Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 40 (2022) 970–976

Contents lists available at ScienceDirect

Vaccine

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

COVID-19 vaccine reactogenicity – A cohort event monitoring study in the Netherlands using patient reported outcomes

Leàn Rolfes, Linda Härmark, Agnes Kant, Leontine van Balveren, Wil Hilgersom, Florence van Hunsel *

Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands

ARTICLE INFO

Article history:
Received 8 September 2021
Received in revised form 6 January 2022
Accepted 10 January 2022
Available online 17 January 2022

Keywords:
COVID-19 vaccine
Reactogenicity
Pyrexia
AEFI
Patient reported outcomes
Pharmacovigilance
Postmarketing
Drug safety

ABSTRACT

Objectives: To explore factors that are associated with reactogenicity in general and systemic after the first dose of COVID-19 vaccine in the Netherlands.
Design: A web-based prospective cohort design using patient reported outcomes (PROs).
Setting: Any person who has been vaccinated with any brand of COVID-19 vaccine in the Dutch COVID immunization programme.
Participants: 22,184 participants. Of these, 13,959 (62.9%) experienced reactogenicity in general and 11,979 (54.0%) systemic reactogenicity within 7 days after vaccination.
Main outcome measures: Factors that are associated with the occurrence of reactogenicity after COVID-19 vaccination.
Results: Compared to the Comirnaty® vaccine, the highest odds ratio (OR) for developing reactogenicity was for the Vaxzevria® vaccine (OR 5.18) followed by Spikevax® (OR 2.16), and Janssen (OR 1.65). Participants with a history of COVID-19 disease had a 3.10 increased odds for reactogenicity. Women had a 2.08 increased odds compared to men. Older participants experienced less reactogenicity. Compared to the age group < 50, the ORs for the age groups 50–60, 61–79, and ≥80 were 0.36, 0.15, and 0.10 respectively. The use of an antipyretic drug, or a drug for nervous system disorders gave an increased odds of 1.34 and 1.16 respectively. A body mass index of 25.0–29.9 and over 30 was negatively associated with reactogenicity (OR 0.87 and OR 0.72 respectively). Comorbidities that were associated with reactogenicity were cardiac disorders (OR 1.26), respiratory disorders (OR 1.31), psychiatric disorders (1.37), reproductive disorders (OR 1.54), and eye disorders (OR 1.55). The factors associated with systemic reactogenicity were mostly comparable, but there were differences for comorbidities, drug use, and the strength of the regression coefficient.
Conclusions: This extensive study with over 22,000 vaccine recipients in the Netherlands demonstrated that, taken into account all factors in the model, the Comirnaty® vaccine gave the least and the Vaxzevria® vaccine the most reactogenicity in general and systemic after the first dose. Also a person with a history of COVID-19 disease, female sex and younger age had an increased odds for experiencing reactogenicity after vaccination.

1. Introduction

The rapid development and deployment of COVID-19 vaccines has put the safety of these vaccines in the spot light. So far four COVID-19 vaccines are approved in the European Union: mRNA vaccines from Pfizer-BioNTech (Comirnaty®) [1] and Moderna (Spikevax®) [2] and viral vector vaccines from AstraZeneca (Vaxzevria®) [3] and Janssen [4]. The vaccines had been tested for efficacy and safety in large clinical trials [5–7]. During the vaccination campaign in the Netherlands, a large amount of vaccines were administered in a time-period of months. This made large scale near real time safety surveillance possible during the vaccine roll-out.

The Netherlands Pharmacovigilance Centre Lareb monitors the safety of COVID-19 vaccines. Similar to other vaccination campaigns, such as the yearly influenza- and the 2009/2010 H1N1 vaccination campaigns [8,9] an ongoing prospective cohort event monitoring (CEM) study was performed in addition to the spontaneous reporting system in the Netherlands. This current CEM study follows people who had been vaccinated with one of the four available COVID-19 vaccines in the Netherlands during a six month period after vaccination [10].

* Corresponding author at: Netherlands Pharmacovigilance Center, Lareb Goudsbloemvallei 7, 5237 MH 's Hertogenbosch, the Netherlands.
E-mail address: f.vanhunsel@lareb.nl (F. van Hunsel).

https://doi.org/10.1016/j.vaccine.2022.01.013
0264-410X/

An adverse event following immunisation (AEFI) is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease [11]. Reactions commonly seen in the registration studies for the COVID-19 vaccines are those referring to reactogenicity [5–7]. Reactogenicity represents the physical manifestation of the inflammatory response to vaccination. It can include local injection site reactions such as swelling, redness, pruritus, and pain, and also systemic symptoms like fever, myalgia and headache [12]. Although these AEFI are considered mild, they can lead to discomfort and absence from work, as was described for medical practitioners in the Netherlands [13]. The occurrence of reactogenicity can be influenced by intrinsic factors (e.g. age, gender, BMI), vaccine factors (e.g. brand, adjuvant), and administration factors (e.g. injection route, needle length) [12].

