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Frequency and timing of adverse reactions to COVID-19 vaccines; A multi-country cohort event monitoring study

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ABSTRACT

Introduction: During the COVID-19 pandemic, EMA set-up a large-scale cohort event monitoring (CEM) system to estimate incidence rates of patient-reported adverse drug reactions (ADRs) of different COVID-19 vaccines across the participating countries. This study aims to give an up to date and in-depth analysis of the frequency of patient-reported ADRs after the 1st, 2nd, and booster vaccination, to identify potential predictors in developing ADRs and to describe time-to-onset (TTO) and time-to-recovery (TTR) of ADRs.

Methods: A CEM study was rolled out in a period ranging from February 2021 to February 2023 across multiple European countries; The Netherlands, Belgium, France, the United Kingdom, Italy, Portugal, Romania, Slovakia and Spain. Analysis consisted of a descriptive analyses of frequencies of COVID-19 vaccine-related ADRs for 1st, 2nd and booster vaccination, analysis of potential predictors in developing ADRs with a generalized linear mixed-effects model, analysis of TTO and TTR of ADRs and a sensitivity analysis for loss to follow-up (L2FU).

Results: A total of 29,837 participants completed at least the baseline and the first follow-up questionnaire for 1st and 2nd vaccination and 7,250 participants for the booster. The percentage of participants who reported at least one ADR is 74.32% (95%CI 73.82–74.81). Solicited ADRs, including injection site reactions, are very common across vaccination moments. Potential predictors for these reactions are the brand of vaccine used, the patient's age, sex and prior SARS-CoV-2 infection. The percentage of serious ADRs in the study is low for 1st and 2nd vaccination (0.24%, 95%CI 0.19—0.31) and booster (0.26%, 95%CI 0.15, 0.41). The TTO was 14 h (median) for dose 1 and slightly longer for dose 2 and booster dose. TTR is generally also within a few days. The effect of L2FU on estimations of frequency is limited.

Conclusion: Despite some limitations due to study design and study-roll out, CEM studies can allow prompt and almost real-time observations of the safety of medications directly from a patient-centered perspective, which can play a crucial role for regulatory bodies during an emergency setting such as the COVID-19 pandemic.

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1. Introduction

Since the COVID-19 virus emerged in December 2019, causing a steep increase in morbidity and mortality due to viral infection complications [1–4], rapid steps have been taken to develop vaccines to combat the pandemic. Development of COVID-19 vaccines was globally fast-tracked by applying the extensive knowledge on vaccine production gained with existing vaccines. Early scientific advice from regulators was offered to speed up development [5]. Vaccine development also involved the application of relatively new vaccine platforms, such as the mRNA vaccines, with which there was no large-scale experience before [6]. Large placebo-controlled trials were conducted at an unprecedented pace, and results were shared with regulatory agencies and the scientific community [7–11]. Accelerated evaluation in authorisation procedures took place in Europe, which included a rolling review allowing the European Medicines Agency (EMA) to assess data as they become available, and a shift towards real world evidence generation in the post-marketing setting [12]. This resulted in the first vaccine (Pfizer/BioNTech) being licensed by the European Medicines Agency (EMA) in December 2020. A few months later, two mRNA vaccines (Comirnaty® (Pfizer/BioNTech) [13], Spikevax® (Moderna) [14] and two viral vector vaccines (Vaxzevria®(AstraZeneca) [15], Jcovden® (Janssen [Johnson & Johnson] [16] were available in Europe.

COVID-19 vaccine development is still ongoing; according to the World Health Organization (WHO), as of March 10, 2023, there are still almost 200 new vaccines for COVID-19 in the clinical development stage and 200 more in the pre-clinical development stage [17]. Vaccine platforms in the clinical development phase are mainly Protein subunit vaccines (32 %), followed by mRNA vaccines (24 %), Viral Vector (non-replicating) (14 %), and Inactivated Virus vaccines (12 %) [17]. Because new variants of the COVID-19 virus (Delta, Omicron, then BA.4, BA.5 and others) emerge, the protection offered by existing vaccines wanes, and the development of booster and adapted vaccines for new variants continues [18,19].

On the other hand, the use of new vaccines in a pandemic situation with large-scale vaccination campaigns requires a solid system for post-marketing surveillance [20]. Spontaneous reporting systems for adverse drug reactions (ADRs) [21] still have a proven important place in this and the volume of safety data from spontaneous reports has been exceptionally high [22].

Complementary to this is the use of cohort event monitoring studies and other sources for real world evidence such as electronic healthcare data [23–25]. The EMA commissioned several independent observational studies using a large network of electronic healthcare databases and cohort event monitoring through safety data collection via mobile and web-based applications. This type of study makes it possible to estimate the incidence of ADRs in daily practice [22] and additionally to implement the information gathered from large registration studies, providing a more complete picture of the safety profile of the vaccines in all types of subpopulations. In contrast to spontaneously reported data, the denominator of the studied cohort is known and well characterized so that ADR frequencies can be calculated, and directly compared to data collected in the pre-licensing phase. In addition, information on timing, duration and burden of adverse reactions as well as patient's medical history and other clinically relevant data elements are available.

During the pandemic, EMA supported a large-scale cohort event monitoring system under the framework of the COVID-19 Vaccine Monitor (CVM) study to estimate, describe and compare incidence rates of patient-reported adverse reactions of different COVID-19 vaccines across the participating countries in the general and special populations (pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy, and people with prior SARS-CoV-2 infection) [26]. This study has the advantage of also including data on booster vaccination. So far, less data have been reported on the safety of the booster vaccines compared to primary vaccinations, especially in data from a real-world setting [27–34].

Herein, we report an up to date and in-depth analysis of the frequency of patient reported ADRs after the 1st, 2nd, and booster vaccination and to identify potential predictors in developing ADRs. Moreover, we explored time to onset (TTO) and duration of COVID-19 vaccine related adverse reactions.

2. Methods

2.1. Study set-up and participating countries

Based on a common protocol (EU PAS Register Number EUPAS39798), we used data from two different data-collection tools; Lareb Intensive Monitoring (LIM), developed by the Dutch pharmacovigilance centre Lareb [35] and Research Online (RO) platform developed by the University Medical Centre Utrecht (UMCU) in the Netherlands. These were adapted for use in multiple countries, to monitor the safety of first, second, and booster doses of EMA-approved COVID-19 vaccines in the general population.

The Netherlands, Belgium, France, the United Kingdom, and Italy participated using the LIM app to collect the first and second doses. Data on booster doses were collected through RO in Italy, France, the United Kingdom, Portugal, Romania, Slovakia and Spain.

Each organization had a country-specific website and questionnaires (Q) were in the local language(s). Participants could be included in more than one subset. Participants registered online within two days of receiving the vaccine and reported demographic data, medical history in a baseline questionnaire, and ADRs up to six months after vaccination in six follow-up questionnaires. Registration took place in a period ranging from February 2021 to February 2023 A custom-made common data model (CDM) was developed to allow the combination of data from different data sources and perform statistical analysis. Although Germany and Croatia worked with the same study protocol [26,36], they did not use the same data collection tools and analysis on aggregated data were possible only for these countries and therefor they could be not be taken into account during this study where we pooled data together using the CDM. Additional details can be found in the CVM final study report [36] and previous publication [26].

