In this analysis, no significant differences in probability of moderate-to-severe side-effects between different booster doses were found.

Discussion

Summary of the findings

In our study population of PHCPs, we found that the most frequently reported side-effects are similar across COVID-19 mRNA doses with fatigue, local pain at the injection site, general pains, and headache most frequently reported. The median duration of those side-effects is similar across booster doses with most symptoms lasting for a median of 2 days.

The prediction model includes five predictors: sex, alcohol consumption, recent COVID-19 infection, history of moderate-to-severe side-effects after any of the previous COVID-19 vaccines, and the booster dose (first or second). Participants reported moderate-to-severe side-effects for 281 of the 2309 first boosters (12%), and 121 of the 1304 s boosters (9%). The strongest determinant in experiencing moderate-to-severe side-effects following a booster COVID-19 vaccine is having previously reported moderate-to-severe side-effects after one of the earlier COVID-19 vaccine doses with an adjusted odds that is 3.6 times higher. Women are 1.49 times more likely to experience moderate-to-severe side-effects after booster COVID-19 vaccines. The other determinants in the final predictive model (e.g., booster dose, a recent COVID-19 infection and alcohol consumption) showed no statistically significant effect on the probability of

moderate-to-severe side-effects when included in the multivariable model.

Comparison with existing literature

Frequencies of side-effects after COVID-19 booster vaccines were previously investigated among healthcare workers in Saudi Arabia, in a convenience sample in Greece, and in Pfizer's placebo-controlled trial [5, 34, 35]. However, we must exercise caution when comparing relative frequencies in our study to those reported in other studies, as in our analysis we focus on the frequency of side-effects among those participants reporting moderate to severe side effects.

Several studies have investigated risk factors that increase the likelihood of experiencing side-effects after the first two doses of COVID-19 vaccines. These factors include younger age, female sex, vaccine dose, brand of vaccine, a past COVID-19 infection, and severity of those symptoms, all of which have been found to be associated with the occurrence of side-effects [23, 36–38]. To our knowledge, only one study reported risk factors associated with experiencing side-effects after the booster dose. This study found a positive association of side-effects with female sex, younger age, and brand of the vaccine [35]. In our study, we did not find an association between age and side-effects. Consistent with existing literature, we found a strong association of our outcome with female sex, and a weak association with vaccine dose, and a recent COVID-19 infection. None of the aforementioned papers looked at a possible association with alcohol consumption and history of side-effects after any of the previous doses. In our longitudinal study, experiencing moderate-to-severe side-effects after one of the previous doses is a strong determinant.

Strengths and limitations

Our study provides a comprehensive examination of the probability of experiencing moderate-to-severe side-effects following COVID-19 booster doses, considering patient -and vaccine characteristics. The model incorporates a wide range of potential predictors, offering valuable insights into key determinants of side-effects.

A significant strength lies in the substantial dataset, comprising side-effects data reported by 3096 PHCPs. From this study population a more objective evaluation is to be expected compared to the general public. Additionally, having longitudinal data on the same individuals across multiple doses enables us to assess the impact of the booster dose and the influence of a history of side-effects after any of the previous doses. Notably, we are the first to report the substantial influence of a history of side-effects on future risk of side-effects after COVID-19 booster doses.

Our study provides a precise assessment of the risk of side-effects following booster doses of COVID-19 mRNA vaccines. Our prognostic model relies on only four predictors: sex, history of side-effects after any of the previous doses, booster dose, and alcohol consumption. Furthermore, with this externally validated predictive model, we offer detailed insights into the specific impact of each predictor on the likelihood of having moderate-to-severe side-effects after COVID-19 booster doses.

Several limitations must be acknowledged. First, a part of the study involves a retrospective analysis of a prospectively collected cohort, where data were not exclusively gathered for this specific investigation. Consequently, detailed information regarding mild side-effects is lacking. This influenced our decision to focus on moderate-to-severe side-effects. This limitation hinders our ability to assess the overall incidence rates of side-effects within our study population. Moreover, participants were limited to the predefined side-effects presented in the questionnaire. However, we did include an "other" option for responses, yet consistent answers were not identified alongside the provided symptoms.

Second, a substantial time gap exists between the eight measurement of the original study and the ninth, conducted for this research. Consequently, a significant number of participants provided information about their fifth dose while omitting details about their fourth dose. This has led to a lack of interval-length information for the third booster dose and necessitated the use of multiple imputation techniques. Furthermore, the extended time interval between the fourth and fifth dose surveys introduced the potential for recall bias in reporting side-effects.

