Analysis of Coronavirus Prevention Network COVID-19 vaccine efficacy trials: Do vaccine side effects predict better efficacy to prevent COVID-19?

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Abstract

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Many previous studies have investigated the predictiveness of antibody markers on COVID-19 and there are also mixed results indicating the association between immunogenicity and reactogenicity induced by vaccines. However, little is known about the direct association of reactogenicity and clinically relevant endpoints such as symptomatic COVID-19. Among the Moderna trial, the Novavax trial, and the Sanofi Stage 1 and Stage 2 trials, we assessed the associations of reactogenicity variables, specifically the occurrence of any AR, any local AR, any systemic AR, and fever with future risk of COVID-19 among vaccine and placebo recipients using marginal variable importance measures (VIM) analysis, and we examined the vaccine efficacy in the subgroups defined by reactogenicity outcome if assigned vaccine using principal stratification (PS) analysis. By the VIM analysis, we do not find a significant increase in predictiveness for reactogenicity variables across all vaccine trials. By the PS analysis, the results in the Moderna trial suggest improved vaccine efficacy among the subgroup with vaccine-caused reactogenicity compared to the subgroup without reactogenicity, while there's an opposite direction of vaccine efficacy suggested by the Sanofi trials. Although many results are not significant, the opposite pattern we found between mRNA and recombinant protein vaccines can contribute to the design of future vaccines.

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1 Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had an unprecedented impact on global health, economies, and daily life since its outbreak in late 2019. The virus spreads primarily through respiratory droplets and has led to widespread morbidity and mortality, straining healthcare systems worldwide. Vaccination is considered an efficient approach to combat the spread of COVID-19. As of today, several COVID-19 vaccines based on different technologies are available, including mRNA-based vaccines (e.g., Pfizer-BioNTech and Moderna), viral vector vaccines (e.g., Johnson & Johnson and AstraZeneca), and protein subunit vaccines (e.g., Novavax), to meet the global need for vaccine, the wide geographic diversity of the pandemic, and the emergence of variants (Corey et al. [2020]). Vaccination against SARS-CoV-2 has been shown to be effective in reducing SARS-CoV-2 infections, symptomatic COVID-19, hospitalizations, and mortality. Vaccines by Moderna, Johnson & Johnson, AstraZeneca, and Novavax, and Sanofi were developed partly through the six harmonized phase 3 COVID-19 vaccine efficacy trials conducted in public-private partnerships funded by NIAID and BARDA (USG Phase 3 program). The primary publications of all of the USG Phase 3 program can be seen in Baden et al. [2021], El Sahly et al. [2021], Sadoff et al. [2021, 2022], Falsey et al. [2021], Dunkle et al. [2022], Dayan et al. [2023b,a].

A correlates of protection (CoP) is an immune marker statistically correlated with vaccine efficacy (Plotkin and Gilbert [2012]). It can be used to reliably predict vaccine efficacy against clinically relevant endpoints and, thus, is widely pursued in vaccine research, including COVID-19. Some previous research has investigated the association between antibody immune markers and COVID-19 stems from the six harmonized phase 3 COVID-19 VE trials, as mentioned in the previous paragraph. This research was conducted by the NIAID- and BARDA-funded COVID-19 Vaccine Correlates of Protection Program (USG CoP Program). The immune correlates statistical analysis plan (SAP) specified statistical methods within each of the following statistical frameworks, all of which have been applied to some or all of the trial datasets: (1) nonparametric covariate-marginalized assessment of univariable marker correlates of risk (van der Laan et al. [2022]); (2) nonparametric and semiparametric univariable marker controlled vaccine efficacy causal analysis (Gilbert et al. [2022b]); (3) nonparametric univariable marker stochastic interventional vaccine efficacy causal analysis (Hejazi et al. [2021]); (4) nonparametric univariable/multivariable marker mediation analysis based on natural direct and indirect effects (Benkeser et al. [2021]), (5) nonparametric and semiparametric principal stratification correlates of vaccine efficacy analysis (Gilbert et al. [2020], Huang et al. [2022]); (5) nonparametric stochastic interventional vaccine efficacy analysis (Hejazi et al. [2021]); and (6) multivariable marker superlearning correlates of risk analysis that considered all of the measured antibody markers in the same machine learning analysis (Benkeser et al. [2023b]). All immune correlates analyses conducted by all methods supported both IgG binding antibodies to the Spike protein and neutralizing antibody titers as correlates of COVID-19 in vaccine recipients, and also supportive of these antibody markers for use as partially validated surrogate endpoints (Earle et al. [2021], Fong et al. [2022, 2023], Khoury et al. [2022], Benkeser et al. [2023a,b], Hejazi et al. [2023], Huang et al. [2023]). These blinded-phase correlates studies had scope (1) to study antibody markers measured 2–4 weeks post primary vaccination series in SARS-CoV-2 negative individuals (inferred to be never previously infected with SARS-CoV-2); (2) to study the primary study endpoint of virologically-confirmed symptomatic COVID-19 through to between 2.5 and 7

months post primary vaccination series depending on the trial; (3) to study COVID-19 endpoints caused by ancestral and many pre-omicron variants. The paper Gilbert et al. [2022a] summarized the significance and impact of these results, as well as important open challenges that remain to be addressed with future correlates of protection research (Gilbert et al. [2022a]). The results to date have supported that binding antibodies to SARS-CoV-2 spike, binding antibodies to the spike receptor-binding domain (RBD), and pseudovirus neutralizing antibody titers ("ID50 titer") measured 2–4 weeks after the primary vaccination series are all significant inverse correlates of risk and supported to have value as partially valid surrogate endpoints (immune correlate of protection), with ID50 titer standing out as a consistent and highest quality independent correlate of protection across trials and vaccine platforms. The results provided the insight that generally across the vaccine platforms, vaccine recipients with lowest antibody levels (near or below assay detection limits) were particularly vulnerable to failure of vaccination to protect, with impact to raise special concern for sub-populations with low frequencies of detectable neutralizing antibodies. Impact of these results has included undergirding use of ID50 titer as a surrogate endpoint for many vaccine recommendation, authorization, and approval decisions.

In addition to predicting the efficacy of the vaccines, safety is another big concern in COVID-19 vaccine development. Previous research has studied the relationship between immunogenicity and reactogenicity (solicited adverse reactions). The results in Siangphoe et al. [2023] suggest that solicited systemic adverse reactions (ARs) predict higher neutralizing antibody (nAb) geometric mean titers (GMTs) after a second mRNA-1273 injection. Another research project studied the association between self-reported solicited ARs after receiving SARS-CoV-2 mRNA vaccines (Pfizer-BioNTech and Moderna) and serum concentration of IgG antibody against the spike protein (IgG spike antibody) among participants in the Framingham Heart Study (FHS). The result suggests that systemic solicited ARs are associated with greater antibody response (Hermann et al. [2022]). Moreover, Dutcher et al. [2024] examined the association between solicited ARs and neutralizing antibody (nAB) response at 1 month and 6 months after the second vaccine dose among participants who received either BNT162b2 or mRNA-1273. The study found that chills, tiredness, feeling unwell, and headache after the second dose were each associated with higher nAB at 1 and 6 months after vaccination. The study also suggests a significant positive association between the number of distinct symptoms, vaccination-induced change in skin temperature and heart rate, and nAB at both follow-up time points. In contrast, the research conducted by Choi et al. [2023] among mRNA-1273 recipients found that neither experiencing any solicited local nor Systemic ARs after both injections were predictive of higher antibody response (IgG spike antibody). Only participants with a headache after the first injection showed significantly stronger antibody response after 8 weeks.

Despite the prior publications investigating the predictiveness of antibody markers on SARS-CoV-2 infection as well as the association between reactogenicity and antibody response, little is known about the direct association between reactogenicity and clinically relevant endpoints such as symptomatic COVID-19. Therefore, in this project, our objectives are:

1. To characterize associations of reactogenicity variables with future risk of COVID-19 among vaccine and placebo recipients separately;

2. To characterize the vaccine vs. placebo effect on COVID-19 in subgroups defined by reactogenicity outcome if assigned vaccine.

This project will analyze multiple phase 3 trials in the US Government's public-private partnership COVID-19 vaccine effiacy trials program, including all trials with enough reactogenicity data to support the analysis: the P3001 Moderna COVE trial, the P3004 Novavax PREVENT-19 trial, the P3005 Sanofi VAT00008 Stage 1 trial, and the P3005 Sanofi VAT00008 Stage 2 trial. It is another cross-protocol analysis of multiple phase 3 trials, with other research projects with this objective published in Lora et al. [2023], Theodore et al. [2023], Rick et al. [2023], Turley et al. [2023].

2 Methods

2.1 Study Cohorts

For the Moderna and Novavax trials, the cohort analyzed is the protocol-specified per-protocol cohort which is the same cohort used for primary efficacy analysis, consisting of randomized baseline SARS-CoV-2 negative participants who received all planned immunizations without major protocol violations. In both cases, the per-protocol analysis set and baseline negative vs. positive are defined the same as in the protocol and primary papers, as also defined in Rick et al. [2023]. Note that for the Moderna trial, the primary paper Baden et al. [2021] used the data cutoff on November 11, 2020 (interim analysis), while the primary paper El Sahly et al. [2021] used the data cutoff on March 26, 2021 (final analysis). In our work, we focus on the most up-to-date data as in El Sahly et al. [2021]. Similarly, for the Novavax trial, the primary paper Dunkle et al. [2022] used the data cutoff on April 19, 2021, while in our work, we focus on the (final) data cutoff on September 27, 2021.

For both Sanofi stage 1 and Sanofi stage 2 trials, separate analyses are done for participants naive at both D01 and D22 in the modified full analysis set post-dose2 (mFAS-PD2) and for participants non-naive at either D01 or D22 in mFAS-PD2. The naive and non-naive cohorts are defined the same as in the protocols and primary analyses Dayan et al. [2023b] and Dayan et al. [2023a], involving RNA PCR and serology testing data at D01 and D22. Participants with undetermined naive/non-naive status were excluded. The data cut-off date we used for Sanofi trials is June 05, 2023. In addition, since reactogenicity data were only collected among participants in the reactogenicity subset (see more details in Section 2.2), all the analyses for Sanofi stage 1 and Sanofi stage 2 are implemented among participants who are in mFAS-PD2 and also in the reactogenicity subset. Since the total number of cases and the incidence rate are both low, additional analyses were conducted on the entire Sanofi Stage 2 cohort, regardless of the previous infection status. This includes participants from both the Sanofi Stage 2 naive analysis set and the Sanofi Stage 2 non-naive analysis set.

2.2 Reactogenicity Assessment

Reactogenicity data were collected from all participants in the P3001 Moderna COVE trial and the P3004 Novavax PREVENT-19 trial, while it was only collected from the reactogenicity subset in the P3005 Sanofi VAT00008 Stage 1 and Stage 2 trials. Reactogenicity was assessed by the severity and duration of solicited local and systemic ARs reported within 7 days after each injection. The severity grading of solicited ARs was based on grading scales modified from the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. The types of solicited ARs collected in the P3001 Moderna COVE trial were arthralgia, chills, erythema, fatigue, fever, headache, myalgia, nausea, pain, swelling, and underarm gland swelling or tenderness; the types of solicited ARs collected in the P3001 Moderna COVE trial were arthralgia, chills, erythema, fatigue, fever, headache, myalgia, nausea, pain, swelling, and underarm gland swelling or tenderness; the types of solicited ARs collected were arthralgia, chills, erythema, fever, headache, myalgia, pain, swelling, and malaise in the P3005 Sanofi VAT00008 Stage 1 and Stage 2 trials.

In this project, the reactogenicity variables we are interested in are the occurrence of any solicited AR, the occurrence of any solicited local AR, the occurrence of any solicited Systemic AR, and fever, for each vaccination (first and second). The occurrence of certain AR endpoints after each vaccination is denoted as an indicator variable where 1 refers to either having duration for at least 1 day or having worst severity grade greater than or equal to grade 1, and 0 refers to having 0 duration and worst severity grade 0. The severity grade 0 is denoted as not having the reactogenicity or having more mild symptoms than grade 1.

2.3 Outcome

For the Moderna and Sanofi trials, the primary endpoint is the protocol-specified primary endpoint, virologically-confirmed symptomatic COVID-19 (referred to as COVID-19), starting 14 days after the second injection and throughout the blinded period of study follow-up. For the Novavax trial, the primary endpoint is the protocol-specified primary endpoint, virologically-confirmed symptomatic COVID-19, starting 7 days after the second injection and throughout the blinded period of study follow-up.

2.4 Statistical Analysis

2.4.1 Objective One: Prediction of COVID-19

Addressing our first objective includes quantification of COVID-19 classification accuracy and variable importance analysis for estimating which reactogenicity variables have the greatest influence in predicting COVID-19.

We will implement the nonparametric variable importance technique from Wolock et al. [2023] to predict the risk of COVID-19 infection in each of the six study cohorts. The analysis will be done for each injection and for each treatment arm. We will use the landmark time area under the ROC curve (AUC) as the predictiveness measure and implement the analysis using cross-fitting with global survival stacking for nuisance estimation. The algorithms included in the global survival stacking are SL.mean, SL.glm, and SL.glmnet. The results of the marginal variable importance measures (VIM) analysis will be presented where the full feature vector includes the baseline characteristics plus all other features or feature groups of interest, and the reduced feature vector includes only the baseline characteristics. The feature or group of features included in each trial can be seen in Table 1 - Table 3. The confounders adjusted for in the analyses to examine the association between reactogenicity variables and future risk of COVID-19 for each trial are adapted from Gilbert et al. [2022c], Fong et al. [2023], Peter B. Gilbert [2024]. The marginal VIM analysis also adjusts for enrollment date where it is denoted as an indicator variable based on the median of the enrollment date among all participants in the certain analysis set.

The analysis will be conducted for each study cohort, treatment arm, and injection. In addition, we require each analysis set to have at least 15 COVID-19 cases. For each type of reactogenicity endpoint, we also require at least one case for each level of the reactogenicity variable. Therefore, the vaccine recipients in the Novavax trial are excluded from this analysis (14 cases). The occurrence of fever is excluded from the Moderna post-dose one analysis, Novavax post-dose one and post-dose two analysis, and Sanofi Stage 2 Naive post-dose one analysis. Complete-case analysis is implemented to deal with the missing values in reactogenicity variables.

Group	Feature(s)
1	occurrence of any type of solicited AR within 7 days after each injection
2	occurrence of any solicited local AR within 7 days after each injection
3	occurrence of any solicited systemic AR within 7 days after each injection
4	occurrence of fever within 7 days after each injection
5	Baseline characteristics: baseline risk score, community of color, risk of exposure to SARS-CoV-2 as per OSHA

Table 1: Groups of Features included in the Moderna Trial

Group	Feature(s)
1	occurrence of any type of solicited AR within 7 days after each injection
2	occurrence of any solicited local AR within 7 days after each injection
3	occurrence of any solicited systemic AR within 7 days after each injection
4	occurrence of fever within 7 days after each injection
5	Baseline characteristics: baseline risk score, risk of exposure to SARS-CoV-2 as per OSHA

Table 2: Groups of Features included in the Novavax Trial

Group	Feature(s)
1	occurrence of any type of solicited AR within 7 days after each injection
2	occurrence of any solicited local AR within 7 days after each injection
3	occurrence of any solicited systemic AR within 7 days after each injection
4	occurrence of fever within 7 days after each injection
5	Baseline characteristics: baseline risk score, force of infection (FOI)

Table 3: Groups of Features included in the Sanofi Trials

Each of the analyses estimates a conditional survival curve $P(T \leq t_0|X)$ with T is the number of days between the time origin and the COVID-19 endpoint and t_0 is the last time by which a COVID-19 endpoint is counted (the so-called landmark time), such that a definition of t_0 is needed for each analysis. For the analyses of the Sanofi vaccines, t_0 is set to 181 days after the time origin for the analyses of post-dose two reactogenicity. For post-dose one reactogenicity analyses, t_0 is defined as 202 days after the time origin. Regarding the analyses of the Moderna and Novavax vaccines, for both post-dose two and post-dose one analyses, t_0 is defined as the latest day of follow-up after the time origin such that at least 5 COVID-19 endpoints occurred in each of the vaccine and placebo arms. In general, follow-up only includes follow-up prior to unblinding, such that at least 5 COVID-19 endpoints must occur during the blinded phase of follow-up. For post-dose one analyses, the time origin is 7 days post dose 1. For post-dose two analyses, the time origin is 7 days post dose 2. The landmark time used for each study cohort and injection can be seen in Table 4.

Vaccine Cohort	Post Dose One (days)	Post Dose Two (days)
Moderna	144	115
Novavax	67	46
Sanofi Stage 1 Naive	202	181
Sanofi Stage 1 Non-Naive	202	181
Sanofi Stage 2 Naive	202	181
Sanofi Stage 2 Non-Naive	202	181

Table 4: Landmark time since time origin for each trial. The time origin for post-dose one analyses is 6 days post dose 1. The time origin for post-dose two analyses is 6 days post dose 2.

2.4.2 Objective Two: Impact of Vaccine-caused Reactogenicity on COVID-19 Vaccine Efficacy

Addressing our second objective focuses on placebo recipients with no reported reactogenicity, comparing vaccine efficacy in the subgroup with a given reactogenicity outcome if assigned vaccine (but not if assigned placebo) to vaccine efficacy in the subgroup without a given reactogenicity outcome under both randomization assignments using principal stratification methods.

Let R be a binary reactogenicity variable measured after dose one or after dose two, with $R(a)$ the potential outcome under assignment to vaccine ($a = 1$) and under assignment to placebo ($a = 0$). Let Y be the indicator of COVID-19 after the time point that R is measured, with $Y(a)$ the potential outcomes for $a = 0, 1$. We consider causal estimands of interest defined exactly as in Gilbert et al. [2020]. In their notation, our objective is to estimate VE(1,0)=CEP(1,0) and VE(0,0)=CEP(0,0) where:

- VE(1,0) $:= 1 - P(Y(1) = 1|R(1) = 1, R(0) = 0)/P(Y(0) = 1|R(1) = 1, R(0) = 0)$ and
- VE(0,0) $:= 1 - P(Y(1) = 1|R(1) = 0, R(0) = 0)/P(Y(0) = 1|R(1) = 0, R(0) = 0)$.

That is, VE(1,0) is vaccine efficacy in the subgroup with vaccine-caused reactogenicity, and VE(0,0) is vaccine efficacy in the subgroup without reactogenicity under both treatment assignments. We also estimate the relative risk ratio [1-VE(0,0)]/[1-VE(1,0)] which is interpreted as the degree (on the multiplicative scale) to which vaccine-reduction of COVID-19 is better for the (1,0) subgroup than for the (0,0) subgroup (i.e., quantifying a vaccine-protection advantage of having vaccine-caused reactogenicity).

The NEE-CB method is applied to the datasets for both post-dose one and post-dose two analyses where NEE refers to the version of the methods that assume "no early efficacy" of the vaccine vs. placebo on COVID-19 by the time reactogenicity is measured, and CB standards for "constant biomarker", which in our context means that $R(0)$ takes the same constant value for all placebo recipients: $R(0) = 0$. Given this assumption, only placebo recipients with no reported reactogenicity are included in the analyses. This method relies on one pre-specified sensitivity parameter, β_0. For our analysis, first, β_0 is set to zero (providing no robustness to potential post-randomization selection bias), and the point estimate and 95% CI are calculated. Then, β_0 is set to vary from $\log(0.75)$ to $-\log(0.75)$ (medium robustness) and $\log(0.5)$ to $-\log(0.5)$ (high robustness), and the ignorance interval (IGI) and 95% estimated uncertainty interval (EUI) are calculated, which account for uncertainty due to partial non-identifiability of the causal parameter being estimated as well as for sampling variability.

The analyses will be implemented for study cohorts in which for both post-dose one and post-dose two analyses, at least 15 vaccine cases occurred before the certain landmark time for a given reactogenicity value and at least one vaccine case occurred for each level of the reactogenicity variable. The analyses will be implemented for study cohorts in which for a given dosing, there are at least 15 vaccine cases, defined as vaccine cases occurred before the certain landmark time, for the given reactogenicity variable and at least one vaccine case for each level of the reactogenicity variable. Therefore, participants in the Novavax trial and Sanofi Stage 1 Non-naive cohort are excluded from this analysis since only 8 and 13 vaccine recipients had symptomatic COVID-19 infection before a certain landmark time, respectively. In addition, we only consider implementing this analysis among trials that have vaccine efficacy of at least 30%, which excludes the Sanofi Stage 1 Naive cohort from this analysis (Dayan et al. [2023b]). The occurrence of fever is excluded from Moderna post-dose one analysis, Sanofi Stage 2 Naive post-dose one analysis, and Sanofi Stage 2 Non-naive post-dose two analysis.

The data analysis is done for the same overall binary reactogenicity variables studied for the prediction objective, that measure any reactogenicity, local reactogenicity, systemic reactogenicity, or fever. The cohorts, landmark times, and included COVID-19 endpoints are the same as for the prediction analyses. Similar to the prediction analysis, complete-case analysis is implemented to deal with the missing values in reactogenicity variables.

3 Results

3.1 Summary of COVID-19 Endpoints among Each Vaccine Trial

The number of COVID-19 endpoints and the incidence of cases stratified by treatment arms in each vaccine trial can be seen in Table 5.

Vaccine Cohort		Vaccine $n/N(\%)$	Placebo $n/N(\%)$
Moderna	Full analysis set	55/14,287 (0.4)	744/14,164 (5.3)
Novavax	Full analysis set	17/17,272 (0.1)	79/8385 (0.9)
Sanofi Stage 1 Naive	Reactogenicity Subset	49/558 (8.8)	57/504 (11.3)
Sanofi Stage 1 Non-Naive	Reactogenicity Subset	24/1530 (1.6)	44/1559 (2.8)
Sanofi Stage 2 Naive	Reactogenicity Subset	20/244 (8.2)	34/257 (13.2)
Sanofi Stage 2 Non-Naive	Reactogenicity Subset	39/2070 (1.9)	82/2009 (4.1)

Table 5: Summary of Symptomatic COVID-19 cases among the full analysis set of each study cohort as defined in Section 2.1. Reactogenicity was only collected among participants in the reactogenicity subset in the Sanofi trials.

3.2 Description of Demographics and Baseline Characteristics among Each Trial Cohort

The following tables provide a description of demographics and baseline characteristics for each study cohort. Separate tables are provided for post-dose one and post-dose two analyses.

