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A comparison of four self-controlled study designs in an analysis of COVID-19 vaccines and myocarditis using five European databases

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ABSTRACT

Introduction: The aim of this study was to assess the possible extent of bias due to violation of a core assumption (event-dependent exposures) when using self-controlled designs to analyse the association between COVID-19 vaccines and myocarditis.

Methods: We used data from five European databases (Spain: BIFAP, FISABIO VID, and SIDIAP; Italy: ARS-Tuscany; England: CPRD Aurum) converted to the ConcePTION Common Data Model. Individuals who experienced both myocarditis and were vaccinated against COVID-19 between 1 September 2020 and the end of data availability in each country were included. We compared a self-controlled risk interval study (SCRI) using a pre-vaccination control window, an SCRI using a post-vaccination control window, a standard SCCS and an extension of the SCCS designed to handle violations of the assumption of event-dependent exposures.

Results: We included 1,757 cases of myocarditis. For analyses of the first dose of the Pfizer vaccine, to which all databases contributed information, we found results consistent with a null effect in both of the SCRI and extended SCCS, but some indication of a harmful effect in a standard SCCS. For the second dose, we found evidence of a harmful association for all study designs, with relatively similar effect sizes (SCRI pre = 1.99, 1.40 – 2.82; SCRI post 2.13, 95 %CI – 1.43, 3.18; standard SCCS 1.79, 95 %CI 1.31 – 2.44, extended SCCS 1.52, 95 %CI = 1.08 – 2.15). Adjustment for calendar time did not change these conclusions. Findings using all designs were also consistent with a harmful effect following a second dose of the Moderna vaccine.

Conclusions: In the context of the known association between COVID-19 vaccines and myocarditis, we have demonstrated that two forms of SCRI and two forms of SCCS led to largely comparable results, possibly because of limited violation of the assumption of event-dependent exposures.

1. Introduction

Self-controlled study designs are a useful tool for evaluating vaccine safety signals, as they do not require the identification of an external control group and automatically control for all time-invariant confounding [1]. This is an important benefit when studying vaccinations,

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as those who choose to get vaccinated are often very different in terms of their underlying health from those who are unvaccinated [2]. Two commonly used self-controlled designs in vaccine safety are the self-controlled case series (SCCS) and the self-controlled risk interval (SCRI) designs. In these study designs only people with the outcome (cases) are included, and the risk of an event occurring during a pre-specified risk window after the exposure is compared to an unexposed control period. In a typical SCCS, all time except the risk window is considered as the control period, that is, observation does not stop at the occurrence of the outcome. The SCRI is a special case of the SCCS in which the control period is fixed relative to the vaccination date [3].

Arguably the most important assumption for SCCS is that the occurrence of the outcome does not impact the probability of subsequent exposure [4,5]. In the vaccine setting, this may be violated if future doses are delayed following the event of interest. For example, the occurrence of myocarditis may delay the receipt of a COVID-19 vaccine, resulting in an upward bias in the association between COVID-19 vaccines and myocarditis if ignored in analyses [6]. A pre-exposure window can be used to correct for delays but will not suffice if the event delays the exposure for indeterminate periods of time or contraindicates it [7]. Alternative solutions include only analysing pre-event exposures and starting the observation time at the exposure [7], or using extensions of the SCCS based on a pseudo-likelihood approach [5]. Starting the observation time at the exposure only works for a single vaccine dose, and simulation studies have demonstrated that it may introduce bias in the multi-dose setting [8]. A less commonly used option involves truncating the SCCS observation time to only include a pre-specified time period between doses, during which another vaccination would not be expected to occur [9]. This method represents a special case of an SCRI using one or more post-vaccination control windows, in which the length of the control windows is fixed by the vaccination schedule.

Another important source of potential differences between SCCS and SCRI designs relates to calendar time trends: as the SCCS typically includes a longer study period, it may be more sensitive to variations in the occurrence of the outcome over time unless these are adequately controlled for in the analysis. However, the SCRI is theoretically more vulnerable to rapid changes in outcome incidence, as comparisons are typically, if not always, mono-directional. For example, an SCRI using a control period prior to a vaccine being administered might overestimate the risk of a safety event if the incidence of the safety event increases over calendar time.

The choice of study design is of key importance for studies of vaccine safety, but comparisons of versions of the SCRI and SCCS in settings where the assumption of event-dependent exposures may be violated are limited. We, therefore, compared these study designs using a case study of multidose COVID-19 vaccination and myocarditis, in which we were concerned that violation of the event-dependent exposure assumption, and therefore, the specification of the control periods, may be an issue.

2. Methods

2.1. Description of the SCCS and SCRI designs

All study designs were self-controlled, that is, they included only cases. In all designs, the risk period after each dose started on day 1 and lasted until day 28. The focus was on the first and second doses, as COVID-19 booster doses had not been rolled out at the time of design of this study. Where relevant, doses were assigned a pre-exposure period of 30 days to account for potential short violations of the assumption of event-dependent exposures. The day of vaccination was modelled as a separate risk window. In the case of overlaps, risk periods always took precedence over pre-exposure periods, and latter risk periods took precedence over earlier risk periods. All designs are described in more detail below and illustrated in Fig. 1.

a. Pre-vaccination SCRI.

The pre-vaccination SCRI used a 60-day period before the 1st vaccine dose lasting from days [-89, −30] as control time. A 30-day period before each vaccine dose [-29, 0] was considered a pre-exposure period (Fig. 1a). In practice, both pre-exposure periods and time in between doses, where this occurred, were treated as separate levels of the exposure variable. This means that individuals who experienced events in these time periods were included in the analysis, and will have contributed to the calendar time adjustment (although they did not directly contribute to the contrast of interest of risk versus control period).

b. Post-vaccination SCRI.

The post-vaccination SCRI used time after the second vaccine dose as control time, or time after the first vaccine dose for those without a second vaccine dose. A control period of 60 days was used, lasting from days [29, 88] after the relevant vaccine dose (the first 28 days constituted the risk period). The design is illustrated in Fig. 1b below.

c. Standard SCCS.

