**Poster code:** CO139

# Reactogenicity of Nuvaxovid and Other Commercialised COVID-19 Vaccines: A Systematic Review of Randomised Controlled Trials

**Alice Sanderson, MPhil[1], José Bartelt-Hofer, PhD[2]*, Manuela Gschwend, PhD[3], Paul Miller, MSc[1], Katie Reddish, BSc[1], Joe W. E. Moss, PhD[1], Neil Hansell BSc[1], Clotilde El Guerche-Séblain, PhD[2], Charalampos Valmas, PhD[2], Rachael McCool BSc[1]**

*[1]York Health Economics Consortium, York, UK; [2]Sanofi Vaccines, Lyon, France; [3]Novavax Inc, Gaithersburg, MD, United States*

*Presenting Author: José Bartelt-Hofer (Jose.Bartelt-Hofer@sanofi.com)

## Key takeaways

This literature review of COVID-19 vaccines demonstrates that Nuvaxovid has the largest evidence base from randomised controlled trials, while also supporting a favourable reactogenicity profile compared to mRNA vaccines

## BACKGROUND

- COVID-19 vaccines demonstrate distinct reactogenicity profiles, with evidence suggesting protein-based vaccines may result in fewer adverse events (AEs) compared to mRNA vaccines[1-2]
- Nuvaxovid™, a protein-based COVID-19 vaccine, has shown comparable efficacy and effectiveness to mRNA vaccines with evidence of reduced reactogenicity[2-4]
- However, evidence on the reactogenicity profiles of commercialised COVID-19 vaccines capturing the newest post-market authorisation studies is limited, necessitating updated systematic evidence synthesis

## OBJECTIVE

This systematic literature review (SLR) presents clinical evidence on the reactogenicity profile of commercialised COVID-19 vaccines from randomised controlled trials (RCTs)

## METHODS

**Study registration**
PROSPERO (CRD420251084936)

**Eligible population**
Adults[d]

**Comparator**
Placebo, any of the interventions of interest

**Data sources**
Databases[a], trial registries[b] and HTA/regulatory agency webpages[c]

**Study types**
RCTs

**Outcomes**
- Post-vaccination solicited AEs

**Stratified, when available by**
- Severity (grades 1–4)
- AE site (local or systemic)
- Prior immune status (primary vs booster doses)

**Search dates**
**Initial search:** July 2025
**Supplementary search:** September 2025 (MEDLINE)

**Intervention**
Currently commercialised mRNA or protein-based COVID-19 vaccines[e]

[a]Databases include MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment database (HTA), Cochrane Database of Systematic Reviews (CDSR)
[b]Trial Registries include ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP)
[c]HTA/Regulatory Agency Webpages include Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (CDC ACIP), European Medicines Agency (EMA), U.S. Food and Drug Administration Drug Database (Drugs@FDA), National Institute for Health and Care Excellence (NICE), Canada's Drug Agency (CDA-AMC), Institute for Clinical and Economic Review (ICER)
[d]Adults with no contraindication for receiving a COVID-19 vaccine
[e]Nuvaxovid (NVX-CoV2373 and NVX-CoV2601); Comirnaty (BNT162b2); Spikevax (mRNA-1273); mNEXSPIKE (mRNA-1283); Kostaive (ARCT-154, ARCT-2301); Bimervax (PHH-1V, PHH-1V81)

## CONCLUSIONS

Descriptive SLR data support favourable reactogenicity profile for Nuvaxovid relative to mRNA vaccines