	Placebo	Treatment
	(N=8598)	(N=13633)
Sex		
Female	4337 (50.4%)	6627 (48.6%)
Male	4261 (49.6%)	7006 (51.4%)
Age category and risk for severe Covid-19		
>=18 and <65 Years and at Risk	1489 (17.3%)	2274 (16.7%)
>=18 and <65 Years and Not at Risk	5162 (60.0%)	7975 (58.5%)
>=65 Years	1947 (22.6%)	3384 (24.8%)
Body Mass Index		
Mean (SD)	29.4 (6.72)	29.2 (6.77)
Median [Min, Max]	28.2 [12.3, 72.7]	28.0 [9.78, 82.0]
Community of Color		
Yes	3013 (35.0%)	4786 (35.1%)
No	5585 (65.0%)	8823 (64.9%)
Risk Exposure		
High exposure risk	4478 (52.1%)	7215 (52.9%)
Medium exposure risk	4120 (47.9%)	6418 (47.1%)
Chronic lung disease		
No	8066 (93.8%)	12870 (94.4%)
Yes	532 (6.2%)	763 (5.6%)
Significant cardiac disease		
No	6015 (70.0%)	9442 (69.3%)
Yes	2583 (30.0%)	4191 (30.7%)
Severe obesity		
No	5235 (60.9%)	8413 (61.7%)
Yes	3363 (39.1%)	5220 (38.3%)
Diabetes		
No	7759 (90.2%)	12268 (90.0%)
Yes	839 (9.8%)	1365 (10.0%)
Liver disease		
No	8528 (99.2%)	13525 (99.2%)
Yes	70 (0.8%)	108 (0.8%)
HIV		
No	6139 (71.4%)	9643 (70.7%)
Yes	2459 (28.6%)	3990 (29.3%)
Standardized risk score		
Mean (SD)	0.08 (0.99)	0.03 (0.99)
Median [Min, Max]	0.25 [-7.00, 3.12]	0.19 [-4.19, 3.27]

Table 6: Demographic and clinical characteristics at baseline summarized among participiants in the Moderna analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after first injection.

	Placebo	Treatment
	(N=8584)	(N=13620)
Sex		
Female	4329 (50.4%)	6615 (48.6%)
Male	4255 (49.6%)	7005 (51.4%)
Age category and risk for severe Covid-19		
>=18 and <65 Years and at Risk	1485 (17.3%)	2269 (16.7%)
>=18 and <65 Years and Not at Risk	5156 (60.1%)	7967 (58.5%)
>=65 Years	1943 (22.6%)	3384 (24.8%)
Body Mass Index		
Mean (SD)	29.4 (6.72)	29.2 (6.76)
Median [Min, Max]	28.2 [12.3, 72.7]	28.0 [9.78, 82.0]
Community of Color		
Yes	3008 (35.0%)	4778 (35.1%)
No	5576 (65.0%)	8842 (64.9%)
Risk Exposure		
High exposure risk	4471 (52.1%)	7210 (52.9%)
Medium exposure risk	4113 (47.9%)	6410 (47.1%)
Chronic lung disease		
No	8053 (93.8%)	12856 (94.4%)
Yes	531 (6.2%)	764 (5.6%)
Significant cardiac disease		
No	6006 (70.0%)	9434 (69.3%)
Yes	2578 (30.0%)	4186 (30.7%)
Severe obesity		
No	5228 (60.9%)	8407 (61.7%)
Yes	3356 (39.1%)	5213 (38.3%)
Diabetes		
No	7746 (90.2%)	12258 (90.0%)
Yes	838 (9.8%)	1362 (10.0%)
Liver disease		
No	8515 (99.2%)	13513 (99.2%)
Yes	69 (0.8%)	107 (0.8%)
HIV		
No	6130 (71.4%)	9636 (70.7%)
Yes	2454 (28.6%)	3984 (29.3%)
Standardized risk score		
Mean (SD)	0.08 (0.99)	0.03 (0.99)
Median [Min, Max]	0.25 [-7.00, 3.12]	0.19 [-4.19, 3.27]

Table 7: Demographic and clinical characteristics at baseline summarized among participants in the Moderna analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after second injection.

	Placebo
	(N=4654)
Sex	
Female	2532 (54.4%)
Male	2122 (45.6%)
Age Group	
<65 Years	4215 (90.6%)
>=65 Years	439 (9.4%)
Race	
White	3649 (78.4%)
Black or African American	430 (9.2%)
American Indian or Alaska native	237 (5.1%)
Asian	222 (4.8%)
Multiple	83 (1.8%)
Other	33 (0.7%)
Ethnic	
Not Hispanic or Latino	3709 (79.7%)
Hispanic or Latino	945 (20.3%)
Risk exposure	
High exposure risk	444 (9.5%)
Lower exposure risk (caution)	2693 (57.9%)
Medium exposure risk	1517 (32.6%)
Chronic lung disease	
No	3878 (83.3%)
Yes	776 (16.7%)
Significant cardiac disease	
No	3629 (78.0%)
Yes	1025 (22.0%)
Diabetes	
No	4214 (90.5%)
Yes	440 (9.5%)
Liver disease	
No	4622 (99.3%)
Yes	32 (0.7%)
Kidney disease	
No	4625 (99.4%)
Yes	29 (0.6%)
HIV	
No	3655 (78.5%)
Yes	999 (21.5%)
Standardized risk score	
Mean (SD)	0.11 (0.93)
Median [Min, Max]	0.19 [-3.03, 3.78]
Country	
Mexico	247 (5.3%)
United States	4407 (94.7%)

Table 8: Demographic and clinical characteristics at baseline summarized among participants in the Novavax placebo recipients who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after first injection. Novavax vaccine recipients are excluded from both VIM analysis and Principal Stratification analysis.

	Placebo
	(N=4556)
Sex	
Female	2466 (54.1%)
Male	2090 (45.9%)
Age Group	
<65 Years	4120 (90.4%)
>=65 Years	436 (9.6%)
Race	
White	3549 (77.9%)
Black or African American	425 (9.3%)
American Indian or Alaska Native	252 (5.5%)
Asian	218 (4.8%)
Multiple	80 (1.8%)
Other	32 (0.7%)
Ethnic	
Not Hispanic or Latino	3618 (79.4%)
Hispanic or Latino	938 (20.6%)
Risk exposure	
High exposure risk	430 (9.4%)
Lower exposure risk (caution)	
Medium exposure risk	1472 (32.3%)
Chronic lung disease	
No	3797 (83.3%)
Yes	759 (16.7%)
Significant cardiac disease	
No	3546 (77.8%)
Yes	1010 (22.2%)
Diabetes	
No	4120 (90.4%)
Yes	436 (9.6%)
Liver disease	
No	4524 (99.3%)
Yes	32 (0.7%)
Kidney disease	
No	4525 (99.3%)
Yes	31 (0.7%)
HIV	
No	3574 (78.4%)
Yes	982 (21.6%)
Standardized risk score	
Mean (SD)	0.10 (0.93)
Median [Min, Max]	0.15 [-3.03, 3.78]
Country	
Mexico	258 (5.7%)
United States	4298 (94.3%)

Table 9: Demographic and clinical characteristics at baseline summarized among participants in the Novavax placebo recipients who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after second injection. Novavax vaccine recipients are excluded from both VIM analysis and Principal Stratification analysis.

	Placebo	Treatment
	(N=500)	(N=556)
Sex		
Female	198 (39.6%)	248 (44.6%)
Male	302 (60.4%)	308 (55.4%)
Age		
Mean (SD)	43.1 (15.9)	42.5 (15.4)
Median [Min, Max]	41.0 [18.0, 86.0]	42.0 [18.0, 86.0]
Age Group		
>=60 years	90 (18.0%)	88 (15.8%)
18-59 years	410 (82.0%)	468 (84.2%)
Body Mass Index		
Mean (SD)	25.3 (5.79)	25.0 (5.79)
Median [Min, Max]	24.4 [14.5, 54.2]	23.9 [14.5, 52.1]
Missing	1 (0.2%)	0 (0%)
Race		
Asian	205 (41.0%)	219 (39.4%)
Black or African American	166 (33.2%)	197 (35.4%)
American Indian or Alaska Native	105 (21.0%)	119 (21.4%)
White	22 (4.4%)	21 (3.8%)
Multiple	1 (0.2%)	0 (0%)
Native Hawaiian or Other Pacific Islander	1 (0.2%)	0 (0%)
Ethnic		
Not Hispanic or Latino	388 (77.6%)	428 (77.0%)
Hispanic or Latino	108 (21.6%)	128 (23.0%)
Not Reported	3 (0.6%)	0 (0%)
Unknown	1 (0.2%)	0 (0%)
Country		
Ghana	149 (29.8%)	159 (28.6%)
Japan	117 (23.4%)	121 (21.8%)
Honduras	61 (12.2%)	74 (13.3%)
Nepal	72 (14.4%)	69 (12.4%)
Colombia	45 (9.0%)	47 (8.5%)
United States	37 (7.4%)	32 (5.8%)
India	15 (3.0%)	26 (4.7%)
Kenya	4 (0.8%)	28 (5.0%)
Force of Infection		
Mean (SD)	18.8 (31.8)	15.4 (25.8)
Median [Min, Max]	3.56 [1.23, 147]	3.56 [0, 146]
Standardized risk score		
Mean (SD)	-0.26 (0.84)	-0.32 (0.48)
Median [Min, Max]	-0.36 [-1.83, 7.39]	-0.43 [-1.13, 0.80]

Table 10: Demographic and clinical characteristics at baseline summarized among participants in the Sanofi Stage 1 Naive cohort who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after first injection.

	Placebo	Treatment
	(N=501)	(N=555)
Sex		
Female	199 (39.7%)	248 (44.7%)
Male	302 (60.3%)	307 (55.3%)
Age		
Mean (SD)	43.0 (15.9)	42.5 (15.4)
Median [Min, Max]	41.0 [18.0, 86.0]	42.0 [18.0, 86.0]
Age Group		
>=60 years	90 (18.0%)	88 (15.9%)
18-59 years	411 (82.0%)	467 (84.1%)
Body Mass Index		
Mean (SD)	25.3 (5.78)	24.9 (5.78)
Median [Min, Max]	24.3 [14.5, 54.2]	23.9 [14.5, 52.1]
Missing	1 (0.2%)	0 (0%)
Race		
Asian	206 (41.1%)	219 (39.5%)
Black or African American	166 (33.1%)	196 (35.3%)
American Indian or Alaska Native	106 (21.2%)	120 (21.6%)
White	21 (4.2%)	20 (3.6%)
Multiple	1 (0.2%)	0 (0%)
Native Hawaiian or Other Pacific Islander	1 (0.2%)	0 (0%)
Ethnic		
Not Hispanic or Latino	388 (77.4%)	426 (76.8%)
Hispanic or Latino	109 (21.8%)	129 (23.2%)
Not Reported	3 (0.6%)	0 (0%)
Unknown	1 (0.2%)	0 (0%)
Country		
Ghana	149 (29.7%)	159 (28.6%)
Japan	117 (23.4%)	121 (21.8%)
Nepal	72 (14.4%)	69 (12.4%)
Honduras	61 (12.2%)	74 (13.3%)
Colombia	46 (9.2%)	48 (8.6%)
United States	37 (7.4%)	30 (5.4%)
India	15 (3.0%)	26 (4.7%)
Kenya	4 (0.8%)	28 (5.0%)
Force of Infection		
Mean (SD)	18.7 (31.8)	15.1 (25.6)
Median [Min, Max]	3.56 [1.23, 147]	3.56 [0, 146]
Standardized risk score		
Mean (SD)	-0.26 (0.84)	-0.32 (0.49)
Median [Min, Max]	-0.36 [-1.83, 7.39]	-0.43 [-1.13, 0.80]

Table 11: Demographic and clinical characteristics at baseline summarized among participants in the Sanofi Stage 1 Naive cohort who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after second injection.

	Placebo	Treatment
	(N=1550)	(N=1521)
Sex		
Female	693 (44.7%)	661 (43.5%)
Male	857 (55.3%)	860 (56.5%)
Age		
Mean (SD)	38.2 (14.6)	38.0 (14.5)
Median [Min, Max]	36.0 [18.0, 95.0]	36.0 [18.0, 89.0]
Age Group		
>=60 years	145 (9.4%)	143 (9.4%)
18-59 years	1405 (90.6%)	1378 (90.6%)
Body Mass Index		
Mean (SD)	23.7 (4.62)	23.8 (4.70)
Median [Min, Max]	22.9 [13.6, 46.2]	23.0 [14.1, 50.2]
Race		
Black or African American	725 (46.8%)	712 (46.8%)
Asian	589 (38.0%)	562 (36.9%)
American Indian or Alaska Native	226 (14.6%)	239 (15.7%)
Multiple	3 (0.2%)	2 (0.1%)
White	3 (0.2%)	5 (0.3%)
Unknown	3 (0.2%)	1 (0.1%)
Native Hawaiian or Other Pacific Islander	1 (0.1%)	0 (0%)
Ethnic		
Not Hispanic or Latino	1308 (84.4%)	1274 (83.8%)
Hispanic or Latino	231 (14.9%)	237 (15.6%)
Unknown	11 (0.7%)	10 (0.7%)
Country		
Ghana	679 (43.8%)	683 (44.9%)
India	428 (27.6%)	408 (26.8%)
Nepal	156 (10.1%)	149 (9.8%)
Colombia	146 (9.4%)	160 (10.5%)
Honduras	83 (5.4%)	75 (4.9%)
Kenya	44 (2.8%)	31 (2.0%)
United States	8 (0.5%)	11 (0.7%)
Japan	6 (0.4%)	4 (0.3%)
Force of Infection		
Mean (SD)	8.62 (16.69)	8.39 (15.21)
Median [Min, Max]	3.56 [0, 135]	3.56 [0.27, 133]
Standardized risk score		
Mean (SD)	0.32 (0.64)	0.12 (0.49)
Median [Min, Max]	0.30 [-1.05, 2.93]	0.01 [-0.66, 3.70]

Table 12: Demographic and clinical characteristics at baseline summarized among participants in the Sanofi Stage 1 Non-naive cohort who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after first injection.

	Placebo	Treatment
	(N=1544)	(N=1520)
Sex		
Female	693 (44.9%)	659 (43.4%)
Male	851 (55.1%)	861 (56.6%)
Age		
Mean (SD)	38.3 (14.6)	38.0 (14.4)
Median [Min, Max]	36.0 [18.0, 95.0]	36.0 [18.0, 89.0]
Age Group		
>=60 years	145 (9.4%)	141 (9.3%)
18-59 years	1399 (90.6%)	1379 (90.7%)
Body Mass Index		
Mean (SD)	23.7 (4.63)	23.8 (4.73)
Median [Min, Max]	22.9 [13.6, 46.2]	23.0 [14.1, 50.2]
Race		
Black or African American	726 (47.0%)	711 (46.8%)
Asian	589 (38.1%)	562 (37.0%)
American Indian or Alaska Native	219 (14.2%)	239 (15.7%)
Multiple	3 (0.2%)	2 (0.1%)
White	3 (0.2%)	5 (0.3%)
Unknown	3 (0.2%)	1 (0.1%)
Native Hawaiian or Other Pacific Islander	1 (0.1%)	0 (0%)
Ethnic		
Not Hispanic or Latino	1309 (84.8%)	1274 (83.8%)
Hispanic or Latino	224 (14.5%)	236 (15.5%)
Unknown	11 (0.7%)	10 (0.7%)
Country		
Ghana	679 (44.0%)	682 (44.9%)
India	428 (27.7%)	408 (26.8%)
Nepal	156 (10.1%)	149 (9.8%)
Colombia	140 (9.1%)	160 (10.5%)
Honduras	82 (5.3%)	75 (4.9%)
Kenya	44 (2.8%)	31 (2.0%)
United States	9 (0.6%)	11 (0.7%)
Japan	6 (0.4%)	4 (0.3%)
Force of Infection		
Mean (SD)	8.62 (16.69)	8.39 (15.21)
Median [Min, Max]	3.56 [0, 135]	3.56 [0.273, 133]
Standardized risk score		
Mean (SD)	0.32 (0.66)	0.12 (0.49)
Median [Min, Max]	0.3 [-1.05, 2.93]	0.01 [-0.66, 3.70]

Table 13: Demographic and clinical characteristics at baseline summarized among participants in the Sanofi Stage 1 Non-naive cohort who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after second injection.

	Placebo	Treatment
	(N=257)	(N=244)
Sex		
Female	113 (44.0%)	113 (46.3%)
Male	144 (56.0%)	131 (53.7%)
Age		
Mean (SD)	39.1 (16.7)	38.1 (14.7)
Median [Min, Max]	34.0 [18.0, 91.0]	34.5 [18.0, 93.0]
Age Group		
>=60 years	38 (14.8%)	27 (11.1%)
18-59 years	219 (85.2%)	217 (88.9%)
Body Mass Index		
Mean (SD)	23.3 (3.93)	23.7 (4.93)
Median [Min, Max]	22.5 [14.5, 41.5]	22.4 [15.1, 48.6]
Race		
Asian	124 (48.2%)	108 (44.3%)
Black Or African American	92 (35.8%)	96 (39.3%)
Unknown	37 (14.4%)	38 (15.6%)
American Indian Or Alaska Native	3 (1.2%)	1 (0.4%)
White	1 (0.4%)	0 (0%)
Multiple	0 (0%)	1 (0.4%)
Ethnic		
Not Hispanic Or Latino	217 (84.4%)	204 (83.6%)
Hispanic Or Latino	40 (15.6%)	39 (16.0%)
Not Reported	0 (0%)	1 (0.4%)
Country		
Nepal	119 (46.3%)	108 (44.3%)
Kenya	82 (31.9%)	89 (36.5%)
Mexico	37 (14.4%)	38 (15.6%)
Ghana	8 (3.1%)	6 (2.5%)
India	5 (1.9%)	0 (0%)
Colombia	3 (1.2%)	1 (0.4%)
Uganda	3 (1.2%)	2 (0.8%)
Force of Infection		
Mean (SD)	5.89 (12.48)	5.86 (11.75)
Median [Min, Max]	1.90 [0.10, 11]	1.90 [0.11, 92.7]
Standardized risk score		
Mean (SD)	-0.06 (1.23)	0.26 (1.73)
Median [Min, Max]	-0.44 [-2.23, 3.66]	-0.40 [-1.05, 4.65]

Table 14: Demographic and clinical characteristics at baseline summarized among participants in the Sanofi Stage 2 Naive cohort who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after first injection.

	Placebo	Treatment
	(N=251)	(N=240)
Sex		
Female	112 (44.6%)	113 (47.1%)
Male	139 (55.4%)	127 (52.9%)
Age		
Mean (SD)	39.1 (16.7)	38.3 (14.7)
Median [Min, Max]	34.0 [18.0, 91.0]	35.0 [18.0, 93.0]
Age Group		
>=60 years	38 (15.1%)	27 (11.3%)
18-59 years	213 (84.9%)	213 (88.8%)
Body Mass Index		
Mean (SD)	23.3 (3.95)	23.7 (4.96)
Median [Min, Max]	22.5 [14.5, 41.5]	22.4 [15.1, 48.6]
Race		
Asian	119 (47.4%)	106 (44.2%)
Black Or African American	91 (36.3%)	95 (39.6%)
Unknown	37 (14.7%)	37 (15.4%)
American Indian Or Alaska Native	3 (1.2%)	1 (0.4%)
White	1 (0.4%)	0 (0%)
Multiple	0 (0%)	1 (0.4%)
Ethnic		
Not Hispanic Or Latino	211 (84.1%)	201 (83.8%)
Hispanic Or Latino	40 (15.9%)	38 (15.8%)
Not Reported	0 (0%)	1 (0.4%)
Country		
Nepal	114 (45.4%)	106 (44.2%)
Kenya	82 (32.7%)	88 (36.7%)
Mexico	37 (14.7%)	37 (15.4%)
Ghana	7 (2.8%)	6 (2.5%)
India	5 (2.0%)	0 (0%)
Colombia	3 (1.2%)	1 (0.4%)
Uganda	3 (1.2%)	2 (0.8%)
Force of Infection		
Mean (SD)	5.89 (12.48)	5.86 (11.75)
Median [Min, Max]	1.90 [0.10, 11]	1.90 [0.11, 92.7]
Standardized risk score		
Mean (SD)	-0.06 (1.23)	0.26 (1.73)
Median [Min, Max]	-0.44 [-2.23, 3.66]	-0.40 [-1.05, 4.65]

Table 15: Demographic and clinical characteristics at baseline summarized among participants in the Sanofi Stage 2 Naive cohort who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after second injection.

	Placebo	Treatment
	(N=2009)	(N=2069)
Sex		
Female	929 (46.2%)	928 (44.9%)
Male	1080 (53.8%)	1141 (55.1%)
Age		
Mean (SD)	38.9 (14.8)	39.2 (15.0)
Median [Min, Max]	37.0 [18.0, 93.0]	36.0 [18.0, 90.0]
Age Group		
>=60 years	269 (13.4%)	302 (14.6%)
18-59 years	1740 (86.6%)	1767 (85.4%)
Body Mass Index		
Mean (SD)	23.7 (4.37)	23.6 (4.29)
Median [Min, Max]	22.7 [13.4, 48.5]	22.7 [11.7, 52.1]
Race		
Asian	921 (45.8%)	935 (45.2%)
Black Or African American	912 (45.4%)	956 (46.2%)
Unknown	149 (7.4%)	148 (7.2%)
American Indian Or Alaska Native	12 (0.6%)	13 (0.6%)
Multiple	4 (0.2%)	3 (0.1%)
White	11 (0.5%)	14 (0.7%)
Ethnic		
Not Hispanic Or Latino	1824 (90.8%)	1877 (90.7%)
Hispanic Or Latino	173 (8.6%)	179 (8.7%)
Not Reported	7 (0.3%)	5 (0.2%)
Unknown	5 (0.2%)	8 (0.4%)
Country		
Kenya	608 (30.3%)	642 (31.0%)
India	523 (26.0%)	538 (26.0%)
Nepal	399 (19.9%)	399 (19.3%)
Ghana	255 (12.7%)	272 (13.1%)
Mexico	159 (7.9%)	160 (7.7%)
Uganda	53 (2.6%)	45 (2.2%)
Colombia	12 (0.6%)	13 (0.6%)
Force of Infection		
Mean (SD)	2.88 (6.41)	2.66 (5.69)
Median [Min, Max]	1.04 [0.04, 91.9]	1.04 [0.0426, 80.6]
Standardized risk score		
Mean (SD)	0.12 (1.08)	0.16 (1.24)
Median [Min, Max]	-0.03 [-2.31, 4.46]	-0.19 [-1.35, 4.43]
Missing	170 (8.5%)	189 (9.1%)

Table 16: Demographic and clinical characteristics at baseline summarized among participants in the Sanofi Stage 2 Non-naive cohort who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after first injection.