The standard SCCS used all calendar time, from a fixed start date in calendar time (1 September 2020 until the last available follow-up

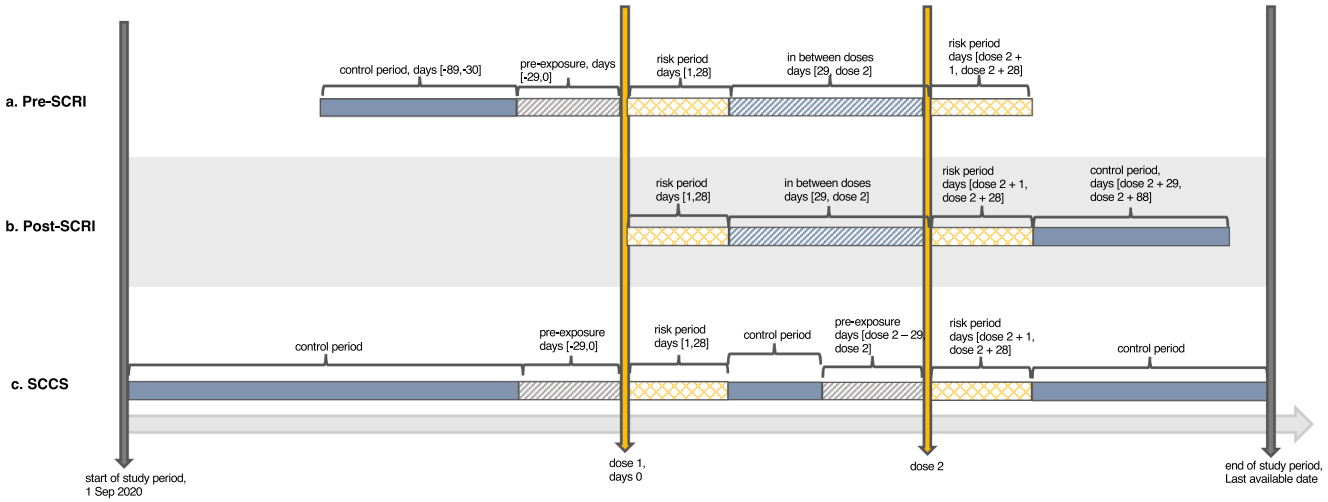

Fig. 1. Illustration of the study designs. (For interpretation to colours in this figure, the reader is referred to the web version of this paper.)

(Fig. 1c). The start of follow-up was set to provide enough time to implement a pre-vaccination SCRI before the receipt of the first vaccine in the contributing databases (8 December 2020. All time not designated as a pre-exposure period, a risk period or a vaccination day was used as the control period.

d. Extended SCCS.

This used the same design as the standard SCCS (Fig. 1c) but with an analysis method based on a pseudo-likelihood approach. This method was developed specifically to account for bias that might be introduced due to event-dependent exposures [5], and is described in detail by Farrington, Whitaker and Gebhremichael Weldeselassie [10]. The implementation of this method in this database was restricted to individuals with at least one vaccine dose due to the nature of the data cuts used for the analysis.

Our hypothesis was that the occurrence of myocarditis would delay the receipt of vaccination. Although it is possible that some of the consequences of myocarditis would move individuals into a risk group, thereby moving their vaccination forward, acute myocarditis was not considered a chronic heart disease for the purposes of identifying risk groups in the UK [11]. Our expectations regarding the extent of bias based on the event delaying the exposure can be seen in Table 1.

2.2. Case study

We compared these designs as part of an evaluation of COVID-19 vaccination and myocarditis completed as part of the Covid Vaccine Monitoring (CVM) project, a collaboration between the EU PE&PV (Pharmacoepidemiology and Pharmacovigilance) Research Network (led by Utrecht University) and the Vaccine Monitoring Collaboration for Europe network (VAC4EU). The clinical findings using a pre-vaccination SCRI have been published [11].

2.2.1. Data

Data were included from the Spanish Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP) database (end of data; April 2022), the Italian ARS-Tuscany database (end of data; December 2021), the Spanish FISABIO VID database (end of data; December 2021), the Spanish SIDIAP database (end of data; June 2022) and the British Clinical Practice Research Datalink CPRD Aurum (end of data; March 2022). Data was included from 1 September 2020 for all databases. All five data providers converted their data to the ConcePTION Common Data Model which resulted in structurally harmonised local datasets [12], and have been described in greater detail in previous publications [13].

Table 1
Expected bias under each design if the assumption of event-dependent exposures is violated.

Design		Expected bias	Rationale
Pre-SCRI	Dose 1	Biased upwards	Using reference time before vaccination would bias (both) rate ratios upwards, because cases occurring during the reference time would be preferentially excluded (lower event probability during the reference time, given that vaccination occurred).
	Dose 2	Biased upwards	
Post-SCRI	Dose 1	Unbiased	Using reference time after the last vaccine dose would allow us to make inferences about the last dose. Because cases were included if they did not have a second vaccine dose, we would expect that estimates for both dose one and two were unbiased.
	Dose 2	Unbiased	
Standard SCCS	Dose 1	Biased upwards	As for the pre-SCRI, but possibly a weaker bias because the reference time now includes cases occurring after vaccination as well.
	Dose 2	Biased upwards	
Extended SCCS	Dose 1	Unbiased	As the extended SCCS has been developed specifically to allow unbiased estimates of the rate ratio when the assumption of event-dependent exposures is violated, we were not expecting bias in this scenario.
	Dose 2	Unbiased	

2.2.2. Study design and analysis

The core methods have been previously described [13]. Briefly, individuals who experienced both the outcome of interest and were vaccinated between 1 September 2020 and the end of data availability (which varied in the different databases) were eligible for inclusion. We further required individuals to have at least one year of baseline time prior to the start of the study period, have non-missing age and sex, be aged 18 years or older at the start of the study period, have a known vaccine brand for their first dose, and no history of myocarditis in the 365 days leading up to the start of the study period. The outcome of interest was the first code of myocarditis during the study period [14]. The vaccines of interest were Comirnaty (Pfizer/BioNtech), Spikevax (Moderna), Vaxzevria (AstraZeneca) and the Jcovden COVID-19 vaccine (Janssen). Due to small numbers and because our interest was primarily in the comparison of the different designs, we excluded individuals who received different brands of vaccine for their first and second vaccine doses.

Third and fourth doses were not considered as exposures of interest in this analysis, as the number of booster vaccinations in the data was very low at the time of the design of this study. Nevertheless, the presence of further doses needed to be accounted for in the analysis. How this was handled varied depending on the design. In the post-vaccination SCRI, we curtailed the control period at the start of the third dose, if this occurred. We expected such instances to be relatively rare given the minimum time required between second and booster doses but nevertheless quantified the occurrence of such curtailment in each database. For the standard and extended SCCS, we considered third and fourth doses, and their pre-exposure periods, as separate levels of the exposure variable to remove periods of potential increased risk from the reference time.