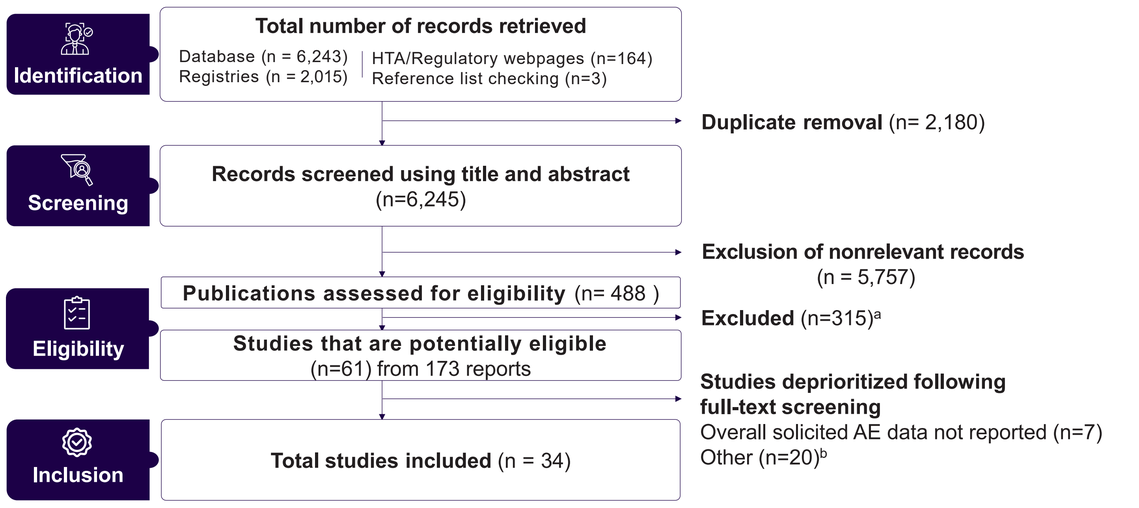
These heterogeneous trial data establish the foundational framework for an ongoing network meta-analysis that isolates and compares relative reactogenicity profiles across different severity grades, AE site and prior immune status

## RESULTS

### Study Selection

- Out of 6,245 screened records, 34 RCTs (17 placebo-controlled; 17 active comparator trials) were eligible (**Figure 1**)

**Figure 1. PRISMA Flowchart for study identification process**




[a]Excluded due to ineligible study design, outcomes, intervention, comparator, or patient population; clinical trials without results; ongoing trials without results; ongoing studies; preprints; and systematic reviews
[b]Studies with Non-COVID comparators, strain comparisons, terminated vaccine ARCT-021, or no reactogenicity data (n=20)

### Study Characteristics

**6,245**
Records screened

**34**
RCTs eligible[5-38](17 placebo controlled; 17 active comparator)

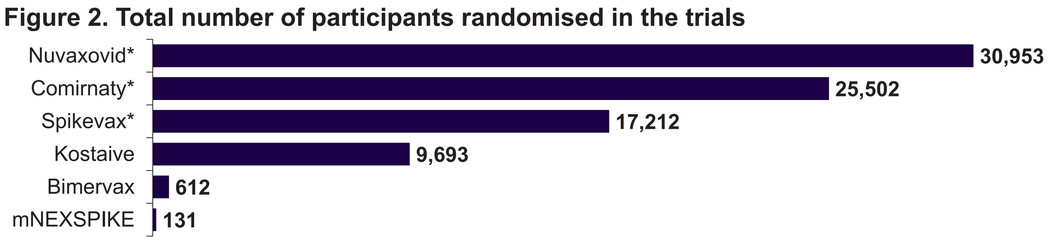
**The most common trial phase**

Phase 4 (n=7)
**Overall**

Phase 1/2 (n=4)
**Placebo-controlled trials**

Phase 4 (n=5)
**Active-comparator trials**

**Figure 2. Total number of participants randomised in the trials**




Note: Placebo arms are excluded
*Does not include patients primed with BNT162b2 in PICOBOO as the number randomised is unclear