Given the vaccination strategy in the Netherlands [14] together with the inclusions strategy for the LIM cohort, the population which was vaccinated with mRNA and vector vaccines and those included during the study period were very different in terms of gender and age during. Participants who received Comirnaty® were men and women of working age [18–65] and people over 80 years, while dose included in the LIM cohort were mostly people over 80 years. For Vaxzevria® mostly women of a working age [18–65] were included. In the UK, analysis of self-reported AEFIs following COVID-19 vaccination indicated that mRNA vaccines were associated with an increased incidence of local reactions and considerably lower incidence of systemic reactions compared to viral vector-based vaccines [15]. In this study, participants who received the mRNA vaccine were mostly health professionals of a working age, while recipients of a viral vector-based vaccine were relatively older.

Given these differences in vaccinated populations, it is unknown if the difference in occurrence of reactogenicity can be explained by the type of vaccine or by other factors. Given the importance of COVID-19 vaccination in order to help stop this pandemic, and also the future use of COVID-19 vaccines, it is important to improve our understanding about the occurrence of reactogenicity after COVID-19 vaccination. The primary aim of this study was to explore factors that are associated with the occurrence of COVID-19 vaccine reactogenicity after the first dose in the Netherlands, including the use of different brands of vaccines. The secondary aim was to explore factors associated with the occurrence of COVID-19 vaccine related systemic reactogenicity.

2. Methods

2.1. Setting and study population

This is a web-based prospective cohort design using patient reported outcomes (PROs) in the Netherlands that started in February 2021 and will include data until 2022. All Dutch residents above 16 years of age who were vaccinated with a COVID-19 vaccine in the Dutch COVID immunisation programme during the study period from February to beginning of August 2021 were eligible to participate in this particular study. Participation was possible if participants were able to read and write Dutch, if they were able to provide informed consent, and had access to the internet.

2.2. Data collection

Participants were invited for participation to this study by means of a flyer, which was handed over at a subset of vaccination sites nationally, including the municipal health service and general practitioners, and some hospitals. The flyer contained information about the study and an URL for registration on the website. Participants were able to register for this study before they were vaccinated and with a maximum of 2 days after vaccination.

Data were collected by means of online questionnaires using the Lareb Intensive Monitoring (LIM) system [8,9]. See also Supplementary materials 1 for items included in the questionnaires. After registration, participants filled in the baseline questionnaire with questions about participant characteristics (age, gender, length, weight), comorbidities, concomitant medication, use of an antipyretic drug several hours before or after vaccinations, and a history of experienced COVID-19 disease. For the latter it was specified if the participant had a positive polymerase chain reaction (PCR)-test, or the participants had answered this question with 'yes' or 'probable' but no PCR-test was done. In the registration form, the vaccination date was asked. If the participant wasn't yet vaccinated at time of registration, the vaccination date was asked in the baseline questionnaire.

It was expected that most AEFIs occur within 72 h after vaccination. In addition, most of the well-known AEFIs recover within five days after vaccination. Therefore, the first questionnaire on AEFIs was send on the seventh day after vaccination to retrieve most information on recovery and reduce recall bias.

For the complete study, participants receive a total of six online questionnaires about patient reported events attributed to the vaccination of COVID-19 over a period of six months. For the current analysis, only data from the first AEFI questionnaire have been used. Participants were able to fill in the questionnaire with a maximum of 6 days after receiving the first questionnaire (or 13 days after vaccination). All reported experienced AEFIs were coded using the the Medical Dictionary for Regulatory Activities (MedDRA®) terminology 23.0 and 24.0 [16]. Although the participant was asked to report those reactions related to the use of the vaccine, we will refer to the reported reactions as AEFIs. For AEFIs that are related to reactogenicity, AEFIs on Preferred Term (PT) MedDRA level related to injection site reactions and well-known systemic AEFIs (chills, fatigue, headache, joint pain, malaise, myalgia, nausea. and pyrexia) were included (Supplementary materials 2). [17].

2.3. Statistical analysis

Descriptive statistics were used to gain insight into the study population. Potential factors associated with the occurrence of reactogenicity were tested using multivariable logistic regression analysis. Independent variables included in the analysis were: brand of COVID-19 vaccine, gender, age, body mass index (BMI), a history of COVID-19 disease based on a positive PCR-test, comorbidities based on MedDRA system organ class (SOC), and use of specific concomitant medication based on ATC-classification [18], see Table 1. Possible interaction has been tested for 'gender*age group' and 'gender*brand of COVID-19 vaccine'.

According to the rule of thumb to have adequate statistical power to develop a multivariable model we opted for at least 10 cases per independent variable [9]. Backward selection procedures were used. The Hosmer–Lemeshow goodness of fit was assessed as a measure of calibration of the final model. Expert opinion was used for the selection of the variables that were tested, and the results of the statistical testing were used to ultimately determine which factors influenced the reactogenicity. Data were analysed using R, a software environment for statistical computing and graphics.

3. Results

3.1. Baseline characteristics

A total of 22,184 participants were included in this study; 10,724 for Comirnaty®, 8,778 for Vaxzevria®, 1,508 for Jansen,

Table 1
Type and number of independent variables in the full cohort.