For each study design, we generated basic summary data for the people included in each analysis, plotted histograms showing the time between event and each vaccination (exposure-centred interval plots[1]), and fit conditional Poisson regression models to calculate incidence rate ratios for the association between the first and second vaccine dose and myocarditis, stratified by DAP and vaccine brand using the *{SCCS}* package in R. Finally, we added a random-effect meta-analysis across the data sources using the *{meta}* package in R. It was not feasible to apply all designs for all vaccines and doses, as not all vaccines were widely used in the included databases. Although this means that the meta-analysed estimates for some vaccines include different countries, we nevertheless felt it was appropriate to present results following meta-analysis, as we were primarily interested in whether the application of one design over and other would have led to different regulatory conclusions. The inability of some databases to contribute to some designs was considered an important part of this assessment. The databases contributing to each estimate are marked in the forest plots, and, given the methodological focus of this manuscript, we also emphasise findings for the Pfizer vaccine for which all databases contributed.

Agreement between designs was assessed informally, by considering

[1] *These plots are "centred" on vaccination, that is, the time of vaccination is subtracted from each event time and the histogram therefore displays the event times relative to each vaccination date. Time zero is the time of each vaccination, a positive time represents an event occurring after vaccination, and a negative time an event occurring before vaccination.*

what the interpretation of findings would be from a public health perspective. All code for preparing the data and running these models is available on Github (https://github.com/VAC4EU/CVM/releases/tag/SCCS_v1.0.1).

3. Results

3.1. Description of study population

In total, we included 1,757 cases of myocarditis: 191 cases from ARS, 642 from CPRD, 240 from FISABIO, 404 from SIDIAP and 280 from BIFAP-PC. A flowchart showing the selection of individuals from each country is provided in Table 2.

Most cases received the Pfizer/BioNtech vaccine (Table 3) and < 5 received the Janssen vaccine (meaning further analysis of this vaccine was not feasible) The second dose coverage was around 80 % or higher for all vaccine brands in all countries, although the number of third doses was relatively low for all brands. The post-vaccine SCRI, as planned, required a minimum of 89 days between the second and third vaccine dose (28 day risk period, plus a 60 day control period), and it was reassuring that the minimum time between the second and third dose was longer than 90 days for all brands in all countries, apart from for Moderna in the FISABIO database where the minimum time was 85 days (but the lower quartile 132 days). It is worth noting that because our interest was in the first two doses, we didn't specify selection based on the brand of the third dose so this may be of a different brand to the first two doses (likely explaining the apparent third AZ doses for many of these cases).

3.2. Graphical assessment of model assumptions

We used exposure-centred interval plots to assess the violation of the event-dependent exposure assumption for the first and second vaccine dose, of each brand, in each country. Not all of these plots could be released due to small numbers and disclosure rules for each data provider. Plots that could be released are provided in Fig. 2a-f for the Pfizer vaccine. Plots for other vaccines are provided in the supplementary materials.

The key trend observed in these graphical assessments of the Pfizer vaccine was that there was some evidence of a short but temporary delay of both the first and second doses in the ARS database. This can be seen by a short "drop" in the number of events shortly before both vaccine doses in Fig. 2a-b. However, this appeared short-lived and the number of events increased with increasing distance from the vaccine doses. The graphical assessment was less clear in FISABIO and CPRD, with no clear drop preceding the either dose in these database (Fig. 2c – 2f). However, the number of cases was relatively low in all databases, meaning that trends were relatively difficult to discern.

3.3. Regression models comparing the different designs

The meta-analysed results for all vaccines and doses, with and without calendar time adjustments, can be seen in Figs. 3–6. As described in the methods, our write-up focuses on the Pfizer vaccine as all databases contributed data for this vaccine. Country-specific results can be found in the supplementary materials.

3.3.1. Pfizer

For analyses of the first dose, we found results consistent with a null effect in both of the SCRI and extended SCCS, but some indication of a harmful effect in a standard SCCS. For the second dose, we found evidence of a harmful association for all study designs, with relatively similar effect sizes (SCRI pre = 1.99, 1.40 – 2.82; SCRI post 2.13, 95 %CI – 1.43, 3.18; standard SCCS 1.79, 95 %CI 1.31 – 2.44, extended SCCS 1.52, 95 %CI = 1.08 – 2.15). Adjustment for calendar time in 60-day increments did not change these conclusions.

3.3.2. Moderna and AstraZeneca

The databases contributing to each design for analyses of AstraZeneca and Moderna vaccines varied. For AstraZeneca, all designs were consistent with a null effect for both doses, both before and after calendar time adjustment. For Moderna, we found some evidence of a harmful association between the first dose and myocarditis using the standard and extended SCCS, but not in the SCRIs. Calendar time adjustment did not change these conclusions, but confidence intervals were very wide. For the second dose, all designs resulted in consistently harmful associations both before and after calendar time adjustment, apart from the pre-vaccine SCRI after calendar time adjustment, where a small number of cases resulted in very wide confidence intervals (2.61, 0.55 – 12.44).

4. Discussion

4.1. Summary

In this study, we compared the ability of four different self-controlled study designs to detect the known association between some COVID-19 vaccines and myocarditis using data from five European countries. All designs were able to detect the association between the second dose of the Pfizer and Moderna vaccines and an increased risk of myocarditis, although control for calendar time was more challenging in the SCRIs, resulting in wider confidence intervals after covariate adjustment. There was no indication of systematic overestimates of the rate ratio in the pre-SCRI and standard SCCS compared to the post-SCRI or the extended SCCS.

4.2. Comparison to prior literature

Other authors have also compared different study designs for the

Table 2
Selection into the case series, by DAP.

	ARS	CPRD	FISABIO	SIDIAP	BIFAP-PC
	N (%)	N (%)	N (%)	N(%)	N(%)
Total individuals in dataset	3,704,289	15,214,165	5,607,181	6,220,172	12,912,064
non-missing gender	3,704,289 (100)	15,214,165 (100)	5,607,181 (100)	6,220,172 (100)	12,912,064 (100)
non-missing age	3,704,289 (100)	15,214,165 (100)	5,607,181 (100)	6,220,172 (100)	12,912,064 (100)
age over 18	3,083,301 (83.24)	11,682,705 (76.79)	4,522,073 (80.65)	4,995,184 (80.31)	10,462,443 (80.31)
non-missing first dose	2,527,061 (68.22)	7,652,699 (50.3)	3,715,022 (66.25)	4,066,912 (65.38)	8,402,992 (65.38)
non-missing type of first dose	2,527,061 (68.22)	7,652,699 (50.3)	3,715,022 (66.25)	4,066,912 (65.38)	8,402,992 (65.38)
dose 1 and 2 the same brand	2,436,048 (65.76)	7,459,138 (49.03)	3,527,140 (62.9)	3,776,589 (60.72)	7,946,432 (60.72)
non-missing outcome	511 (0.01)	1295 (0.01)	763 (0.01)	738 (0.01)	603 (0.01)
outcome occurs after start	233 (0.01)	[redacted]	281 (0.01)	404 (0.01)	280 (0.01)
outcome occurs before censor	191 (0.01)	642 (0)	240 (0)	404 (0.01)	280 (0.01)
Cases included	**191 (0.01)**	**642 (0)**	**240 (0)**	**404 (0.01)**	**280 (0.01)**

Table 3
Distribution of vaccine doses, by brand and DAP.