	Placebo	Treatment
	(N=1962)	(N=2028)
Sex		
Female	906 (46.2%)	904 (44.6%)
Male	1056 (53.8%)	1124 (55.4%)
Age		
Mean (SD)	39.1 (14.8)	39.3 (15.1)
Median [Min, Max]	37.0 [18.0, 93.0]	37.0 [18.0, 90.0]
Age Group		
>=60 years	269 (13.7%)	302 (14.9%)
18-59 years	1693 (86.3%)	1726 (85.1%)
Body Mass Index		
Mean (SD)	23.7 (4.37)	23.6 (4.29)
Median [Min, Max]	22.7 [13.4, 48.5]	22.7 [11.7, 52.1]
Race		
Asian	903 (46.0%)	923 (45.5%)
Black or African American	890 (45.4%)	928 (45.8%)
Unknown	142 (7.2%)	147 (7.2%)
White	11 (0.6%)	14 (0.7%)
American Indian or Alaska Native	12 (0.6%)	13 (0.6%)
Multiple	4 (0.2%)	3 (0.1%)
Ethnic		
Not Hispanic or Latino	1784 (90.9%)	1837 (90.6%)
Hispanic or Latino	166 (8.5%)	178 (8.8%)
Not Reported	7 (0.4%)	5 (0.2%)
Unknown	5 (0.3%)	8 (0.4%)
Country		
Kenya	592 (30.2%)	620 (30.6%)
India	523 (26.7%)	538 (26.5%)
Nepal	381 (19.4%)	387 (19.1%)
Ghana	249 (12.7%)	266 (13.1%)
Mexico	152 (7.7%)	159 (7.8%)
Uganda	53 (2.7%)	45 (2.2%)
Colombia	12 (0.6%)	13 (0.6%)
Force of Infection		
Mean (SD)	2.88 (6.41)	2.66 (5.69)
Median [Min, Max]	1.04 [0.04, 91.9]	1.04 [0.0426, 80.6]
Standardized risk score		
Mean (SD)	0.12 (1.08)	0.16 (1.24)
Median [Min, Max]	-0.03 [-2.31, 4.46]	-0.19 [-1.35, 4.43]

Table 17: Demographic and clinical characteristics at baseline summarized among participants in the Sanofi Stage 2 Non-naive cohort who are in the analysis set as defined in Section 2.1 and who have records of any type of solicited AR (having at least one type of solicited AR) after second injection.

3.3 Summary of the Relative Frequency of Reactogenicity Variables among Each Trial Cohort

The following tables summarize the relative frequency of each type of reactogenicity variable analyzed for each study cohort. Separate figures are provided for reactogenicity induced by the first and second injection.

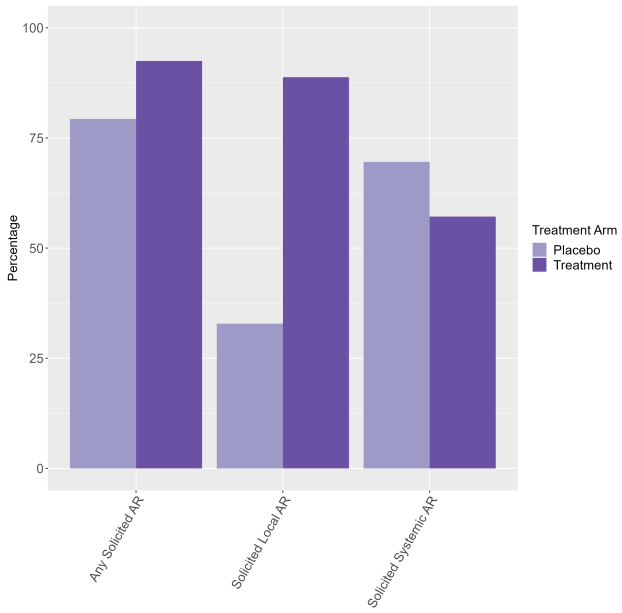


Figure 1: Relative frequency of post-dose one reactogenicity variables analyzed in the VIM and/or PS analysis in the Moderna cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

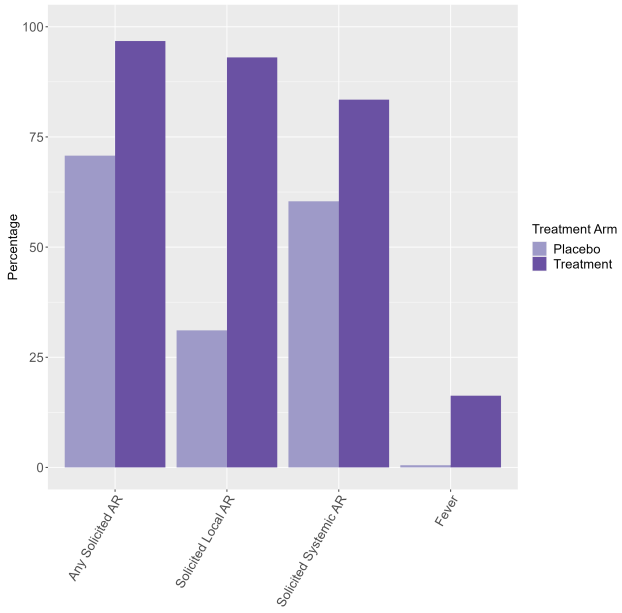


Figure 2: Relative frequency of post-dose two reactogenicity variables analyzed in the VIM and/or PS analysis in the Moderna cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

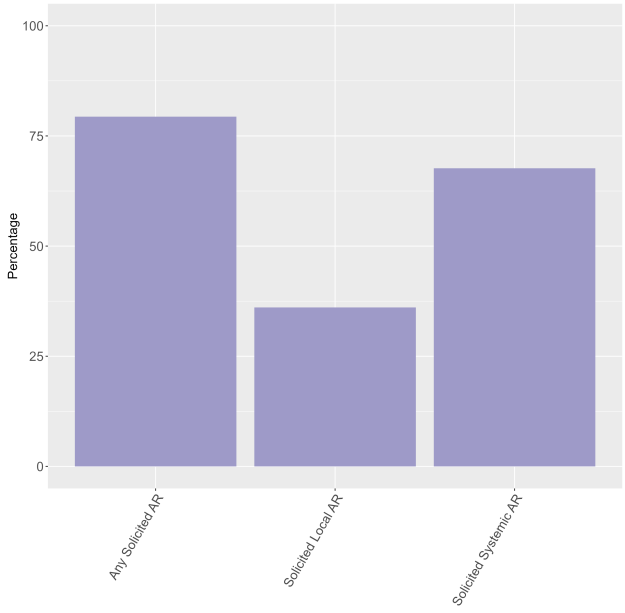


Figure 3: Relative frequency of post-dose one reactogenicity variables analyzed in the VIM and/or PS analysis among the Novavax placebo recipients who are in the study cohort as defined in Section 2.1 and who have records of all reactogenicity variables. Novavax vaccine recipients are excluded from both VIM and PS analysis.

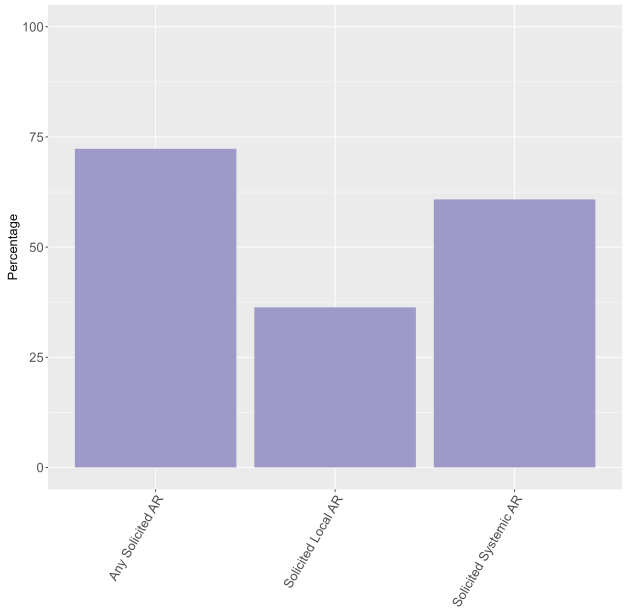


Figure 4: Relative frequency of post-dose two reactogenicity variables analyzed in the VIM and/or PS analysis among the Novavax placebo recipients who are in the study cohort as defined in Section 2.1 and who have records of all reactogenicity variables. Novavax vaccine recipients are excluded from both VIM and PS analysis.

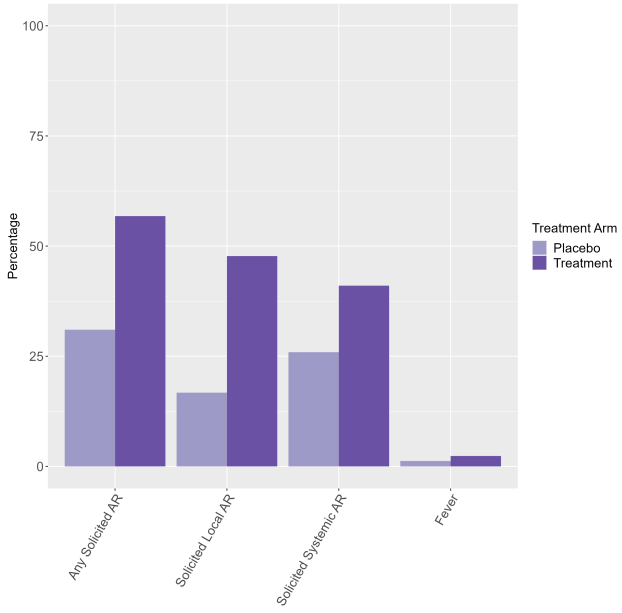


Figure 5: Relative frequency of post-dose one reactogenicity variables analyzed in the VIM and/or PS analysis in the Sanofi Stage 1 Naive cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

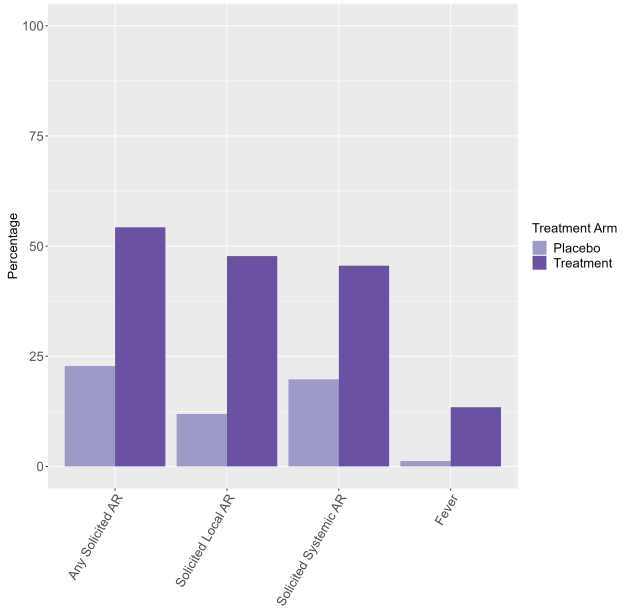


Figure 6: Relative frequency of post-dose two reactogenicity variables analyzed in the VIM and/or PS analysis in the Sanofi Stage 1 Naive cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

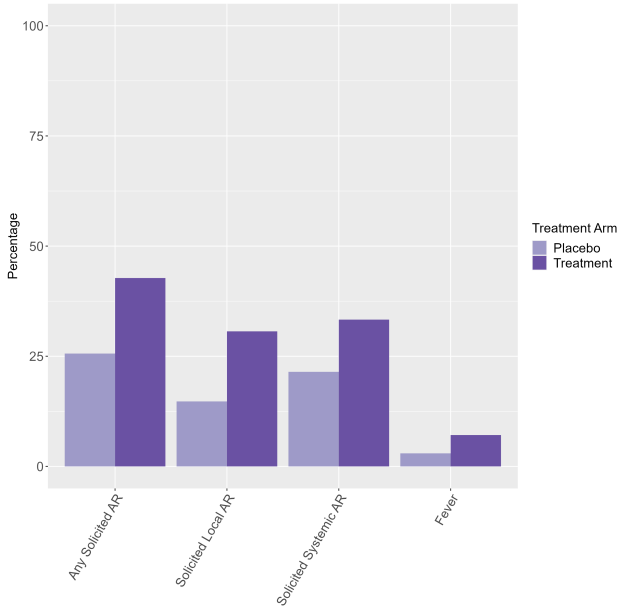


Figure 7: Relative frequency of post-dose one reactogenicity variables analyzed in the VIM and/or PS analysis in the Sanofi Stage 1 Non-naive cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

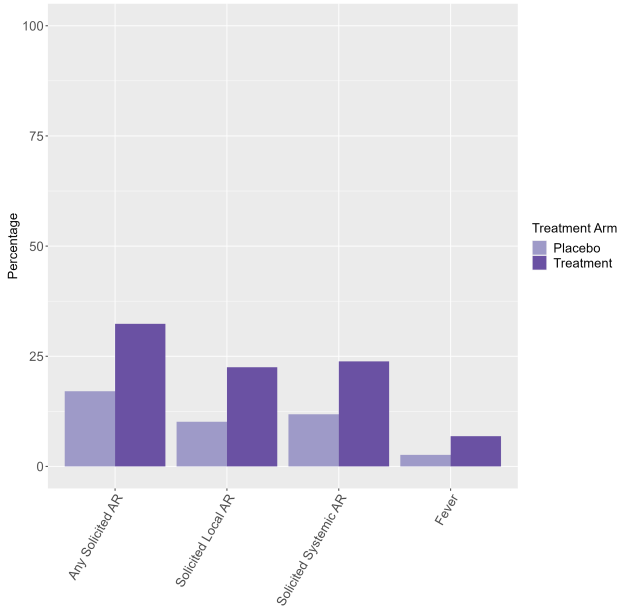


Figure 8: Relative frequency of post-dose two reactogenicity variables analyzed in the VIM and/or PS analysis in the Sanofi Stage 1 Non-naive cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

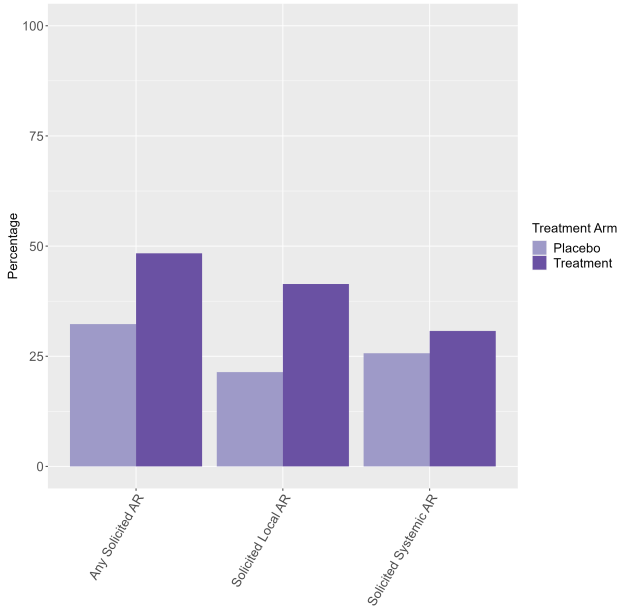


Figure 9: Relative frequency of post-dose one reactogenicity variables analyzed in the VIM and/or PS analysis in the Sanofi Stage 2 Naive cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

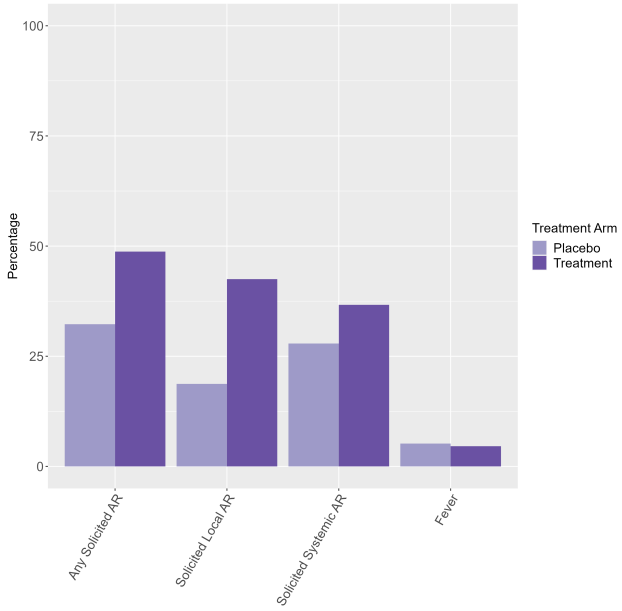


Figure 10: Relative frequency of post-dose two reactogenicity variables analyzed in the VIM and/or PS analysis in the Sanofi Stage 2 Naive cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

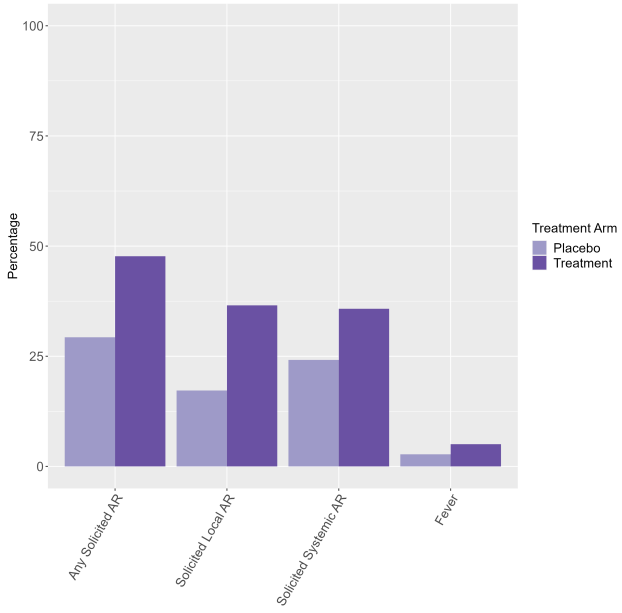


Figure 11: Relative frequency of post-dose one reactogenicity variables analyzed in the VIM and/or PS analysis in the Sanofi Stage 2 Non-naive cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

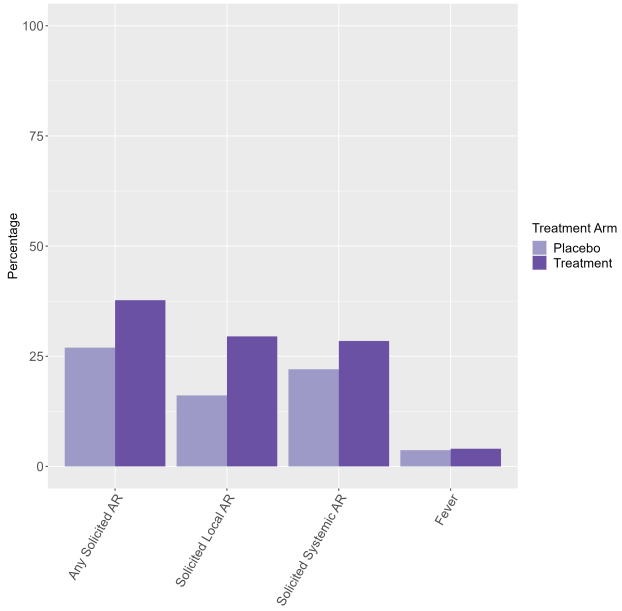


Figure 12: Relative frequency of post-dose two reactogenicity variables analyzed in the VIM and/or PS analysis in the Sanofi Stage 2 Non-naive cohort as defined in Section 2.1 and who have records of all reactogenicity variables.

Overall, the vaccine recipients exhibit a higher relative frequency of each type of reactogenicity compared to the placebo recipients in each vaccine trial, which is unsurprising. It is worth mentioning that the second injection in the Moderna trial (mRNA vaccine) induced a substantially higher amount of solicited systemic AR and fever compared to the Novavax and Sanofi trials (recombinant protein vaccines). The difference in

the frequency of fever between the treatment arms is also significantly larger in the Moderna trial than in the other trials. However, it is noteworthy that solicited systemic AR caused by the first injection is more commonly seen in the placebo recipients than in the vaccine recipients. This surprising observation could be due to the fact that a majority of the missing reactogenicity data comes from the placebo group, and many of these placebo recipients may not have experienced any reactogenicity.

3.4 Variable Importance Measures of Reactogenicity Variables on the Prediction of COVID-19

3.4.1 Moderna Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1680	100
	Yes	6457	360
Any Solicited Local AR			
	No	5448	325
	Yes	2689	135
Any Solicited Systemic AR			
	No	2489	127
	Yes	5648	333

Table 18: Summary of cases by post-dose one reactogenicity among Moderna placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	2401	109
	Yes	5722	350
Any Solicited Local AR			
	No	5584	329
	Yes	2539	130
Any Solicited Systemic AR			
	No	3252	147
	Yes	4871	312
Fever			
	No	8083	457
	Yes	40	2

Table 19: Summary of cases by post-dose two reactogenicity among Moderna placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1024	2
	Yes	12552	50
Any Solicited Local AR			
	No	1525	3
	Yes	12051	49
Any Solicited Systemic AR			
	No	5821	18
	Yes	7755	34

Table 20: Summary of cases by post-dose one reactogenicity among Moderna vaccine recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	437	3
	Yes	13123	49
Any Solicited Local AR			
	No	938	8
	Yes	12622	44
Any Solicited Systemic AR			
	No	2240	11
	Yes	11320	41
Fever			
	No	11348	49
	Yes	2212	3

Table 21: Summary of cases by post-dose two reactogenicity among Moderna vaccine recipients in the analysis set.

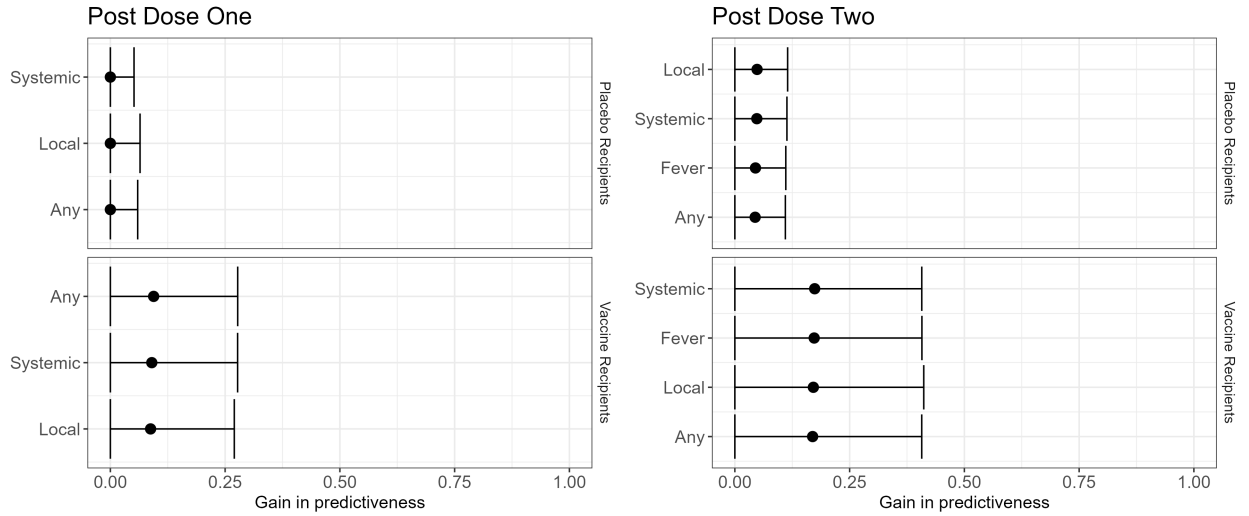


Figure 13: Marginal VIM analysis for Moderna cohort. Columns correspond, from left to right, to VIM evaluated for post-dose one reactogenicity, and post-dose two reactogenicity. Predictiveness is evaluated relative to AUC for only the set of baseline characteristics, including baseline risk score, membership in a community of color, and at elevated risk of COVID-19. The AUC of the oracle prediction function with only baseline characteristics is (1) 0.596 for placebo recipients for post-dose one reactogenicity; (2) 0.468 for vaccine recipients for post-dose one reactogenicity; (3) 0.566 for placebo recipients for post-dose two reactogenicity; (4) 0.410 for vaccine recipients for post-dose two reactogenicity.

