Comparative reactogenicity of recombinant protein-based and mRNA COVID-19 vaccines: a real-world active surveillance study

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BACKGROUND

Real-world comparative data on the reactogenicity of different COVID-19 vaccine platforms remain limited, particularly for newer vaccine technologies such as recombinant protein-based vaccines.

Active surveillance approaches provide detailed and timely information on adverse events (AEs) following vaccination, including their frequency and potential impact on daily life.

Understanding differences in reactogenicity between vaccine platforms may help inform vaccination strategies, especially in populations where tolerability is an important consideration.

Objective: To compare the frequency and clinical impact of adverse events following mRNA-based and recombinant protein-based COVID-19 vaccines using real-world active surveillance data.

METHODS

Study design and population

- This is an interim analysis of an observational study using active surveillance electronic questionnaires distributed to individuals vaccinated against COVID-19 during the 2025–2026 vaccination campaign, starting on November 25, 2025, including data up to January 21, 2026.

Data collection

- Questionnaires were sent by mobile phone text messages 7 days after vaccination and collected information on:
  - Local AEs
  - Systemic AEs
  - Interference with daily activities
  - Need for symptomatic treatment
  - Healthcare consultation

AEs were analyzed, distinguishing between:

- Any adverse event
- Local adverse events
- Systemic adverse events

Analyses were also stratified by age group.

RESULTS

A total of 4248 SMS invitations were sent, of which 578 questionnaires were completed, corresponding to an overall response rate of 13.6%.

Response rates were:

- 14.4% for the mRNA-based vaccine (297/2060)
- 12.8% for the recombinant protein-based vaccine (281/2188)

Baseline characteristics

Baseline characteristics differed mainly in **age distribution**, with recipients of the recombinant protein-based vaccine being older overall.

In contrast:

- **Sex distribution was similar between groups**
- **Coadministration rates were also comparable**

Table 1. Baseline characteristics of participants receiving recombinant protein–based and mRNA-based vaccines

Characteristic	*Recombinant protein–based (n=281)*	*mRNA-based (n=297)*	*p-values*
Age group			<0.001
<20	2 (0.7%)	–	
20–29	3 (1.1%)	6 (2.0%)	
30–39	14 (7.7%)	23 (7.7%)	
40–49	32 (11.4%)	62 (20.9%)	
50–59	76 (27.0%)	96 (32.3%)	
60–69	98 (34.9%)	72 (24.2%)	
70–79	45 (16.0%)	35 (11.8%)	
>80	11 (3.9%)	3 (1.0%)	
Female sex	133 (47.3%)	154 (52.0%)	0.27
Coadministration	227 (80.8%)	236 (79.5%)	0.70

Adverse events

At least one adverse event was reported by **27.3%** of individuals receiving the mRNA vaccine and **14.6%** of individuals receiving the recombinant protein-based vaccine ($p < 0.001$). Both local and systemic adverse events were reported **less frequently** among recipients of the recombinant protein-based vaccine. Detailed comparisons of adverse events are shown in Table 2.

Clinical impact of adverse events

Adverse events with potential clinical impact were also **less frequent** among recipients of the recombinant protein-based vaccine (detailed comparison is shown in Table 2). Healthcare consultation was uncommon and similar between groups (**2.4% vs 1.4%**; p = 0.41).

Table 2. Adverse events following COVID-19 vaccination by vaccine platform.