			N (%)	Time from previous vaccine dose	
				Median (Q1; Q2)	Min; Max
ARS	AstraZeneca	Dose 1	7 (100)	–	–
		Dose 2	7 (100)	84 (76; 84)	53; 84
		Dose 3	<5	–	–
	Janssen	Dose 1	<5	–	–
		Dose 2	<5	–	–
		Dose 3	<5	–	–
	Moderna	Dose 1	42 (100)	–	–
		Dose 2	34 (80.95)	41 (28; 42)	28; 191
		Dose 3	12 (28.57)	183 (150; 201)	126; 258
	Pfizer	Dose 1	139 (100)	–	–
		Dose 2	116 (83.45)	42 (21; 42)	21; 235
		Dose 3	30 (21.58)	206 (186; 264)	132; 330
CPRD	AstraZeneca	Dose 1	306 (100)	–	–
		Dose 2	295 (96.41)	77 (70; 80)	27; 238
		Dose 3	228 (74.51)	193 (185; 206)	127; 293
	Moderna	Dose 1	28 (100)	–	–
		Dose 2	19 (67.86)	63 (57; 84)	38; 162
		Dose 3	9 (32.14)	149 (147; 162)	137; 232
	Pfizer	Dose 1	308 (100)	–	–
		Dose 2	277 (89.94)	74 (60; 78)	19; 322
		Dose 3	174 (56.49)	192 (182; 206)	117; 307
FISABIO	AstraZeneca	Dose 1	16 (100)	–	–
		Dose 2	15 (93.75)	82 (72; 84)	54; 99
		Dose 3	7 (43.75)	164 (158; 172)	148; 198
	Janssen	Dose 1	<5	–	–
		Dose 2	<5	–	–
		Dose 3	<5	–	–
	Moderna	Dose 1	45 (100)	–	–
		Dose 2	40 (88.89)	28 (28; 28)	27; 118
		Dose 3	17 (37.78)	190 (132; 199)	85; 214
	Pfizer	Dose 1	175 (100)	–	–
		Dose 2	152 (85.98)	21 (21; 21)	19; 190
		Dose 3	41 (21.34)	199 (186; 219)	141; 311
SIDIAP	AstraZeneca	Dose 1	56 (100)	–	–
		Dose 2	55 (98.21)	79 (70; 88)	54; 110
		Dose 3	48 (85.71)	173 (160; 182)	126; 250
	Janssen	Dose 1	10 (100)	–	–
		Dose 2	<5	–	–
		Dose 3	<5	–	–
	Moderna	Dose 1	84 (100)	–	–
		Dose 2	72 (85.71)	28 (28; 29)	28; 168
		Dose 3	37 (44.05)	200 (176; 221)	90; 318
	Pfizer	Dose 1	254 (100)	–	–
		Dose 2	230 (90.55)	21 (21; 22)	20; 199
		Dose 3	146 (57.48)	206 (191; 226)	100; 360
BIFAP-PC	AstraZeneca	Dose 1	18 (100)	–	–
		Dose 2	16 (88.89)	78 (73; 84)	65; 91
		Dose 3	13 (72.22)	163 (154; 171)	135; 202
	Janssen	Dose 1	<5	–	–
		Dose 2	<5	–	–
		Dose 3	<5	–	–
	Moderna	Dose 1	59 (100)	–	–
		Dose 2	46 (77.97)	28 (28; 30)	27; 182
		Dose 3	12 (20.34)	189 (171; 230)	108; 265
	Pfizer	Dose 1	200 (100)	–	–
		Dose 2	169 (84.5)	21 (21; 22)	20; 197
		Dose 3	38 (19)	198 (184; 218)	132; 326