In the questionnaires, solicited adverse reactions that were known to occur frequently were explicitly named, as they are linked to the injection itself or reactogenicity of the immune system. These consisted of: *Fever/feverishness, Shivering/chills, Headache, Nausea, Myalgia/muscle pain, Arthralgia/joint pain, Malaise*, *Fatigue* and *Injection site reaction (redness, warmth, pain, itch, hematoma, swelling, induration, ELS (extensive limb swelling))*. If two or more of the following adverse reactions were flagged by a study participant (redness, warmth, pain, swelling), it was also asked whether the redness and/or swelling went past the elbow or shoulder. In addition, it was asked in each questionnaire whether any *other* (unsolicited) suspected adverse reactions occurred as free text. Adverse reactions were coded with the Medical Dictionary for Regulatory Activities (MedDRA®) [37]. Solicited ADRs could be automatically MedDRA®-coded, the unsolicited events were manually assessed and coded, and the seriousness was classified based on international criteria [38].

2.2. Descriptive analyses of frequencies of COVID-19 vaccine-related adverse reactions

Firstly, an overview table of respondents who filled in at least one Questionnaire (Q1) was made, including participants per country, vaccine brand, across men vs women and age groups. The table provides the number and percentage of any ADR, serious ADRs [38] and Adverse Events of Special Interest (AESI) [39]. For percentages of ADRs corresponding 95 % Confidence Intervals (CI) were calculated.

For the participants *with complete vaccination data of the primary vaccinations*, a heatmap of the percentage of participants who reported at least one ADR, one solicited ADR, and one solicited ADR without

injection site reactions was generated; the data were stratified by vaccine brand, vaccination moment, age group and sex. The same strata were used to calculate the percentages of participants with a reported body temperature of 38.0 °C or higher. We also stratified for a medical history of prior COVID-19 infection. Separate heatmaps are also available for booster doses. The denominator for these calculations was the number of participants with completed questionnaires from baseline to Q6 for 1st and 2nd vaccination or Q5 in case of booster vaccination.

2.3. Analysis of potential predictors in developing COVID-19 vaccine-related adverse reactions

A generalized linear mixed-effects model (GLMM) was used, which can fit random intercepts and random slopes for each unit of measurement for the different predictors which vary across the different measurement units. The random intercept/slopes suggest in particular variance–covariance structures across different measurements within a unit [40]. With the GLMM, we could examine the occurrence of ADRs after receipt of the first or the second vaccine dose or booster dose and estimate the contribution of vaccine brand, sex, age, or a history of prior COVID-19 infection. The dependent variable was either any ADR, any solicited ADR, or fever. A mixed-effects logistic regression was used due to the binary outcome of the dependent variable. Fixed-effect covariates included vaccine brand, sex, age (as a numerical variable), and prior COVID-19 infection confirmed with a polymerase chain reaction (PCR) test. We included 'country' as a random intercept because of the variance in terms of vaccination rates and study enrollment both temporally and geographically. Again, the denominator for these calculations was the number of participants with completed questionnaires from baseline to Q6 for 1st and 2nd vaccination and completed questionnaires from baseline to Q5 for booster vaccination.

2.4. Analysis of time-to-onset and duration of COVID-19 vaccine-related adverse reactions

For the participants with *complete vaccination data of the primary vaccinations or booster*, the TTO and time to recovery (TTR) of reported ADRs (median and 1st interquartile range and 3rd interquartile range in hours) were analyzed and visualized with a combination of violin plots and boxplots. Participants could report the TTO) of an ADR and TTR as number of seconds, minutes, hours, days, weeks or months. All analyses were performed using R statistical software (version 4.3.1). The mixed-effects logistic regression was conducted using the lme4 R package. Statistical significance was declared if $p < 0.05$. For heatmaps and TTO/TTR plots, the ggplot2 R package was used, for TTO/TTR tables the flextable R package.

2.5. Sensitivity analysis

Sensitivity analyses were performed to get insight in the effect of loss to follow-up (LTFU). For these sensitivity analyses, we calculated the percentage of participants who reported at least one ADR in the period from Q1 to, Q2, Q3, Q4 or Q5. The denominator for these calculations was the number of participants who had filled in the questionnaire at the stratified moment.

3. Results

For this study, a total of 29,837 participants were included with LIM at first vaccination in the general population, who completed at least the baseline and the first follow-up questionnaire. Due to loss to follow-up (not responding to subsequent questionnaires) the number of participants who received dose 1 is higher than those who received dose 2 (Table 1). Through RO, 7,250 participants who completed at least the baseline and the first follow-up questionnaire were included for the booster.

3.1. Descriptive analyses of frequencies

Table 2 provides an overview of the participants with a primary vaccination in the study across countries including participants per country, vaccine brand, across men vs women and age groups. The percentage of participants who reported at least one ADR is 74.32 % (95 %CI 73.82—74.81). The percentage of serious ADRs in the study is low (0.24 %, 95 %CI 0.19—0.31) based on participants who filled in at least Q1 and the number of AESI is even lower (0.19 %, 95 %CI 0.14, 0.25).

Table 3 provides similar data for the Booster vaccination. The percentage of participants who reported at least one ADR is 64.45 % (95 % CI 63.31—65.57). The percentage of serious ADRs and AESI after booster vaccination in the study is low (0.26 %, 95 %CI 0.15, 0.41) based on participants who filled in at least Q1.

Fig. 1 shows a heatmap of the percentages of participants with complete vaccination data who reported any adverse reaction after the 1st and 2nd doses across vaccine brands and age groups and stratified by sex. This shows that adverse reactions were more frequent after the 1st than the 2nd dose of AstraZeneca, across all strata and after the second dose for Moderna. With increasing age fewer ADRs are reported, across all vaccines, and women report more frequently than men. A similar pattern was observed when focusing only on the solicited adverse reactions: older participants reported fewer adverse reactions than younger age groups. Participants report more adverse reactions after the first dose across all vaccine brands except Moderna, where most participants report more reactions after the second dose. This pattern is not as marked in the age categories above 60 years. Electronic Supplemental Material Figs. 1-4 show stratifications of the Heatmap for solicited ADRs, with and without injection site reactions and pyrexia, pyrexia only, and stratified for prior SARS-CoV-2 infection. When looking at pyrexia, defined as a body temperature increase above 38 °C, vaccinees who received AstraZeneca reported fever rates, higher after dose 1 than 2, both in males and females, and mostly in younger persons. Participants who had a prior SARS-CoV-2 infection (confirmed with a positive test) experienced at least one adverse reaction more often after the 1st dose compared to participants who did not have prior COVID-19. This pattern was observed in both men and women and across vaccine brands.

