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Adverse drug reactions following SARS-CoV-2 vaccination of 3805 healthcare workers cause substantial sick-leave and are correlated to vaccine regimen, age, sex and serological response

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ABSTRACT

Background: Although SARS-CoV-2 vaccination was a critical component to mitigate impact of the pandemic, it also brought specific challenges related to adverse drug reactions (ADRs) when large cohorts of healthcare workers were vaccinated.

Methods and findings: This study reports solicited ADRs and IgG anti-SARS-CoV-2 levels from 3805 healthcare workers in Sweden following primary immunization during 2021. Differences in systemic reactions at a level where study participants needed sick-leave or rescheduling of work shifts differed substantially between vaccine regimens, ranging from 12 % (Comirnaty) to 48 % (heterologous vaccination with Vaxzevria/Spikevax). Multivariable linear regression showed that the anti-S IgG response was dependent on vaccine label and that higher age and increased time from vaccination significantly correlated with lower antibody titers. Multivariable logistic regression models describing the risk for each ADR category in relation to vaccine label, age, sex, anti-S IgG levels post vaccination and time from vaccination showed vaccine label-dependent statistically significant differences in adjusted odds ratios for wide range of ADR categories, as high as OR 10 (95 % CI 7.6–13.5) for fever and chills when comparing Vaxzevria to Comirnaty. Among the mRNA vaccines, use of Spikevax (compared to Comirnaty) correlated with a statistically significant 1.3 to 3.5-fold increase in adjusted ORs for several ADR categories.

Conclusions: Based on a large cohort of health workers, our study confirms that adverse reactions after COVID-19 vaccination can lead to a substantial amount of missed work shifts, potentially causing organizational-level disturbances in staffing. There are significant differences in ADR frequencies related to vaccine type, age and sex, at overall levels not observed for other commonly used vaccines for adults.

1. Introduction

The COVID-19 pandemic has brought unprecedented challenges to healthcare systems worldwide, due to an overall significant morbidity and mortality, but also due to shortenings in personnel due to illness and quarantine. In the beginning of October 2023, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been confirmed in more than 776 million people and has caused more than 7.1 million deaths worldwide [1].

One of the cornerstones in mitigating the consequences of the pandemic has been vaccination, with development efforts started as soon as the virus genome was published in early January 2020 [2,3].

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Already in December 2022, the WHO had documented more than 240 COVID-19 vaccine candidates [4]. The surprisingly fast development of effective vaccines against SARS-CoV-2 has been a crucial step in controlling the pandemic and mortality rates have fallen substantially during 2022 and 2023 [5]. It is estimated that the different vaccines saved more than 20 million lives already in the first year of use [6] and according to WHO, more than 13.5 billion doses from around 40 different vaccines have been administered worldwide up until the beginning of October 2023 [1].

Currently there are four types of COVID-19 vaccines available worldwide: nucleic acid (mRNA and DNA) vaccines, vector vaccines, inactivated vaccines and adjuvanted protein vaccines [4]. In Sweden the following vaccines have been used: Comirnaty (Pfizer-BioNTech), Spikevax (Moderna) and Vaxzevria (Oxford-AstraZeneca) and, in very limited quantities, Nuvaxovid (Janssen).

There have however been concerns about potential adverse events associated with COVID-19 vaccines, both short- and long-term effects, partly due to the extremely fast development of vaccines. Reported common adverse drug reactions (ADRs) resemble those of most other vaccines, including pain or swelling at the injection site, fever, fatigue, headache and muscle aches, and are mild and resolve within a few days. Serious ADRs have been rare, but they do occur and include anaphylaxis, Guillain-Barré syndrome, transverse myelitis, myocarditis, and blood clotting disorders [7–10].

Given the widespread use of COVID-19 vaccines, several systematic reviews have summarized the effectiveness and reported ADRs associated with vaccination [11,12]. Previous experience in other countries has also described that, during vaccination, it was common for healthcare workers to miss work shifts due to ADRs [13–17].

In addition to the registrational clinical trials, cohort event monitoring (CEM) or survey studies have been performed, investigating ADRs in daily practice on a large scale, next to data from spontaneous reporting systems [18]. However, findings from these data collections have generally not put this in relation to antibody levels received through vaccination.