In Figure 13, we display the results of the marginal VIM analysis for the Moderna cohort. Among the placebo recipients, the reactogenicity induced by the first injection is not estimated to add any predictiveness of COVID-19 given the AUC of the baseline characteristics. However, among this cohort, experiencing any type of solicited local AR after the second injection is estimated to be the most important feature among all four types of solicited AR, although the magnitude is quite small, with a gain in predictiveness of 0.05. Following this, experiencing any type of solicited systemic AR after the second injection is of secondary

importance. Among the vaccine recipients, experiencing any type of solicited AR after the first injection has the largest estimated marginal importance with a gain in predictiveness of 0.09 AUC. In contrast, experiencing any type of solicited systemic AR after the second injection has the largest estimated marginal importance with a gain in predictiveness of 0.17 AUC, and experiencing fever after the second injection is of secondary importance. Experiencing any type of solicited AR after the second injection ranks last among all four types of reactogenicity. We performed tests of the null hypothesis of zero importance for each type of reactogenicity, none of which achieved statistical significance at a 0.05 level. However, the p-values of the reactogenicity induced by the second injection nearly reach the significance level ($p = 0.09$, $p = 0.08$, $p = 0.08$, $p = 0.09$ for any solicited AR, any solicited local AR, any solicited systemic AR, and fever among placebo recipients, respectively; $p = 0.08$, $p = 0.08$, $p = 0.07$, $p = 0.07$ for any solicited AR, any solicited local AR, any solicited systemic AR, and fever among vaccine recipients, respectively).

In general, the ranking of all types of reactogenicity variables analyzed is different across both treatment arms and injections. However, although with different rankings, the magnitude of the estimated gain in predictiveness of each type of reactogenicity variable is very similar among each panel (each treatment arm and injection). In addition, the magnitude of the gain in predictiveness of each type of reactogenicity relative to the baseline characteristics is estimated to be higher among vaccine recipients than in placebo recipients, and higher among reactogenicity induced by the second injection than the first injection. In both vaccine and placebo cohorts, the confidence intervals are wider in post-dose two analyses than in post-dose one analyses.

3.4.2 Novavax Placebo Recipients Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	950	10
	Yes	3655	39
Any Solicited Local AR			
	No	2945	30
	Yes	1660	19
Any Solicited Systemic AR			
	No	1490	15
	Yes	3115	34

Table 22: Summary of cases by post-dose one reactogenicity among Novavax placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1245	17
	Yes	3262	32
Any Solicited Local AR			
	No	2868	33
	Yes	1639	16
Any Solicited Systemic AR			
	No	1761	24
	Yes	2746	25

Table 23: Summary of cases by post-dose two reactogenicity among Novavax placebo recipients in the analysis set.

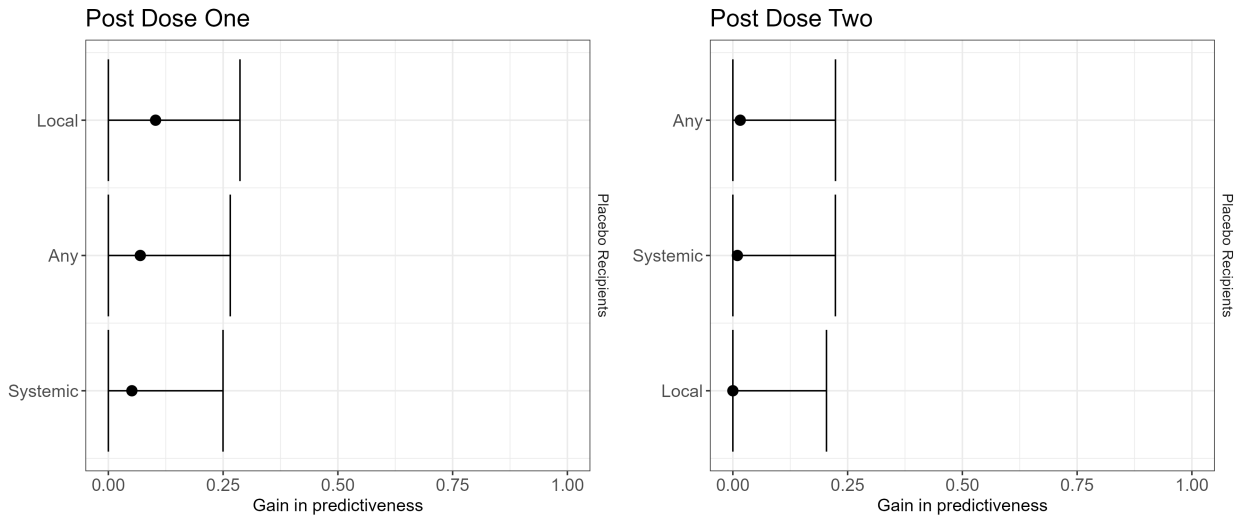


Figure 14: Marginal VIM analysis for Novavax placebo recipients. Columns correspond, from left to right, to VIM evaluated for post-dose one reactogenicity, and post-dose two reactogenicity. Predictiveness is evaluated relative to AUC for only the baseline characteristics, including baseline risk score and risk of exposure. The AUC of the oracle prediction function with only baseline characteristics is (1) 0.463 for post-dose one reactogenicity and (2) 0.461 for post-dose two reactogenicity.

In Figure 14, we display the results of the marginal VIM analysis for the Novavax placebo recipients. Having any type of solicited local AR after the first injection is estimated to be the most important with a gain in predictiveness of 0.10 AUC, while having any type of solicited systemic AR after the first injection is estimated to be the least important. In contrast, having any type of solicited AR has the largest estimated marginal importance with a small gain in predictiveness of 0.02 AUC, while having any type of solicited local AR ranks last with no gain in predictiveness. In both vaccine and placebo cohorts, the confidence intervals are similar among post-dose one and post-dose two analyses. Hypothesis tests of non-zero importance for both treatment arms and both post-dose one and post-dose two analyses do not reach statistical significance.

3.4.3 Sanofi Stage 1 Naive Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	300	38
	Yes	137	15
Any Solicited Local AR			
	No	360	48
	Yes	77	5
Any Solicited Systemic AR			
	No	325	38
	Yes	112	15
Fever			
	No	432	52
	Yes	5	1

Table 24: Summary of cases by post-dose one reactogenicity among Sanofi Stage 1 Naive placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	346	37
	Yes	94	19
Any Solicited Local AR			
	No	392	45
	Yes	48	11
Any Solicited Systemic AR			
	No	359	39
	Yes	81	17
Fever			
	No	435	55
	Yes	5	1

Table 25: Summary of cases by post-dose two reactogenicity among Sanofi Stage 1 Naive placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	225	13
	Yes	277	36
Any Solicited Local AR			
	No	267	21
	Yes	235	28
Any Solicited Systemic AR			
	No	307	18
	Yes	195	31
Fever			
	No	490	48
	Yes	12	1

Table 26: Summary of cases by post-dose one reactogenicity among Sanofi Stage 1 Naive vaccine recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	237	15
	Yes	265	34
Any Solicited Local AR			
	No	271	17
	Yes	231	32
Any Solicited Systemic AR			
	No	282	18
	Yes	220	31
Fever			
	No	438	39
	Yes	64	10

Table 27: Summary of cases by post-dose two reactogenicity among Sanofi Stage 1 Naive vaccine recipients in the analysis set.

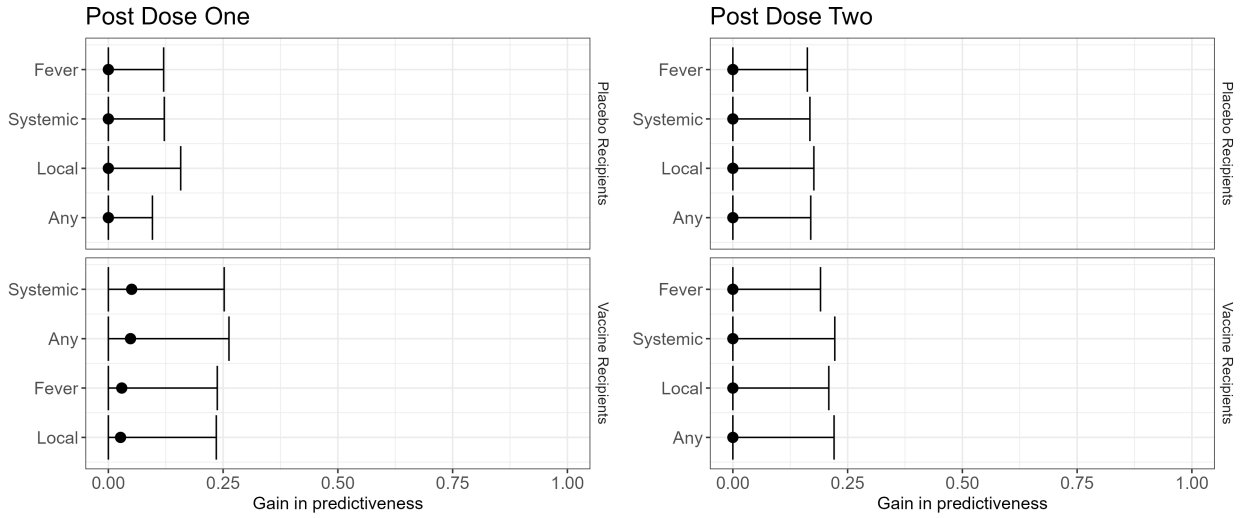


Figure 15: Marginal VIM analysis for Sanofi stage 1 Naive cohort. Columns correspond, from left to right, to VIM evaluated for post-dose one reactogenicity, and post-dose two reactogenicity. Predictiveness is evaluated relative to AUC for only baseline characteristics, including baseline risk score and FOI. The AUC of the oracle prediction function with only baseline characteristics is (1) 0.773 for placebo recipients for post-dose one reactogenicity; (2) 0.659 for vaccine recipients for post-dose one reactogenicity; (3) 0.744 for placebo recipients for post-dose two reactogenicity; (4) 0.693 for vaccine recipients for post-dose two reactogenicity.

In Figure 15, we display the results of the marginal VIM analysis for the Sanofi Stage 1 Naive cohort. Among vaccine recipients, the reactogenicity induced by the first injection is estimated to increase predictiveness relative to baseline characteristics. Specifically, experiencing any type of solicited systemic AR has the highest marginal importance, with a small gain in predictiveness of 0.05 AUC. In contrast, experiencing any type of solicited local AR has the lowest gain in predictiveness, with an increase of 0.03 AUC. However, the reactogenicity induced by both injections among placebo recipients, as well as the reactogenicity induced by the second injection among vaccine recipients, are not estimated to achieve any gain in predictiveness relative to baseline characteristics. In both vaccine and placebo cohorts, the confidence intervals are similar among post-dose one and post-dose two analyses. Hypothesis tests of non-zero importance in both treatment arms and both post-dose one and post-dose two analyses do not reach statistical significance.

3.4.4 Sanofi Stage 1 Non-naive Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1098	32
	Yes	379	10
Any Solicited Local AR			
	No	1258	37
	Yes	219	5
Any Solicited Systemic AR			
	No	1159	34
	Yes	318	8
Fever			
	No	1433	41
	Yes	44	1

Table 28: Summary of cases by post-dose one reactogenicity among Sanofi Stage 1 Non-naive placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1241	28
	Yes	245	16
Any Solicited Local AR			
	No	1337	38
	Yes	149	6
Any Solicited Systemic AR			
	No	1319	30
	Yes	167	14
Fever			
	No	1448	42
	Yes	38	2

Table 29: Summary of cases by post-dose two reactogenicity among Sanofi Stage 1 Non-naive placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	847	14
	Yes	633	10
Any Solicited Local AR			
	No	1026	17
	Yes	454	7
Any Solicited Systemic AR			
	No	988	15
	Yes	492	9
Fever			
	No	1375	22
	Yes	105	2

Table 30: Summary of cases by post-dose one reactogenicity among Sanofi Stage 1 Non-naive vaccine recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1003	13
	Yes	476	10
Any Solicited Local AR			
	No	1149	15
	Yes	330	8
Any Solicited Systemic AR			
	No	1128	16
	Yes	351	7
Fever			
	No	1379	20
	Yes	100	3

Table 31: Summary of cases by post-dose two reactogenicity among Sanofi Stage 1 Non-naive vaccine recipients in the analysis set.

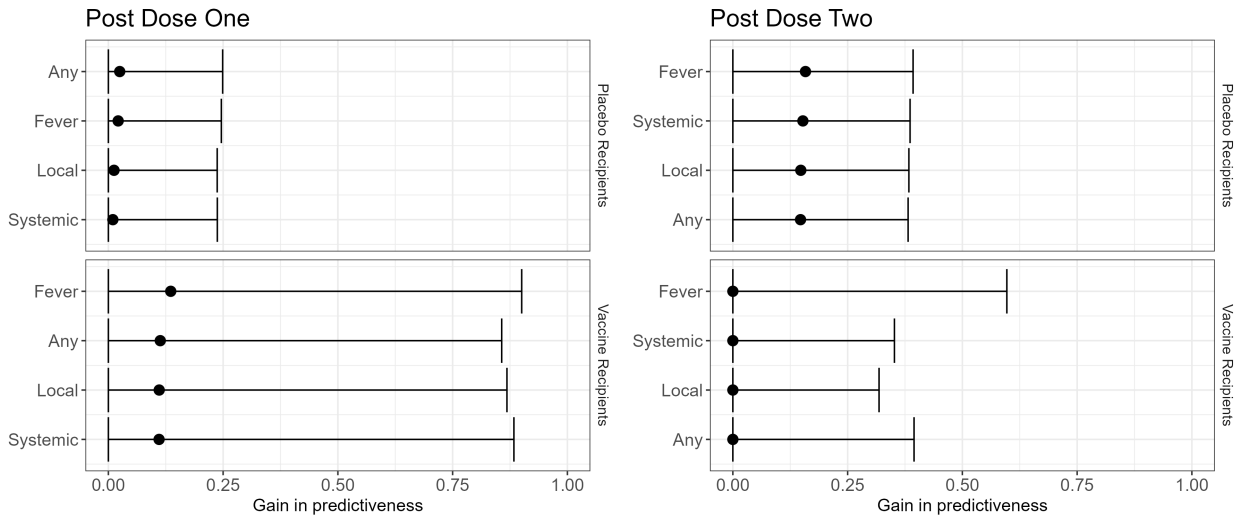


Figure 16: Marginal VIM analysis for Sanofi Stage 1 Non-naive cohort. Columns correspond, from left to right, to VIM evaluated for post-dose one reactogenicity, and post-dose two reactogenicity. Predictiveness is evaluated relative to AUC of only baseline characteristics, including baseline risk score and FOI. The AUC of the oracle prediction function with only baseline characteristics is (1) 0.637 for placebo recipients for post-dose one reactogenicity; (2) 0.695 for vaccine recipients for post-dose one reactogenicity; (3) 0.581 for placebo recipients for post-dose two reactogenicity; (4) 0.707 for vaccine recipients for post-dose two reactogenicity.

In Figure 16, we display the results of the marginal VIM analysis for the Sanofi Stage 1 Non-naive cohort. Among the placebo recipients, experiencing any type of solicited AR after the first injection has the largest estimated marginal importance with a very small gain in predictiveness of 0.02, followed by experiencing a fever. Experiencing any type of solicited systemic AR after the first injection ranks last among all four types of reactogenicity. The ranking of the reactogenicity is different than that observed in the post-dose one analysis among the placebo recipients. In particular, having a fever after the second injection is estimated to be the most important with a gain in predictiveness of 0.16. Experiencing any type of solicited systemic AR after the second injection is of secondary importance, whereas experiencing any type of solicited AR is of the least importance. As in the placebo cohort, the confidence intervals are wider in post-dose two analyses than in post-dose one analyses. Among the vaccine participants, having a fever after the first injection is estimated to be the most important with a gain in predictiveness of 0.14. Experiencing any type of solicited AR after the first injection is of secondary importance, and experiencing any type of solicited systemic AR is of the least importance. Reactogenicity induced by the second injection is estimated to have no gain in predictiveness relative to baseline characteristics. As in the vaccine cohort, the confidence intervals are wider in the post-dose one analyses compared to those in the post-dose two analyses. Hypothesis tests of non-zero importance in both treatment arms and both post-dose one and post-dose two analyses do not reach statistical significance.

3.4.5 Sanofi Stage 2 Naive Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	158	16
	Yes	65	18
Any Solicited Local AR			
	No	178	24
	Yes	45	10
Any Solicited Systemic AR			
	No	171	20
	Yes	52	14

Table 32: Summary of cases by post-dose one reactogenicity among Sanofi Stage 2 Naive placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	149	21
	Yes	68	13
Any Solicited Local AR			
	No	179	25
	Yes	38	9
Any Solicited Systemic AR			
	No	158	23
	Yes	59	11
Fever			
	No	206	32
	Yes	11	2

Table 33: Summary of cases by post-dose two reactogenicity among Sanofi Stage 2 Naive placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	117	9
	Yes	107	11
Any Solicited Local AR			
	No	133	10
	Yes	91	10
Any Solicited Systemic AR			
	No	158	11
	Yes	66	9

Table 34: Summary of cases by post-dose one reactogenicity among Sanofi Stage 2 Naive vaccine recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	117	6
	Yes	103	14
Any Solicited Local AR			
	No	129	9
	Yes	91	11
Any Solicited Systemic AR			
	No	143	9
	Yes	77	11
Fever			
	No	212	17
	Yes	8	3

Table 35: Summary of cases by post-dose two reactogenicity among Sanofi Stage 2 Naive vaccine recipients in the analysis set.

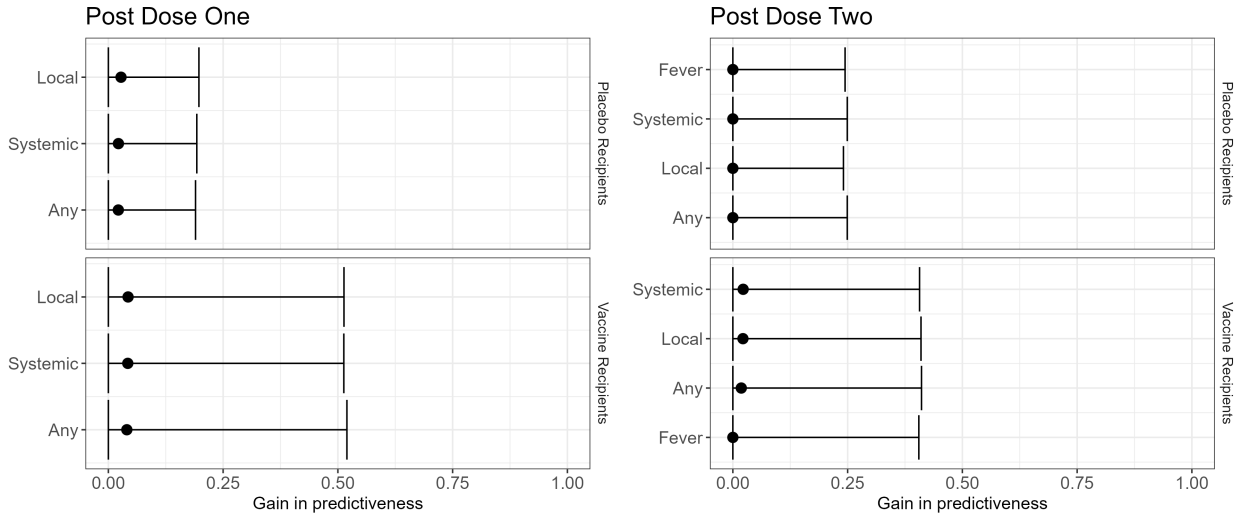


Figure 17: Marginal VIM analysis for Sanofi Stage 2 Naive cohort. Columns correspond, from left to right, to VIM evaluated for post-dose one reactogenicity, and post-dose two reactogenicity. Predictiveness is evaluated relative to AUC for only baseline characteristics, including baseline risk score and FOI. The AUC of the oracle prediction function with only baseline characteristics is (1) 0.881 for placebo recipients for post-dose one reactogenicity; (2) 0.759 for vaccine recipients for post-dose one reactogenicity; (3) 0.864 for placebo recipients for post-dose two reactogenicity; (4) 0.729 for vaccine recipients for post-dose two reactogenicity.

In Figure 17, we present the results of the marginal VIM analysis for the Sanofi Stage 2 Naive cohort. Among the placebo recipients, experiencing any type of solicited local AR after the first injection is estimated to be the most important feature with a small gain in predictiveness of 0.03, while experiencing any type of solicited AR is estimated to be the least important. The reactogenicity induced by the second injection is not estimated to achieve any gain in predictiveness, but the confidence intervals are wider than those in post-dose one analyses. Among the vaccine recipients, the ranking of reactogenicity in the post-dose one analysis is the same as the ranking observed among placebo recipients. However, the magnitude of the estimated gain in predictiveness is relatively higher in the vaccine cohort, with the increase in predictiveness of 0.04 for experiencing any type of solicited local AR. In contrast, among vaccine recipients, experiencing any type of solicited systemic AR is estimated be have the largest marginal importance with a gain in predictiveness of 0.02, followed by experiencing any type of solicited local AR. Fever induced by the second injection is estimated to be the least important and has no gain in predictiveness relative to baseline characteristics. The confidence intervals are wider in post-dose one analyses compared to those in post-dose two analyses. In addition, although with different rankings, the magnitude of the estimated gain in predictiveness of each type of reactogenicity is very similar in each of the four analyses. Hypothesis tests of non-zero importance in both treatment arms and both post-dose one and post-dose two analyses do not reach statistical significance.