1a. Full cohort

COVID vaccine brand	Comirnaty®		Vaxzevria®		Janssen		Spikevax®		Unknown	
Participants	3763	35.1%	7962	90.7%	935	84.4%	1275	84.5%	24	33.3%
Age Group										
Age 0–50	499	13.3%	4415	55.5%	695	74.3%	802	62.9%	8	33.3%
Age 51–60	340	9.0%	2098	26.4%	233	24.9%	414	32.5%	5	20.8%
Age 61–79	2019	53.7%	1447	18.2%	7	0.7%	59	4.6%	7	29.2%
Age 80+	905	24.0%	2	0.0%	0	0.0%	0	0.0%	4	16.7%
Sex										
Male	1774	47.1%	1014	12.7%	128	13.7%	275	21.6%	8	33.3%
Female	1989	52.9%	6948	87.3%	807	86.3%	1000	78.4%	16	66.7%
Use of an antipyretic several hours drug before or after vaccination	324	8.6%	1729	21.7%	256	27.4%	218	17.1%	0	0.0%
Experienced COVID-19 disease with positive test	260	6.9%	922	11.6%	131	14.0%	197	15.5%	3	12.5%
Body Mass Index (BMI)										
BMI < 18.5	59	1.6%	142	1.8%	16	1.7%	27	2.1%	1	4.2%
BMI 18.5–24.9	1823	48.4%	3758	47.2%	552	59.0%	632	49.6%	12	50.0%
BMI 25.0–29.9	1373	36.5%	2487	31.2%	270	28.9%	413	32.4%	12	50.0%
BMI 30+	476	12.6%	1492	18.7%	96	10.3%	193	15.1%	2	8.3%
Comorbidities (MedDRA System Organ Class)										
Vascular	1458	38.7%	990	12.4%	84	9.0%	152	11.9%	4	16.7%
Immune	184	4.9%	299	3.8%	39	4.2%	109	8.5%	1	4.2%
Cardiac	728	19.3%	293	3.7%	25	2.7%	61	4.8%	3	12.5%
Musculoskeletal and connective	141	3.7%	183	2.3%	13	1.4%	38	3.0%	0	0.0%
Respiratory	472	12.5%	706	8.9%	70	7.5%	220	17.3%	1	4.2%
Ear and labyrinth	12	0.3%	10	0.1%	0	0.0%	1	0.1%	0	0.0%
Metabolism	361	9.6%	377	4.7%	21	2.2%	80	6.3%	2	8.3%
Endocrine	353	9.4%	362	4.5%	24	2.6%	84	6.6%	2	8.3%
Psychiatric	117	3.1%	401	5.0%	53	5.7%	61	4.8%	2	8.3%
Renal and urinary	96	2.6%	51	0.6%	0	0.0%	18	1.4%	0	0.0%
Skin and subcataneous	32	0.9%	65	0.8%	11	1.2%	16	1.3%	0	0.0%
Neoplasms	144	3.8%	85	1.1%	8	0.9%	46	3.6%	0	0.0%
Gastrointestinal	65	1.7%	106	1.3%	15	1.6%	18	1.4%	0	0.0%
Surgical and medical procedures	37	1.0%	32	0.4%	0	0.0%	9	0.7%	0	0.0%
Infections and infestations	17	0.5%	43	0.5%	3	0.3%	8	0.6%	0	0.0%
Eye	41	1.1%	34	0.4%	4	0.4%	3	0.2%	0	0.0%
Cognenital. familial genetic	2	0.1%	20	0.3%	0	0.0%	0	0.0%	0	0.0%
Hepatobiliary disorders	22	0.6%	23	0.3%	2	0.2%	5	0.4%	0	0.0%
Reproducive system and systems	353	9.4%	362	4.5%	24	2.6%	84	6.6%	2	8.3%
Injury. poisening and procedural complication	15	0.4%	26	0.3%	0	0.0%	3	0.2%	0	0.0%
General disorders and administration site conditions	20	0.5%	24	0.3%	0	0.0%	6	0.5%	0	0.0%
Investigations	30	0.8%	21	0.3%	1	0.1%	5	0.4%	0	0.0%
Social circumstances	7	0.2%	26	0.3%	6	0.6%	12	0.9%	0	0.0%
Concomitant medication based on Anatomical Therapeutic Chemical (ATC) Classification System										
ATC L - Antineoplastic and immunomodulating agents	99	2.6%	110	1.4%	15	1.6%	54	4.2%	1	4.2%
ATC *H*01 - Pituitary and hypothalamic hormones and analogues	90	2.4%	178	2.2%	18	1.9%	37	2.9%	0	0.0%
ATC H02 - Corticosteroids for systemic use	62	1.6%	26	0.3%	2	0.2%	8	0.6%	0	0.0%
ATC N - Nervous system	460	12.2%	1066	13.4%	99	10.6%	124	9.7%	5	20.8%