In this study we present a solicited and systematic collection of ADR reports and associated sick leave following COVID-19 vaccination, relating these to antibody levels, vaccine regimen and demographic factors in a cohort of healthcare workers in the Uppsala County of Sweden.

2. Materials and methods

2.1. Study subjects and sampling

Uppsala County, located on the eastern coast of Sweden, has a population of just above 404,000 residents. The County Council, Region Uppsala, has roughly 11,300 employees working in the healthcare sector. Starting in January 2021, healthcare workers in Region Uppsala were vaccinated for COVID-19 and were offered a free SARS-CoV-2 serology test for follow-up between February 15 and October 15, 2021. All healthcare workers, including those who chose not to get vaccinated and those who abstained from taking the second vaccine dose, were invited to participate. In total, 4051 subjects (3468 women and 583 men) were screened for inclusion. Of these, 3805 met the inclusion criteria for this study, which meant they had received two doses of vaccine and had completed the ADR questionnaire.

Blood sampling for antibody testing for participants in the study was recommended, but not restricted to, 1–3 months after the second vaccine dose. The sampling was performed in line with clinical routines at the healthcare worker's unit of employment, where they also were invited to participate in the study. However, the per protocol analysis dataset was restricted to the 3312 subjects sampled 30 to 100 days after completing a two-dose primary vaccination regimen.

The study sampling referral included a questionnaire (Supplementary Table 1) for structured collection of ADRs along with dates of vaccination and type of vaccine. Solicited ADRs included a broad spectrum of symptoms and in addition allowed reports of other types of ADRs outside the categories provided in the form, as free text.

The study was approved by the Swedish Ethical Review Authority (no 2021–00384).

2.2. Vaccine regimens

Initially, Comirnaty was the only vaccine available in Sweden, but subsequently Vaxzevria and Spikevax also became available, while Nuvaxovid was not used for healthcare workers in Uppsala County. The three vaccines used were available in different quantities during different periods and due to changes in recommendations during the vaccination campaign, healthcare professionals in Uppsala County were vaccinated with these three vaccines in a total of five homo- and heterologous combinations.

2.3. SARS-CoV-2 serology

IgG antibodies against SARS-CoV-2 were assessed at the Laboratory of Clinical Microbiology, Uppsala University Hospital, utilizing both the SARS-CoV-2 IgG II Quant assay for the quantitative determination of IgG antibodies to SARS-CoV-2 (spike receptor-binding domain/anti-S) and the SARS-CoV-2 IgG for the qualitative determination of IgG antibodies to SARS-CoV-2 (nucleocapsid domain/anti-N). Both assays were conducted on the Abbott Architect i2000SR Analyzer (Abbott, Illinois, USA). The cutoff was established at 100 AU/mL (Abbott Units/ml) for a positive result in the quantitative method and 1.4 S/CO (Signal to Cutoff Value) for the qualitative method. The results were stored in the electronic health records and the researchers accessed the data on IgG anti-SARS-CoV-2 analyses, both during a previous screening in 2020 [19] and following vaccination.

2.4. Statistical analyses

A multivariable linear regression model was fitted to regress log10-transformed antibody levels on type of vaccine, time from vaccination, age, and sex. Predictors were selected based on biological rationale and previously published data, prior to opening the dataset. Key model assumptions regarding linearity, homoscedasticity, and normality were evaluated using residual plots, showing only a slightly long-tailed residual distribution. The results are presented after back-transformation of the regression coefficients by anti-logging, meaning they can be interpreted as differences in geometric means. *P*-values below 0.05 were considered statistically significant.

A set of multivariable logistic regression models, one predicting each ADR category, were fitted using type of vaccine, anti-S IgG levels post vaccination, time from vaccination to sampling, age, and sex. Deviations from the modelling assumptions on linearity were explored using spline modelling for the predictors, not showing any substantial increase in performance as estimated by C-scores over a linearity assumption.

R version 4.2.2 with packages dplyr version 1.1.0, vtable version 1.4.1, ggplot2 version 3.4.1 and pheatmap version 1.0.12 were used for all statistical analyses and visualisations. The heatmap was clustered for both columns (ADRs) and rows (study participants) using Manhattan distance.

