Severity of self-reported systemic reactions following SARS-CoV-2 vaccination and immunological response in the Danish National Cohort Study of Effectiveness and Safety of SARS-CoV-2/COVID-19 Vaccines (ENFORCE)

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BACKGROUND

- Major side effects after vaccination can be caused by a reactive immune system.
- With the introduction of COVID-19 vaccines, an assumption has been that severe side effects after vaccination mean that the vaccine is working.

AIM

- To investigate statistical association between severity of self-reported systemic reactions to SARS-CoV-2 vaccination and immunological response, assessed by total serum immunoglobulin G [IgG] antibodies against SARS-CoV-2 spike protein.

METHODS

- Data are from ENFORCE, an open-label, non-randomised, parallel group, phase IV study that enrolled Danish adult citizens prior to their first SARS-CoV-2 vaccination.
- Figure 1 displays the analysis inclusion criteria.
- A severity score was defined based on 7 systemic reactions (muscle pain, joint pain, fatigue, fever, headache, nausea, chills) counting +1 for each reaction reported with moderate severity and +2 for each severe, up to a maximum score of 14.
- Linear regression was used to assess the association between severity score and $\log_{10}$transformed spike IgG level after first and second vaccinations, adjusted for potential confounders (primary analysis).
- We also tested the impact of adjusting for spike IgG level measured prior to each vaccination.
- Logistic regression was used to further explore any association between pre-vaccination $\log_{10}$transformed spike IgG level and self-reported systemic reactions.

RESULTS

- 6194 and 5940 participants were included for first and second vaccinations, respectively (Table 1).
- Fatigue, muscle pain, and headache were the most commonly reported systemic reactions, occurring more frequently after second vaccination and with a higher chance of being reported as moderate/severe (Figure 2).

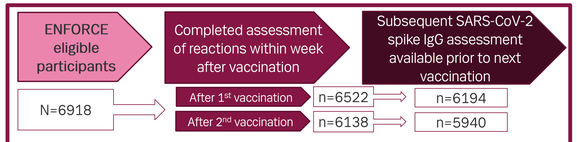


Figure 1 Selection of participants

	First vaccination (N=6194)	Second vaccination (N=5940)
Age at enrolment (years), median (IQR)	64 (54, 75)	64 (54, 75)
Sex, n (%)		
Male	2684 (43.3)	2566 (43.2)
Female	3509 (56.7)	3374 (56.8)
CCI score categories [1], n (%)		
0	4896 (79.1)	4707 (79.2)
1-2	1105 (17.8)	1049 (17.7)
>2	192 (3.1)	184 (3.1)
First vaccine type, n (%)		
BTN162b2	3455 (55.8)	3567(60.1)
mRNA-1237	2397 (38.7)	2373 (39.9)
ChAdOx1	341 (5.5)	0 (0.0)
Evidence of prior SARS-CoV-2 infection [2], n (%)	309 (5.0)	319 (5.4)
Time from vaccination to spike IgG assessment (weeks), median (IQR)	4 (3, 5)	9 (8, 10)
Pre-vaccination SARS-CoV-2 spike IgG level (AU/mL), median (IQR)	77 (40, 173)	30713 (9589, 90874)

Table 1 Characteristics

[1] Charlson comorbidity index (CCI) based on comorbidities in the 5 years prior to enrolment.

[2] Infection prior to first vaccination defined by positive antibody result from ELISA (Wantai) test or positive PCR test and prior to second vaccination included any positive PCR tests after first dose.

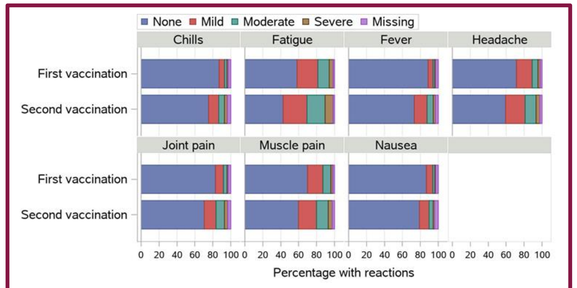
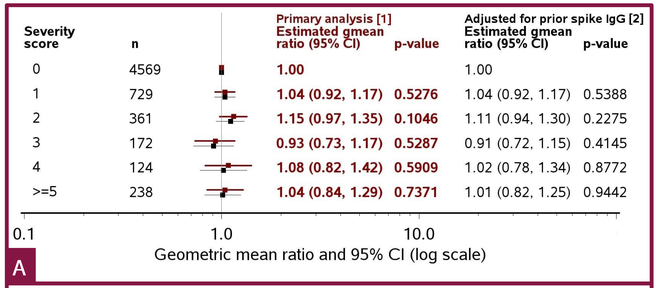