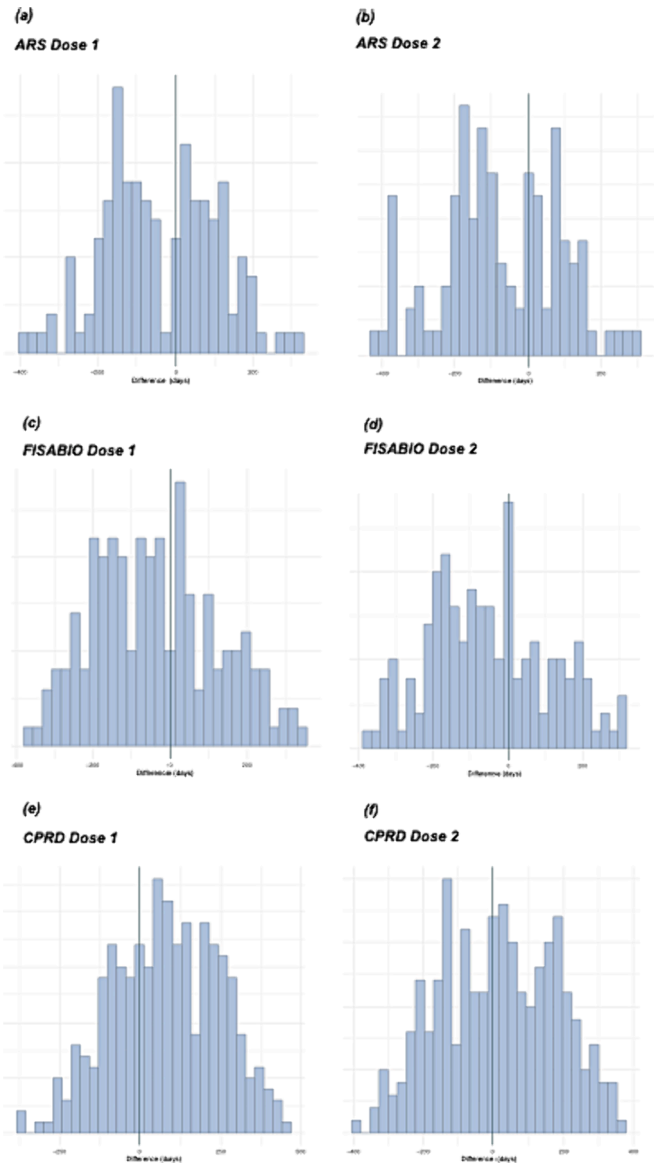

Fig. 2. a-f. Exposure-centred intervals plot for Pfizer dose 1 and dose 2 in the ARS (a - b), FISABIO (c – d) and CPRD (e – f). [1]*These plots show the time to event for each person, "centred" on the vaccination (i.e, subtracting the vaccination from the event time). A time of zero means the event and vaccine happened on the same date, a positive time means the event happened after vaccination and a negative event time means the event happened before vaccination. A "drop" before day 0 indicates an absence of events before vaccination, and indicates potential bias due to event-dependency of the exposure. Each bar represents a fixed period of time of more than one day, with the same width (automatically determined) used within each database.*

purpose of detecting vaccine safety effects, most recently Schuemie et al in an evaluation of 25 different study designs in four different US health insurance databases [2]. The evaluation included a comparison between a standard SCCS, post-vaccine SCCS, pre-vaccine SCRI, and post-vaccine SCRI. Performance was compared in terms of the ability of each method to detect associations between six different vaccines and three simulated positive controls; and their ability to not detect associations for 93 l negative controls. This resulted in over a million effect size estimates, on which performance metrics such as type I and type II errors were computed. The authors concluded that the self-controlled methods generally performed better than historical cohort and case-control methods given the performance metrics calculated in the paper, although the SCCS and SCRI were not explicitly compared [2]. From the

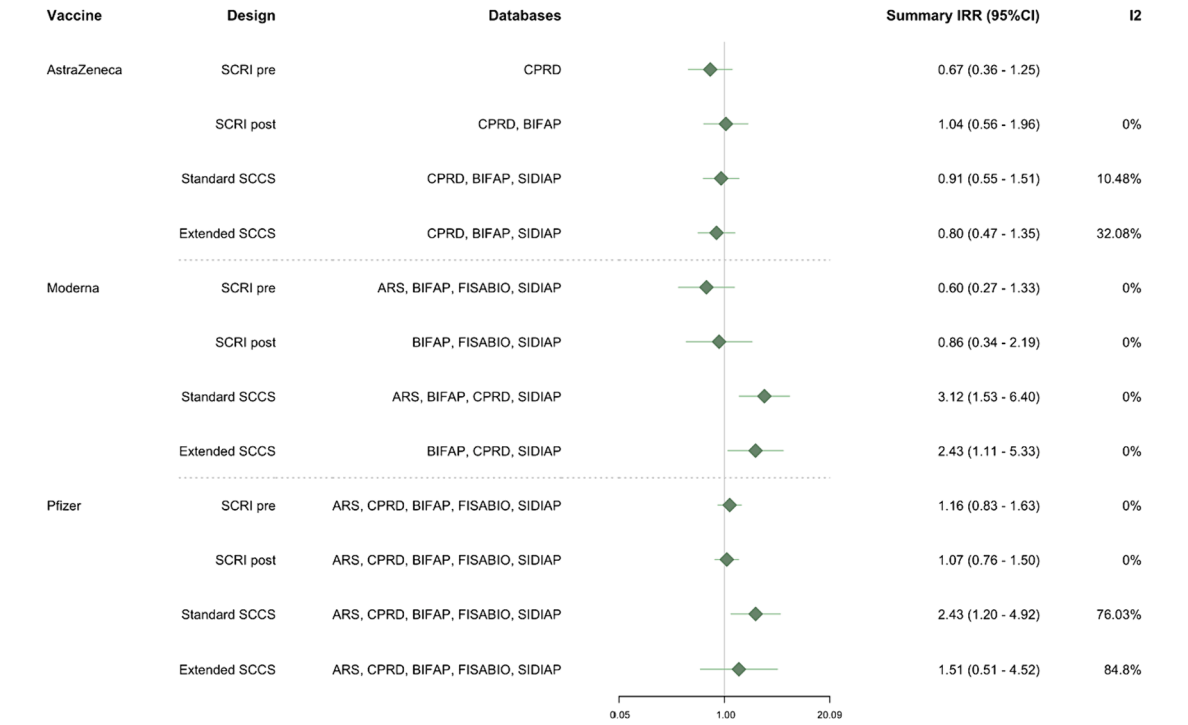

Fig. 3. Meta-analysed association between the first dose of each vaccine and myocarditis, unadjusted for calendar time.