3.4.6 Sanofi Stage 2 Non-naive Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1362	54
	Yes	560	27
Any Solicited Local AR			
	No	1590	68
	Yes	332	13
Any Solicited Systemic AR			
	No	1464	55
	Yes	458	26
Fever			
	No	1870	78
	Yes	52	3

Table 36: Summary of cases by post-dose one reactogenicity among Sanofi Stage 2 Non-naive placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1368	60
	Yes	505	22
Any Solicited Local AR			
	No	1569	71
	Yes	304	11
Any Solicited Systemic AR			
	No	1460	64
	Yes	413	18
Fever			
	No	1806	77
	Yes	67	5

Table 37: Summary of cases by post-dose two reactogenicity among Sanofi Stage 2 Non-naive placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1069	10
	Yes	955	29
Any Solicited Local AR			
	No	1292	17
	Yes	732	22
Any Solicited Systemic AR			
	No	1311	14
	Yes	713	25
Fever			
	No	1923	36
	Yes	101	3

Table 38: Summary of cases by post-dose one reactogenicity among Sanofi Stage 2 Non-naive vaccine recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1240	18
	Yes	741	21
Any Solicited Local AR			
	No	1402	22
	Yes	579	17
Any Solicited Systemic AR			
	No	1421	24
	Yes	560	15
Fever			
	No	1903	36
	Yes	78	3

Table 39: Summary of cases by post-dose two reactogenicity among Sanofi Stage 2 Non-naive vaccine recipients in the analysis set.

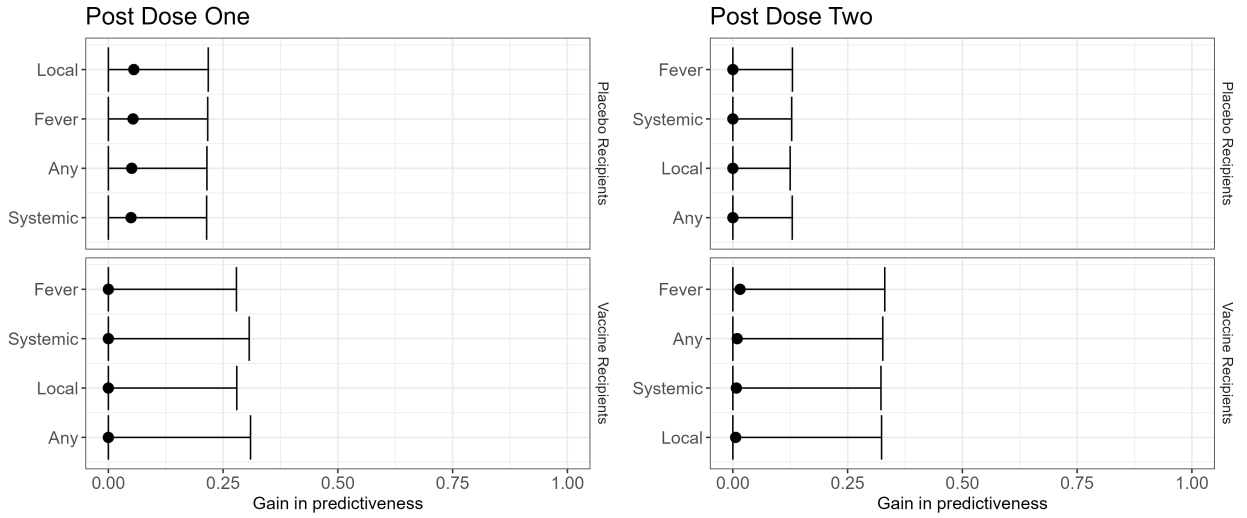


Figure 18: Marginal VIM analysis for Sanofi Stage 2 Non-naive cohort. Columns correspond, from left to right, to VIM evaluated for post-dose one reactogenicity, and post-dose two reactogenicity. Predictiveness is evaluated relative to AUC for only baseline characteristics, including baseline risk score and FOI. The AUC of the oracle prediction function with only baseline characteristics is (1) 0.698 for placebo recipients for post-dose one reactogenicity; (2) 0.685 for vaccine recipients for post-dose one reactogenicity; (3) 0.748 for placebo recipients for post-dose two reactogenicity; (4) 0.671 for vaccine recipients for post-dose two reactogenicity.

In Figure 18, we present the results of the marginal VIM for the Sanofi Stage 2 Non-naive cohort. Among the placebo recipients, having any type of solicited local AR after the first injection is estimated to be the most important reactogenicity with a gain in predictiveness of 0.06, and having a fever after the first injection is of secondary importance. Having any type of solicited systemic AR after the first injection ranks last, but the magnitude of the gain in predictiveness of each type of reactogenicity is very similar. The reactogenicity induced by the second injection is not estimated to achieve any gain in predictiveness relative to the baseline characteristics, and the confidence intervals are narrower in post-dose two analyses than those in post-dose one analyses. Among the vaccine recipients, the reactogenicity induced by the first injection is not estimated to achieve any gain in predictiveness relative to the baseline characteristics. Having a fever after the second injection is estimated to be the most important reactogenicity, although with a very small gain in predictiveness of 0.02. The estimated gain in predictiveness of other types of reactogenicity induced by the second injection is almost 0. The confidence intervals are similar among post-dose one and post-dose two analyses. Hypothesis tests of non-zero importance in both treatment arms and both post-dose one and post-dose two analyses do not reach statistical significance.

3.4.7 Sanofi Stage 2 Combined Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1520	70
	Yes	625	45
Any Solicited Local AR			
	No	1768	92
	Yes	377	23
Any Solicited Systemic AR			
	No	1635	75
	Yes	510	40
Fever			
	No	2088	112
	Yes	57	3

Table 40: Summary of cases by post-dose one reactogenicity among Sanofi Stage 2 placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1517	81
	Yes	573	35
Any Solicited Local AR			
	No	1748	96
	Yes	342	20
Any Solicited Systemic AR			
	No	1618	87
	Yes	472	29
Fever			
	No	2012	109
	Yes	78	7

Table 41: Summary of cases by post-dose two reactogenicity among Sanofi Stage 2 placebo recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1186	19
	Yes	1062	40
Any Solicited Local AR			
	No	1425	27
	Yes	823	32
Any Solicited Systemic AR			
	No	1469	25
	Yes	779	34
Fever			
	No	2141	56
	Yes	107	3

Table 42: Summary of cases by post-dose one reactogenicity among Sanofi Stage 2 vaccine recipients in the analysis set.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1357	24
	Yes	844	35
Any Solicited Local AR			
	No	1531	31
	Yes	670	28
Any Solicited Systemic AR			
	No	1564	33
	Yes	637	26
Fever			
	No	2115	53
	Yes	86	6

Table 43: Summary of cases by post-dose two reactogenicity among Sanofi Stage 2 vaccine recipients in the analysis set.

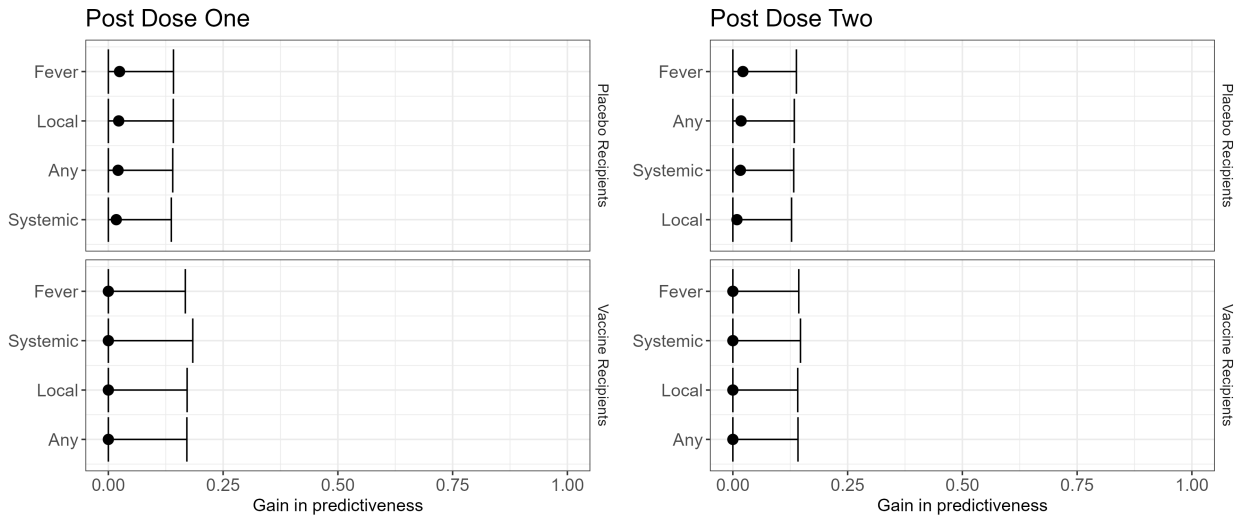


Figure 19: Marginal VIM analysis for Sanofi Stage 2 combined cohort regardless of previous infection status. Columns correspond, from left to right, to VIM evaluated for post-dose one reactogenicity, and post-dose two reactogenicity. Predictiveness is evaluated relative to AUC for only baseline characteristics, including baseline risk score and FOI. The AUC of the oracle prediction function with only baseline characteristics is (1) 0.776 for placebo recipients for post-dose one reactogenicity; (2) 0.761 for vaccine recipients for post-dose one reactogenicity; (3) 0.783 for placebo recipients for post-dose two reactogenicity; (4) 0.763 for vaccine recipients for post-dose two reactogenicity.

In Figure 19, we present the results of the marginal VIM analysis for the Sanofi Stage 2 cohort that combines participants in the Sanofi Stage 2 regardless of their previous infection status. Among the placebo recipients, experiencing a fever after the first injection is estimated to be the most important with a gain in predictiveness of 0.02. Experiencing any type of solicited local AR after the first injection is of secondary importance and having any type of solicited systemic AR is of the least importance. Similarly, fever after the second injection has the largest estimated marginal importance with a gain in predictiveness of 0.02. Experiencing any type of solicited AR after the second injection is of secondary importance and having any type of solicited local AR is of the least importance. However, the reactogenicity induced by both injections among vaccine recipients is not estimated to achieve any gain in predictiveness relative to baseline characteristics. As in both treatment arms, the confidence intervals are similar among post-dose one and post-dose two analyses. Hypothesis tests of non-zero importance in both treatment arms and both post-dose one and post-dose two analyses do not reach statistical significance.

3.5 Principal Stratification Analysis of the Impact of Reactogenicity Variables on Vaccine Efficacy Against COVID-19

3.5.1 Moderna Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1687	94
Any Solicited Local AR			
	No	5462	311
Any Solicited Systemic AR			
	No	2498	119

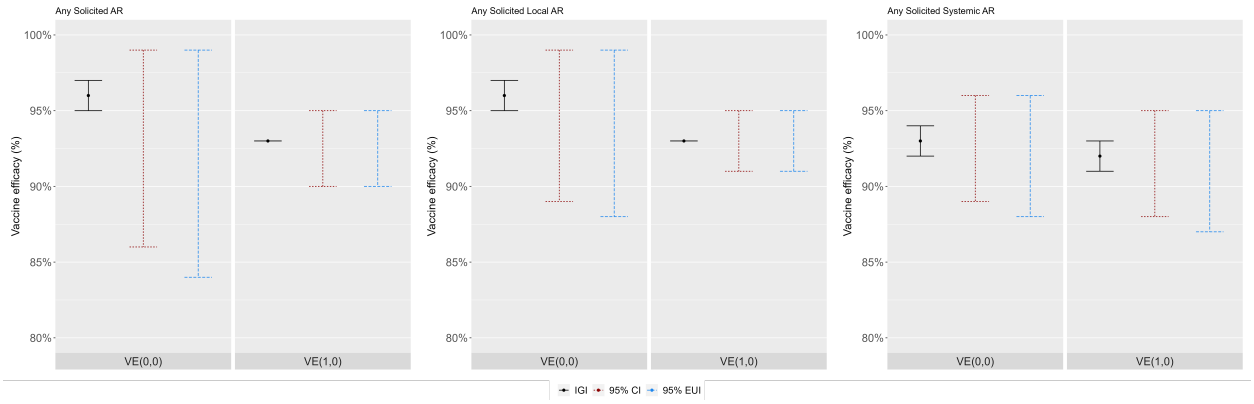
Table 44: Summary of cases by post-dose one reactogenicity among placebo recipients. Only placebo recipients without reported reactogenicity are included. Cases in this table are defined as endpoints occurred before the landmark time.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1027	2
	Yes	12559	45
Any Solicited Local AR			
	No	1526	3
	Yes	12057	44
Any Solicited Systemic AR			
	No	5824	18
	Yes	7762	29

Table 45: Summary of cases by post-dose one reactogenicity among vaccine recipients. Cases in this table are defined as endpoints occurred before the landmark time.

		VE(0, 0)		VE(1, 0)		(1-VE(0,0))/(1-VE(1,0))	
Solicited AR	Sens	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval
Any Solicited AR	None	(0.96, 0.96)	(0.86, 0.99)	(0.93, 0.93)	(0.90, 0.95)	(0.54, 0.54)	(0.14, 2.16)
Any Solicited AR	Med	(0.95, 0.97)	(0.84, 0.99)	(0.93, 0.93)	(0.90, 0.95)	(0.42, 0.72)	(0.12, 2.39)
Any Solicited AR	High	(0.93, 0.98)	(0.78, 0.99)	(0.93, 0.93)	(0.90, 0.95)	(0.29, 1.06)	(0.09, 3.38)
Solicited Local AR	None	(0.96, 0.96)	(0.89, 0.99)	(0.93, 0.93)	(0.91, 0.95)	(0.54, 0.54)	(0.17, 1.69)
Solicited Local AR	Med	(0.95, 0.97)	(0.88, 0.99)	(0.93, 0.93)	(0.91, 0.95)	(0.41, 0.71)	(0.15, 1.90)
Solicited Local AR	High	(0.93, 0.98)	(0.83, 0.99)	(0.93, 0.94)	(0.90, 0.95)	(0.28, 1.05)	(0.11, 2.73)
Solicited Systemic AR	None	(0.93, 0.93)	(0.89, 0.96)	(0.92, 0.92)	(0.88, 0.95)	(0.83, 0.83)	(0.46, 1.48)
Solicited Systemic AR	Med	(0.92, 0.94)	(0.88, 0.96)	(0.91, 0.93)	(0.87, 0.95)	(0.63, 1.09)	(0.39, 1.77)
Solicited Systemic AR	High	(0.90, 0.95)	(0.84, 0.97)	(0.89, 0.94)	(0.84, 0.95)	(0.43, 1.61)	(0.26, 2.61)

Table 46: Moderna COVE: Vaccine efficacy results for different types of reactogenicity post dose one under No Early Efficacy (NEE) assumption with sensitivity analysis scenarios. Sensitivity parameter settings on the degree of potential post-randomization selection bias were: None, β_0 sensitivity parameter set to zero; Med, β_0 sensitivity parameter ranging from log(0.75) to -log(0.75); High, β_0 sensitivity parameter ranging from log(0.5) to - log(0.5).



(a)

	For RR Ratio (1-VE(0,0))/(1-VE(1,0))			
Solicited AR	Point Estimate	95% CI	IGI	95% EUI
Any Solicited AR	0.54	(0.14, 2.16)	(0.42, 0.72)	(0.12, 2.39)
Solicited Local AR	0.54	(0.17, 1.69)	(0.41, 0.71)	(0.15, 1.90)
Solicited Systemic AR	0.83	(0.46, 1.48)	(0.63, 1.09)	(0.39, 1.77)

(b)

Figure 20: Vaccine efficacy (VE) against COVID-19 by subgroups with vs. without reported reactogenicity for the Moderna post-dose one analysis. **(a)** The black dot in each panel corresponds to the VE estimate for the relevant subgroups for three types of reactogenicity when the sensitivity parameter is set to zero. The vertical black line denotes the ignorance interval (IGI) when the sensitivity parameter ranges from log(0.75) to -log(0.75), the vertical red dashed line denotes the 95% confidence interval (CI) when the sensitivity parameter is set to zero, and the vertical blue dashed line denotes the 95% estimated uncertainty interval (EUI) when the sensitivity parameter ranges from log(0.75) to - log(0.75). **(b)** Relative risk (RR) ratio for each type of solicited AR. The measurements presented are under the same setting as **(a)**.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	2405	106
Any Solicited Local AR			
	No	5598	317
Any Solicited Systemic AR			
	No	3257	142
Fever			
	No	8101	438

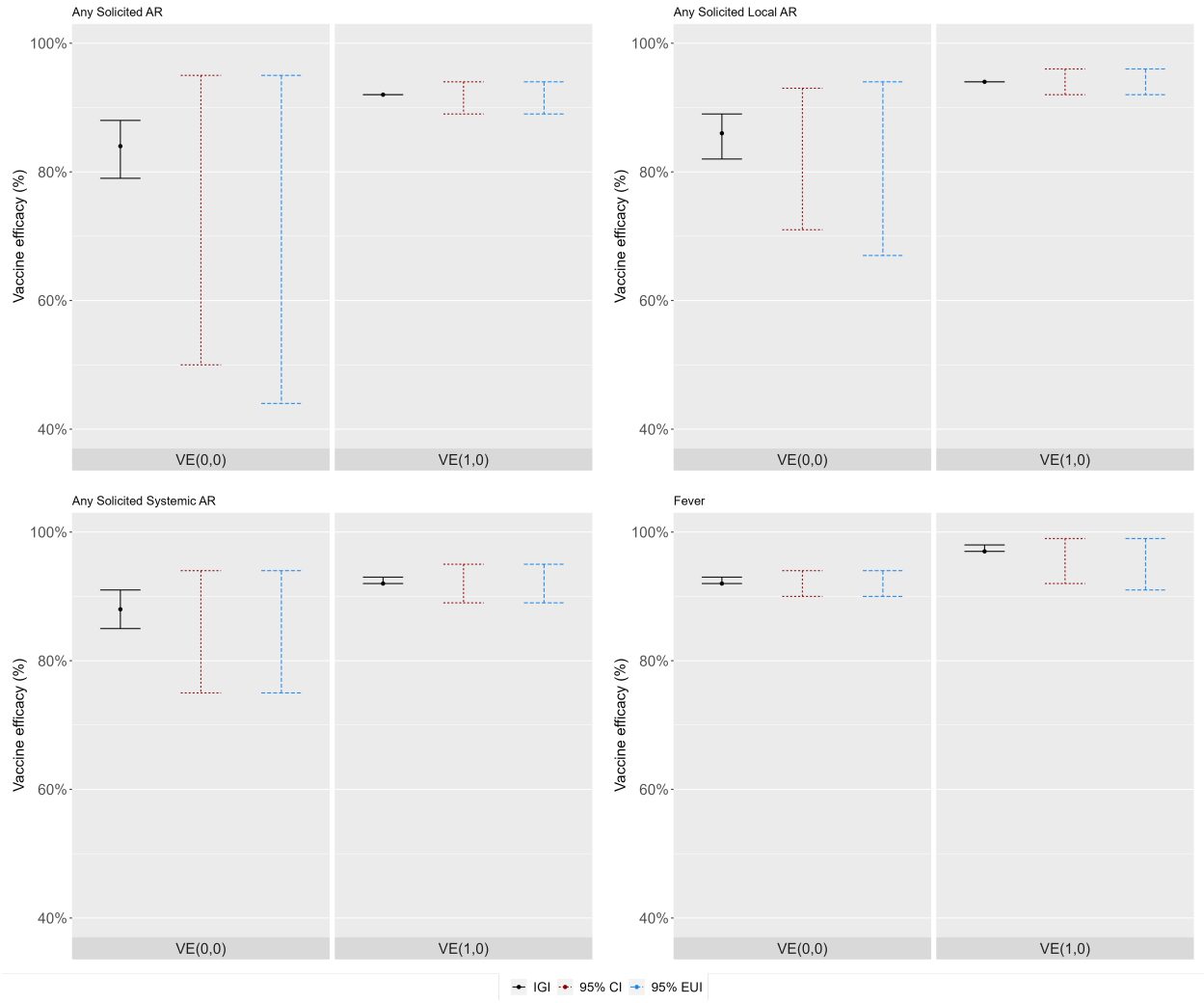
Table 47: Summary of cases by post-dose two reactogenicity among placebo recipients. Only placebo recipients without reported reactogenicity are included.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	439	3
	Yes	13134	44
Any Solicited Local AR			
	No	940	7
	Yes	12631	40
Any Solicited Systemic AR			
	No	2242	11
	Yes	11330	36
Fever			
	No	11355	44
	Yes	2212	3

Table 48: Summary of cases by post-dose two reactogenicity among vaccine recipients.

		VE(0, 0)		VE(1, 0)		(1-VE(0,0))/(1-VE(1,0))	
Solicited AR	Sens	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval
Any Solicited AR	None	(0.84, 0.84)	(0.50, 0.95)	(0.92, 0.92)	(0.89, 0.94)	(2.03, 2.03)	(0.64, 6.46)
Any Solicited AR	Med	(0.79, 0.88)	(0.44, 0.95)	(0.92, 0.92)	(0.89, 0.94)	(1.55, 2.68)	(0.57, 7.26)
Any Solicited AR	High	(0.69, 0.91)	(0.20, 0.97)	(0.92, 0.92)	(0.89 ,0.94)	(1.06, 3.98)	(0.40, 10.51)
Solicited Local AR	None	(0.86, 0.86)	(0.71, 0.93)	(0.94, 0.94)	(0.92, 0.96)	(2.34, 2.34)	(1.06, 5.18)
Solicited Local AR	Med	(0.82, 0.89)	(0.67, 0.94)	(0.94, 0.94)	(0.92, 0.96)	(1.79, 3.08)	(0.91, 6.03)
Solicited Local AR	High	(0.74, 0.92)	(0.52, 0.96)	(0.94, 0.94)	(0.92, 0.96)	(1.23, 4.55)	(0.63, 8.86)
Solicited Systemic AR	None	(0.88, 0.88)	(0.79, 0.94)	(0.92, 0.92)	(0.89, 0.95)	(1.54, 1.54)	(0.79, 3.00)
Solicited Systemic AR	Med	(0.85, 0.91)	(0.75, 0.94)	(0.92, 0.93)	(0.89, 0.95)	(1.17, 2.03)	(0.67, 3.56)
Solicited Systemic AR	High	(0.79, 0.93)	(0.65, 0.96)	(0.91, 0.93)	(0.88, 0.95)	(0.80, 3.01)	(0.46, 5.27)
Fever	None	(0.92, 0.92)	(0.90, 0.94)	(0.97, 0.97)	(0.92, 0.99)	(2.85, 2.85)	(0.92, 8.82)
Fever	Med	(0.92, 0.93)	(0.90, 0.94)	(0.97, 0.98)	(0.91, 0.99)	(2.17, 3.74)	(0.82, 9.88)
Fever	High	(0.91, 0.93)	(0.89, 0.95)	(0.95, 0.98)	(0.88, 0.99)	(1.47, 5.46)	(0.57, 14.08)

Table 49: Moderna COVE: Vaccine efficacy results for different types of reactogenicity post dose 2 under the No Early Efficacy (NEE) assumption with sensitivity analysis scenarios. Sensitivity parameter settings on the degree of potential post-randomization selection bias were: None, β_0 sensitivity parameter set to zero; Med, β_0 sensitivity parameter ranging from log(0.75) to -log(0.75); High, β_0 sensitivity parameter ranging from log(0.5) to - log(0.5).