3. Results

3.1. Baseline characteristics

The cohort of 3805 participants were divided into five groups based on obtained vaccine regimen. The largest group received two doses of Comirnaty (2094), followed by smaller groups who received two doses of Vaxzevria (745), two doses of Spikevax (627), one dose of Vaxzevria and one dose of Spikevax (350) or one dose of Vaxzevria and one dose of

Comirnaty (89), both heterogenous regimens in named order. The participants were between 18 and 88 years old, indicating that a limited number of elderly subjects previously affiliated with the hospital may have joined the study, and 14 % were male. The distribution in each group is shown in Table 1.

3.2. SARS-CoV-2 serology

Anti-N and anti-S IgG levels, before and after vaccination are shown in Fig. 1. Before vaccination, in samples collected in our screening study made in 2020 [19], the vast majority of subjects did not have any significant levels of SARS-CoV-2 anti-N or anti-S IgG antibodies. The anti-S IgG response post-vaccination varied depending on vaccine regimen. Participants receiving two doses of Spikevax presented with the highest antibody levels, while those receiving two doses of Vaxzevria had the lowest serologic response to vaccination.

Antibody levels were generally lower in participants with a longer time from vaccination to sampling with the trend continuing up to the analysis cut-off at 100 days post vaccination (Fig. 2). This effect was most prominent for regimens inducing high antibody levels, reducing differences between regimens over time. The trend was slightly less clear for participants that had received two doses of Vaxzevria, where levels were generally lower.

The linear regression model (Table 2) shows that the type of vaccine, together with age and time from vaccination, is associated with the anti-S IgG response following vaccination. All regimens containing Spikevax induced higher anti-S IgG levels than Comirnaty (coefficient 1.78 for Spikevax and 1.18 for Vaxzevria+Spikevax) while the Vaxzevria-only regimen resulted in lower levels (coefficient 0.19) except for when sequenced with Spikevax (coefficient 1.18). As expected, antibody levels were lower with increasing age (coefficient 0.90 per 10 years) and with longer time from vaccination (coefficient 0.98 per day).

3.3. Adverse drug reactions

As shown in Table 3, the vast majority of participants, regardless of vaccine regimen, stated that they experienced local reactions at the injection site such as pain, swelling and/or redness after vaccination. The highest incidence of local reactions was seen in the group that received two doses of Spikevax (90.9 %) and among those that received the combination of Vaxzevria + Spikevax (87.8 %). The second most common adverse reaction was fever and/or chills, which a majority (64–77 %) of the participants in all groups experienced, except those receiving two doses of Comirnaty, where only 29 % reported this type of event. Fatigue/weakness/dizziness and headache were also very common side effects, reported by a majority (54–72 %) in all groups, except in the group receiving two doses of Comirnaty, where less than 40 % reported this kind of side effects. Muscle and joint pain were also commonly reported by all groups (48–66 %) except the double Comirnaty group (27 %).

More unusual side effects, such as rash and/or itching, were reported by <5 % in all groups except those receiving two doses of Spikevax, where nearly 11 % reported this. Respiratory symptoms were reported by less than 7 % of the participants. GI symptoms were reported by around 6–14 % of participants, with those receiving two doses of Comirnaty reporting the lowest (5.8 %), and those receiving Vaxzevria + Spikevax the highest, frequency (13.6 %).

Anaphylactic reactions were reported in a very low number, where 0–0.6 % stated that they had received such kind of side effects. Since it was not asked about, we do not know the severity of the anaphylactic reactions reported.

As shown in Supplementary Table 1, participants were asked about other, non-listed ADRs and also asked to describe them in free text. Depending to group, between 2 and 12 % stated that they had experienced other ADRs. However, most of the described ADRs were ones already asked about in the questionnaire but in other or less descriptive words, for example nausea or vomiting (GI symptoms), vertigo (dizziness) or hematoma and numbness in site of injection (pain/redness/swelling). In most cases the participants had also answered affirmatively at the fixed answers were these, in free text described, ADRs would fit, and we did not code the free text answers further. In addition to this, there was a wide range of symptoms described, including menstrual disturbances, sciatic pain and dry mouth. There were however 17 people stating that they experienced some kind of cardiac effects (from slightly higher pulse to palpitations and, in one case, chest pain). Non-non-solicited ADR reports were not further evaluated, given the substantial risk of under-reporting.