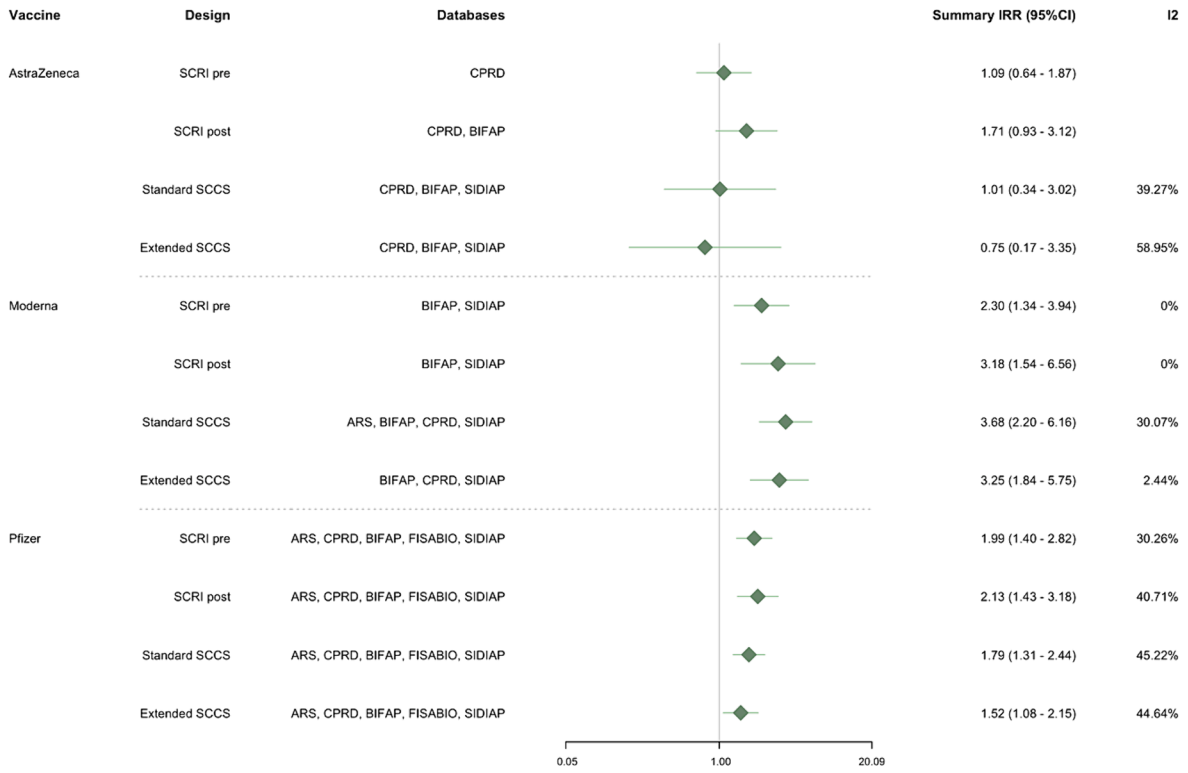

Fig. 4. Meta-analysed association between the second dose of each vaccine and myocarditis, unadjusted for calendar time.

data presented performance appears relatively similar, although multiple vaccine doses were considered as separate individuals in this analysis and therefore potential violations of the self-controlled study assumptions could not be addressed.

Focusing specifically on the choice of design in the context of violations of the event-dependent exposure assumption, Hua et al evaluated the performance of the standard SCCS, a post-vaccination SCCS and the extended SCCS in a simulation study of two vaccinations and a rare adverse event [8]. They found that for a single vaccine dose and no seasonal confounders, the post-vaccination and extended SCCS were both unbiased whereas use of the standard SCCS resulted in an upward bias. However, in the multidose setting, only the extended SCCS was

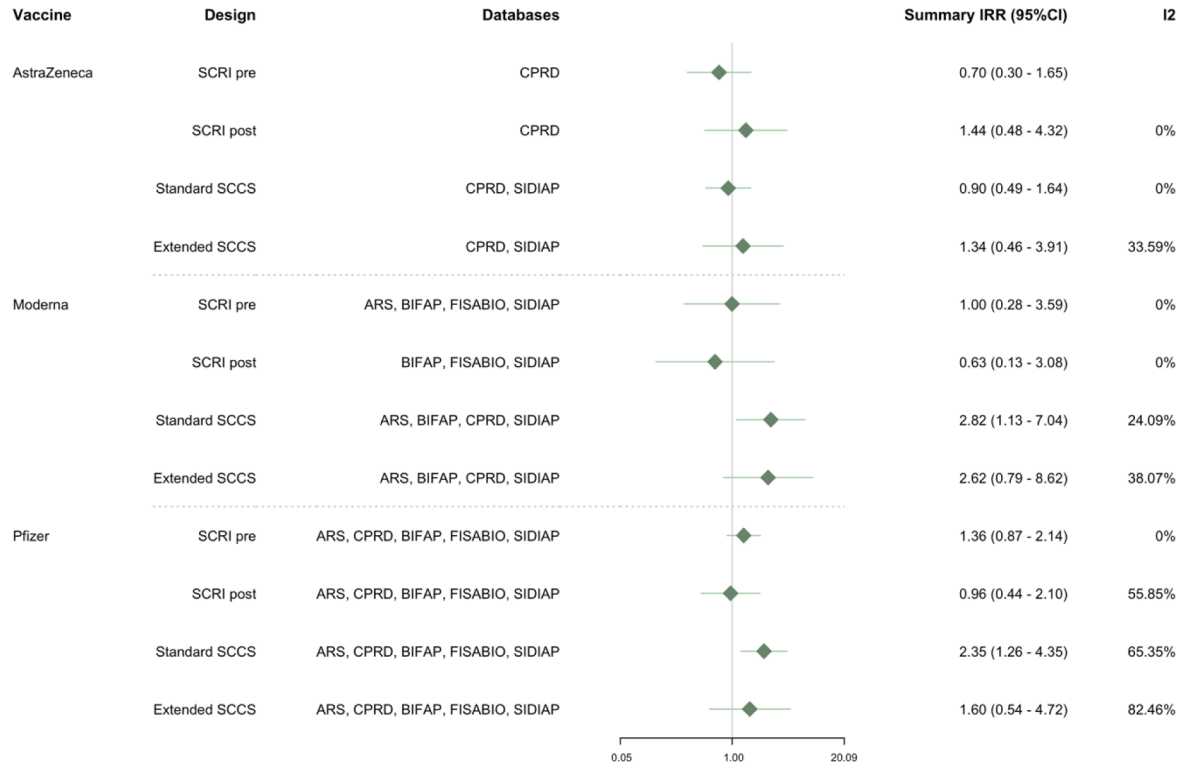

Fig. 5. Meta-analysed adjusted association between the first dose of each vaccine and myocarditis, after adjustment for calendar time in 60-day increments.

