Effectiveness and Reactogenicity of Protein Subunit COVID-19 Vaccine: Findings From BEEHIVE and SHIELD Studies§

KEY TAKEAWAYS

Real-world evidence showed that protein subunit COVID-19 vaccine demonstrated lower reactogenicity compared to Pfizer-BioNTech mRNA COVID-19 vaccine during the first week post-vaccination

BACKGROUND

- The COVID-19 pandemic prompted the development of multiple vaccine platforms, with both protein-based and mRNA vaccines demonstrating ≥90% efficacy against severe COVID-19[1]
- Vaccine reactogenicity, defined as local and systemic reactions, is a leading factor for COVID-19 vaccine hesitancy in adults[2]
- Comparative reactogenicity data has been limited among approved COVID-19 vaccines[3]

Two studies were conducted, which assessed effectiveness and reactogenicity of approved COVID-19 vaccines: *BEEHIVE* (**B**ooster **E**pidemiological **E**valuation of **H**ealth, **I**llness, and **V**accine **E**fficacy [NCT06065176]), a randomized controlled trial in the general adult population, and *SHIELD* (**S**tudy of **H**ealthcare Workers and First Responders **I**nvestigating **E**ffects Systemic and **L**ocal of COVID-19 Vaccine **D**oses [NCT06633835]), a real-world interventional study among healthcare workers and first responders[4-7]

OBJECTIVES

BEEHIVE: To compare vaccine effectiveness of 2023-2024 protein subunit (NVX) or mRNA (PFZ) booster COVID-19 vaccines against symptomatic SARS-CoV-2 infection vs non-boosted individuals, and to examine relative vaccine efficacy between vaccine types[4,5]

To report on local and systemic reactogenicity in the first week after receipt of a vaccine[4,5]

SHIELD: To compare the percentage of participants experiencing systemic reactogenicity symptoms (fever, fatigue, malaise, muscle pain, joint pain, nausea/vomiting, headache) within 2- and 7-days following a single dose of an updated 2024-2025 protein subunit (NVX) or mRNA (PFZ) COVID-19 vaccines and examine its disrupting impact on daily life[6,7]

STUDY METHODS

Study design

BEEHIVE[4,5]: Double-blinded, partially randomized, controlled trial

SHIELD[6,7]: Prospective, interventional, open-label, real-world study

Study duration

BEEHIVE[4,5]: Nov 2023 - Aug 2024

SHIELD[6,7]: Sep 2024 – Dec 2024

Vaccines

BEEHIVE[4,5]: 2023-2024 protein subunit (NVX, XBB.1.5) and mRNA (PFZ, XBB.1.5)

SHIELD[6,7]: 2024-2025 protein subunit (NVX, JN.1) and mRNA (PFZ, KP.2)

Inclusion criteria

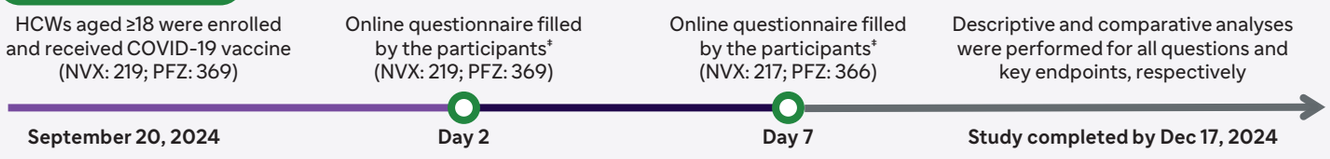
BEEHIVE[4,5]:
- Age ≥18 years
- Previously received ≥2 doses of mRNA COVID-19 vaccine

SHIELD[6,7]:
- Age ≥18 years
- HCW/FR† with direct patient contact
- Previous COVID-19 vaccination within 4 years

BEEHIVE[4,5]

- Post-vaccination surveys on Days 1, 2, and 6 to capture solicited adverse events
- RAT to detect a SARS-CoV-2 infection every week for 24 weeks

SHIELD[6,7]



OUTCOMES

BEEHIVE[4,5]

Primary Endpoint
- Time to onset of a COVID-19 infection (confirmed by RAT)

Additional Outcomes
- Local and systemic reactogenicity (Days 1, 2, and 6)
- Relative vaccine efficacy
- Safety of NVX and PFZ

SHIELD[6,7]

Primary Endpoint
- Percentage of participants experiencing systemic reactogenicity symptoms within 2 days post-vaccination

Secondary Endpoints
- Percentage of participants who experienced any local reactogenicity symptoms
- Participant's mean number of any systemic reactogenicity symptoms
- Percentage of participants reporting systemic or local reactogenicity of grade 2 or higher, and
- Disruptions in participants' work/social/family life, all within 2-days post-vaccination