Persistence of symptoms was defined as whether any symptom described was still present at time of answering the ADR questionnaire. Among those reports, the majority described headache, fatigue or remaining pain at injection site.

It was common for staff to miss work shifts due to ADRs, but there was a great variation between the groups. In the group that received two doses of Comirnaty, only 12.3 % stated that they missed a shift, while almost half, 48.2 %, of those in the group who had received the combination Vaxzevria + Spikevax were affected to this extent.

Results from the logistic regression models describing risk factors for each group of adverse drug reaction (ADR) are presented in full in Supplementary Table 2. The risk factors studied were - type of vaccine regimen, age at second dose, male sex and anti-S IgG levels post vaccination. In summary, compared to two doses of Comirnaty, all other vaccine regimens were associated with a statistically significant 2 to 10-fold increase in risk of fever/chills, headache, fatigue/weakness/dizziness and pain in joints/muscles. The odds ratios were overall higher for the two heterogenous vaccine regimens. Younger age was also significantly correlated with an increased risk of vaccine reactivity, while male sex significantly correlated with a lower risk. As to the risk of missing work shifts, compared to Comirnaty, the odds ratios were between 3 (Spikevax) and 6 (Vaxzevria+Spikevax) with the homologous Vaxzevria regimen in between (OR 4.7).

A heatmap clustering analysis was performed to further investigate the adverse reactions patterns (Fig. 3). Overall, local pain/redness/swelling separated from systemic reactivity. Further, a clear correlation was seen within a subset of systemic ADR categories in a cluster containing headache, fatigue/weakness/dizziness, fever/chills, and muscle/joint pain. From the participant clustering, it can be concluded that a substantial proportion of the participants receiving two doses of Comirnaty presented with no adverse reactions whatsoever or local reactions only.

4. Discussion

In this study we present the safety profile the COVID-19 vaccination regimens provided to a large cohort of Swedish healthcare workers and

Table 1
Baseline characteristics in the total cohort of 3805 participants. Time from vaccination and age given as median (min-max).

	Comirnaty	Vaxzevria	Spikevax	Vaxzevria + Spikevax	Vaxzevria + Comirnaty
Total (n)	2094	645	627	350	89
Male sex (proportion)	14.9 %	12.9 %	17.9 %	11.4 %	10.1 %
Time from vaccination (d)	51 (15–261)	70 (20–207)	49 (14–236)	68 (23–211)	68 (19–168)
Age at vaccination (y)	48 (18–88)	48 (20–78)	41 (19–76)	43 (23–65)	43 (24–87)