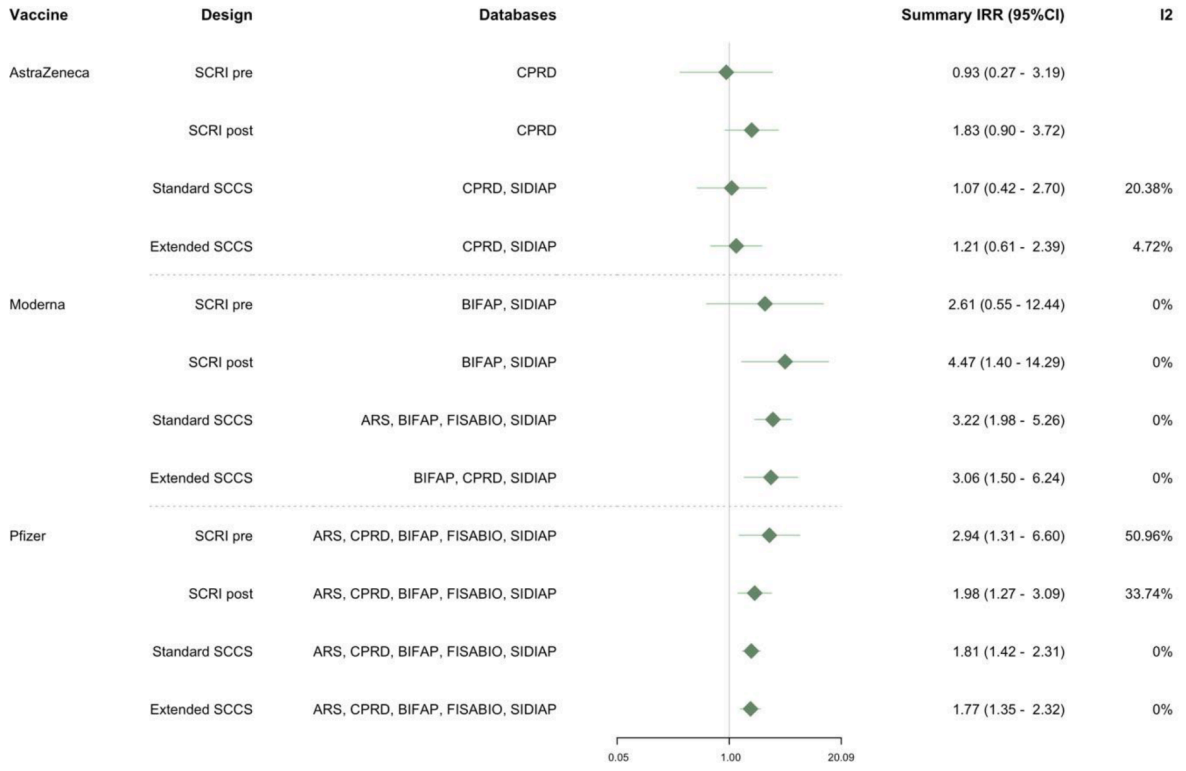

Fig. 6. Meta-analysed adjusted association between the second dose of each vaccine and myocarditis, after adjustment for calendar time in 60-day increments.

able to recover unbiased estimates for both vaccine doses [8].

4.3. Interpretation

Taken together, our results extend findings from previous comparisons of study designs for determining vaccine safety by providing a detailed comparison of different SCCS and SCRI design options in a clinical setting where we expected exposures to be event-dependent. Our key finding is that there was generally good agreement between these designs, implying that the extent of violations of

this assumption might be limited in our setting. This was confirmed through a graphical investigation, which suggested that any violation of the assumption of event-dependent exposures was likely to be limited in most databases, and short-lived if violated. Our results are therefore in agreement with those from Schuemie and colleagues, which showed similar performance of both SCRI and SCCS designs [2].

An interesting and unexpected finding was that the Moderna and Pfizer first dose rate ratios were somewhat higher using both the standard and extended SCCS, with both of the SCRI finding results closer to the null. This was particularly marked before the adjustment for calendar time. Although findings should be interpreted cautiously as confidence intervals overlapped between the different study designs, the SCCS may be more sensitive to inadequately controlled calendar time trends than the SCRI, as it includes a significantly longer follow-up period than the SCRIs. An increase in the rate of myocarditis over time, for example, due to increasing COVID-19 prevalence, might have been expected to produce the observed results. Nevertheless, differences in study designs were not consistent between doses, and we cannot rule out that some of the variation may be due to random error.

Another difference worth commenting on is that although both the standard and extended SCCS included a greater number of events, we found wider confidence intervals for AstraZeneca adjusted first dose estimates using these designs than using either the pre- or post-vaccine SCRIs. This appeared to be due to the fact that some SCCS, but not SCRI, ran with a very low number of events in databases where the AstraZeneca vaccines were not widely used. These estimates therefore contributed to the meta-analyses for the SCCS, but not for the SCRI. Comparing estimates in the CPRD database only showed narrower confidence intervals for the SCCS than the SCRI for these comparisons, as expected..

When choosing a certain study design, there are also important pragmatic considerations to take into account. For example, the post-vaccination SCRI required the accumulation of sufficient time after the second vaccine dose, and for urgent questions, it may not be feasible to wait for follow-up time to accumulate. The SCCS may offer practical advantages compared to SCRI designs when attempting to adjust for covariates. We struggled to control for calendar time in the country-specific SCRI due to a low number of events and a relatively short follow-up period (<120 days), which resulted in collinearity between the proposed calendar time variables and the risk intervals and in turn very wide confidence intervals in the SCRI, but not the SCCS. There are alternative options for adjusting for calendar time in an SCRI [15], and these options may be useful where time-varying confounding by calendar time is a particular concern. More generally, time-varying confounders such as SARS-CoV-2 infection may be less problematic in an SCRI as the observation periods are shorter than in the SCCS.

4.4. Limitations

There are some important limitations to this work. Firstly, within each country, there was often a small number of cases available. This was reflected in convergence problems and increased variance in the post-vaccine SCRI for some vaccines and countries. Secondly, we were restricted to implementing the designs in datasets in which all cases received at least one vaccine dose, which might have limited the SCCS extension's ability to correct for potential bias, particularly for the first dose. We also found that currently available software for fitting the SCCS extension did not always notify the user of convergence issues and had limited options for covariate adjustment. An important avenue for future work may be to improve guidance and software for fitting SCCS extensions. Our experience also highlights that there may be pragmatic reasons for using a simpler, design-based solution such as a truncated SCCS or post-vaccine SCRI to tackle the issue of event-dependent exposures. In our implementation of the post-vaccine SCRI, we also defined a control window following the last vaccine dose. This means that the control window specification was technically different for individuals receiving a single dose, compared to those receiving more than one. Ideally, we would have used a consistent control window definition, but given the short time between doses for COVID-19 vaccines it was not possible to add this after the first dose. Using a fixed time period after the first dose (for example, 6 months or 1 year), was also not feasible as the time between the first, second and third doses varied between countries. In general, the control periods in an SCRI should be as close to the risk periods as possible to minimise sensitivity to calendar time trends. It's also important to note that we only compared four possible design options that we considered particularly relevant for our case study. There are of course other potential study designs that could be used to address the study question, including between-person study designs such as cohort or case-control studies. The most reliable inferences can likely be made by triangulating findings from multiple different study designs, subject to different underlying assumptions [16]. It should be noted that our results here were generated for methodological purposes and we therefore did not stratify our analyses by age, study heterologous dosing, or attempt to control for time-varying confounding by SARS-CoV-2 infection status. This means that we caution against a clinical interpretation of these results, particularly as strong effect modification by age has been shown for this safety signal [13]. Our control of calendar time trends was likely imperfect, as small numbers meant we had to use relatively crude categories of 60-days to model this. Infection with SARS-CoV-2 has also been shown to increase the risk of myocarditis [17], which might cause a downward bias in the pre-vaccine SCRI as individuals gain some protection after vaccination. Although we typically observed good agreement between the pre and post vaccine SCRI in this study, this possibility suggests that a post vaccine SCRI might be a useful sensitivity analyses when the safety event is also strongly linked to the infection the vaccine is designed to prevent. Finally, we note that this is a single case study. Although our results provide reassurance regarding the results previously reported by our team [13] and report on our experience using a number of different methods in the context of a distributed network analysis, they cannot be used to draw more general conclusions regarding the performance of these designs.