Heatmaps were also made for participants who filled in all questionnaires after receiving the booster vaccination. It should be noted that for the booster vaccination, the number of inclusions in the study is much lower than for 1st and 2nd doses and data are generally only available for the Pfizer and Moderna vaccines. Even if the booster vaccines' dosage is lower than for 1st and 2nd doses [41], we observed a similar pattern of ADR frequency for Pfizer and Moderna boosters compared to primary vaccination, with more ADRs being reported for the Moderna than Pfizer across strata. For the booster vaccination, heatmaps for frequencies of reported ADRs across strata (solicited with and without injection site reactions, pyrexia only, and with/without prior COVID-19) are shown in Electronic Supplemental Material Figs. 5-8.

Table 1
Respondents per questionnaire (Q) for 1st, 2nd and booster vaccination.

1st and 2nd vaccination data with LIM		Booster vaccination data with RO	
Questionnaire	Respondents	Questionnaire	Respondents
baseline	34,051 (100.0 %)	baseline	9747
Q1	29,837 (87.6 %)	Q1	6984
Q2	27,391 (80.4 %)	Q2	5679
Q3	24,569 (72.2 %)	Q3	4714
Q4	22,411 (65.8 %)	Q4	3594
Q5	20,261 (59.5 %)	Q5	3206
Q6	17,913 (52.6 %)		

Table 2
Overview table of respondents with a *primary vaccination (1st and 2nd vaccination)* who filled in at least one Questionnaire (Q1) and total number of ADRs in the study compared to Q1 in LIM.

	N_AstraZeneca (%)	N_BioNtech/Pfizer (Comirnaty) (%)	N_Moderna (%)	N_Johnson&Johnson (Janssen) (%)	N_Novavax (Nuvaxovid) (%)	N_Unknown (%)	N_total (%)	N_Any_ADR (%)	N_Any_sollicited (%)	N_Any_serious (%)	N_Any_AESI (%)
Country											
BELGIUM	1 (0.01)	28 (0.19)	1 (0.03)	8 (0.32)	0 (0.00)	0 (0.00)	38 (0.13)	25 (65.79)	25 (65.79)	1 (2.63)	0 (0.00)
FRANCE	3 (0.03)	1118 (7.51)	52 (1.44)	3 (0.12)	0 (0.00)	4 (6.90)	1180 (3.95)	839 (71.10)	814 (68.98)	6 (0.51)	3 (0.25)
ITALY	3 (0.03)	622 (4.18)	110 (3.05)	8 (0.32)	2 (100.00)	6 (10.34)	751 (2.52)	495 (65.91)	478 (63.65)	9 (1.20)	0 (0.00)
NETHERLANDS	8805 (99.88)	12,907 (86.75)	3432 (95.12)	2455 (99.23)	0 (0.00)	41 (70.69)	27,640 (92.64)	20,668 (74.78)	20,017 (72.42)	57 (0.21)	54 (0.20)
UK	4 (0.05)	204 (1.37)	13 (0.36)	0 (0.00)	0 (0.00)	7 (12.07)	228 (0.76)	147 (64.47)	145 (63.60)	0 (0.00)	0 (0.00)
Sex											
Female	7531 (85.42)	6685 (44.93)	2380 (65.96)	1767 (71.42)	1 (50.00)	34 (58.62)	18,398 (61.66)	15,829 (86.04)	15,498 (84.24)	54 (0.29)	41 (0.22)
Male	1285 (14.58)	8194 (55.07)	1228 (34.04)	707 (28.58)	1 (50.00)	24 (41.38)	11,439 (38.34)	6345 (55.47)	5981 (52.29)	19 (0.17)	16 (0.14)
Age											
Age 0 – 19 years	63 (0.71)	597 (4.01)	39 (1.08)	31 (1.25)	0 (0.00)	6 (10.34)	736 (2.47)	508 (69.02)	492 (66.85)	3 (0.41)	0 (0.00)
Age 20 – 29 years	1193 (13.53)	1227 (8.25)	468 (12.97)	363 (14.67)	0 (0.00)	6 (10.34)	3257 (10.92)	2991 (91.83)	2967 (91.10)	5 (0.15)	6 (0.18)
Age 30 – 39 years	1368 (15.52)	1388 (9.33)	669 (18.54)	383 (15.48)	0 (0.00)	5 (8.62)	3813 (12.78)	3501 (91.82)	3455 (90.61)	11 (0.29)	9 (0.24)
Age 40 – 49 years	1787 (20.27)	992 (6.67)	1048 (29.05)	586 (23.69)	0 (0.00)	15 (25.86)	4428 (14.84)	4015 (90.67)	3956 (89.34)	12 (0.27)	6 (0.14)
Age 50 – 59 years	2302 (26.11)	756 (5.08)	1252 (34.70)	1061 (42.89)	1 (50.00)	4 (6.90)	5376 (18.02)	4620 (85.94)	4507 (83.84)	10 (0.19)	16 (0.30)
Age 60 – 69 years	2072 (23.50)	762 (5.12)	107 (2.97)	46 (1.86)	1 (50.00)	8 (13.79)	2996 (10.04)	2430 (81.11)	2350 (78.44)	14 (0.47)	7 (0.23)
Age 70 – 79 years	27 (0.31)	5458 (36.68)	24 (0.67)	4 (0.16)	0 (0.00)	5 (8.62)	5518 (18.49)	2612 (47.34)	2407 (43.62)	10 (0.18)	9 (0.16)
Age 80 + years	4 (0.05)	3699 (24.86)	1 (0.03)	0 (0.00)	0 (0.00)	9 (15.52)	3713 (12.44)	1497 (40.32)	1345 (36.22)	8 (0.22)	4 (0.11)
Total	8816 (100.00)	14,879 (100.00)	3608 (100.00)	2474 (100.00)	2 (100.00)	58 (100.00)	29,837 (100.00)	22,174 (74.32)	21,479 (71.99)	73 (0.24)	57 (0.19)

Table 3
Overview table of respondents with a *booster vaccination* who filled in at least one Questionnaire (Q1) and total number of ADRs in the study compared to Q1 in RO.