†HCWs and FRs were defined as anyone having direct face-to-face contact (defined as being within 3 feet, or about an arm's length) with patients as part of their full- or part-time (≥20h per week) job responsibilities
‡Participants self-reported on 11 vaccine-related reactogenicity symptoms and functional impairment using a 5-item modified Sheehan Disability Scale

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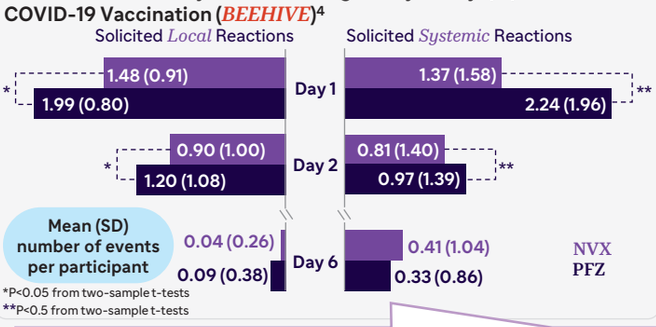
RESULTS

Vaccine Effectiveness (*BEEHIVE*)[5]

- The boosted group vaccinated with either NVX or PFZ vaccine demonstrated a ***lower SARS-CoV-2 infection event rate*** vs the non-boosted group; adjusted ***VE over 24 weeks***: ***43.5%*** (95% CI: 18.3–61.0%)
- The study was unable to assess with precision non-inferiority between NVX and PFZ due to lower-than-expected enrollment number and attack rate, as well as higher assumed relative efficacy

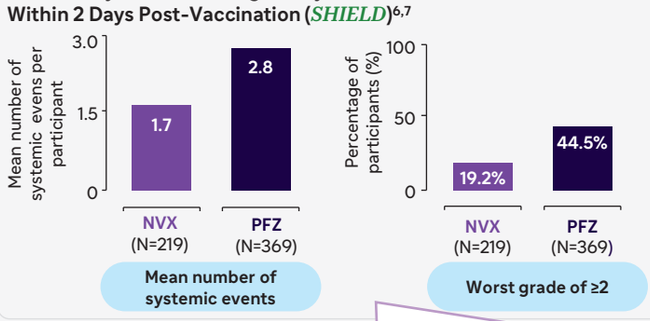
Reactogenicity

Solicited Local and Systemic Reactogenicity at Day 1, 2, and 6 Since COVID-19 Vaccination (*BEEHIVE*)[4]



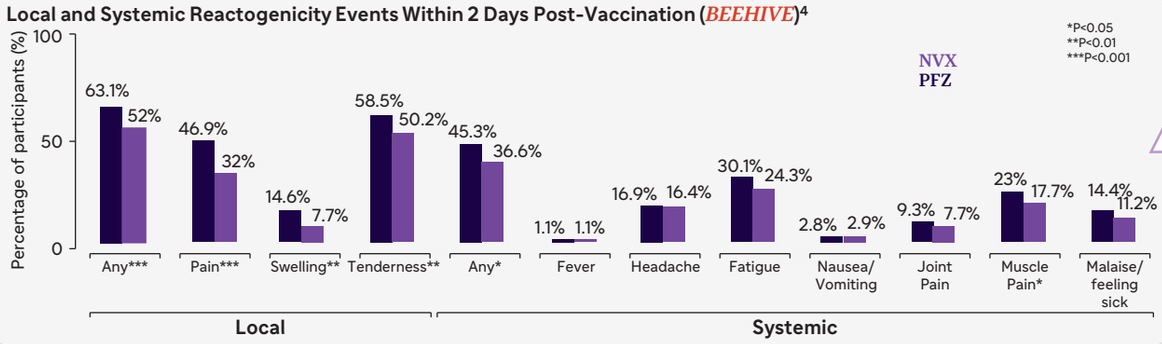
NVX booster recipients reported ***fewer local and systemic reactions than with PFZ booster*** in first two days post-vaccination

Solicited Systemic Reactogenicity Events After NVX or PFZ Vaccines Within 2 Days Post-Vaccination (*SHIELD*)[6,7]



Two-days post-vaccination, fewer NVX recipients reported at least one systemic (***73.6%*** vs ***87.5%***; OR: 0.40) and at least one local (***82.4%*** vs ***98.0%***; OR: 0.10) reactogenicity symptom than PFZ recipients