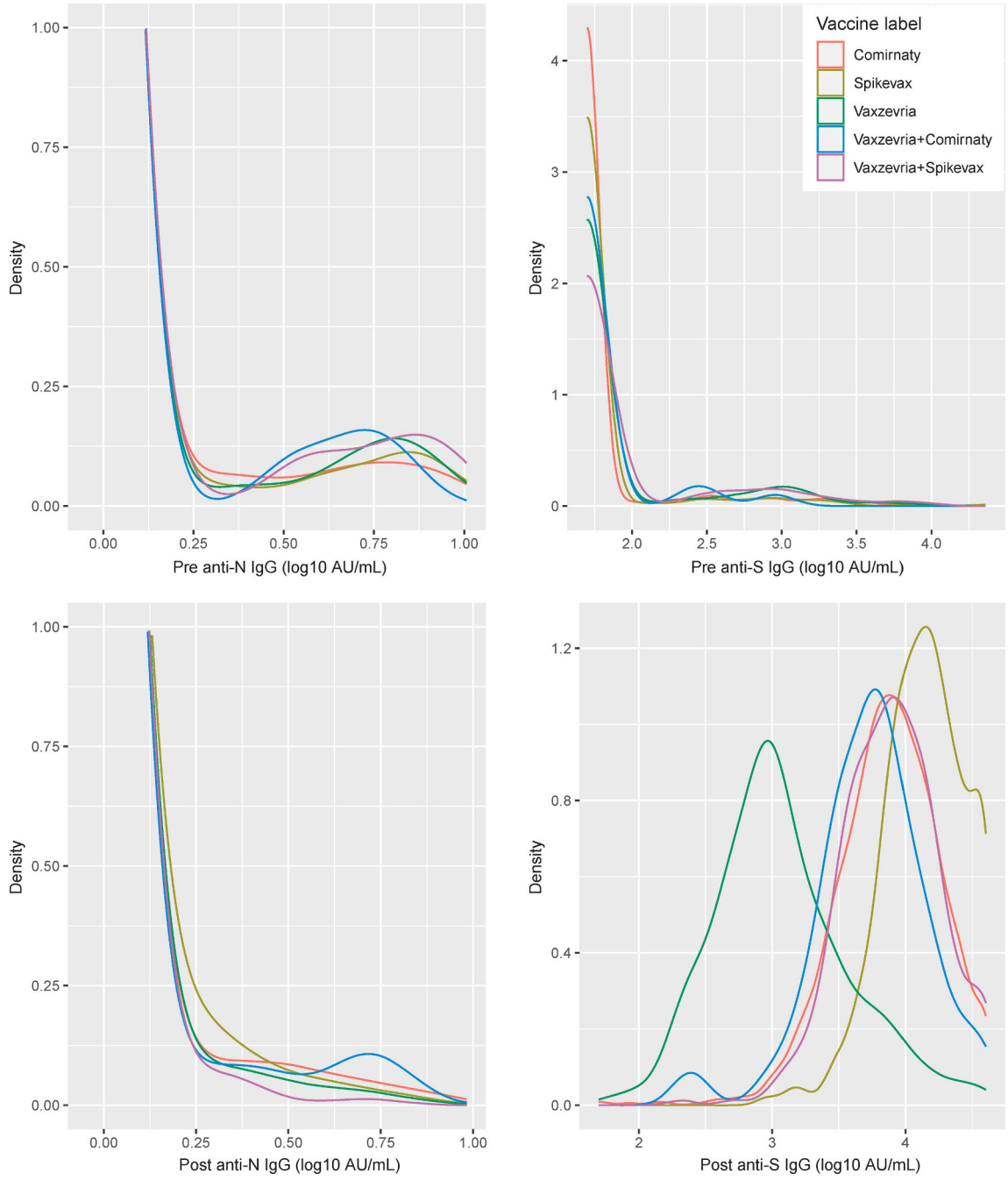

Fig. 1. Density plot showing the distribution in antibody titers of SARS-CoV-2 anti-N (left) and anti-S (right) levels the year before (top) and 30–100 days after (bottom) vaccination.

show that experienced ADRs, to a significant degree, caused a need for sick leave or rescheduling of work shifts.

We found that the risk of missing work shifts, as well as risk for all ADRs except from anaphylactic reactions (very few reported), correlated with type of vaccine and vaccine regimen, with heterogenous regimens counting for the highest risk for ADRs. For several ADR categories, higher levels of anti-S IgG post vaccination correlated with a higher risk of ADRs which is in line with previous studies [20] but could not fully explain the differences observed between different vaccine regimens. The heatmap show a clustering of adverse drug reactions including as headache, fever/chills, fatigue and muscle/joint pain. This may be because these are systemic reactions that are physiologically related, such as fever and chills causing fatigue or headache.

Apart from impact of what type of vaccine, or combination of vaccines, used, the regression analyses show that older age and male sex correlated with a lower incidence of ADRs and thus with a lower risk for missing work. The results are consistent with other similar studies [13–17,21].

Many studies have pointed out the beneficial effects of vaccination regarding severe COVID-19 disease and the relatively low incidence of serious adverse effects of mass vaccination [7–9,11,12]. In terms of serious adverse events, this study confirms the same low incidence. As to the types of drug reactions described, we believe our data are well in line with what is described in the respective product information documents and that the risk/benefit balance for all approved products are clearly positive in comparison with acquiring COVID-19 disease. However, one important dimension that is not captured in the regulatory safety assessment, is the burden of each reaction and what practical impact