1b. Participants with at least one AEFI related to systemic reactogenicity

COVID vaccine brand	Comirnaty®		Vaxzevria®		Janssen		Spikevax®		Unknown	
Participants	2484	23.2%	7641	87.0%	894	81.1%	939	62.3%	21	29.2%
Age Group										
Age 0–50	408	16.4%	4303	56.3%	670	74.9%	615	65.5%	8	38.1%
Age 51–60	246	9.9%	1991	26.1%	218	24.4%	284	30.2%	4	19.0%
Age 61–79	1229	49.5%	1345	17.6%	6	0.7%	40	4.3%	6	28.6%
Age 80+	601	24.2%	2	0.0%	0	0.0%	0	0.0%	3	14.3%
Sex										
Male	1095	44.1%	957	12.5%	125	14.0%	191	20.3%	6	28.6%
Female	1389	55.9%	6684	87.5%	769	86.0%	748	79.7%	15	71.4%
Use of an antipyretic several hours drug before or after vaccination	255	10.3%	1666	21.8%	246	27.5%	175	18.6%	0	0.0%
Experienced COVID-19 disease with positive test	218	8.8%	882	11.5%	127	14.2%	175	18.6%	3	14.3%
Body Mass Index (BMI)										
BMI <18.5	37	1.5%	137	1.8%	15	1.7%	17	1.8%	0	0.0%
BMI 18.5–24.9	1164	46.9%	3621	47.4%	532	59.5%	457	48.7%	11	52.4%
BMI 25.0–29.9	911	36.7%	2384	31.2%	263	29.4%	310	33.0%	9	42.9%
BMI 30+	352	14.2%	1419	18.6%	84	9.4%	146	15.5%	1	4.8%
Comorbidities (MedDRA System Organ Class)										
Vascular	976	39.3%	929	12.2%	78	8.7%	110	11.7%	4	19.0%

Table 1 (*continued*)

1b. Participants with at least one AEFI related to systemic reactogenicity									
COVID vaccine brand	Comirnaty®		Vaxzevria®		Janssen		Spikevax®		Unknown	
Immune	126	5.1%	280	3.7%	38	4.3%	85	9.1%	1	4.8%
Cardiac	489	19.7%	276	3.6%	22	2.5%	42	4.5%	3	14.3%
Musculoskeletal and connective	102	4.1%	176	2.3%	13	1.5%	30	3.2%	0	0.0%
respiratory	332	13.4%	677	8.9%	67	7.5%	176	18.7%	1	4.8%
Ear and labyrinth	11	0.4%	10	0.1%	0	0.0%	1	0.1%	0	0.0%
Metabolism	234	9.4%	359	4.7%	21	2.3%	64	6.8%	2	9.5%
Endocrine	229	9.2%	343	4.5%	24	2.7%	68	7.2%	2	9.5%
Psychiatric	91	3.7%	386	5.1%	51	5.7%	52	5.5%	2	9.5%
Renal and urinary	67	2.7%	50	0.7%	0	0.0%	16	1.7%	0	0.0%
Skin and subcataneous	19	0.8%	61	0.8%	11	1.2%	13	1.4%	0	0.0%
Neoplasms	99	4.0%	81	1.1%	8	0.9%	37	3.9%	0	0.0%
Gastrointestinal	48	1.9%	102	1.3%	14	1.6%	18	1.9%	0	0.0%
Surgical and medical procedures	26	1.0%	29	0.4%	0	0.0%	8	0.9%	0	0.0%
Infections and infestations	11	0.4%	41	0.5%	3	0.3%	7	0.7%	0	0.0%
Eye	27	1.1%	32	0.4%	4	0.4%	3	0.3%	0	0.0%
Cognenital. familial genetic	2	0.1%	20	0.3%	0	0.0%	0	0.0%	0	0.0%
Hepatobiliary	14	0.6%	22	0.3%	2	0.2%	5	0.5%	0	0.0%
Reproducive system and systems	229	9.2%	343	4.5%	24	2.7%	68	7.2%	2	9.5%
Injury. poisening and procedural complication	13	0.5%	25	0.3%	0	0.0%	3	0.3%	0	0.0%
General disorders and administration site conditions	15	0.6%	22	0.3%	0	0.0%	3	0.3%	0	0.0%
Investigations	20	0.8%	20	0.3%	1	0.1%	3	0.3%	0	0.0%
Social circumstances	7	0.3%	23	0.3%	5	0.6%	5	0.5%	0	0.0%
Concomitant medication based on Anatomical Therapeutic Chemical (ATC) Classification System										
ATC L - Antineoplastic and immunomodulating agents	62	2.5%	102	1.3%	13	1.5%	41	4.4%	1	4.8%
ATC *H*01 - Pituitary and hypothalamic hormones and analogues	59	2.4%	169	2.2%	17	1.9%	33	3.5%	0	0.0%
ATC H02 - Corticosteroids for systemic use	39	1.6%	23	0.3%	2	0.2%	7	0.7%	0	0.0%
ATC N - Nervous system	318	12.8%	1020	13.3%	96	10.7%	103	11.0%	4	19.0%

and 1,508 for Spikevax®. Of these, 13,959 (62.9%) experienced at least one AEFI related to reactogenicity and 11,979 (54.0%) experienced at least one systemic AEFI after the first dose of the COVID-19 vaccine. Table 1 presents the number of independent variables included in the analyses for the whole cohort. Participants were vaccinates between February 1st 2021 to May 9th 2021. They registered between February 1st 2021 and May 9th 2021, and completed the first questionnaire between March 1st 2021 and May 9th 2021.

3.2. Multivariable logistic regression analysis

Table 2**a and 2b** present the results from the multivariabele regression analysis. There was a positive association with the vaccine brand and occurrence of reactogenicity. Compared to the Comirnaty® vaccine, the highest odds ratio (OR) for developing reactogenicity in general was for the Vaxzevria® vaccine (OR 5.18) followed by Spikevax® (OR 2.16), and Janssen® (OR 1.65). For systemic reactogenicity, the ORs were even higher for the vaccines of Vaxzevria® and Janssen®; 7.62 and 3.02 respectively. For the Spikevax® vaccine the OR for systemic reactogenicity (1.29) was lower as compared to the OR for reactogenicity in general.