	N_AstraZeneca (%)	N_BioNtech/Pfizer (Comirnaty) (%)	N_Moderna (%)	N_Johnson&Johnson (Janssen) (%)	N_Novavax (Nuvaxovid) (%)	N_Unknown (%)	N_total (%)	N_Any_ADR (%)	N_Any_sollicited (%)	N_Any_serious (%)	N_Any_AESI (%)
Country											
France	5 (17.86)	1638 (45.88)	2198 (65.34)	1 (20.00)	0 (0.00)	1 (7.69)	3843 (55.03)	2455 (63.88)	2326 (60.53)	2 (0.05)	10 (0.26)
Ireland	1 (3.57)	138 (3.87)	38 (1.13)	0 (0.00)	0 (0.00)	0 (0.00)	177 (2.53)	81 (45.76)	79 (44.63)	1 (0.56)	0 (0.00)
Italy	12 (42.86)	1175 (32.91)	678 (20.15)	2 (40.00)	4 (100.00)	2 (15.38)	1873 (26.82)	1243 (66.36)	1198 (63.96)	12 (0.64)	6 (0.32)
Portugal	0 (0.00)	63 (1.76)	38 (1.13)	0 (0.00)	0 (0.00)	0 (0.00)	101 (1.45)	62 (61.39)	61 (60.40)	1 (0.99)	0 (0.00)
Romania	0 (0.00)	134 (3.75)	60 (1.78)	2 (40.00)	0 (0.00)	0 (0.00)	196 (2.81)	144 (73.47)	142 (72.45)	0 (0.00)	0 (0.00)
Slovakia	0 (0.00)	8 (0.22)	1 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	9 (0.13)	4 (44.44)	3 (33.33)	0 (0.00)	0 (0.00)
Spain	1 (3.57)	72 (2.02)	121 (3.60)	0 (0.00)	0 (0.00)	3 (23.08)	197 (2.82)	145 (73.60)	140 (71.07)	0 (0.00)	0 (0.00)
Switzerland	0 (0.00)	42 (1.18)	54 (1.61)	0 (0.00)	0 (0.00)	1 (7.69)	97 (1.39)	66 (68.04)	66 (68.04)	1 (1.03)	0 (0.00)
United Kingdom	9 (32.14)	300 (8.40)	176 (5.23)	0 (0.00)	0 (0.00)	6 (46.15)	491 (7.03)	301 (61.30)	285 (58.04)	1 (0.20)	2 (0.41)
Sex											
Female	12 (42.86)	2335 (65.41)	1981 (58.89)	3 (60.00)	2 (50.00)	8 (61.54)	4341 (62.16)	3034 (69.89)	2916 (67.17)	13 (0.30)	13 (0.30)
Male	16 (57.14)	1235 (34.59)	1383 (41.11)	2 (40.00)	2 (50.00)	5 (38.46)	2643 (37.84)	1467 (55.51)	1384 (52.36)	5 (0.19)	5 (0.19)
Age											
Age 0 – 19 years	0 (0.00)	202 (5.66)	18 (0.54)	0 (0.00)	0 (0.00)	2 (15.38)	222 (3.18)	121 (54.50)	115 (51.80)	1 (0.45)	1 (0.45)
Age 20 – 29 years	3 (10.71)	736 (20.62)	189 (5.62)	0 (0.00)	0 (0.00)	3 (23.08)	931 (13.33)	647 (69.50)	625 (67.13)	1 (0.11)	2 (0.21)
Age 30 – 39 years	4 (14.29)	719 (20.14)	821 (24.41)	1 (20.00)	3 (75.00)	1 (7.69)	1549 (22.18)	1103 (71.21)	1068 (68.95)	10 (0.65)	3 (0.19)
Age 40 – 49 years	8 (28.57)	634 (17.76)	922 (27.41)	0 (0.00)	1 (25.00)	3 (23.08)	1568 (22.45)	1084 (69.13)	1041 (66.39)	2 (0.13)	4 (0.26)
Age 50 – 59 years	6 (21.43)	615 (17.23)	795 (23.63)	2 (40.00)	0 (0.00)	1 (7.69)	1419 (20.32)	885 (62.37)	842 (59.34)	2 (0.14)	2 (0.14)
Age 60 – 69 years	4 (14.29)	493 (13.81)	505 (15.01)	1 (20.00)	0 (0.00)	0 (0.00)	1003 (14.36)	534 (53.24)	496 (49.45)	1 (0.10)	5 (0.50)
Age 70 – 79 years	3 (10.71)	149 (4.17)	107 (3.18)	0 (0.00)	0 (0.00)	3 (23.08)	262 (3.75)	119 (45.42)	106 (40.46)	1 (0.38)	1 (0.38)
Age 80 + years	0 (0.00)	22 (0.62)	7 (0.21)	1 (20.00)	0 (0.00)	0 (0.00)	30 (0.43)	8 (26.67)	7 (23.33)	0 (0.00)	0 (0.00)
Total	28 (100.00)	3570 (100.00)	3364 (100.00)	5 (100.00)	4 (100.00)	13 (100.00)	6984 (100.00)	4501 (64.45)	4300 (61.57)	18 (0.26)	18 (0.26)

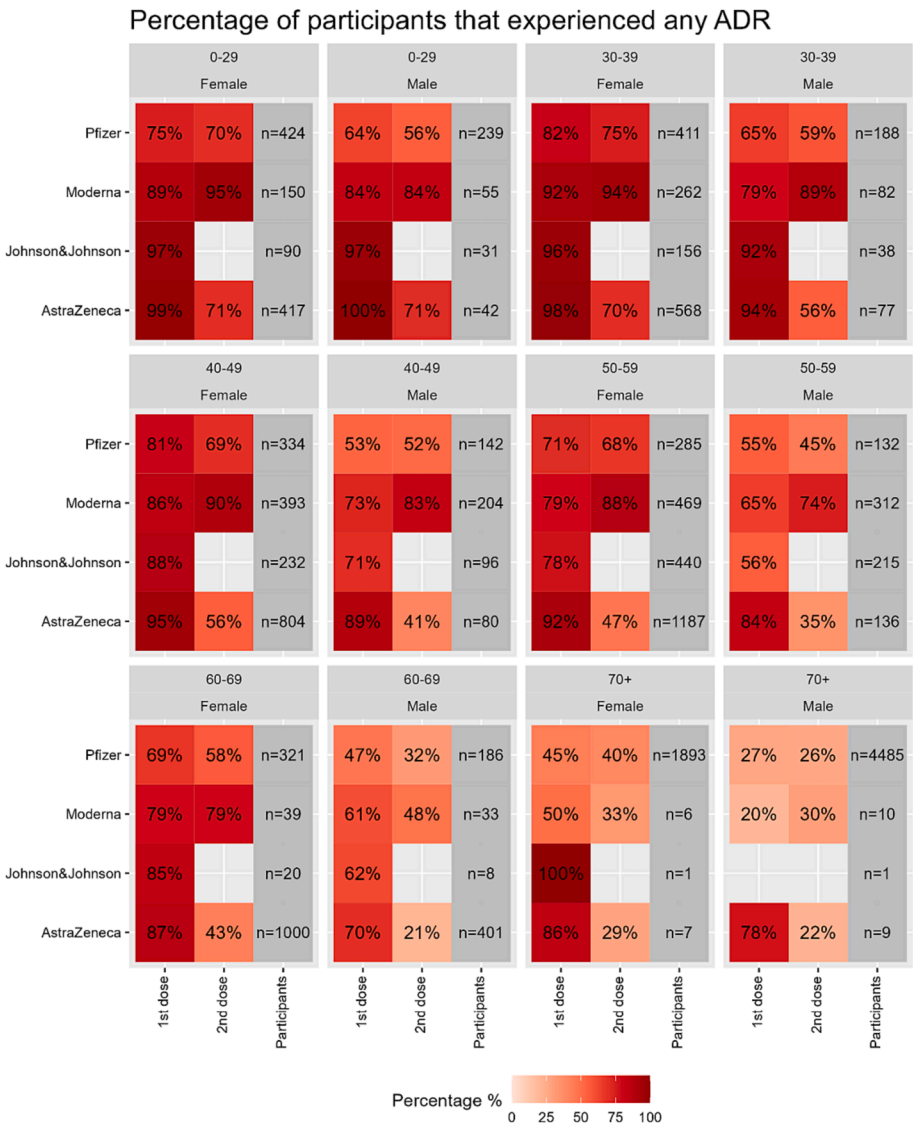

Fig. 1. Heatmap for any ADR in total population stratified for dose 1 and 2.