(a)

	For RR Ratio (1-VE(0,0))/(1-VE(1,0))			
Solicited AR	Point Estimate	95% CI	IGI	95% EUI
Any Solicited AR	2.03	(0.64, 6.46)	(1.55, 2.68)	(0.57, 7.26)
Solicited Local AR	2.34	(1.06, 5.18)	(1.79, 3.08)	(0.91, 6.03)
Solicited Systemic AR	1.54	(0.79, 3.00)	(1.17, 2.03)	(0.67, 3.56)
Fever	2.85	(0.92, 8.82)	(2.17, 3.74)	(0.82, 9.88)

(b)

Figure 21: Vaccine efficacy (VE) against COVID-19 by subgroups with vs. without reported reactogenicity for the Moderna post-dose two analysis. **(a)** The black dot in each panel corresponds to the VE estimate for the relevant subgroups for four types of reactogenicity when the sensitivity parameter is set to zero. The vertical black line denotes the ignorance interval (IGI) when the sensitivity parameter ranges from log(0.75) to -log(0.75), the vertical red dashed line denotes the 95% confidence interval (CI) when the sensitivity parameter is set to zero, and the vertical blue dashed line denotes the 95% estimated uncertainty interval (EUI) when the sensitivity parameter ranges from log(0.75) to - log(0.75). **(b)** Relative risk (RR) ratio for each type of solicited AR. The measurements presented are under the same setting as **(a)**.

For a given type of reactogenicity, PS analysis estimates VE for each of two subgroups defined by reactogenicity potential outcomes under assignment to vaccine and placebo (i.e., the subgroup with vaccine-caused reactogenicity and the subgroup without reactogenicity under both treatment assignments). PS analysis is applied under the NEE-CB assumption (Gilbert et al. [2020]). We present the results using ignorance

intervals (IGIs) and 95% estimated uncertainty intervals (EUIs). The IGI is the range of VE point estimates that are calculated under specific values of the sensitivity parameters. The 95% EUI is the union of 95% CIs, with each 95% CI calculated under specific values of the sensitivity parameters. Results are presented under three sensitivity analysis scenarios in which the sensitivity parameter β_0 is set to three different possible ranges: [log(1.0), log(1.0) = 0, 0] (none robustness), [log(0.75), $-\log(0.75)$] (medium robustness), and [log(0.5), $-\log(0.5)$] (high robustness), to account for different types and degrees of post-randomization selection bias.

For each of the reactogenicity induced by the first dosage, the estimated VE is higher among the subgroup without reactogenicity (VE(0,0)) compared to the subgroup with vaccine-caused reactogenicity (VE(1,0)). In the special case of setting the sensitivity parameter to 0 (none robustness), IGIs collapse to point estimates and EUIs collapse to CIs, in which case the estimated VE (95% CI) for VE(0,0) vs. VE(1,0) for having any type of solicited AR is 96% (86%, 99%) vs. 93% (90%, 95%), and results for the other two types of reactogenicity are similar (Table 46, Figure 20). To access the vaccine-protection advantage of having vaccine-caused reactogenicity, the relative risk ratios $(1 - VE(0, 0))/(1 - VE(1, 0))$ are calculated. In the scenario of non-robustness, the point estimate (95% CI) for any type of solicited AR is 0.54 (0.14, 2.16), which suggests higher VE among the subgroup without reactogenicity but it is not statistically significant. This inference is also not robust to the moderate amount of allowed uncertainty (95% EUI 0.12, 2.39), and not robust to the higher amount of allowed uncertainty (95% EUI 0.09, 3.38). Similar results are obtained for the other two types of reactogenicity.

Conversely, for each of the reactogenicity induced by the second dosage, the estimated VE is higher among the subgroup with vaccine-caused reactogenicity compared to the subgroup without reactogenicity. In the special case of none robustness, the estimated VE (95% CI) for VE(0,0) vs. VE(1,0) for having any type of solicited AR is 84% (90%, 95%) vs. 92% (89%, 94%), and results for having any type of solicited local AR and having any type of solicited systemic AR are similar. The estimated VEs for both subgroups for having fever are relatively higher, with the estimated VE (95% CI) for VE(0,0) vs. VE(1,0) for having any type of solicited AR being 92% (90%, 94%) vs. 97% (92%, 99%) (Table 49, Figure 21). As for the RR ratio, in the scenario of non-robustness, the point estimate (95% CI) for any type of solicited AR is 2.03 (0.64, 6.46), which suggests higher VE among the subgroup with vaccine-caused reactogenicity but it is not statistically significant. This inference is also not robust to the moderate amount of allowed uncertainty (95% EUI 0.57, 7.26), and not robust to the higher amount of allowed uncertainty (95% EUI 0.40, 10.51). Similar results are obtained for any type of solicited systemic AR and fever, but note that the lower bound of the 95% CI for fever is 0.92 which is very close to 1. Other than that, in the scenario of non-robustness, the estimated RR ratio (95% CI) for any solicited local AR is 2.34 (1.06, 5.18), supporting higher VE among the subgroup with vaccine-caused solicited local AR, whereas this result is not robust to the moderate amount of allowed uncertainty (95% EUI 0.91, 6.03), and not robust to the higher amount of allowed uncertainty (95% EUI 0.63, 8.86).

3.5.2 Sanofi Stage 2 Naive Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	161	13
Any Solicited Local AR			
	No	185	17
Any Solicited Systemic AR			
	No	176	15

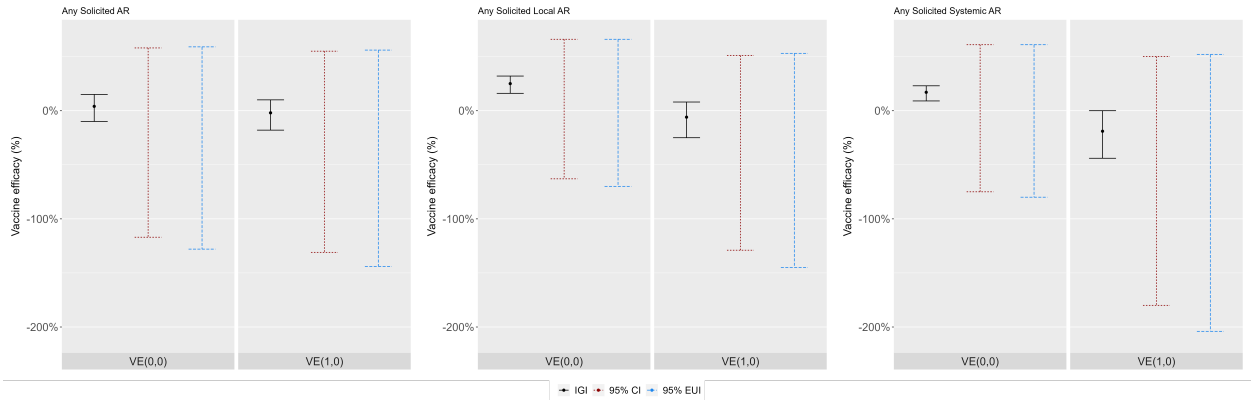
Table 50: Summary of cases by post-dose one reactogenicity among placebo recipients. Only placebo recipients without reported reactogenicity are included. Cases in this table are defined as endpoints occurred before the landmark time.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	117	9
	Yes	109	9
Any Solicited Local AR			
	No	134	9
	Yes	92	9
Any Solicited Systemic AR			
	No	158	11
	Yes	68	7

Table 51: Summary of cases by post-dose one reactogenicity among vaccine recipients. Cases in this table are defined as endpoints occurred before the landmark time.

		VE(0, 0)		VE(1, 0)		(1-VE(0,0))/(1-VE(1,0))	
Solicited AR	Sens	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval
Any Solicited AR	None	(0.04, 0.04)	(-1.17, 0.58)	(-0.02, -0.02)	(-1.31, 0.55)	(0.94, 0.94)	(0.39, 2.28)
Any Solicited AR	Med	(-0.10, 0.15)	(-1.28, 0.59)	(-0.18, 0.10)	(-1.44, 0.56)	(0.72, 1.22)	(0.34, 2.60)
Any Solicited AR	High	(-0.37, 0.26)	(-1.76, 0.63)	(-0.05, 0.23)	(-2.01, 0.61)	(0.49, 1.78)	(0.23, 3.75)
Solicited Local AR	None	(0.25, 0.25)	(-0.63, 0.66)	(-0.06, -0.06)	(-1.29, 0.51)	(0.71, 0.71)	(0.29, 1.72)
Solicited Local AR	Med	(0.16, 0.32)	(-0.70, 0.66)	(-0.25, 0.08)	(-1.45, 0.53)	(0.54, 0.92)	(0.25, 1.96)
Solicited Local AR	High	(-0.02, 0.40)	(-0.99, 0.69)	(-0.61, 0.23)	(-2.12, 0.60)	(0.37, 1.33)	(0.18, 2.80)
Solicited Systemic AR	None	(0.17, 0.17)	(-0.75, 0.61)	(-0.19, -0.19)	(-1.80, 0.50)	(0.70, 0.70)	(0.28, 1.73)
Solicited Systemic AR	Med	(0.09, 0.23)	(-0.80, 0.61)	(-0.44, 0)	(-2.04, 0.52)	(0.53, 0.91)	(0.25, 1.97)
Solicited Systemic AR	High	(-0.05, 0.29)	(-1.02, 0.63)	(-0.94, 0.20)	(-3.01, 0.61)	(0.37, 1.31)	(0.17, 2.81)

Table 52: Sanofi Stage 2 Naive Cohort: Vaccine Efficacy Results for Different Types of reactogenicity Post Dose 1 Under No Early Efficacy (NEE) Assumption with sensitivity analysis scenarios. Sensitivity parameter settings on the degree of potential post-randomization selection bias were: None, β_0 sensitivity parameter set to zero; Med, β_0 sensitivity parameter ranging from log(0.75) to -log(0.75); High, β_0 sensitivity parameter ranging from log(0.5) to - log(0.5).



(a)

	For RR Ratio (1-VE(0,0))/(1-VE(1,0))			
Solicited AR	Point Estimate	95% CI	IGI	95% EUI
Any Solicited AR	0.94	(0.39, 2.28)	(0.72, 1.22)	(0.34, 2.60)
Solicited Local AR	0.71	(0.29, 1.72)	(0.54, 0.92)	(0.25, 1.96)
Solicited Systemic AR	0.70	(0.28, 1.73)	(0.54, 0.91)	(0.25, 1.97)

(b)

Figure 22: Vaccine efficacy (VE) against COVID-19 by subgroups with vs. without reported reactogenicity for the Sanofi Stage 2 Naive post-dose one analysis. **(a)** The black dot in each panel corresponds to the VE estimate for the relevant subgroups for four types of reactogenicity when the sensitivity parameter is set to zero. The vertical black line denotes the ignorance interval (IGI) when the sensitivity parameter ranges from log(0.75) to -log(0.75), the vertical red dashed line denotes the 95% confidence interval (CI) when the sensitivity parameter is set to zero, and the vertical blue dashed line denotes the 95% estimated uncertainty interval (EUI) when the sensitivity parameter ranges from log(0.75) to - log(0.75). **(b)** Relative risk (RR) ratio for each type of solicited AR. The measurements presented are under the same setting as **(a)**.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	152	18
Any Solicited Local AR			
	No	184	20
Any Solicited Systemic AR			
	No	161	20
Fever			
	No	215	83

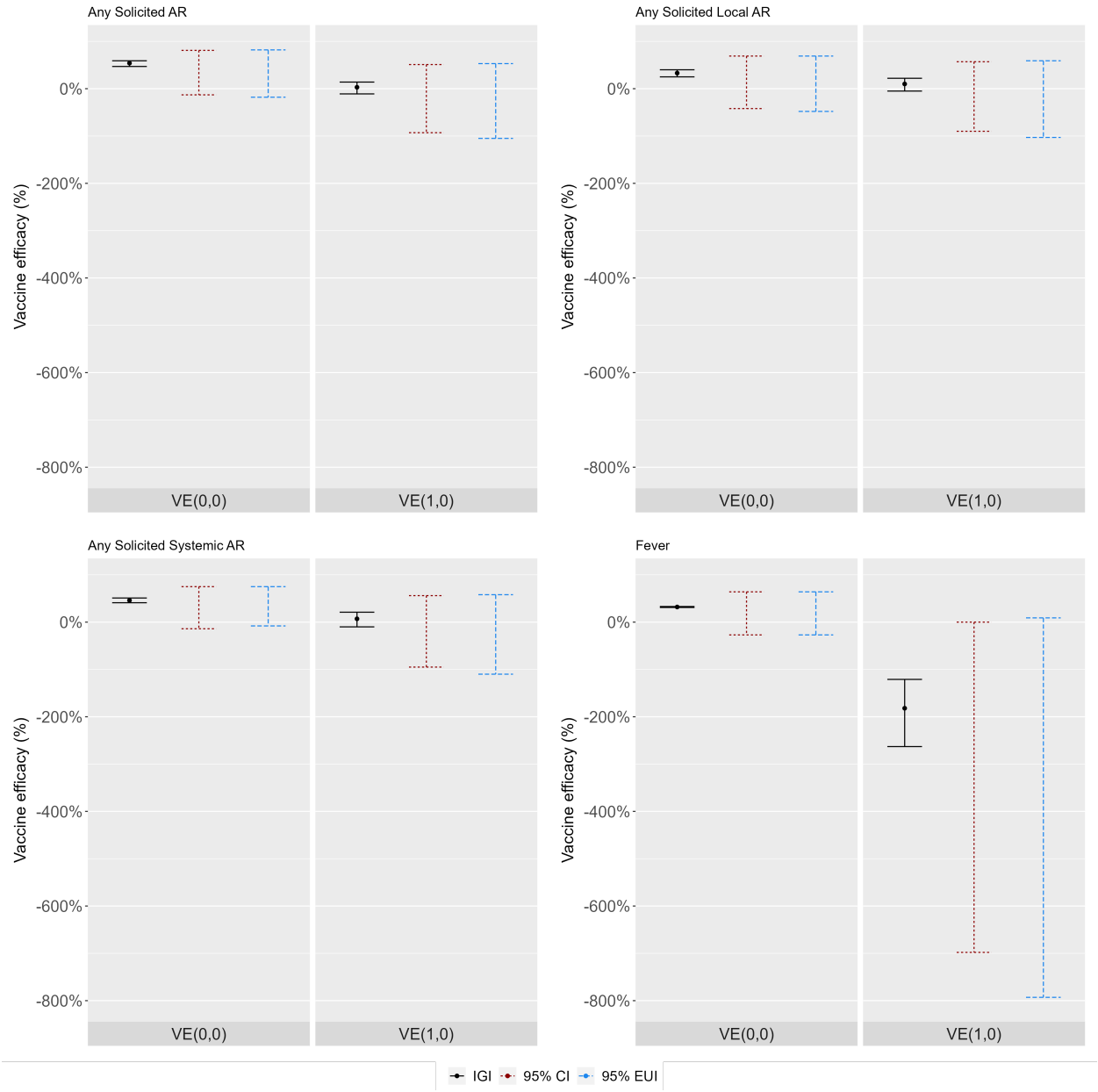
Table 53: Summary of cases by post-dose two reactogenicity among placebo recipients. Only placebo recipients without reported reactogenicity are included. Cases in this table are defined as endpoints occurred before the landmark time.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	117	6
	Yes	105	12
Any Solicited Local AR			
	No	129	9
	Yes	93	9
Any Solicited Systemic AR			
	No	143	9
	Yes	79	9
Fever			
	No	214	15
	Yes	8	3

Table 54: Summary of cases by post-dose two reactogenicity among vaccine recipients. Cases in this table are defined as endpoints occurred before the landmark time.

		VE(0, 0)		VE(1, 0)		(1-VE(0,0))/(1-VE(1,0))	
Solicited AR	Sens	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval
Any Solicited AR	None	(0.54, 0.54)	(-0.13, 0.81)	(0.03, 0.03)	(-0.93, 0.51)	(0.48, 0.48)	(0.18, 1.22)
Any Solicited AR	Med	(0.47, 0.59)	(-0.18, 0.82)	(-0.11, 0.14)	(-1.05, 0.53)	(0.37, 0.62)	(0.16, 1.38)
Any Solicited AR	High	(0.35, 0.64)	(-0.41, 0.83)	(-0.40, 0.26)	(-1.53, 0.58)	(0.26, 0.89)	(0.12, 1.96)
Solicited Local AR	None	(0.33, 0.33)	(-0.42, 0.69)	(0.10, 0.10)	(-0.90, 0.57)	(0.74, 0.74)	(0.30, 1.79)
Solicited Local AR	Med	(0.25, 0.40)	(-0.48, 0.69)	(-0.05, 0.22)	(-1.03, 0.59)	(0.57, 0.96)	(0.27, 2.04)
Solicited Local AR	High	(0.09, 0.47)	(-0.74, 0.72)	(-0.35, 0.34)	(-1.57, 0.65)	(0.39, 1.38)	(0.19, 2.91)
Solicited Systemic AR	None	(0.46, 0.46)	(-0.14, 0.75)	(0.07, 0.07)	(-0.95, 0.56)	(0.58, 0.58)	(0.24, 1.40)
Solicited Systemic AR	Med	(0.41, 0.51)	(-0.18, 0.75)	(-0.10, 0.21)	(-1.10, 0.58)	(0.45, 0.75)	(0.21, 1.59)
Solicited Systemic AR	High	(0.30, 0.56)	(-0.35, 0.77)	(-0.43, 0.34)	(-1.71, 0.65)	(0.31, 1.07)	(0.15, 2.25)
Fever	None	(0.32, 0.32)	(-0.27, 0.64)	(-1.82, -1.82)	(-6.98, 0)	(0.24, 0.24)	(0.08, 0.71)
Fever	Med	(0.31, 0.33)	(-0.27, 0.64)	(-2.63, -1.21)	(-7.93, 0.09)	(0.18, 0.31)	(0.07, 0.79)
Fever	High	(0.30, 0.34)	(-0.28, 0.64)	(-4.24, -0.61)	(-11.63, 0.32)	(0.13, 0.44)	(0.05, 1.09)

Table 55: Sanofi Stage 2 Naive Cohort: Vaccine Efficacy Results for Different Types of reactogenicity Post Dose 2 Under No Early Efficacy (NEE) Assumption with sensitivity analysis scenarios. Sensitivity parameter settings on the degree of potential post-randomization selection bias were: None, β_0 sensitivity parameter set to zero; Med, β_0 sensitivity parameter ranging from log(0.75) to -log(0.75); High, β_0 sensitivity parameter ranging from log(0.5) to - log(0.5).



(a)

	For RR Ratio (1-VE(0,0))/(1-VE(1,0))			
Solicited AR	Point Estimate	95% CI	IGI	95% EUI
Any Solicited AR	0.48	(0.18, 1.22)	(0.37, 0.62)	(0.16, 1.38)
Solicited Local AR	0.74	(0.30, 1.79)	(0.57, 0.96)	(0.27, 2.04)
Solicited Systemic AR	0.58	(0.24, 1.40)	(0.45, 0.75)	(0.21, 1.59)
Fever	0.24	(0.08, 0.71)	(0.18, 0.31)	(0.07, 0.79)

(b)

Figure 23: Vaccine efficacy (VE) against COVID-19 by subgroups with vs. without reported reactogenicity for the Sanofi Stage 2 Naive post-dose two analysis. **(a)** The black dot in each panel corresponds to the VE estimate for the relevant subgroups for four types of reactogenicity when the sensitivity parameter is set to zero. The vertical black line denotes the ignorance interval (IGI) when the sensitivity parameter ranges from log(0.75) to -log(0.75), the vertical red dashed line denotes the 95% confidence interval (CI) when the sensitivity parameter is set to zero, and the vertical blue dashed line denotes the 95% estimated uncertainty interval (EUI) when the sensitivity parameter ranges from log(0.75) to - log(0.75). **(b)** Relative risk (RR) ratio for each type of solicited AR. The measurements presented are under the same setting as **(a)**.

For each of the reactogenicity induced by the first dosage, the estimated VE is higher among the subgroup without reactogenicity compared to the subgroup with vaccine-caused reactogenicity. In the special case of none robustness, the estimated VE (95% CI) for VE(0,0) vs. VE(1,0) for having any type of solicited AR is 4% (-117%, 58%) vs. -2% (-131%, 55%), and results for the other two types of reactogenicity are similar (Table 52, Figure 22). In the scenario of non-robustness, the point estimate of RR ratio (95% CI) for any type of solicited AR is 0.94 (0.39, 2.28), which suggests higher VE among the subgroup without reactogenicity but it is not statistically significant. This inference is also not robust to the moderate amount of allowed uncertainty (95% EUI 0.34, 2.6), and not robust to the higher amount of allowed uncertainty (95% EUI 0.23, 3.75). Similar conclusions are drawn for the other two types of reactogenicity.

Similarly, for each of the reactogenicity induced by the second dosage, the estimated VE is higher among the subgroup without reactogenicity compared to the subgroup with vaccine-caused reactogenicity. In the special case of none robustness, the estimated VE (95% CI) for VE(0,0) vs. VE(1,0) for having any type of solicited AR is 54% (-13%, 81%) vs. 3% (-93%, 51%). Among the subgroup without reactogenicity, the VE point estimates for other types of reactogenicity are lower, with 33% for not experiencing any type of solicited local AR, 46% for not experiencing any type of solicited systemic AR, and 32% for not experiencing a fever (Table 49, Figure 21). As for the RR ratio, in the scenario of non-robustness, the point estimate (95% CI) for any type of solicited AR is 0.48 (0.18, 1.22), which suggests higher VE among the subgroup without reactogenicity but it is not statistically significant. This inference is also not robust to the moderate amount of allowed uncertainty (95% EUI 0.16, 1.38), and not robust to the higher amount of allowed uncertainty (95% EUI 0.12, 1.91). Similar results are obtained for any type of solicited local AR and any type of solicited systemic AR. However, in the scenario of non-robustness, the estimated RR ratio (95% CI) for fever is 0.24 (0.08, 0.71), supporting higher VE among the subgroup without vaccine-caused fever. This inference is robust to the moderate amount of allowed uncertainty (95% EUI 0.07, 0.79), but is not robust to the higher amount of allowed uncertainty (95% EUI 0.05, 1.09).