Older participants experienced less reactogenicity. Compared to the age group < 50, the decrease in OR for reactogenicity in general for the age groups 50–60, 61–79, and ≥80 was 0.36, 0.15, and 0.10 respectively. For systemic reactogenicity, the ORs were 0.41, 0.19, and 0.14 for the age groups 50–60, 61–79, and ≥80 respectively. Women had an increased OR for experiencing general and systemic reactogenicity compared to men (respectively 2.08 and 1.92, recalculated by 1/exp(B)). A BMI of 25.0 to 29.9 and over 30 was negatively associated with reactogenicity in general (OR 0.87 and OR 0.72 respectively). For the analysis on systemic reactogenicity, only a BMI over 30 was associated (OR 0.81). Participants with a history of COVID-19 disease had a 3.10 increased odds for reactogenicity in general, and a 2.77 increased odds for systemic reactogenicity. Participants who used an antipyretic drug several hours drug before or after vaccination had a 1.34 increased odds for reactogenicity in general and 1.37 increased odds for systemic reactogenicity.

For reactogenicity in general, the ATC class nervous disorder was positively associated (OR 1.16). Comorbidities that were associated with reactogenicity in general were cardiac disorders (OR 1.26), respiratory disorders (OR 1.31), psychiatric disorders (1.37), reproductive disorders (OR 154), and eye disorders (OR 1.55). For the systemic reactogenicity, cardiac disorder (OR 1.28), respiratory disorders (OR 1.32), psychiatric disorders (OR 1.42), and neoplasm disorders (OR 1.25) were associated.

There were also factors included in the model without statistical significance. Because they influence other factors in the model, they were considered important to report. We found no statistical interaction for the age groups in combination with gender and for gender in combination with the brand of COVID-19 vaccine. In Supplementary materials 3 a summary of data is provided for each included systemic AEFI.

4. Discussion

Real time and real-world data about the safety of COVID-19 vaccines is extremely important given the rapid deployment of these vaccines. This study specifically explored factors associated with COVID-19 vaccine reactogenicity, as there were signs from clinical practice that viral vector vaccine may have a higher degree of reactogenicity compared to the mRNA vaccines after the first dose.

To answer this question and to provide more insight in the effects of age, gender, and medical history in relation to reactogenicity, data from the Dutch COVID-19 vaccine CEM study were used. Multivariate logistic regression analysis demonstrated that despite difference in the population that was vaccinated with each vaccine brand, and taken into account all factors in the model, the mRNA Comirnaty® vaccine gave the least reactogenicity and the

Table 2
Models from multivariabele logistic regression.

Table 2**a** AEFI related to reactogenicity in general

	Odds Ratios (95% confidence interval)	Regression coefficient (p-value)
Vaccine brand Comirnaty®		
Vaccine brand Vaxzevria®	5.18 (4.68–5.73)	<0.001
Vaccine brand Janssen	1.65 (1.35–2.02)	<0.001
Vaccine brand Spikevax®	2.16 (1.81–2.57)	<0.001
Vaccine brand unknown	0.64 (0.36–1.12)	0.127
Gender (men vs women)	0.48 (0.45–0.52)	<0.001
Age group < 50		
Age group 50–60	0.36 (0.32–0.42)	<0.001
Age group 61–79	0.15 (0.13–0.18)	<0.001
Age group ≥ 80	0.10 (0.08–0.11)	<0.001
BMI < 18.5		
BMI 18.5–24.9	1.13 (0.82–1.57)	0.467
BMI 25.0–29.9	0.87 (0.81–0.95)	0.001
BMI 30+	0.72 (0.65–0.81)	<0.001
Experienced COVID-19 disease with positive test	3.10 (2.58–3.76)	<0.001
Used antipyretic drugs	1.34 (1.18–1.52)	<0.001
Comorbidity cardiac	1.26 (1.14–1.39)	<0.001
Comorbidity repiratory	1.31 (1.17–1.48)	<0.001
Comorbidity psychiatric	1.37 (1.08–1.74)	0.011
Comorbidity reproductive	1.54 (1.05–2.27)	0.028
Comorbidity eye disorder	1.55 (1.01–2.37)	0.043
Comorbidity immune	1.19 (0.99–1.43)	0.066
Comorbidity infections	1.83 (0.94–3.71)	0.085
Comorbidity general	1.74 (0.94–3.25)	0.080
ACT - Nervous system	1.16 (1.03–1.31)	0.019
Intercept	5.00 (4.36–5.75)	<0.001