3.2. Analysis of potential predictors in developing ADRs

The estimated effects of co-variates (vaccine brand, age, sex and a prior SARS-CoV-2 infection) are presented as odds ratios (ORs) with 95 % confidence intervals in Table 4.

For the general population, with increasing age, there is a lower contribution to the occurrence of any ADR, any solicited ADR, or fever; There were significant differences between vaccine brands, with the highest OR found for the 1st dose of AstraZeneca with an OR of 4.37 (95 % CI 3.87–4.94) for all ADRs and an especially high OR for pyrexia of 25.34 (95 %CI 20.26–31.69). Also, for the Janssen vaccine, high ORs for pyrexia were found for dose 1; OR 11.60 (95 %CI 8.97–15.02). On the contrary, for AstraZeneca dose 2, there is a lower OR for the occurrence of an ADR as compared to Pfizer dose 2 but not for Moderna. It should be noted that the J&J vaccine was not given in a 2nd dose. Male sex as a predictor has a lower contribution than female sex, for both doses 1 and 2. A prior SARS-CoV-2 infection as a predictor gives an increased OR for any ADR and any solicited ADR and fever for both doses 1 and 2, although the effect is higher for dose 1. For the booster dose, Moderna again had an increased OR for all ADRs, solicited ADRs, and pyrexia as compared to the Pfizer vaccine. No significant increase in OR for prior COVID-19 was noted. Booster effects for age and sex were similar to dose 1 and 2. For the AstraZeneca vaccine, the number of collected booster dosages in the study was very limited.

3.3. Analysis of time-to-onset and duration of events

The TTO of adverse reactions across doses 1 and 2, for participants with complete vaccination data, is shown in Fig. 3. The median TTO is within a day for the 1st dose (median 14 h) and slightly longer for the 2nd dose (median 24 h). The median TTO is lower for dose 1 and especially for women in comparison to men (12 to 24 h respectively for all ADRs irrespective of vaccine brand). The TTR has a median of 36 h for both the 1st and 2nd dose (Fig. 4). For both TTO and TTR, there is a small group (n = 73 respondents, 0.24 % of all participants who filled in at least Q1) that reported ARDs with either a long TTO after vaccination or with a long duration (TTR) >= 3 months.

The TTO and TTR for the booster dose are shown in Figs. 5 and 6. The median TTO for the booster dose is 24 h, the median TTR is 72 h.

Electronic Supplemental Material Tables 1 and 2 and Figures ESM 9–14 show the TTO and TTR for age strata, for male vs female and for commonly reported ADRs. ESM-15 – 20 shows the TTO and TTR across the same strata for the booster dose.

Electronic Supplemental Material Table 3 gives an overview of the reported MedDRA Preferred Terms (PTs) for reactions with either TTO or TTR >= 3 months. For the ADRs with a long TTR, fatigue was the

Table 4
Estimated effects of co-variates in development of ADRs are presented as odds ratios (ORs) with 95% confidence intervals.

	Coefficient_names	OR	95 %CI_lower_OR	95 %CI_upper_OR
DOSE 1 ANY ADR				
	(Intercept)	10.20	5.99	17.37
Brand	Pfizer (Ref category)			
	Moderna	1.66	1.45	1.91
	Janssen	1.56	1.33	1.83
	AstraZeneca	4.37	3.87	4.94
Age	Age	0.96	0.96	0.96
Sex	Male	0.43	0.39	0.46
Prior SARS-CoV-2 infection	Prior_COVID	2.62	2.08	3.31
DOSE 2 ANY ADR				
	(Intercept)	6.00	4.12	8.73
Brand	Pfizer (Ref category)			
	Moderna	3.87	3.35	4.46
	AstraZeneca	0.59	0.53	0.64
Age	Age	0.97	0.96	0.97
Sex	Male	0.48	0.45	0.52
Prior SARS-CoV-2 infection	Prior_COVID	1.25	1.05	1.49
DOSE 1 SOLLICITED ADR				
	(Intercept)	9.48	5.81	15.46
Brand	Pfizer (Ref category)			
	Moderna	1.63	1.43	1.86
	Janssen	1.51	1.30	1.77
	AstraZeneca	4.40	3.92	4.94
Age	Age	0.96	0.96	0.96
Sex	Male	0.44	0.41	0.47
Prior SARS-CoV-2 infection	Prior_COVID	2.58	2.06	3.22
DOSE 2 SOLLICITED ADRS				
	(Intercept)	5.28	3.72	7.49
Brand	Pfizer (Ref category)			
	Moderna	3.98	3.47	4.57
	AstraZeneca	0.59	0.54	0.65
Age	Age	0.97	0.96	0.97
Sex	Male	0.49	0.45	0.53
Prior SARS-CoV-2 infection	Prior_COVID	1.24	1.05	1.48
DOSE 1 PYREXIA				
	(Intercept)	0.07	0.05	0.09
Brand	Pfizer (Ref category)			
	Moderna	2.11	1.54	2.89
	Janssen	11.60	8.97	15.02
	AstraZeneca	25.34	20.26	31.69
Age	Age	0.97	0.97	0.98
Sex	Male	0.50	0.43	0.59
Prior SARS-CoV-2 infection	Prior_COVID	2.57	2.13	3.10
DOSE 2 PYREXIA				
	(Intercept)	0.17	0.13	0.23
Brand	Pfizer (Ref category)			
	Moderna	6.61	5.51	7.93
	AstraZeneca	0.79	0.64	0.99
Age	Age	0.97	0.97	0.98
Sex	Male	0.52	0.43	0.62
Prior SARS-CoV-2 infection	Prior_COVID	1.78	1.35	2.34
BOOSTER 1 ANY ADR				
	(Intercept)	3.36	2.28	4.96
Brand	Pfizer (Ref category)			
	Moderna	1.62	1.39	1.89
	AstraZeneca	1.58	0.33	7.54
Age	Age	0.98	0.98	0.99
Sex	Male	0.53	0.45	0.62
Prior SARS-CoV-2 infection	Prior_COVID	1.04	0.81	1.33
BOOSTER SOLLICITED ADR				
	(Intercept)	3.11	2.20	4.40
Brand	Pfizer (Ref category)			
	Moderna	1.65	1.42	1.91
	AstraZeneca	0.94	0.19	4.52
Age	Age	0.98	0.98	0.99
Sex	Male	0.55	0.47	0.64
Prior SARS-CoV-2 infection	Prior_COVID	0.98	0.77	1.24
BOOSTER PYREXIA				
	(Intercept)	0.07	0.04	0.12
Brand	Pfizer (Ref category)			
	Moderna	2.53	1.89	3.39
	AstraZeneca	–	–	–
Age	Age	0.99	0.98	1.00
Sex	Male	0.68	0.51	0.90
Prior SARS-CoV-2 infection	Prior_COVID	1.31	0.87	1.97