3.5.3 Sanofi Stage 2 Non-naive Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1372	45
Any Solicited Local AR			
	No	1609	54
Any Solicited Systemic AR			
	No	1474	46
Fever			
	No	1887	62

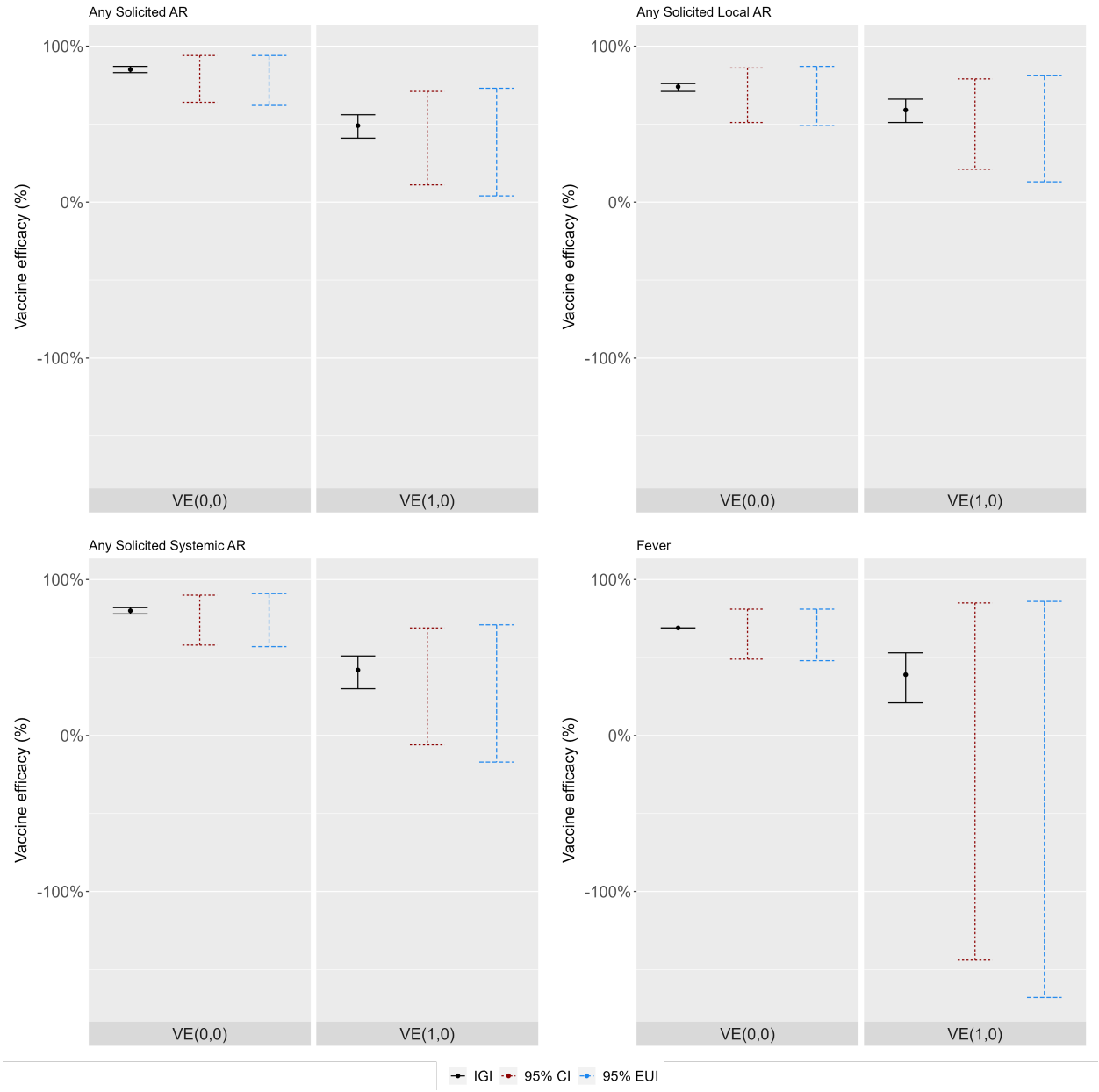
Table 56: Summary of cases by post-dose one reactogenicity among placebo recipients. Only placebo recipients without reported reactogenicity are included. Cases in this table are defined as endpoints occurred before the landmark time.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1074	5
	Yes	974	16
Any Solicited Local AR			
	No	1299	11
	Yes	748	10
Any Solicited Systemic AR			
	No	1317	8
	Yes	731	13
Fever			
	No	1941	19
	Yes	102	2

Table 57: Summary of cases by post-dose one reactogenicity among vaccine recipients. Cases in this table are defined as endpoints occurred before the landmark time. Cases in this table are defined as endpoints occurred before the landmark time.

		VE(0, 0)		VE(1, 0)		(1-VE(0,0))/(1-VE(1,0))	
Solicited AR	Sens	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval
Any Solicited AR	None	(0.85, 0.85)	(0.64, 0.94)	(0.49, 0.49)	(0.11, 0.71)	(0.29, 0.29)	(0.11, 0.77)
Any Solicited AR	Med	(0.83, 0.87)	(0.62, 0.94)	(0.41, 0.56)	(0.04, 0.73)	(0.22, 0.38)	(0.09, 0.88)
Any Solicited AR	High	(0.79, 0.89)	(0.54, 0.95)	(0.24, 0.62)	(-0.23, 0.76)	(0.15, 0.56)	(0.06, 1.29)
Solicited Local AR	None	(0.74, 0.74)	(0.51, 0.86)	(0.59, 0.59)	(0.21, 0.79)	(0.64, 0.64)	(0.27, 1.49)
Solicited Local AR	Med	(0.71, 0.76)	(0.49, 0.87)	(0.51, 0.66)	(0.13, 0.81)	(0.48, 0.84)	(0.23, 1.72)
Solicited Local AR	High	(0.65, 0.79)	(0.40, 0.88)	(0.35, 0.72)	(-0.14, 0.84)	(0.33, 1.24)	(0.16, 2.53)
Solicited Systemic AR	None	(0.80, 0.80)	(0.58, 0.90)	(0.42, 0.42)	(-0.06, 0.69)	(0.35, 0.35)	(0.14, 0.83)
Solicited Systemic AR	Med	(0.78, 0.82)	(0.57, 0.91)	(0.30, 0.51)	(-0.17, 0.71)	(0.26, 0.46)	(0.12, 0.95)
Solicited Systemic AR	High	(0.73, 0.84)	(0.50, 0.91)	(0.07, 0.60)	(-0.56, 0.76)	(0.18, 0.68)	(0.08, 1.40)
Fever	None	(0.69, 0.69)	(0.49, 0.81)	(0.39, 0.39)	(-1.44, 0.85)	(0.51, 0.51)	(0.12, 2.15)
Fever	Med	(0.69, 0.69)	(0.48, 0.81)	(0.21, 0.53)	(-1.68, 0.86)	(0.39, 0.67)	(0.11, 2.37)
Fever	High	(0.68, 0.70)	(0.48, 0.81)	(-0.16, 0.67)	(-2.75, 0.90)	(0.26, 0.99)	(0.08, 3.32)

Table 58: Sanofi Stage 2 Non-Naive Cohort: Vaccine Efficacy Results for Different Types of reactogenicity Post Dose 1 Under No Early Efficacy (NEE) Assumption with sensitivity analysis scenarios. Sensitivity parameter settings on the degree of potential post-randomization selection bias were: None, β_0 sensitivity parameter set to zero; Med, β_0 sensitivity parameter ranging from log(0.75) to -log(0.75); High, β_0 sensitivity parameter ranging from log(0.5) to - log(0.5).



(a)

	For RR Ratio (1-VE(0,0))/(1-VE(1,0))			
Solicited AR	Point Estimate	95% CI	IGI	95% EUI
Any Solicited AR	0.29	(0.11, 0.77)	(0.22, 0.38)	(0.09, 0.88)
Solicited Local AR	0.64	(0.27, 1.49)	(0.48, 0.84)	(0.23, 1.72)
Solicited Systemic AR	0.35	(0.14, 0.83)	(0.26, 0.46)	(0.12, 0.95)
Fever	0.51	(0.12, 2.15)	(0.39, 0.67)	(0.11, 2.37)

(b)

Figure 24: Vaccine efficacy (VE) against COVID-19 by subgroups with vs. without reported reactogenicity for the Sanofi Stage 2 Non-naive post-dose one analysis. **(a)** The black dot in each panel corresponds to the VE estimate for the relevant subgroups for four types of reactogenicity when the sensitivity parameter is set to zero. The vertical black line denotes the ignorance interval (IGI) when the sensitivity parameter ranges from log(0.75) to -log(0.75), the vertical red dashed line denotes the 95% confidence interval (CI) when the sensitivity parameter is set to zero, and the vertical blue dashed line denotes the 95% estimated uncertainty interval (EUI) when the sensitivity parameter ranges from log(0.75) to - log(0.75). **(b)** Relative risk (RR) ratio for each type of solicited AR. The measurements presented are under the same setting as **(a)**.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1379	49
Any Solicited Local AR			
	No	1587	56
Any Solicited Systemic AR			
	No	1471	53

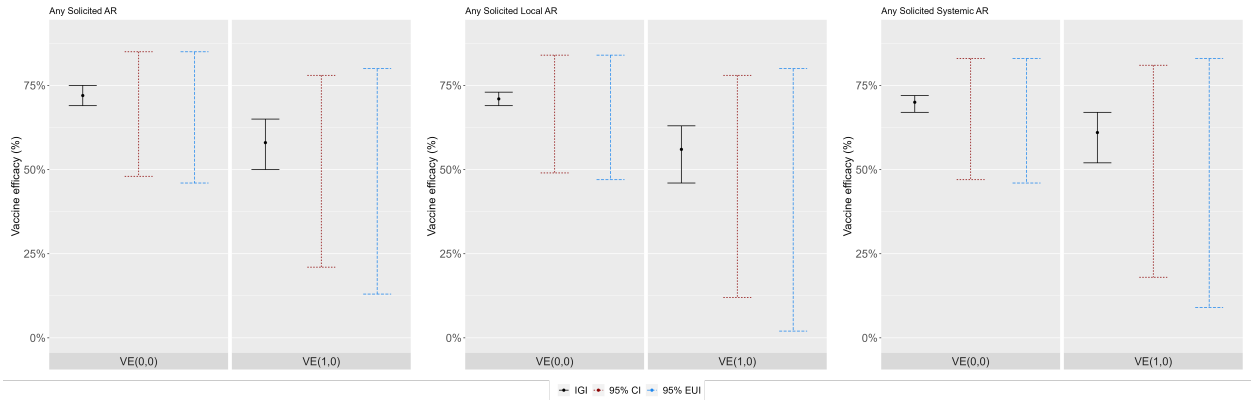
Table 59: Summary of cases by post-dose two reactogenicity among placebo recipients. Only placebo recipients without reported reactogenicity are included. Cases in this table are defined as endpoints occurred before the landmark time.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1246	12
	Yes	759	11
Any Solicited Local AR			
	No	1414	14
	Yes	591	9
Any Solicited Systemic AR			
	No	1430	15
	Yes	575	8

Table 60: Summary of cases by post-dose two reactogenicity among vaccine recipients. Cases in this table are defined as endpoints occurred before the landmark time. Cases in this table are defined as endpoints occurred before the landmark time.

		VE(0, 0)		VE(1, 0)		(1-VE(0,0))/(1-VE(1,0))	
Solicited AR	Sens	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval
Any Solicited AR	None	(0.72, 0.72)	(0.48, 0.85)	(0.58, 0.58)	(0.21, 0.78)	(0.67, 0.67)	(0.30, 1.50)
Any Solicited AR	Med	(0.69, 0.75)	(0.46, 0.85)	(0.50, 0.65)	(0.13, 0.80)	(0.51, 0.88)	(0.25, 1.75)
Any Solicited AR	High	(0.62, 0.77)	(0.36, 0.87)	(0.34, 0.71)	(-0.14, 0.83)	(0.34, 1.30)	(0.17, 2.57)
Solicited Local AR	None	(0.71, 0.71)	(0.49, 0.84)	(0.56, 0.56)	(0.12, 0.78)	(0.65, 0.65)	(0.29, 1.50)
Solicited Local AR	Med	(0.69, 0.73)	(0.47, 0.84)	(0.46, 0.63)	(0.02, 0.80)	(0.49, 0.86)	(0.25, 1.74)
Solicited Local AR	High	(0.63, 0.75)	(0.40, 0.85)	(0.26, 0.71)	(-0.32, 0.84)	(0.33, 1.27)	(0.17, 2.55)
Solicited Systemic AR	None	(0.70, 0.70)	(0.47, 0.83)	(0.61, 0.61)	(0.18, 0.81)	(0.76, 0.76)	(0.32, 1.77)
Solicited Systemic AR	Med	(0.67, 0.72)	(0.46, 0.83)	(0.52, 0.67)	(0.09, 0.83)	(0.57, 1)	(0.28, 2.05)
Solicited Systemic AR	High	(0.62, 0.74)	(0.39, 0.84)	(0.34, 0.74)	(-0.23, 0.86)	(0.39, 1.47)	(0.19, 3)

Table 61: Sanofi Stage 2 Non-Naive Cohort: Vaccine Efficacy Results for Different Types of reactogenicity Post Dose 2 Under No Early Efficacy (NEE) Assumption with sensitivity analysis scenarios. Sensitivity parameter settings on the degree of potential post-randomization selection bias were: None, β_0 sensitivity parameter set to zero; Med, β_0 sensitivity parameter ranging from log(0.75) to -log(0.75); High, β_0 sensitivity parameter ranging from log(0.5) to - log(0.5).



(a)

	For RR Ratio (1-VE(0,0))/(1-VE(1,0))			
Solicited AR	Point Estimate	95% CI	IGI	95% EUI
Any Solicited AR	0.67	(0.30, 1.50)	(0.51, 0.88)	(0.25, 1.75)
Solicited Local AR	0.65	(0.29, 1.50)	(0.49, 0.86)	(0.25, 1.74)
Solicited Systemic AR	0.76	(0.32, 1.77)	(0.57, 1.00)	(0.28, 2.05)

(b)

Figure 25: Vaccine efficacy (VE) against COVID-19 by subgroups with vs. without reported reactogenicity for the Sanofi Stage 2 Non-naive post-dose two analysis. **(a)** The black dot in each panel corresponds to the VE estimate for the relevant subgroups for four types of reactogenicity when the sensitivity parameter is set to zero. The vertical black line denotes the ignorance interval (IGI) when the sensitivity parameter ranges from log(0.75) to -log(0.75), the vertical red dashed line denotes the 95% confidence interval (CI) when the sensitivity parameter is set to zero, and the vertical blue dashed line denotes the 95% estimated uncertainty interval (EUI) when the sensitivity parameter ranges from log(0.75) to - log(0.75). **(b)** Relative risk (RR) ratio for each type of solicited AR. The measurements presented are under the same setting as **(a)**.

For each of the reactogenicity induced by the first dosage, the estimated VE is higher among the subgroup without reactogenicity compared to the subgroup with vaccine-caused reactogenicity. In the special case of none robustness, the estimated VE (95% CI) for VE(0,0) vs. VE(1,0) for having any type of solicited AR is 85% (64%, 94%) vs. 49% (11%, 71%). Among the subgroup without reactogenicity, the VE point estimates for other types of reactogenicity are lower, with 74% for not experiencing any type of solicited local AR, 80% for not experiencing any type of solicited systemic AR, and 69% for not experiencing a fever. Among the subgroup with vaccine-caused reactogenicity, the VE point estimates for other types of reactogenicity are different, with 59% for not experiencing any type of solicited local AR, 42% for not experiencing any type of solicited systemic AR, and 39% for not experiencing a fever. (Table 52, Figure 22). In the scenario of non-robustness, the point estimate of RR ratio (95% CI) for having any type of solicited AR is 0.29 (0.11, 0.77), supporting higher VE among the subgroup without any vaccine-caused solicited AR. This inference is robust to the moderate amount of allowed uncertainty (95% EUI 0.09, 0.88), but is not robust to the higher amount of allowed uncertainty (95% EUI (0.06, 1.29). Similar results can be drawn for any type of solicited systemic AR. The point estimate of RR ratio (95% CI) for any type of solicited systemic AR is 0.35 (0.14, 0.83), supporting higher VE among the subgroup without any vaccine-caused solicited systemic AR. This inference is robust to the moderate amount of allowed uncertainty (95% EUI 0.12, 0.95), but is not robust to the higher amount of allowed uncertainty (95% EUI (0.08, 1.40). In contrast, although the estimated RR ratios for any solicited local AR and fever suggest higher VE among the subgroup without vaccine-caused reactogenicity (RR ratio = 0.64 for any type of solicited local AR, RR ratio = 0.51 for fever), the results are not statistically significant and are also not robust to the moderate amount of allowed uncertainty and the higher amount of allowed uncertainty.

For each of the reactogenicity induced by the second dosage, the estimated VE is higher among the subgroup without reactogenicity compared to the subgroup with vaccine-caused reactogenicity. In the special case of none robustness, the estimated VE (95% CI) for VE(0,0) vs. VE(1,0) for having any type of solicited AR is 72% (48%, 85%) vs. 58% (21%, 78%). The results are similar for the other two types of reactogenicity

(Table 61, Figure 25). As for the RR ratio, in the scenario of non-robustness, the point estimate (95% CI) for any type of solicited AR is 0.67 (0.30, 1.50), which suggests higher VE among the subgroup without reactogenicity but it is not statistically significant. This inference is also not robust to the moderate amount of allowed uncertainty (95% EUI 0.25, 1.75), and not robust to the higher amount of allowed uncertainty (95% EUI 0.17, 2.57). Similar results are obtained for any type of solicited local AR and any type of solicited systemic AR.

3.5.4 Sanofi Stage 2 Combined Cohort

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1533	58
Any Solicited Local AR			
	No	1794	71
Any Solicited Systemic AR			
	No	1650	61
Fever			
	No	2116	85

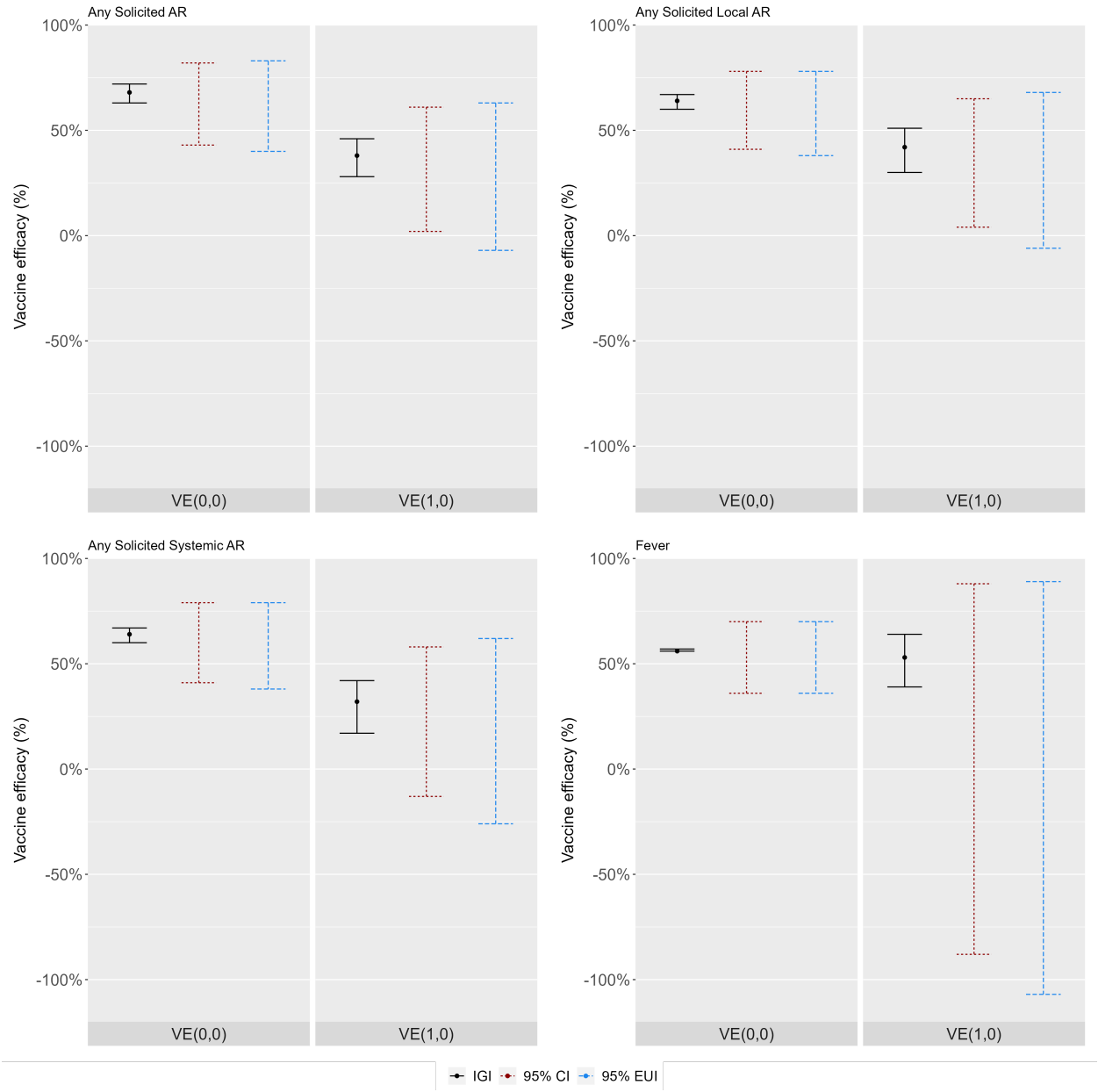
Table 62: Summary of cases by post-dose one reactogenicity among placebo recipients. Only placebo recipients without reported reactogenicity are included. Cases in this table are defined as endpoints occurred before the landmark time.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1191	14
	Yes	1083	25
Any Solicited Local AR			
	No	1433	20
	Yes	840	19
Any Solicited Systemic AR			
	No	1475	19
	Yes	799	20
Fever			
	No	2161	37
	Yes	108	2

Table 63: Summary of cases by post-dose one reactogenicity among vaccine recipients. Cases in this table are defined as endpoints occurred before the landmark time. Cases in this table are defined as endpoints occurred before the landmark time.