Table 2b AEFI related to systemic reactogenicity

	Odds Ratios (95% confidence interval)	Regression coefficient (p-value)
Vaccine brand Comirnaty®		
Vaccine brand Vaxzevria®	7.62 (6.93–8.39)	<0.001
Vaccine brand Janssen	3.02 (2.52–3.64)	<0.001
Vaccine brand Spikevax®	1.29 (1.11–1.48)	0.001
Vaccine brand unknown	1.10 (0.62–1.91)	0.731
Gender (men vs women)	0.52 (0.48–0.57)	<0.001
Age group <50		
Age group 50–60	0.41 (0.37–0.46)	<0.001
Age group 61–79	0.19 (0.17–0.21)	<0.001
Age group ≥80	0.14 (0.12–0.16)	<0.001
BMI <18.5		
BMI 18.5–24.9	0.91 (0.67–1.23)	0.532
BMI 25.0–29.9	0.96 (0.88–1.04)	0.274
BMI 30+	0.81 (0.73–0.90)	<0.001
Experienced COVID-19 disease with positive test	2.77 (2.37–3.26)	<0.001
Used antipyretic drugs	1.37 (1.22–1.54)	<0.001
Comorbidity cardiac	1.28 (1.15–1.42)	<0.001
Comorbidity respiratory	1.32 (1.17–1.48)	<0.001
Comorbidity pshychiatric	1.42 (1.14–1.78)	0.002
Comorbidity neoplasm	1.25 (1.01–1.53)	0.035
Comorbidity musculoskeletal	1.21 (0.97–1.51)	0.088
Comorbidity renal	1.27 (0.97–1.64)	0.074
Comorbidity gastrointestinal	1.35 (0.99–1.84)	0.057
Comorbidity injury and poisoning	1.90 (0.98–3.78)	0.063
ACT - Nervous system	1.10 (0.98–1.25)	0.112
Intercept	1.85 (1.65–2.09)	<0.001

BMI = Body Mass Index, ATC = Anatomical Therapeutic Chemical Classification System.

viral-vector Vaxzevria® vaccine the most. We did not identify clear differences between the type of vaccines (mRNA versus viral vector) for reactogenicity in general. However, for systemic reactogenicity, the viral vector vaccines gave a higher OR compared to the mRNA vaccines.

In a phase-3 clinical trial for Comirnaty® local reactions that occurred within 7 days after vaccination were seen in 83% of participants (age 16–55 years) receiving a first dose of Comirnaty® compared to 14% of those receiving placebo. For participants of 55 years and older this was 71% and 9% respectively. Fever was seen in 4% of younger participants after the first dose and in 1% of older participants [6]. In a phase-3 clinical trial for Spikevax® solicited adverse events at the injection site occurred more frequently than in the placebo group after both the first dose (84.2%, vs. 19.8%) [5]. Both solicited injection-site and systemic adverse events were more common among younger participants (18 to <65 years of age) than among older participants (≥65 years of age). For Vaxzevria®, a single-blind, randomised, controlled, phase 2/3 trial at least one systemic symptom was reported after the first vaccination for 86% of participants in the 18–55 years group, 77% in the 56–69 years group, 65% in the 70 years and older group. Within 7 days after the first vaccination, the incidence of objectively measured fever was low (24%) in patients aged 18–55 years and no fevers were recorded in elderly participant [19]. This was however based on a small number of participants (50 participants aged 18–55 years, 60 aged 56–69 years, and 96 aged 70 years and older).

Mathioudakis et al. [15] and *Mennie et al.* [20] both studied self-reported AEFIs of COVID-19 vaccines in the UK and they found that the Comirnaty® vaccine gave less reactogenicity compared to the Vaxzevria® vaccine, and that female sex and a history of COVID-19 disease were positively associated with experiencing reactogenicity. *Mathioudakis et al.* [15] had included prior use of antipyretic drugs several hours drug before or after vaccination as a variable. This was not found to be associated with the occurrence of reactogenicity. *Mennie et al.* [20] also found that younger people reported a higher rate of AEFIs compared to older people. They included BMI and comorbidities in their analysis, but found no clear trend across the vaccines. In our study, people with a history of COVID-19 also had an increased odds for reactogenicity. We identified comorbidities that give a higher odds for reactogenicity. For respiratory disorders and neoplasms this could possibly be explained by a higher priori change for developing complaints like fever in these group. The medical history categories contain a broad diversity on disorders. Therefor no solid conclusions on the role of the patients' medical history can be drawn from our study and this topic should be further investigated.

A web-based health survey by the US Centers for Disease Control and Prevention (CDC), the V-safe Active Surveillance System, enrolled a total of 3 643 918 persons who completed at least 1 health survey within 7 days following their first vaccine dose with an mRNA vaccine. They found that a greater percentage of participants who received Spikevax® compared with Comirnaty®, reported reactogenicity [21]. Similar to our study, local and systemic reactions were less commonly reported in participants 65 years and older compared with those younger than 65 years. This is likely due to the waning of innate immune defense mechanisms. Also a higher tolerance to pain and illness symptoms gained with life experience has been described in the literature [12].

Compared to men, women have been found to experience higher incidences of (local) reactogenicity after vaccination. Possible explanations could be related to genetic or hormonal differences [12]. For example, differences in skin thickness, blood flow and nervous system structure between men and women may favour the development of injection-site inflammation in women and sex hormones have been shown to influence immune responses [12,22]. Our study found a decreased odds for reactogenicity in the overweight population. In addition to sex and age, BMI could possibly be a factor that influences a persons' immune response, although most studies for COVID-19 vaccines have not found an effect [23–25]. There might also be a relation with vac-

cine administration technique or needle length in persons with obesity [12].