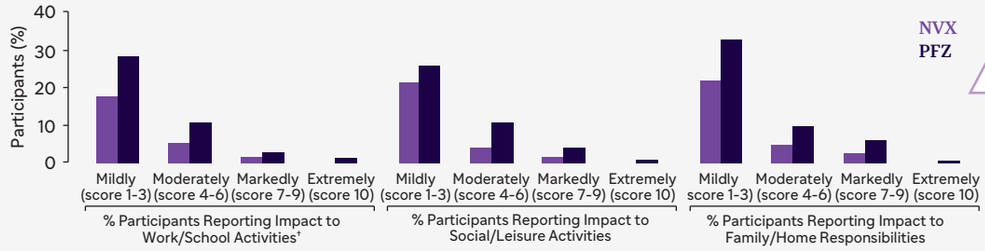
Local and Systemic Reactogenicity Events Within 2 Days Post-Vaccination (*BEEHIVE*)[4]



Local and systemic reactions were ***lower with NVX vaccine than with PFZ vaccine*** on Day 2

Daily Activity Disruption (*SHIELD*)[6,7]

Disruption of Activities Caused by Symptoms Within the First 2 Days Post-Vaccination



†21.5% of NVX and 17.9% of PFZ vaccine recipients did not have work/school scheduled during the days following vaccination and were not included in these results

- NVX vaccine recipients reported less disruption than PFZ vaccine recipients in work/school activities (***39.3%*** vs ***54.3%***), social/leisure activities (***57.5%*** vs ***72.6%***), and family/home responsibilities (***51.2%*** vs ***71.2%***)
- NVX vaccine recipients lost fewer work hours (***0.7*** vs ***1.4 h***; ***50% reduction***) and productive hours (***0.8*** vs ***2.4 h***; ***66% reduction***) compared to PFZ

Safety (*BEEHIVE*)[5]

- No SAE, myocarditis, pericarditis, or death related to either NVX or PFZ vaccines

LIMITATIONS

BEEHIVE[4,5] Single site, 96% Caucasian; majority <60 years; reactogenicity data from patient surveys, which could introduce bias; open-label placebo group

SHIELD[6,7] Observational, real-world study; single site; participants who agree to participate may not be representative of US population

CONCLUSIONS

Protein subunit (NVX) COVID-19 vaccine demonstrated ***lower systemic and local reactogenicity*** than mRNA (PFZ) COVID-19 vaccine across both healthcare workers and general adult populations

The reduced reactogenicity translated into decreases in work disruption, productivity loss, and functional impairment in daily activities

These findings provide valuable insights for policymakers, clinicians, and healthcare systems regarding vaccine selection, particularly for essential workers where ***lower reactogenicity may improve vaccine acceptance***

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; FR, first responder; HCW, healthcare worker; mRNA, messenger ribonucleic acid; NVX, Nuvaxovid; OR, odds ratio; PFZ, Pfizer-BioNTech; RAT, rapid antigen testing; RCTs, randomized controlled trials; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; USA, United States of America; VE, vaccine effectiveness

References: 1. Dunkle LM, *et al.* N Engl J Med. 2022;386(6):531–543; **2. Yoon SK,** *et al.* Poster P1657 presented at: IDWeek; October 19 -22, 2025; Atlanta, USA. https://pmc.ncbi.nlm.nih.gov/articles/PMC12791959/pdf/ofaf695.1832.pdf; **3. Marchese AM,** *et al.* J Infect Dis. 2024;230(2):e496–e502; **4. Yoon SK,** *et al.* Difference in reactogenicity events between mRNA and Protein-subunit Vaccines: Results from the Booster Epidemiological Evaluation of Health, Illness, and Vaccine Efficacy (BEEHIVE) Study, a U.S. randomized trial of 2023 –2024 COVID-19 vaccines (XBB.1.5). Poster P1657 presented at: IDWeek; October 19-22, 2025; Atlanta, USA; **5. Yoon SK,** *et al.* Preliminary Safety and Effectiveness Estimate of 2023–2024 COVID-19 vaccines (XBB.1.5) in Preventing Symptomatic Infections in U.S. adults. Poster P0404 presented at: 35th Congress of European Society of Clinical Microbiology and Infectious Diseases (ESCMID); April 11–15, 2025; Vienna, Austria; **6. Yoon SK,** *et al.* doi: https://doi.org/10.1101/2025.08.25.25334392; **7. Rousculp MD,** *et al.* Impact of Reactogenicity of the 2024-2025 COVID-19 Vaccines on Health Care Workers and First Responders in the United States. Poster P5009 presented at: 35th Congress of European Society of Clinical Microbiology and Infectious Diseases (ESCMID); April 11–15, 2025; Vienna, Austria

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