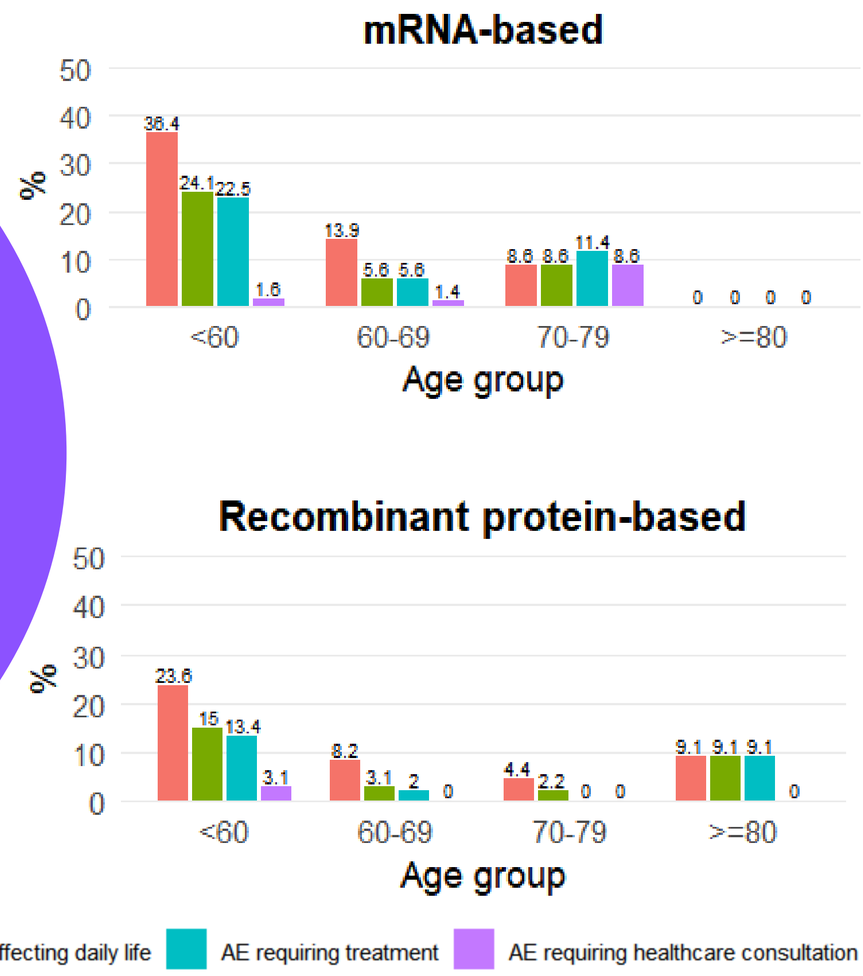
Outcome	*Recombinant protein–based n/N (%)*	*mRNA-based n/N (%)*	*p-value*
More than 1 adverse event (any)	41/281 (14.6%)	81/297(27.3%)	<0.001
More than 1 local AE	36/281 (12.8%)	75/297(25.3%)	<0.001
More than 1 systemic AE	36/281 (12.8%)	77/297 (25.9%)	<0.001
Interference with daily life	24/281 (8.5%)	47/297 (15.9%)	0.07
Need for treatment	20/281 (7.1%)	40/297 (13.5%)	0.12
Healthcare consultation	4/281 (1.4%)	7/297 (2.4%)	0.41

Frequency of any adverse event was **higher** among mRNA vaccine recipients compared with the recombinant protein-based vaccine (**27.3% vs 14.6%**).

This difference was consistent across both **local and systemic adverse events** and across individuals **<80 years**, suggesting a lower overall reactogenicity profile for the recombinant protein-based vaccine.

Adverse events with clinical impact (interference with daily activities and need for treatment) were also **less frequent** in the recombinant protein-based vaccine group.

Despite these differences, **healthcare consultation was rare and similar between groups**, indicating that most adverse events were mild.



CONCLUSIONS

In this real-world active surveillance study, most adverse events following COVID-19 vaccination were **mild and self-limiting**.

The recombinant protein-based COVID-19 vaccine was associated with a **lower frequency of both local and systemic adverse events**, as well as a lower impact on daily activities, compared with the mRNA-based vaccine.

This pattern was consistent across most age groups (**<80 years**), whereas higher reactogenicity rates were observed among individuals aged ≥80 years.

These findings provide valuable **real-world comparative data on vaccine reactogenicity** and may help inform vaccination strategies, particularly in populations where reactogenicity and tolerability are key considerations.

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