The Summary of Product Characteristics (SmPC) for the four vaccines in this study reflects the current insights on AEFI, based on available pre-and post-authorization data. For Comirnaty® [1], the most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%). For Spikevax® [2] the most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%).

For Vaxzevria® [3] the most frequently reported adverse reactions are injection site tenderness (68%), injection site pain (58%), headache (53%), fatigue (53%), myalgia (44%), malaise (44%), pyrexia (includes feverishness (33%) and fever $\geq$ 38 °C (8%), chills (32%), arthralgia (27%) and nausea (22%). For the Janssen vaccine [4], the most common local adverse reactions reported was injection site pain (48.6%). The most common systemic adverse reactions were headache (38.9%), fatigue (38.2%), myalgia (33.2%) and nausea (14.2%). Pyrexia (defined as body temperature $\geq$ 38.0 °C) was observed in 9% of participants.

For all four vaccines the SmPC describes that the majority of these adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. SmPCs [1,2,4] describe that a slightly lower frequency of reactogenicity events was associated with greater age, as is seen in our study. However, the higher odds ratio's that were found for both local and systemic reactogenicity for Vaxzevria® compared to Pfizer are not reflected in the SmPCs. Differences in results between our study and the SmPC could be a result of differences in the included population and the way participant's are asked about the occurrence of AEFI. Also we cannot rule out some form of selection bias.

4.1. Strengths and limitations

The strengths of this study include the large study populations and the inclusion of many variables, like comorbidities and information about a COVID-19 disease history, into the analysis. The Netherlands Pharmacovigilance Centre Lareb has long experience with the CEM system [26]. In our experience, people are able to use the online questionnaire system [27,28]. Another advantage of using PROs is that local and systemic reactogenicity reactions are easily recognizable by the patient, and probably would not be a reason for contact with a medical healthcare professional, so that these effects can be reliably reported by patients themselves. In addition, we were also able to create a linkage with the Dutch vaccination registration system (CIMS) [29], maintained by the National Institute for Public Health and the Environment. Through this linkage, based on the Social Security Number, it was possible to receive the brand of the vaccine in case the patient who filled in the questionnaire did not know this.

A limitation of our study design is that selection bias cannot be ruled out. People who experience AEFIs might be more motivated to participate and registration to the study was possible until two days after vaccination. Therefore exact incidence rates could not be calculated. On the other hand, this selection bias is probably equal for participants vaccinated with the different vaccines. In addition, the study populations for the four vaccines vary in size making it more difficult to have reliable outcomes for the smaller cohorts. Like other studies about COVID-19 vaccine safety, data are limited to the population that has been vaccinated. Due to our selection method, we were only able to include a limited number of people working in hospital setting.

The questionnaire asked participants about a prior infection with the COVID-19 virus. There is a chance for misclassification who answered not having experienced COVID-19 disease or not being tested when they had potential symptoms, because there was not enough test capacity to test all people with COVID-19 disease complaints during the beginning of the COVID-19 pandemic [30].

4.2. Future analysis

Seeing that the vaccination campaign in the Netherlands was still in progress at the time of this first study, future analysis will also provide data on other populations such as younger participants for the mRNA vaccines and the Janssen vaccine. Future analyses will also include the second vaccination moment and more long-term follow-up. Also the role of potential risk factors for developing AEFIs should be further investigated. Similar CEM studies are currently in progress for several other European countries and aggerated data will be analyzed [31]. These studies make it possible to also analyze safety data on a larger scale. Future analysis will also focus on providing insight into characteristics of experienced AEFIs, like time course and severity. These aspects are extremely important for people and could give them more information of what to expect when they experience AEFIs after COVID-19 vaccination. Also information about AEFI after the first and second, and what to expect on an individual level, are important. Such insights might help people to manage expectations and might also influence the vaccination rate positively, this is especially important in the light of possible vaccination campaigns in the future.

5. Conclusion

This extensive study with over 22,000 participants in the Netherlands demonstrated that, taken into account all factors in the model, after the Comirnaty® vaccine the least and the Vaxzevria® vaccine the most reactogenicity in general and systemic was experienced. We did not identify clear differences between the type of vaccines (mRNA versus viral vector) for reactogenicity in general. The viral vector vaccines did however demonstrate to have a higher odds for systemic reactogenicity compared to the mRNA vaccines. Also a person with a history of COVID-19 disease, female sex and younger age had an increased odds for experiencing reactogenicity.

6. Funding/support

Funding for the Cohort event monitoring of COVID-19 vaccine safety was granted by the Dutch Ministry of Health, Welfare and Sport (Grantnumber was 331.880). The Dutch Ministry of Health, Welfare and Sport had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

7. Ethical approval and consent

If a study in the Netherlands is subject to the Medical Research Involving Human Subjects Act (WMO), it must undergo a review by an accredited Medical Research Ethics Committee or the central committee on research involving human subjects (CCMO). After submission to an accredited review committee (METC Brabant), this study was deemed not to fall under the WMO act. Participants in the study fill out a statement of consent at the time of registration.

8. Additional contributions

We acknowledge our colleges of Lareb who helped us with the coding of all data included in this study and Jurriaan Jansen for the data extraction.

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.2022.01.013.