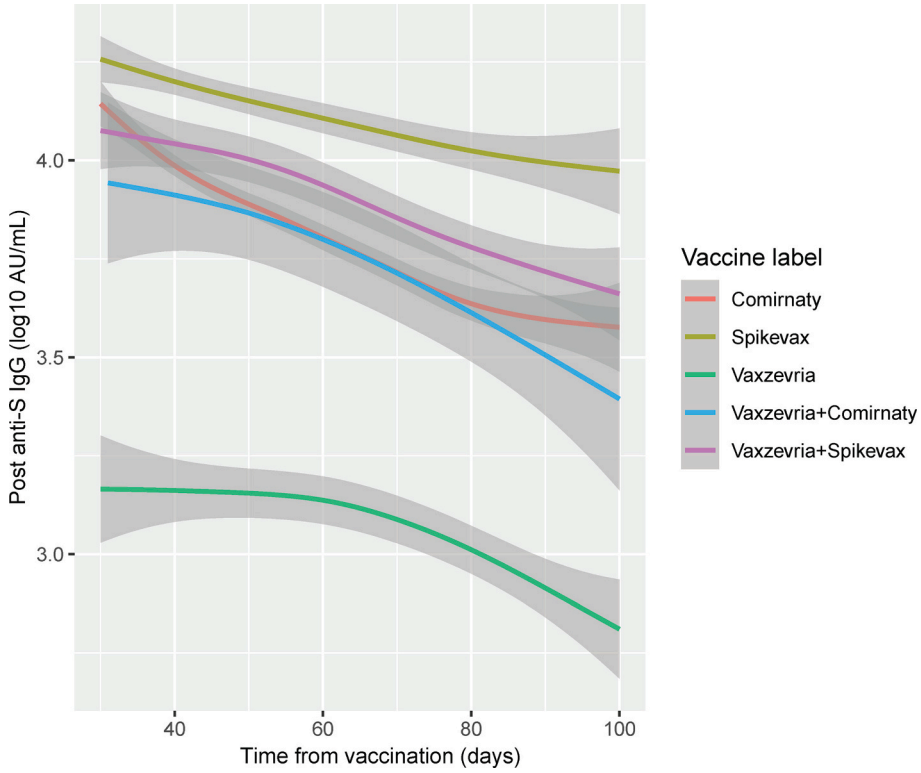

Fig. 2. Modelling of SARS-CoV-2 anti-S IgG levels per vaccine type in relation to time from vaccination. One sample per participant within the day 30–100 post vaccination window included.

Table 2
Multivariable linear regression model, showing independent and statistically significant associations between SARS-CoV-2 anti-S IgG log10-levels and vaccine type, time from vaccination and age. For vaccine type, the largest group (two doses of Comirnaty) is used as a baseline.

	Estimate (95 % CI)	P-value
Comirnaty (base level)	1	
Spikevax	1.78 (1.64–1.93)	< 0.001
Vaxzevria	0.19 (0.18–0.21)	< 0.001
Vaxzevria+Comirnaty	0.84 (0.68–1.04)	0.11
Vaxzevria+Spikevax	1.18 (1.06–1.31)	0.0023
Time from vaccination (days)	0.98 (0.98–0.99)	< 0.001
Age (per 10 years)	0.90 (0.88–0.93)	< 0.001
Male sex	0.93 (0.85–1.01)	0.08

they have on an individual level. Here we can show that, depending on the type of vaccine, between 12 % and 48 % of the participants were affected by post-vaccination symptoms to the degree that they needed to abstain from work in the following day(s). We believe this is a high rate compared to other vaccines offered to health care workers, for example influenza vaccine [22–24].

Following market introduction of the COVID-19 vaccines in 2021, health workers were one of the groups in Sweden first prioritized for vaccination. Both practical considerations, where in most cases it was necessary to organize the injection at each unit or ward, and the handling of the vaccines, led to many units having to vaccinate large parts of their staff at the same time. In several cases, the units therefore had large dropouts after vaccination, due to staff having to stay at home because they suffered from ADRs. This hit hard on units that were already strained both due to a heavy workload and due to illness and rules of quarantine already diminishing their staff group.

As to adverse drug reactions that affected the working capacity,

Table 3
Proportion of participants experiencing adverse drug reactions according to the pre-specified categories (see Supplementary table 1).