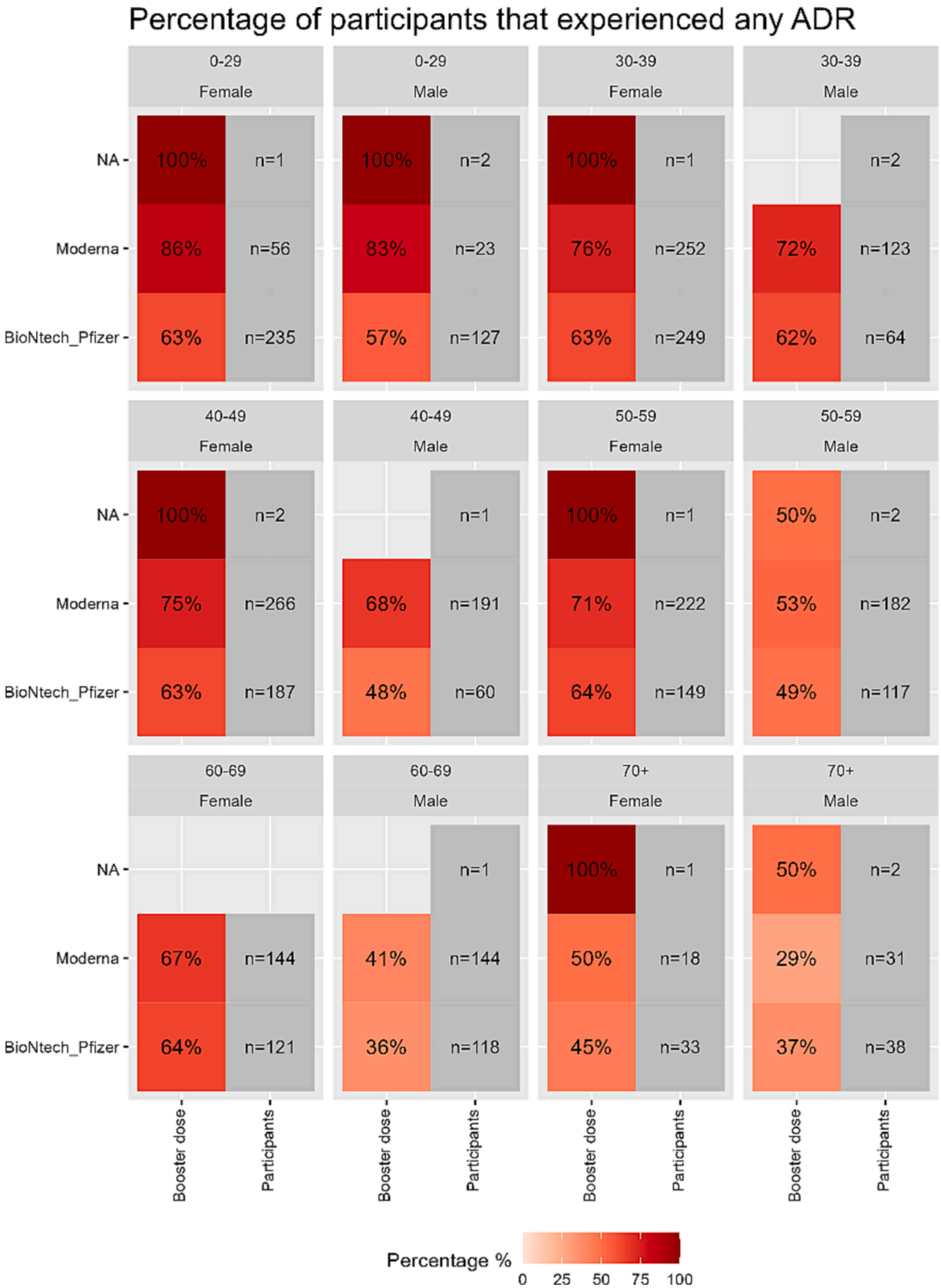

Fig. 2. Heatmap for any ADR in the general population for Booster dose.

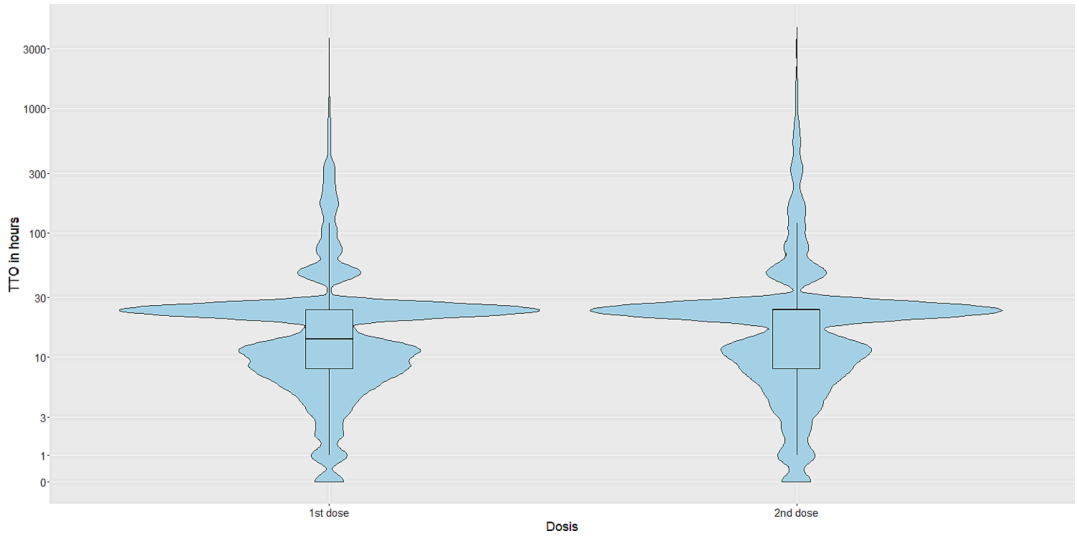

Fig. 3. Combination violin/box-plot showing the Time to Onset (TTO) of adverse reactions for doses 1 and 2 (logarithmic scale).