5. Conclusions

In the context of the known association between COVID-19 vaccines and myocarditis, we have demonstrated that two forms of SCRI and two forms of SCCS led to largely comparable results. This is likely because there was a limited violation of the assumption of event-dependent exposures in all contributing data sources and relatively limited variation in the recording of the outcome over time, and, as a result, the four designs appear equally valid for evaluating this specific clinical question. Pragmatically, the SCCS may offer some advantages compared to the SCRI when there are strong time-varying confounders, for example by SARS-CoV-2 infection status or calendar time trends, and a low number of cases, as the models may be easier to fit. Researchers using pre-vaccination SCRI concerned about event-dependent exposures may find the addition of a post-vaccination SCRI with the control window defined by the scheduled distance between doses a useful complement to evaluate sensitivity of that design to violations of this particular bias. A simulation study of these designs under the presence of multiple different biases, and considering more complex vaccination schedules, would be a valuable area for future research.

6. Disclaimer

The research leading to these results was conducted as part of the activities of the EU PE&PV (Pharmacoepidemiology and Pharmacovigilance) Research Network which is a public academic partnership coordinated by the Utrecht University, The Netherlands. Scientific work for this project was coordinated by the University Medical Center Utrecht in collaboration with the Vaccine Monitoring Collaboration for Europe network (VAC4EU). The project has received support from the

European Medicines Agency under the Framework service contract nr EMA/2018/23/PE. The content of this paper expresses the opinion of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

7. Ethics

This work was conducted as part of a larger programme of work, and this specific methodological sub-study was approved by the LSHTM ethics committee (ref 28222). The larger programme of work had ethics approval from each contributing DAP, as shown below. The protocol was pre-registered on ENCEPP (EUPAS42467).

DAP	EC approval number
ARS	None required
FISABIO	PI 90/2021
SIDIAP	21/199-PCV
BIFAP	Aprobación (22–07-21, acta CEIm 14/21)
CPRD/UU	21_000643

Conflicts of interest

AS is employeed by LSHTM on a fellowship sponsored by GSK. ID owns shares in and reports research grants from GSK, and research grants from AstraZeneca, both unrelated to the current work. FR is an employee of TEAMIT Institute, a research management organisation that participates in financially supported studies for the European Medicines Agency and related healthcare authorities, pharmaceutical companies, and the European Union. FV, MPM, CAB and ES are salaried employees at Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), which receives institutional research funding from public and private partners, pharmaceutical companies and regulatory agencies, administered by IDIAPJGol. MS is head of a department that conducts studies for the European Medicines Agency, the European Commission and medicine manufacturers, all according to the ENCePP code of conduct. MS does not hold personal financial relations with the companies. Carlos E. Durán (CED) is salaried employee by University Medical Center Utrecht, the Netherlands, which receives institutional research funding from pharmaceutical companies and regulatory agencies. CED is involved only in research projects funded by regulatory authorities. RG and DM are employees of ARS Tuscany, which reports funding from the Innovative Medicines Initiative, RTI, PHARMO, University of Southern Denmark, University of Utrecht, Eli Lilly, Pfizer, Novartis, AstraZeneca, Galapagos, and LeoPharma, for studies unrelated to the current work, and conducted in compliance with the ENCePP code of conduct.

CRediT authorship contribution statement

Anna Schultze: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Ivonne Martin:** Writing – review & editing, Methodology. **Davide Messina:** Writing – review & editing, Software, Formal analysis, Data curation. **Sophie Bots:** Writing – review & editing, Methodology. **Svetlana Belitser:** Writing – review & editing, Methodology, Formal analysis. **Juan José Carreras-Martínez:** Writing – review & editing, Data curation. **Elisa Correcher-Martinez:** Writing – review & editing, Data curation. **Arantxa Urchueguía-Fornes:** Writing – review & editing, Data curation. **Mar Martín-Pérez:** Writing – review & editing, Data curation. **Patricia García-Poza:** Writing – review & editing, Data curation. **Felipe Villalobos:** Writing – review & editing, Data curation. **Meritxell Pallejà-Millán:** Writing – review & editing, Data curation. **Carlo Alberto Bissacco:** Writing – review & editing, Data curation. **Elena Segundo:** Writing – review & editing, Data curation. **Patrick Souverein:** Writing – review & editing, Data curation. **Fabio Riefolo:** Writing – review & editing, Project administration. **Carlos E. Durán:** Writing – review & editing, Methodology. **Rosa Gini:** Writing – review & editing, Supervision, Software, Conceptualization. **Miriam Sturkenboom:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Olaf Klungel:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Ian Douglas:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: University Medical Center Utrecht in collaboration with the Vaccine Monitoring Collaboration for Europe network (VAC4EU). reports financial support was provided by European Medicines Agency. Anna Schultze reports a relationship with GSK that includes: funding grants. Ian Douglas reports a relationship with GSK that includes: equity or stocks and funding grants. Fabio Riefolo reports a relationship with TEAMIT Institute, a research management organisation that participates in financially supported studies for the European Medicines Agency and related healthcare authorities, pharmaceutical companies, and the European Union that includes: employment. Felipe Villalobos, Meritxell Palleja-Millan, Carlo Alberto Bissacco and Elena Segundo reports a relationship with IDIAPJGol, which receives institutional research funding from public and private partners, pharmaceutical companies and regulatory agencies that includes: employment. Miriam Sturkenboom reports a relationship with University Medical Center Utrecht, which conducts studies for the European Medicines Agency, the European Commission and medicine manufacturers, all according to the ENCePP code of conduct that includes: employment. Carlos E. Duran reports a relationship with University Medical Center Utrecht, which receives institutional research funding from pharmaceutical companies and regulatory agencies that includes: employment. Rosa Gini and Davide Messina reports a relationship with ARS Tuscany, which reports funding from the Innovative Medicines Initiative, RTI, PHARMO, University of Southern Denmark, University of Utrecht, Eli Lilly, Pfizer, Novartis, AstraZeneca, Galapagos, and LeoPharma that includes: employment. 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.

Data availability

The data that has been used is confidential. The analytical code used to generate the results is archived and available at https://doi.org/10.5281/zenodo.8272057.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.03.043.

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