Third, maximum likelihood-based model selection methods cannot be used to select variables in GEE models. We used QIC to select a correlation structure for the model and for backwards selection for the final model. This is less optimal than using the Correlation Information Criterion (CIC) which could be addressed in the future [31, 39].

Fourth, it is important to note that we cannot establish a definitive causal relationship between the reported side-effects and the vaccines. This limitation arises from several factors. Firstly, the surveys were conducted days to months after their last vaccine, making it challenging to attribute the reported side-effects exclusively to the vaccines. Additionally, we lack information regarding participants' mental health status and other potential past infections, which could have influenced the occurrence of those symptoms. However, it is worth mentioning that the side-effects reported in the questionnaire align with those documented in the existing literature.

Fifth, we acknowledge the reducing response rate to our surveys over the first eight time points, which may

introduce selection bias, potentially limiting the generalizability of our findings. For T9, only those PHCPs who consented to further contact were included, further contributing to potential selection bias. Additionally, as our study aim deviates from the primary focus for which the participants were initially enrolled, the reduced response rate at T9 could affect the results. Particularly if those experiencing fewer and less severe side-effects were less likely to respond (over time), the probability of moderate-to-severe side-effects is overestimated and such selection bias may result in biased estimates of the effect of predictors on the probability of moderate-to-severe side-effects after different vaccine doses.

The last important possible limitation is the subjective nature of assessing side-effect severity. The participants were asked to report the severity of their self-perceived side-effect using response options (none, negligible, mild, moderate or severe) that were not further defined in the survey. Experts caution that risk factors for side-effects may be difficult to generalize between different vaccines and even between doses of the same vaccine (P Van Damme, personal communication, 2023). Our finding, that a history of moderate-to-severe side-effects has a major influence on future side-effects, may be influenced by participants' perceptions.

Interpretation and implication of the results

COVID-19 booster vaccines may potentially be administered seasonally. Vaccine hesitancy often arises due to concerns regarding side-effects [40]. The significance of this study lies in its contribution to understanding the factors that influence the occurrence of moderate-to-severe side-effects following COVID-19 booster vaccination. The low prevalence of moderate-to-severe side-effects and short duration of those symptoms can be used to communicate to hesitant people and health care providers. In our population of PHCPs we found during the nineth measurement that even 14% of them would not take a next booster dose [17].

Given our emphasis on primary healthcare providers, who generally have a younger age profile compared to the more vulnerable population, age was not found as a determinant in our findings. Therefore, prudence is warranted when applying this prognostic model to an elderly and frail population. It remains uncertain whether the determinants identified in our study remain consistent within this group, and additionally, whether their risk profile significantly differs.

The misclassification rate in our test set is 14% with a sensitivity of 65% and a specificity of 87%. This suggests that our model is only moderately able to identify those participants with an elevated risk on developing moderate-to-severe side-effects. However, it has a high ability to correctly identify the true negative cases. These insights can aid in risk assessment, informed counseling, and decision-making regarding booster vaccinations in PHCPs.

It is important to acknowledge that a substantial number of concerns and theories concerning COVID-19 vaccinations relate to the potential long-term effects of these vaccines. However, our study does not provide any specific insight into this aspect. To address these concerns, active surveillance systems such as the Vaccine Safety Datalink are implemented to closely monitor vaccine long-term safety [41].

Conclusion

We developed a prediction model to investigate the probability of moderate-to-severe side-effects after COVID-19 booster mRNA vaccines. Our findings can assist health care providers and policy makers to communicate the low prevalence of moderate-to-severe side-effects, the short duration of those symptoms, and their strongest predictors, mainly the history of side-effects after any of the previous doses and female sex. These valuable insights provide an additional reassuring factor to address concerns about booster vaccination and encourage their uptake.

Abbreviations

AUC	Area under the receiver operating characteristic curve
CIC	Correlation information criterion
EMA	European Medicines Agency
GEE	Generalized estimating equations
IQR	Inter-quartile range
PHCPs	Primary health care providers
QIC	Quasi-log-likelihood under the independence model information criterion
RCT	Randomized clinical trials
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis

Supplementary Information

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Supplementary Material 1

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Author contributions

All authors, JD, SA, MD, PVN, ED, BS and SC, contributed to the study conception and design. Material preparation and data collection were performed by JD, MD, PVN, ED, BS and SC. Analysis of the data was performed by JD, SA and SC. The first draft of the manuscript was written by JD and all co-authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are not openly available, but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical Approval has been granted by the Ethics Committee of the University Hospital of Antwerp/University of Antwerp (Belgian registration number: 3002020000237). Informed consent was obtained from all individual participants in the study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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