References

[1] European Medicines Agency EMA. SmPC Comirnaty; 2021 [updated 12-07-2021]. Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf.
[2] European Medicines Agency EMA. SmPC Spikevax; 2021 [updated 12-07-2021]. Available from: https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf.
[3] European Medicines Agency EMA. SmPC Vaxzevria; 2021 [updated 2021]. Available from: https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf.
[4] European Medicines Agency EMA. SmPC Covid-19 vaccine Janssen; 2021 [updated 07-07-2021]. Available from: https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf.
[5] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403–16.
[6] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603–15.
[7] Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet 2021;397(10277):881–91.
[8] van Balveren-Slingerland L, Kant A, Härmark L. Web-based intensive monitoring of adverse events following influenza vaccination in general practice. Vaccine. 2015;33(19):2283–8.
[9] Härmark L, van Hunsel F, Hak E, van Grootheest K. Monitoring the safety of influenza A (H1N1) vaccine using web-based intensive monitoring. Vaccine. 2011;29(10):1941–7.
[10] BijwerkingencentrumLareb. Mijn Coronavaccin; 2021 [updated 2021]. Available from: https://mijncoronavaccin.nl/.
[11] European Medicines Agency EMA. Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 4); 2017. https://wwwemaeuropaeu/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_enpdf.
[12] Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how's and what's of vaccine reactogenicity. NPJ Vacc 2019;4(1). https://doi.org/10.1038/s41541-019-0132-6.
[13] Kleijne I. Veel huisartsen grieperig na Moderna-inentingen. Medisch Contact; 2021 [15-03-2021].
[14] Rijksoverheid. 2021 Vaccinatieplanning [updated 2021]. Available from: https://www.rijksoverheid.nl/onderwerpen/coronavirus-vaccinatie/volgorde-van-vaccinatie-tegen-het-coronavirus.
[15] 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. https://doi.org/10.3390/life11030249.
[16] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Welcome to MedDRA; 2021 [updated 2017/06/16/]. Available from: https://www.meddra.org/.
[17] Scholl J, van Hunsel F, Hilgersom W, van Puijenbroek EP. Vaxbatch: A stratified disproportionality analysis tool for batch-related AEFI monitoring in vaccines. Pharmacoepidemiol Drug Saf 2020:650–84.
[18] Norwegian Institute of Public. ATC Structure and principles; 2011 [updated 2017/06/01/]. Available from: https://www.whocc.no/atc/structure_and_principles/.
[19] Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2020;396(10267):1979–93.
[20] 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.
[21] Chapin-Bardales J, Gee J, Myers T. Reactogenicity Following Receipt of mRNA-Based COVID-19 Vaccines. JAMA 2021;325(21):2201–2.
[22] Di Resta C, Ferrari D, Viganò M, Moro M, Sabetta E, Minerva M, et al. The Gender Impact Assessment among Healthcare Workers in the SARS-CoV-2 Vaccination-An Analysis of Serological Response and Side Effects. Vaccines (Basel) 2021;9(5):522. https://doi.org/10.3390/vaccines9050522.
[23] Pellini R, Venuti A, Pimpinelli F, Abril E, Blandino G, Campo F, et al. Early Onset of SARS-COV-2 Antibodies after First Dose of BNT162b2: Correlation with Age, Gender and BMI. Vaccines (Basel) 2021;9(7):685. https://doi.org/10.3390/vaccines9070685.
[24] Pellini R, Venuti A, Pimpinelli F, Abril E, Blandino G, Campo F, et al. Initial observations on age, gender, BMI and hypertension in antibody responses to SARS-CoV-2 BNT162b2 vaccine. EClinicalMedicine. 2021;36:100928. https://doi.org/10.1016/j.eclinm.2021.100928.
[25] Kipshidze N, Kipshidze N, Fried M. COVID-19 Vaccines: Special Considerations for the Obese Population. Obes Surg. 2021;31(8):3854–6.
[26] Harmark L. Web-based Intensive Monitoring; a patient based pharmacovigilance tool: Rijksuniversiteit Groningen; 2012.
[27] Thomas PWA, West RL, Russel MGVM, Jansen JM, Kosse LJ, Jessurun NT, et al. Inflammatory bowel disease patients provide reliable self-reported medical information: A multicentre prospective pharmacovigilance monitoring system. Pharmacoepidemiol Drug Saf. 2021;30(4):520–4.
[28] Kosse LJ, Jessurun NT, Hebing RCF, Huiskes VJB, Spijkers KM, van den Bemt BJF, et al. Patients with inflammatory rheumatic diseases: quality of self-reported medical information in a prospective cohort event monitoring system. Rheumatology (Oxford) 2020;59(6):1253–61.
[29] RIVM. Vaccinatieregistratie bij het RIVM en uw privacy; 2021 [updated 2021]. Available from: https://www.rivm.nl/covid-19-vaccinatie/privacy.
[30] RTL Nieuws. Tijdlijn: hoe Nederland te laat het testen op corona uitbreidde; 2021 [updated 21-08-2020]. Available from: https://www.rtlnieuws.nl/nieuws/artikel/5136981/reconstructie-testen-traceren-corona.
[31] Cohort Event Monitoring of safety of COVID-19 vaccines (Early-Covid-Vaccine-Monitor) [Internet]; 2021 [cited 14-07-2021]. Available from: http://www.encepp.eu/encepp/viewResource.htm?id=40288.