	Comirnaty	Spikevax	Vaxzevria	Vaxzevria+Comirnaty	Vaxzevria+Spikevax
Total (n)	2094	627	645	89	350
Missed work	12.0 %	36.0 %	29.0 %	31.0 %	48.0 %
Pain/redness/swelling	78.0 %	91.0 %	72.0 %	75.0 %	88.0 %
Lymph node swelling	5.5 %	7.8 %	2.9 %	3.4 %	10.0 %
Fever/chills	29.0 %	66.0 %	65.0 %	69.0 %	77.0 %
Headache	34.0 %	57.0 %	54.0 %	63.0 %	63.0 %
Fatigue/weakness/dizziness	37.0 %	68.0 %	56.0 %	67.0 %	72.0 %
GI-symptoms	5.9 %	11.0 %	7.3 %	11.0 %	13.0 %
Respiratory symptoms	2.7 %	4.5 %	3.9 %	6.7 %	4.0 %
Pain in joint/muscle	27.0 %	57.0 %	49.0 %	54.0 %	67.0 %
Muscle weakness/numbness	4.3 %	12.0 %	8.8 %	7.9 %	14.0 %
Rash/itching	3.0 %	11.0 %	4.2 %	4.5 %	4.9 %
Anaphylactic reactions	0.2 %	0.5 %	0.5 %	0.0 %	0.6 %
Persistent symptoms	3.4 %	6.9 %	3.4 %	5.6 %	1.7 %
Other symptoms	4.3 %	12.0 %	7.0 %	2.2 %	8.9 %