		VE(0, 0)		VE(1, 0)		(1-VE(0,0))/(1-VE(1,0))	
Solicited AR	Sens	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval
Any Solicited AR	None	(0.68, 0.68)	(0.43, 0.82)	(0.38, 0.38)	(0.02, 0.61)	(0.51, 0.51)	(0.27, 0.98)
Any Solicited AR	Med	(0.63, 0.72)	(0.40, 0.83)	(0.28, 0.46)	(-0.07, 0.63)	(0.39, 0.68)	(0.23, 1.17)
Any Solicited AR	High	(0.54, 0.76)	(0.25, 0.85)	(0.07, 0.54)	(-0.37, 0.69)	(0.26, 1)	(0.15, 1.73)
Solicited Local AR	None	(0.64, 0.64)	(0.41, 0.78)	(0.42, 0.42)	(0.04, 0.65)	(0.62, 0.62)	(0.33, 1.16)
Any Solicited Local AR	Med	(0.60, 0.67)	(0.38, 0.78)	(0.30, 0.51)	(-0.06, 0.68)	(0.47, 0.82)	(0.28, 1.38)
Solicited Local AR	High	(0.51, 0.70)	(0.26, 0.80)	(0.07, 0.60)	(-0.41, 0.73)	(0.32, 1.21)	(0.19, 2.04)
Solicited Systemic AR	None	(0.64, 0.64)	(0.41, 0.79)	(0.32, 0.32)	(-0.13, 0.58)	(0.52, 0.52)	(0.28, 0.97)
Solicited Systemic AR	Med	(0.60, 0.67)	(0.38, 0.79)	(0.17, 0.42)	(-0.26, 0.62)	(0.39, 0.69)	(0.23, 1.16)
Solicited Systemic AR	High	(0.52, 0.70)	(0.27, 0.81)	(-0.11, 0.53)	(-0.68, 0.69)	(0.27, 1.01)	(0.16, 1.71)
Fever	None	(0.56, 0.56)	(0.36, 0.70)	(0.53, 0.53)	(-0.88, 0.88)	(0.93, 0.93)	(0.23, 3.78)
Fever	Med	(0.56, 0.57)	(0.36, 0.70)	(0.39, 0.64)	(-1.07, 0.89)	(0.70, 1.22)	(0.21, 4.16)
Fever	High	(0.54, 0.57)	(0.35, 0.70)	(0.10, 0.74)	(-1.89, 0.92)	(0.47, 1.78)	(0.14, 5.81)

Table 64: Sanofi Stage 2 Cohort: Vaccine Efficacy Results for Different Types of reactogenicity Post Dose 1 Under No Early Efficacy (NEE) Assumption with sensitivity analysis scenarios. Sensitivity parameter settings on the degree of potential post-randomization selection bias were: None, β_0 sensitivity parameter set to zero; Med, β_0 sensitivity parameter ranging from log(0.75) to -log(0.75); High, β_0 sensitivity parameter ranging from log(0.5) to - log(0.5).



(a)

	For RR Ratio (1-VE(0,0))/(1-VE(1,0))			
Solicited AR	Point Estimate	95% CI	IGI	95% EUI
Any Solicited AR	0.51	(0.27, 0.98)	(0.39, 0.68)	(0.23, 1.17)
Solicited Local AR	0.62	(0.33, 1.16)	(0.47, 0.82)	(0.28, 1.38)
Solicited Systemic AR	0.52	(0.28, 0.97)	(0.39, 0.69)	(0.23, 1.16)
Fever	0.93	(0.23, 3.78)	(0.70, 1.22)	(0.21, 4.16)

(b)

Figure 26: Vaccine efficacy (VE) against COVID-19 by subgroups with vs. without reported reactogenicity for the Sanofi Stage 2 combined cohort post-dose one analysis. **(a)** The black dot in each panel corresponds to the VE estimate for the relevant subgroups for four types of reactogenicity when the sensitivity parameter is set to zero. The vertical black line denotes the ignorance interval (IGI) when the sensitivity parameter ranges from log(0.75) to -log(0.75), the vertical red dashed line denotes the 95% confidence interval (CI) when the sensitivity parameter is set to zero, and the vertical blue dashed line denotes the 95% estimated uncertainty interval (EUI) when the sensitivity parameter ranges from log(0.75) to - log(0.75). **(b)** Relative risk (RR) ratio for each type of solicited AR. The measurements presented are under the same setting as **(a)**.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1531	67
Any Solicited Local AR			
	No	1771	76
Any Solicited Systemic AR			
	No	1632	73
Fever			
	No	2037	84

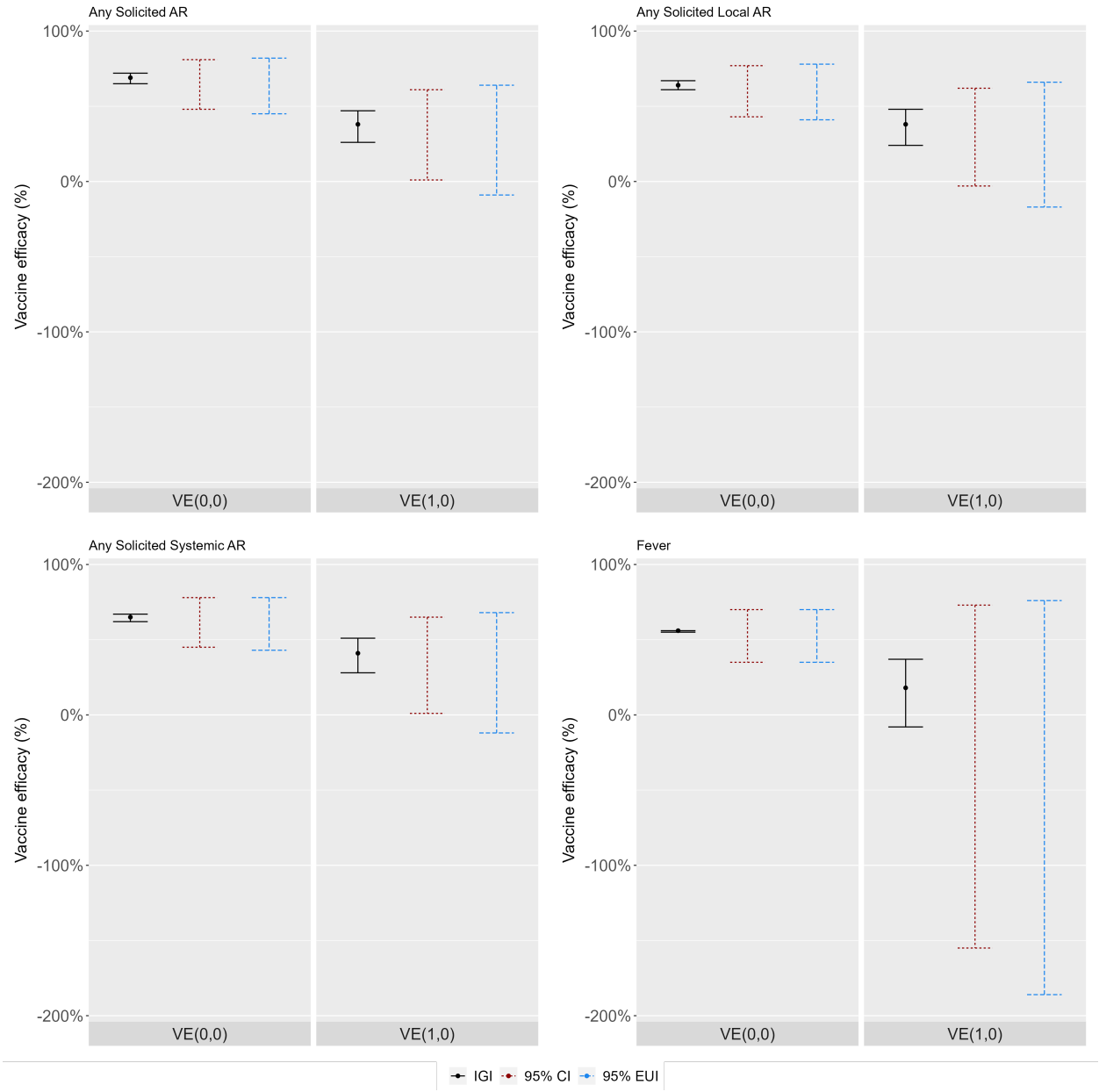
Table 65: Summary of cases by post-dose two reactogenicity among placebo recipients. Only placebo recipients without reported reactogenicity are included. Cases in this table are defined as endpoints occurred before the landmark time.

		Case (No)	Case (Yes)
Any Solicited AR			
	No	1363	18
	Yes	864	23
Any Solicited Local AR			
	No	1543	23
	Yes	684	18
Any Solicited Systemic AR			
	No	1573	24
	Yes	654	17
Fever			
	No	2130	38
	Yes	89	3

Table 66: Summary of cases by post-dose two reactogenicity among vaccine recipients. Cases in this table are defined as endpoints occurred before the landmark time. Cases in this table are defined as endpoints occurred before the landmark time.

		VE(0, 0)		VE(1, 0)		(1-VE(0,0))/(1-VE(1,0))	
Solicited AR	Sens	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval	Ignorance Interval	95% Estimated Uncertainty Interval
Any Solicited AR	None	(0.69, 0.69)	(0.48, 0.81)	(0.38, 0.38)	(0.01, 0.61)	(0.50, 0.50)	(0.27, 0.92)
Any Solicited AR	Med	(0.65, 0.72)	(0.45, 0.82)	(0.26, 0.47)	(-0.09, 0.64)	(0.38, 0.66)	(0.23, 1.10)
Any Solicited AR	High	(0.57, 0.75)	(0.34, 0.84)	(0.03, 0.56)	(-0.44, 0.70)	(0.26, 0.98)	(0.15, 1.63)
Solicited Local AR	None	(0.64, 0.64)	(0.43, 0.77)	(0.38, 0.38)	(-0.03, 0.62)	(0.57, 0.57)	(0.31, 1.05)
Solicited Local AR	Med	(0.61, 0.67)	(0.41, 0.78)	(0.24, 0.48)	(-0.17, 0.66)	(0.43, 0.75)	(0.26, 1.26)
Solicited Local AR	High	(0.54, 0.70)	(0.32, 0.79)	(-0.03, 0.59)	(-0.58, 0.73)	(0.29, 1.11)	(0.18, 1.85)
Solicited Systemic AR	None	(0.65, 0.65)	(0.45, 0.78)	(0.41, 0.41)	(0.01, 0.65)	(0.59, 0.59)	(0.32, 1.10)
Solicited Systemic AR	Med	(0.62, 0.67)	(0.43, 0.78)	(0.28, 0.51)	(-0.12, 0.68)	(0.45, 0.78)	(0.27, 1.31)
Solicited Systemic AR	High	(0.55, 0.7)	(0.34, 0.79)	(0.01, 0.61)	(-0.53, 0.75)	(0.30, 1.15)	(0.18, 1.92)
Fever	None	(0.56, 0.56)	(0.35, 0.70)	(0.19, 0.19)	(-1.51, 0.74)	(0.55, 0.55)	(0.17, 1.74)
Fever	None	(0.56, 0.56)	(0.35, 0.70)	(0.18, 0.18)	(-1.55, 0.73)	(0.54, 0.54)	(0.17, 1.71)
Fever	Med	(0.55, 0.56)	(0.35, 0.70)	(-0.08, 0.37)	(-1.86, 0.76)	(0.41, 0.71)	(0.15, 1.91)
1Fever	High	(0.54, 0.57)	(0.35, 0.7)	(-0.58, 0.56)	(-3.09, 0.83)	(0.27, 1.03)	(0.1, 2.73)

Table 67: Sanofi Stage 2 Cohort: Vaccine Efficacy Results for Different Types of reactogenicity Post Dose 2 Under No Early Efficacy (NEE) Assumption with sensitivity analysis scenarios. Sensitivity parameter settings on the degree of potential post-randomization selection bias were: None, β_0 sensitivity parameter set to zero; Med, β_0 sensitivity parameter ranging from log(0.75) to -log(0.75); High, β_0 sensitivity parameter ranging from log(0.5) to - log(0.5).



(a)

	For RR Ratio (1-VE(0,0))/(1-VE(1,0))			
Solicited AR	Point Estimate	95% CI	IGI	95% EUI
Any Solicited AR	0.50	(0.27, 0.92)	(0.38, 0.66)	(0.23, 1.10)
Solicited Local AR	0.57	(0.31, 1.05)	(0.43, 0.75)	(0.26, 1.26)
Solicited Systemic AR	0.59	(0.32, 1.10)	(0.45, 0.78)	(0.27, 1.31)
Fever	0.51	(0.12, 2.15)	(0.39, 0.67)	(0.08, 3.32)

(b)

Figure 27: Vaccine efficacy (VE) against COVID-19 by subgroups with vs. without reported reactogenicity for the Sanofi Stage 2 combined cohort post-dose two analysis. **(a)** The black dot in each panel corresponds to the VE estimate for the relevant subgroups for four types of reactogenicity when the sensitivity parameter is set to zero. The vertical black line denotes the ignorance interval (IGI) when the sensitivity parameter ranges from log(0.75) to -log(0.75), the vertical red dashed line denotes the 95% confidence interval (CI) when the sensitivity parameter is set to zero, and the vertical blue dashed line denotes the 95% estimated uncertainty interval (EUI) when the sensitivity parameter ranges from log(0.75) to - log(0.75). **(b)** Relative risk (RR) ratio for each type of solicited AR. The measurements presented are under the same setting as **(a)**.

For each of the reactogenicity induced by the first dosage, the estimated VE is higher among the subgroup without reactogenicity compared to the subgroup with vaccine-caused reactogenicity. In the special case of none robustness, the estimated VE (95% CI) for VE(0,0) vs. VE(1,0) for having any type of solicited AR is 68% (43%, 82%) vs. 38% (2%, 61%), and the results for the other types of reactogenicity are similar. (Table 64, Figure 26). In the scenario of non-robustness, the point estimate of RR ratio (95% CI) for having any type of solicited AR is 0.51 (0.27, 0.98), supporting higher VE among the subgroup without any vaccine-caused solicited AR. However, this inference is not robust to the moderate amount of allowed uncertainty (95% EUI 0.23, 1.17), and is not robust to the higher amount of allowed uncertainty (95% EUI (0.15, 1.73). Similar results can be drawn for any type of solicited systemic AR. The point estimate of RR ratio (95% CI) for any type of solicited systemic AR is 0.52 (0.28, 0.97), supporting higher VE among the subgroup without any vaccine-caused solicited systemic AR. This inference is not robust to the moderate amount of allowed uncertainty (95% EUI 0.23, 1.16), and is not robust to the higher amount of allowed uncertainty (95% EUI (0.16, 1.17). In contrast, although the estimated RR ratios for any solicited local AR and fever suggest higher VE among the subgroup without vaccine-caused reactogenicity (RR ratio = 0.62 for any type of solicited local AR, RR ratio = 0.93 for fever), the results are not statistically significant and are also not robust to the moderate amount of allowed uncertainty and the higher amount of allowed uncertainty.

For each of the reactogenicity induced by the second dosage, the estimated VE is higher among the subgroup without reactogenicity compared to the subgroup with vaccine-caused reactogenicity. In the special case of none robustness, the estimated VE (95% CI) for VE(0,0) vs. VE(1,0) for having any type of solicited AR is 69% (48%, 81%) vs. 38% (1%, 61%). The results are similar for the other types of reactogenicity (Table 67, Figure 27). As for the RR ratio, in the scenario of non-robustness, the point estimate (95% CI) for any type of solicited AR is 0.50 (0.27, 0.92), supporting higher VE among the subgroup without reactogenicity. This inference is not robust to the moderate amount of allowed uncertainty (95% EUI 0.23, 1.10), and not robust to the higher amount of allowed uncertainty (95% EUI 0.15, 1.63). On the other hand, although the estimated RR ratios for any solicited local AR, any solicited systemic AR, and fever suggest higher VE among the subgroup without vaccine-caused reactogenicity (RR ratio = 0.57 for any type of solicited local AR, RR ratio = 0.59 for any type of solicited systemic AR, RR ratio = 0.51 for fever), the results are not statistically significant and are also not robust to the moderate amount of allowed uncertainty and the higher amount of allowed uncertainty.

4 Discussion

In this project, we investigate the association of reactogenicity side effects with future risk of COVID-19 among vaccine and placebo recipients using marginal VIM analysis and assess the vaccine efficacy in the vaccine-caused reactogenicity subgroup (i.e. R(1)=1, R(0)=0) and the subgroup without reactogenicity under both treatment assignments (i.e., R(1)=R(0)=0) using PS analysis. In the marginal VIM analysis, the extent to which different types of reactogenicity variables are important for predicting COVID-19 differs across vaccine trials, post-dose one and post-dose two analyses, and between treatment arms. However, although with different ranks in different analyses, the magnitude of the estimated gain in predictiveness of each type of reactogenicity variable compared to baseline factors in each analysis tends to be very similar, which can be in part due to the correlation between the reactogenicity variables. In general, fever and solicited local AR are estimated to be the most important types of reactogenicity among a majority of the analyses, even though the hypothesis tests of non-zero importance in all the analyses implemented do not reach statistical significance. To illustrate our findings, we focus on the results from the Moderna trial since the hypothesis tests of reactogenicity caused by the second injection in the marginal VIM analysis of the Moderna trial almost reach statistical significance (p-values very close to 0.05). For reactogenicity caused by the second injection, there is a gain in predictiveness of about 0.1 AUC for all types of reactogenicity variables with the AUC of the oracle prediction function with only baseline characteristics of 0.566 AUC and solicited local AR estimated to be the most important among the placebo recipients. Among the vaccine recipients, there is a gain in predictiveness of about 0.17 AUC for all types of reactogenicity variables, with the AUC of the oracle prediction function with only baseline characteristics of 0.410 AUC and solicited systemic AR estimated to be the most important. In general, this result is suggestive of more gain in predictiveness for the vaccine group than the placebo group. A potential explanation is that the reactogenicity for placebo

recipients is less connected to immunological mechanisms related to COVID-19 than the reactogenicity for vaccine recipients because it measures mostly a behavioral feature. In contrast, reactogenicity in the vaccine arm measures a behavioral and/or biological feature, and these biological features are more correlated (and potentially more connected to mechanisms) with COVID-19.

In the PS analysis, considering a moderate selection bias, only fever in the Sanofi Stage 2 Naive post-dose two analysis, any solicited AR, and any solicited systemic AR in the Sanofi Stage 2 Non-naive cohort post-dose one analysis indicate higher vaccine efficacy in the subgroup without reactogenicity under both vaccine and placebo, with robust inference. In contrast, in the scenario of no selection bias and considering the results to be hypothesis-generating, we can draw the following conclusions: As in the Moderna trial, there is around 0.5 times the vaccine efficacy among the subgroup having vaccine-caused reactogenicity than among the subgroup without reactogenicity under both treatment assignments after the first injection for all the reactogenicity analyzed, but the results are not statistically significant. Conversely, the post-dose two analysis suggests that the vaccine-caused reactogenicity is connected to improved vaccine efficacy, with around 2 times the vaccine efficacy among the subgroup with vaccine-caused reactogenicity than among the subgroup without reactogenicity under both treatment assignments for all the reactogenicity variables analyzed, but the results are not statistically significant except for experiencing any solicited local AR. Notably, there is a point estimate of 2.85 times vaccine-protection advantage of having vaccine-caused fever after the second injection than not having fever under both treatment assignments, and this result is very close to attaining statistical significance. On the contrary, the analyses in the Sanofi Stage 2 trial indicate the opposite direction of vaccine efficacy. Specifically, the results suggest higher vaccine protection among the subgroup without reactogenicity under both treatment assignments compared to the subgroup with vaccine-caused reactogenicity for all the reactogenicity variables analyzed. Notably, as in the Sanofi Stage 2 Naive cohort, the vaccine provides approximately 0.8 times the protection when reactogenicity is caused by the first vaccine injection compared to when there is no reactogenicity under both treatment assignments. After the second injection, the vaccine offers around 0.5 times the protection with vaccine-caused reactogenicity. In particular, the subgroup who experiences vaccine-caused fever after the second injection has only 0.24 times the protection compared to those who do not have a fever under both treatment assignments. As in the Sanofi Stage 2 Non-naive cohort, there is around 0.5 times vaccine protection of having vaccine-caused reactogenicity after the first injection, and there is around 0.6 times vaccine projection of having vaccine-caused reactogenicity after the second injection. As in the Sanofi Stage 2 combined cohort, there is around 0.5 times vaccine protection of having vaccine-caused reactogenicity after both injections compared to not having it under both treatment assignments. A potential explanation of the opposite results seen from the mRNA vaccine (Moderna), specifically the post-dose two analysis, and the recombinant protein vaccine (Sanofi) is that CD8 T cells induced by mRNA vaccine play a role in preventing COVID-19 (Wherry and Barouch [2022], Stephens and McElrath [2020])and reactogenicity is correlated with a quantitatively or qualitatively more useful CD8 T cell response. In addition, when investigating the association of immunogenicity and reactogenicity of the mRNA-1273 vaccine, Siangphoe and colleagues found higher nAb titers after the second injection, accompanied by more frequent and severe local and systemic ARs compared to the first injection. They propose that this may be due to the immunity acquired after the first injection (Siangphoe et al. [2023]). This explanation may also apply to the improved vaccine efficacy observed among the vaccine-caused reactogenicity subgroup in the analysis of reactogenicity induced by the second injection.

The main strength of this project is that the four trials we analyze are harmonized, randomized, and double-blinded clinical trials. They all share a similar COVID-19 primary endpoint and took place over a fairly similar calendar period of time. Because of the randomization, differences in VIM results that compare the placebo vs. vaccine group can be attributed to being caused by vaccination, and one of the key assumptions of the PS methods is a randomized trial. However, one main limitation of this project is low power and precision due to the low incidence rate and the small number of cases in all four trials, thus warranting implementing the analyses in other randomized clinical trials or cohort studies that have a larger number of cases (or greater sample size) and have the requisite reactogenicity data. Moreover, the results obtained in the marginal VIM analysis have a large amount of uncertainty, and replications of the analyses in other studies are needed. As for the PS analysis, we only implement the analysis among placebo recipients without reported reactogenicity under the NEE-CB assumption made by the methodology employed, and future work is needed to extend the current method to allow reported reactogenicity among placebo recipients and study VE(0) and VE(1). Some other future work is to study whether our current results can extend

to new variants of SARS-CoV-2 and other kinds of vaccines besides COVID-19 vaccines, to understand the mechanism of how reactogenicity impacts vaccine efficacy (e.g., whether it is because reactogenicity increases certain immunological response or is correlated with immune response), and to study whether the impact of reactogenicity on vaccine efficacy is mediated through immunological markers.

5 Software and Code

R code available at Charles Wolock's Github repository *surv_vim_supplementary* using *survML* R package is used to implement the VIM analyses. R code for the *psbinary* R package available at Bryan Blette's Github repository is used to carry out the PS analysis. All data analysis was performed in R (version 4.3.0).

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