### Population Characteristics

**Sex**
40–60% male in 71% of trials

**Ethnicity**
Predominantly White (44%) and Asian (29%)

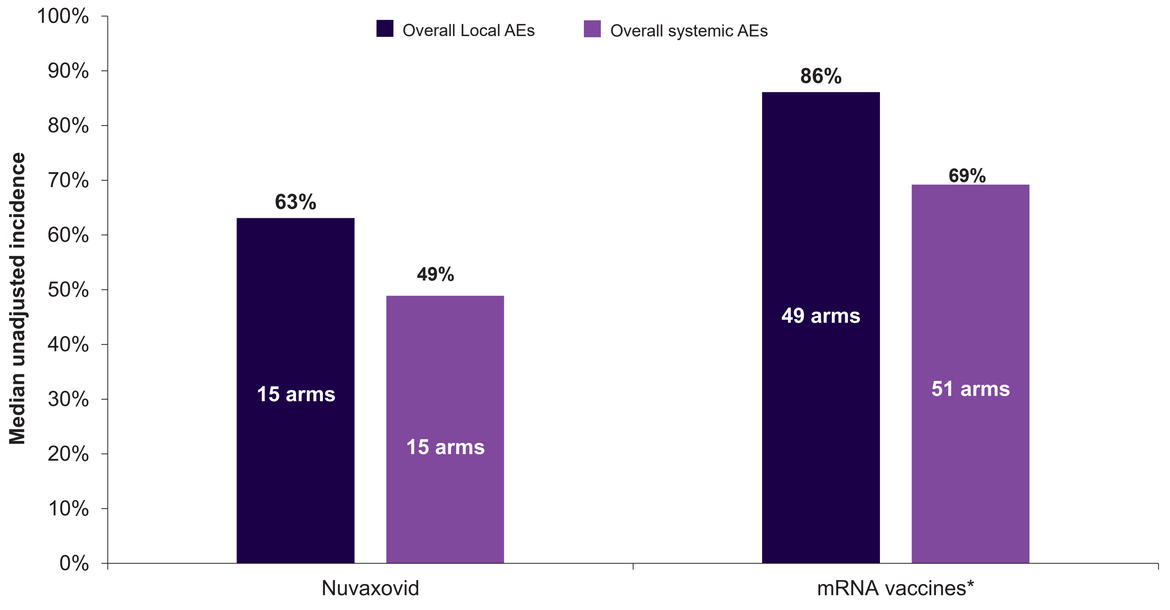
**Age**
Mean age ranges ≈30–70 years

**Chronic conditions**
0% to 92% across arms

### Reactogenicity

- The number of trials reporting some level of granularity concerning solicited AE by grading and site, to different heterogeneous levels, was found as follow:
  - **Placebo-controlled trials**: Nuvaxovid (n=4), Spikevax (n=2), Comirnaty (n=1), Kostaive (n=1)
  - **Active comparator trials**: Nuvaxovid vs Comirnaty (n=2), Nuvaxovid vs Spikevax (n=2), Comirnaty vs Spikevax (n=4), Comirnaty vs Kostaive (n=2), Bimervax vs Comirnaty (n=1), and Spikevax vs mNEXSPIKE (n=1)
  - The median, unadjusted incidence of overall solicited AEs for mRNA vs Nuvaxovid arms was 69% vs 49% for systemic, and 86% vs 63% for local AEs **(Figure 3)**

**Figure 3. Incidence of Solicited Adverse Events: Nuvaxovid vs mRNA* Vaccines**




Note: By the time of the review, the Phase 4 study COMPARE (NCT07051031), comparing Nuvaxovid vs mNEXSPIKE was still ongoing, and therefore not captured in the SLR *Includes Comirnaty, Spikevax and mNEXSPIKE

## STRENGTH

To the best of our knowledge, this is the first study to provide a comprehensive body of evidence on granular reactogenicity profiles of Nuvaxovid and other commercialised COVID-19 vaccines, including the newest post-market authorisation studies

## LIMITATIONS

- This SLR presents descriptive, unadjusted median incidence rates across heterogeneous trials; direct comparative conclusions will be addressed in the planned network meta-analysis
- Heterogeneity in AE reporting standards and grading scales across included studies may have affected the comparability of reactogenicity data; moreover, predominance of White/Asian populations may have limited applicability to broader populations

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**DISCLOSURES:** JBH, CES and CV are full-time employees of Sanofi and may own shares and/or stock options in the company. MG is a consultant to Novavax and may own shares and/or stock options in the company. AS, PM, KR, JWEM, NH, and RM are employees of the York Health Economics Consortium and received consulting fees from Sanofi for the development of this systematic literature review

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