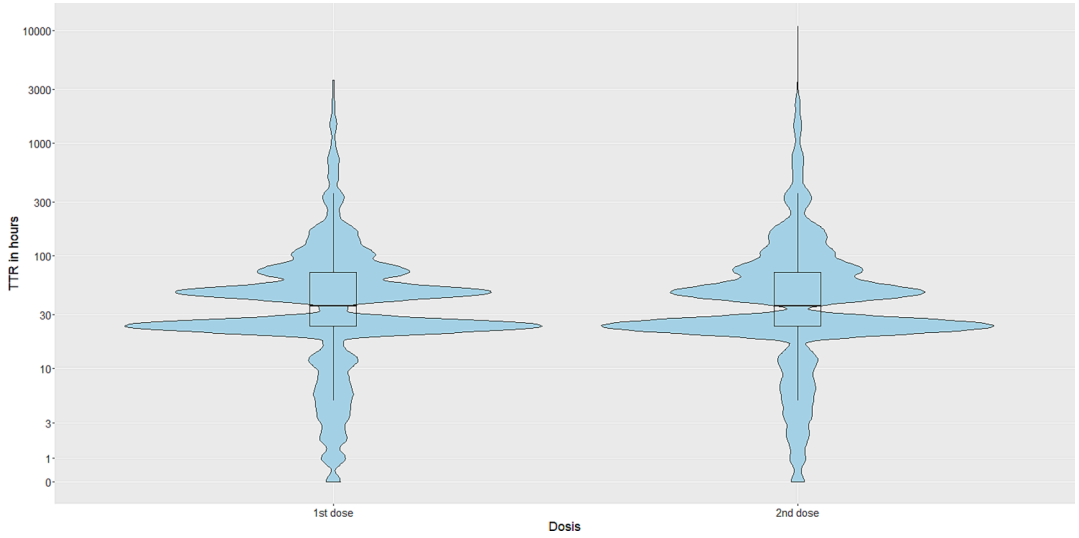

Fig. 4. Combination violin/box-plot showing the Time to Recovery (TTR) of adverse reactions for doses 1 and 2 (logarithmic scale).

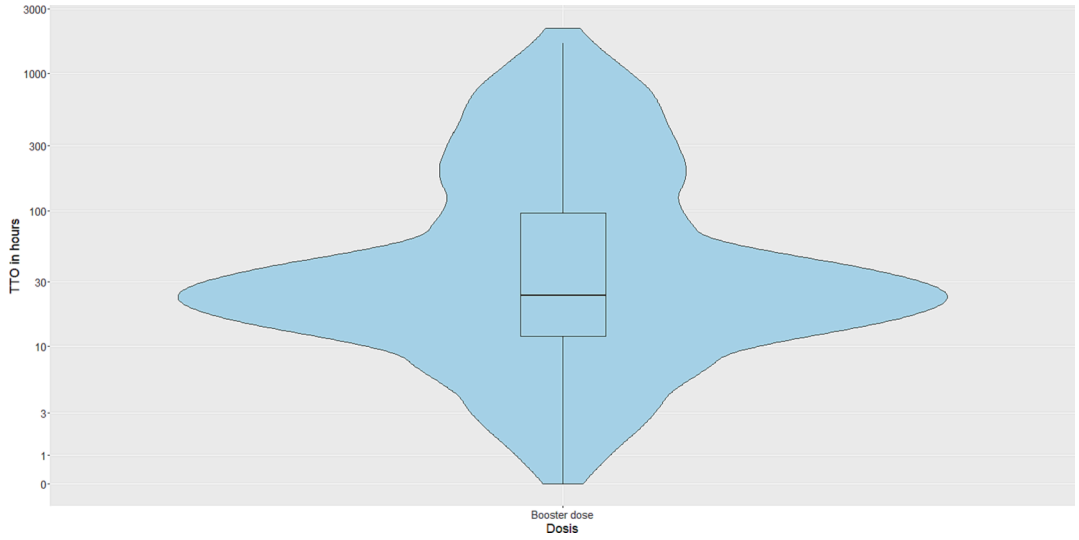

Fig. 5. Combination violin/box-plot showing the Time to Onset (TTO) of adverse reactions for Booster dose (logarithmic scale).

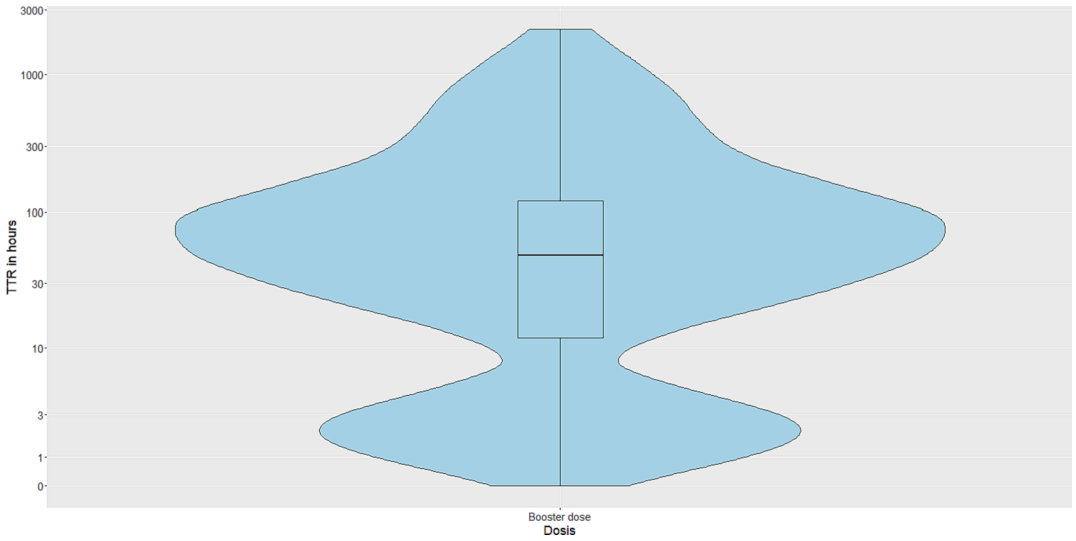

Fig. 6. Combination violin/box-plot showing the Time to Recovery (TTR) of adverse reactions for Booster dose (logarithmic scale).

most frequently reported, followed by headache.

3.4. Sensitivity analysis

For the sensitivity analysis, heatmaps show the percentage of participants who reported at least one ADR in the period from Q1 to Q2, Q3, Q4 or Q5. Compared to the results for participants with full vaccination data, meaning those who have filled in Q1 to Q6, the stratified heatmaps show only minor differences. Based on these heatmaps, the effects of Loss to Follow-up (L2FU) or participants reporting at least one ADR are deemed limited. Electronic Supplemental Material Figure 21 shows the stratified heatmaps.

4. Discussion

This European multi-Country Cohort Event Monitoring Study, based on patient-reported outcomes (PROs), provides insight into the pattern of adverse reactions following COVID-19 vaccines across age groups, vaccine brands and doses, sex, and prior SARS-CoV-2 infection and use a mixed-effects model analysis to look at the contribution of each of these factors as a predictor for the development of ADRs. This was possible thanks to data available on an individual patient level and not only on an aggregated level as in a previous study for this cohort [26]. A major advantage of this study is the inclusion of data on booster vaccination and not only on the primary vaccination.

Solicited local ADRs were very frequent, especially injection site reactions. Fever was highest after AstraZeneca vaccination dose 1. In the youngest age group (up to 29 years old), 45 and 44 % of men and women respectively reported pyrexia after dose 1. In general, frequency of any ADRs was higher after the 1st dose of all vaccine brands, except for Moderna where participants were more likely to report an ADR after dose 2. This was confirmed in the mixed effects model analysis where potential predictors in developing ADRs were studied. Results from our study are similar to other cohort event monitoring studies on the primary vaccinations, such as the V-Safe study in the USA [10] and the UK study using the COVID Symptom Study app [42].