Figure 2 Severity of self-reported systemic reactions within 1 week after vaccination



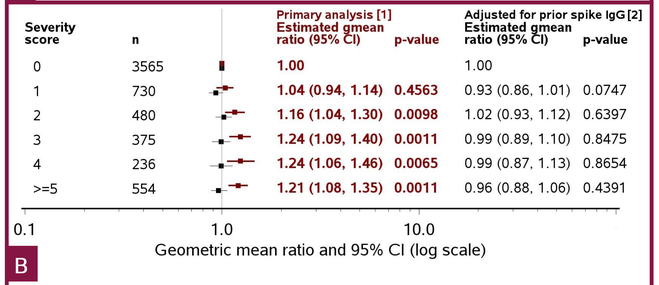


Figure 3 Comparison of SARS-CoV-2 spike IgG levels according to severity score of self-reported systemic reactions following first vaccination (A) and second vaccination (B)

[1] Primary: adjusted for time from vaccination to spike IgG assessment, age, sex, CCI, vaccine type, and evidence of prior SARS-CoV-2 infection.

[2] As per primary analysis but with additional adjustment for pre-vaccination SARS-CoV-2 spike IgG level.

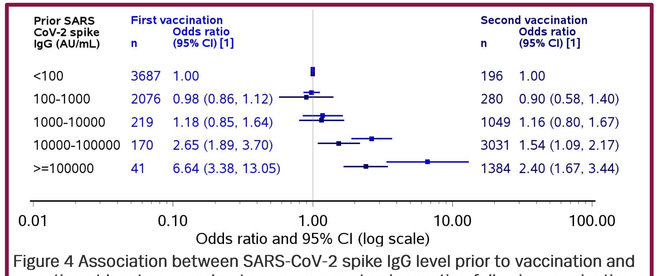


Figure 4 Association between SARS-CoV-2 spike IgG level prior to vaccination and reporting at least one moderate or severe systemic reaction following vaccination.

[1] Adjusted for age, sex, CCI, and vaccine type.

RESULTS (CONT.)

- Following first vaccination, no significant association was found between severity score and spike IgG level, before or after adjustment for pre-vaccination spike IgG, global p-values of 0.595 and p=0.760, respectively (Figure 3A).
- Following second vaccination, the association in the primary analysis was highly significant (global p<0.001). Compared to a zero score, there were significantly higher spike IgG levels for scores of 2 or more, up to an estimated 24% increase for scores of 3 or 4 (Figure 3B). However, the association disappeared after adjusting for pre-vaccination spike IgG (p=0.534).
- We tested the effect of different scoring methods for severity of reactions in sensitivity analyses (e.g. incorporating mild systemic reactions) with broadly consistent findings.
- In a further exploratory analysis of pre-vaccination spike IgG level and reporting at least 1 moderate or severe systemic reaction, we found a significant association (p<0.001); participants with levels of at least 10,000 AU/mL were significantly more likely to report a reaction than those with <100 (Figure 4).

CONCLUSIONS

- An average of 4 weeks after first vaccination, the antibody response to SARS-CoV-2 was similar regardless of the severity of systemic reactions reported.
- Around 9 weeks after second vaccination, those who had at least 2 moderate or 1 severe reaction had a significantly higher response than those with none.
- However, adjustment for pre-vaccination spike IgG level attenuated the association and was found to be related to reporting moderate/severe reactions.
- Therefore, although symptoms appear to be an indicator for a subsequent higher antibody response after the second vaccination, this may be attributed to higher levels of pre-existing immunity in these participants following the first vaccination.