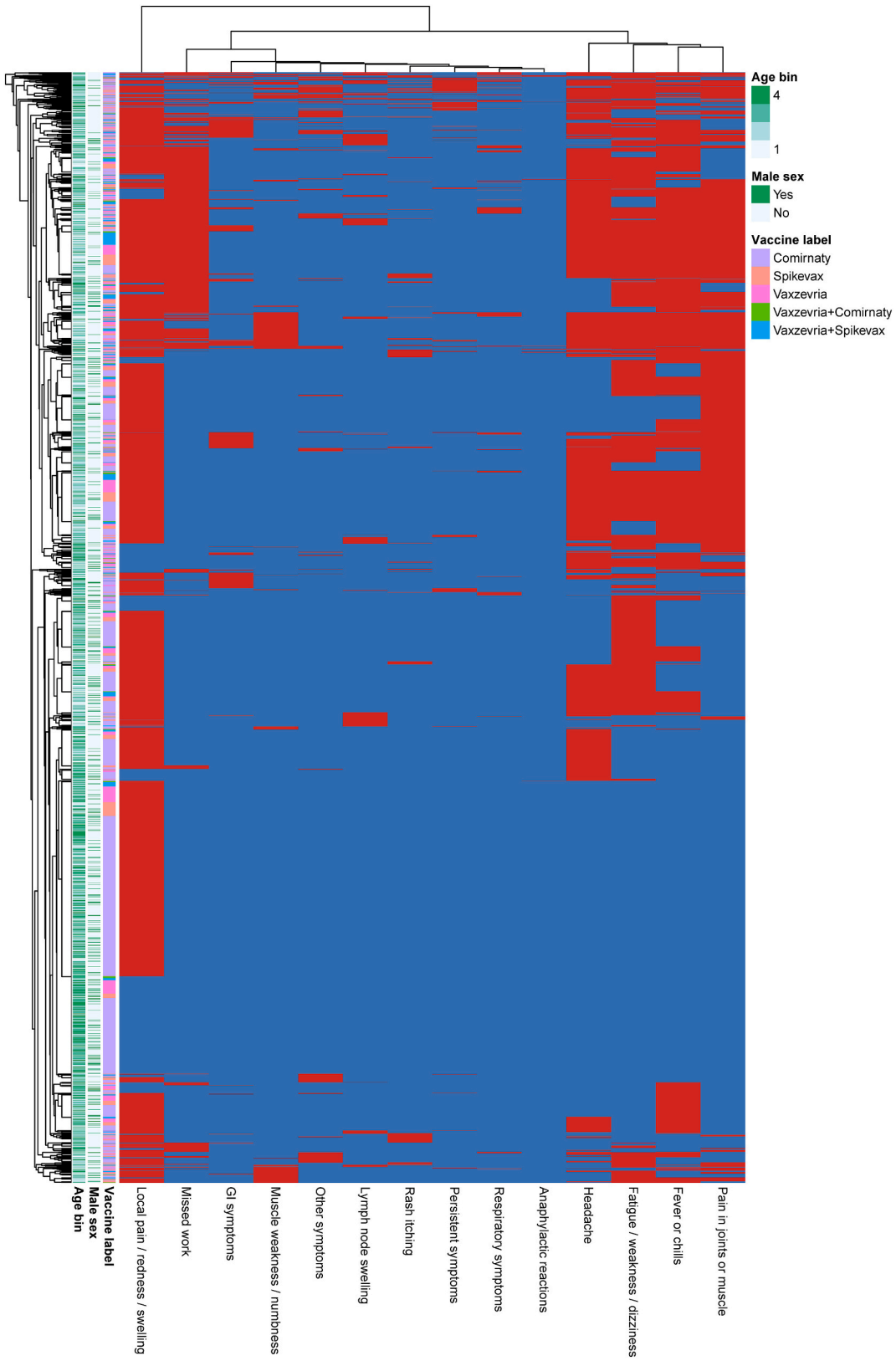

Fig. 3. Heatmap showing the individual ADR profiles with clustering both horizontally (ADR level) and vertically (participant level) using Manhattan distance. Color coding of participant characteristics such as age bin (quartiles), sex and type of vaccine shown to the left.

including fever and fatigue, our observational data suggests that healthcare workers receiving Comirnaty were least affected. Our results support similar findings as other studies from different countries [13,15,16,21].

The characteristics of the study population, with an over-representation of younger women, are a limitation of the study but also representative of how most healthcare systems are currently staffed. The observational nature of the study, where real-world factors such as availability affected which types of vaccines were used, is an obvious limitation compared to a randomized controlled trial. As to the method of actively collecting information on symptoms post vaccination, there is a risk of recall bias, but we also believe it is a strength compared to analyzing only spontaneous ADR reports where there is no known denominator and incidences of ADRs cannot be calculated. The questionnaire used was designed before vaccination of health care personnel started in Sweden and were based on the safety profile established in registrational studies together with reports from countries that started vaccination ahead of Sweden [25]. However, there was room in the questionnaire to describe additional side effects not covered by the questionnaire, which very few participants did, indicating that our set of questions covered the panorama of side effects well. Previous studies have seen a correlation between previous COVID-19 infection and occurrence of ADRs after vaccination [26,27]. In our dataset, no information on previous infection was available.

There have, to our knowledge, already been a few studies that has been studying the substantial amount of missed work shifts due to COVID-19 vaccination [13–17,21]. As the Swedish healthcare system has a high proportion of young female employees, mass vaccination might have a higher risk of effecting the work units negatively than in other work settings in society. More specific differences in adverse drug reactions between men and women is an interesting aspect that we did not specifically focus on in this study, but which would be interesting to look at in a future study.

We have not performed any health economic calculations regarding the missed work shifts, but the absence of health care workers, regardless of reason, during the second and third wave of the pandemic enhanced the problems experienced in the hospitals and some units, especially smaller ones, experienced major staffing problems days after vaccination. For the future, it is important that hospitals and other organizations with round-the-clock services have this in mind when planning for vaccinations of their personnel.

In conclusion, based on a large cohort of health workers, our study confirms that adverse reactions after COVID-19 vaccination can lead to a substantial amount of missed work shifts that can cause organizational-level disturbances in staffing. Further, these risks differ substantially depending on vaccine type, age and sex. In the case of future mass vaccination of healthcare workers, in particular with vaccines based on mRNA or other novel platforms where real-world experience is limited, staggered approaches and pre-planned reduction in planned patient visits could be considered to reduce the organizational impact.

CRediT authorship contribution statement

Anna-Karin Lidström: Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Bo Albinsson:** Writing – review & editing, Resources, Methodology, Investigation. **Fredrik Sund:** Writing – review & editing, Supervision, Resources, Conceptualization. **Johan Lindbäck:** Writing – review & editing, Methodology. **Florence van Hunsel:** Writing – review & editing. **Tove Fall:** Writing – review & editing, Supervision. **Gabriel Westman:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Anna-Karin Lidstrom reports financial support was provided by Olinder-Nielsen Family Foundation. If there are other authors, they 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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127553.

Data availability

Data will be made available on request.

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