Data on booster vaccination mainly included the Pfizer and Moderna vaccines. Reported ADR ORs for the booster in the mixed-model analysis were similar to dose 1, although the OR of a prior COVID-19 infection as a predictor in the mixed model is lower for the booster than for dose 1. These results confirm results from other studies, which have found a high degree of similarity in local and systemic ADRs per vaccination moment overall [32,41]. In a large longitudinal, prospective, community-based study (ZOE COVID Study) in the UK, in which data were self-reported through an app, 73.4 % of participants reported one or more local ADRs within 8 days of the booster vaccination and 15.9 % reported having at least one systemic ADR [32].

For this study an extensive analysis was also performed for the TTO and TTR of ADRs. This is information that is useful to inform vaccinated persons on what to expect after vaccination. In addition, the TTO or TTR distribution of ADRs can be used for the detection of previously unknown events [43,44]. TTO was within an hour for injection site pain and within one day for most other solicited reactions. For systemic reactions median onset time often exceeded a day. For the solicited ADRs, the reported TTO fits with the time frame of immune response induction which is the mechanism underlying these ADRs and is similar to TTO reported in other studies [42]. On the other hand, some recall bias is likely to occur with an increasing TTO since the reporter does not always associate an event with a previous vaccination. Additionally, coincidental events with a short latency may be reported unjustly and may therefore be misclassified as true ADRs. Additionally, TTO clustering may occur depending on the unit reported, for instance, reactions occurring after 20 h, or 27 h may both be reported as 1 day [45]. Very infrequently ADRs in the cohort with either a long TTO or a long TTR have been reported. For the ADRs with a long TTR, fatigue was most frequently reported. It should be noted that some of these ADRs with a long TTO or TTR might be due to errors while filling in the questionnaire by respondents. In the context of COVID-19 vaccinations, there have been literature descriptions and spontaneous reports of prolonged symptoms that have occurred in vaccinated individuals with a temporal relationship to vaccination [46–48].

In this manuscript, the focus was not on serious ADRs and adverse events of special interest (AESI), which have been already largely described elsewhere [26,36]. It should be noted that the percentage of both serious ADRs and AESI was low and no new safety signals about unknown serious ADRs were found in this study.

4.1. Strengths and limitations

Cohort Event Monitoring studies have the benefit of having a proper denominator, which allows for quantification of adverse reactions. A major strength of this study was that we were able to roll out a Cohort Event Monitoring study across multiple European countries with a common protocol and a common data model was developed which allowed us to pool LIM and RO data and analyze data on individual patient level. Also, we have been able to analyse data on booster vaccination in addition to doses 1 and 2.

In addition to the frequency of events and potential predictors for

developing adverse reactions after COVID-19 vaccination, we focused on the TTO and TTR of reported reactions. Characteristics of adverse reactions, such as the time course, are important for the public as it provides them with information and awareness on what to expect after receiving a drug or vaccine [49,50].

The readiness of data collection infrastructure and ethical approval timings were challenging in this study. Countries that had existing data collection tools before the vaccines were launched such as the Netherlands, managed to deploy the systems earlier, leading to a large inclusion of vaccinated persons at the start of the vaccine roll-out while other countries deployed the systems in a later phase of the roll-out and had difficulties to enroll a large cohort. This stresses the importance of a timely data collection infrastructure, ethical approval, and (government) support in setting-up a study such as this. Due to the variation between countries, we opted for a generalized linear mixed-effects model (GLMM). By including a random-effects intercept grouped by country, we accounted for differences in the occurrence of ADRs that might exist due to country-specific variations such as variance in terms of vaccination rates and study enrollment both temporally and geographically.

Unfortunately, considering the inclusion of four data-collection tools in the whole CVM cohort event monitoring study [26,36], we were not able to include here and pool data in the CDM from the SafeVac 2.0 platform developed by the Paul-Ehrlich-Institute in Germany and web-application OPeN developed by the Agency for Medicinal Products and Medical Devices of Croatia (HALMED). Data from these countries could only be available as aggregated data, thus, the performed analyses in this work were not applicable to them as done for LIM and RO data.

Cohort Event Monitoring studies may suffer from selection bias and L2FU We performed crude sensitivity analyses for L2FU where the denominator was the number of persons "observed" from Q1 to Q and the percentage of participants with at least one ADR was calculated. However, this percentage can still be biased if the ADR proportion in the corresponding unobserved subgroup of participants differs from this percentage. Therefore, more L2FU scenarios could be further explored for a better quantification of the risk in different scenarios of this observational study.

5. Conclusion

Solicited adverse reactions, including injection site reactions, are very common across vaccination moments, including booster vaccination. Potential predictors for these reactions are the brand of vaccine used, the patient's age, sex and prior SARS-CoV-2 infection. As expected, the time-to-onset of reported reactions has a median of a day for dose 1 and slightly longer for dose 2. Time to Recovery is generally also within a few days.

Despite some limitations due to study design and study-roll out, Cohort Event Monitoring studies can allow prompt and almost real-time observations of the safety of medications directly from a patient-centered perspective, which can play a crucial role for regulatory bodies during an emergency setting such as the COVID-19 pandemic.

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Ethical approval

The study in France was approved by the Comité de Protection des personnes (CPP – 21.00821.210217) and the Commission nationale de l'informatique et des libertés (CNIL – DR-2021-209) under the name EVANESCO.

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.

The study in Italy was approved by the Comitato Etico dell'Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani I.R.C.C.S. under the name "Cohort Event Monitoring of safety of COVID-19 vaccines".

For the UK, NHS Research Ethics Committee (REC) and Health Research Authority (HRA) approval was obtained for the study.

The study in Slovakia was approved by the Ethics committee of the Children's University Hospital Košice (DFN KE).

The study in Spain was approved by the IDIAP Jordi Gol ethics committee (code 4R21/109).

The study in Romania was approved by the Ethics committee of the Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca (no 246/30.06.2021).

CRediT authorship contribution statement

Monika Raethke: Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Florence van Hunsel:** Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Nicoletta Luxi:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Thomas Lieber:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Chiara Bellitto:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Erik Mulder:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Francesco Ciccimarra:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Fabio Riefolo:** Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Nicolas H. Thurin:** Writing – review & editing, Supervision. **Debabrata Roy:** Writing – review & editing, Supervision. **Kathryn Morton:** Writing – review & editing, Supervision. **Felipe Villalobos:** Writing – review & editing, Supervision. **Francisco Batel Marques:** Writing – review & editing, Supervision. **Andreea Farcas:** Writing – review & editing, Supervision. **Simona Sonderlichová:** Writing – review & editing, Supervision. **Svetlana Belitser:** Writing – review & editing, Methodology, Formal analysis. **Olaf Klungel:** Writing – review & editing, Supervision. **Gianluca Trifirò:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Miriam C. Sturkenboom:** Conceptualization, Funding acquisition, Writing – review & editing, Methodology, Supervision, Investigation, Formal analysis.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.03.001.

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