GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

A Single Shot for Two Threats: Combined mRNA Vaccine Shows Promise for Older Adults

Mental Roadblocks in Recovery:

Factors Associated with Persistent Symptoms After a Concussion

Probiotics Shorten Fever Duration Among Children with URIs

FPIN
Family Physicians Inquiries Network

Volume 6 Issue 15

A Single Shot for Two Threats: Combined mRNA Vaccine Shows Promise for Older Adults

Immunogenicity and Safety of Influenza and COVID-19 Multicomponent Vaccine in Adults ≥50 Years: A Randomized Clinical Trial

Rudman Spergel AK, Wu I, Deng W, et al. Immunogenicity and Safety of Influenza and COVID-19 Multicomponent Vaccine in Adults ≥50 Years: A Randomized Clinical Trial. JAMA. 2025;333(22):1977-1987. doi:10.1001/jama.2025.5646

KEY TAKEAWAY: A single dose of the investigational mRNA-1083 vaccine produces noninferior immunogenicity at day 29 compared with co-administered standard influenza and COVID-19 vaccines in adults ≥50 years old.

STUDY DESIGN: Phase three, randomized, observer-blind, active-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Influenza and COVID-19 cause significant morbidity and mortality in adults >50 years old, yet vaccine uptake remains suboptimal. Coadministration of vaccines is recommended but requires two injections. This study evaluated an investigational single-injection mRNA vaccine that combines components of both influenza and SARS-CoV-2 (mRNA-1083) for immunogenicity and safety.

PATIENTS: Adults ≥50 years old

INTERVENTION: Single intramuscular dose of the investigational mRNA-1,083 vaccine + placebo

CONTROL: Licensed seasonal influenza vaccine and licensed COVID-19 vaccine

PRIMARY OUTCOME: Immunogenicity at day 29

Secondary Outcome: Safety, reactogenicity

METHODS (BRIEF DESCRIPTION):

- A multicenter trial conducted at 146 US sites
- Adults ≥50 years old in good health or with stable chronic medical conditions were included in the study.
- Participants stratified by age groups (50–64 years and ≥65 years) and randomized 1:1 to the following:
  - Single intramuscular dose of the investigational mRNA-1083 vaccine (influenza + SARS-CoV-2) + placebo
  - Licensed seasonal influenza vaccine (SD-IIV4 for ages 50–64 years old; HD-IIV4 for ages ≥65 years old) and licensed COVID-19 vaccine (mRNA-1273)
- The primary immunogenicity outcome was noninferiority of mRNA-1083 vs comparator vaccines for influenza and SARS-CoV-2 strains at day 29 post-vaccination.
- Immunogenicity was assessed separately for four influenza strains (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) and for SARS-CoV-2.
- Noninferiority was defined as the lower bound of the 98% confidence interval for the geometric mean ratio (GMR) >0.67 and for the sero-response rate difference > –10%.
- Antibody levels were measured by hemagglutination inhibition assay (influenza) and pseudo-virus neutralization assay (SARS-CoV-2).
- Safety was assessed by solicited local and systemic adverse reactions for seven days and unsolicited adverse events for 28 days.

INTERVENTION (# IN THE GROUP):

- Adults 50–64 years old and received mRNA-1083: 2,009
- Adults ≥65 years old and received mRNA-1083: 2,025

COMPARISON (# IN THE GROUP):

- Adults 50–64 years old and received SD-IIV4 + mRNA-1273: 2,015
- Adults ≥65 years old and received HD-IIV4 + mRNA-1273: 2,012

FOLLOW-UP PERIOD: Primary immunogenicity and safety outcomes were assessed at 29 days. Total safety follow-up was planned for 181 days, however this interim analysis reports data through 91 days.

RESULTS:

Primary Outcome –

- The mRNA-1083 vaccine produced immune responses that were noninferior to licensed influenza and COVID-19 vaccines for all four influenza strains and SARS-CoV-2. For each antigen, the GMR comparisons met noninferiority criteria, with the lower bound of the 98% CI exceeding the prespecified margin of 0.67:
  - A/H1N1 (GMR 1.1; 97.5% CI, 1.1–1.2)
  - A/H3N2 (GMR 1.1; 97.5% CI, 1.0–1.2)

- B/Victoria (GMR 1.2; 97.5% CI, 1.1–1.3)
- B/Yamagata (GMR 1.0; 97.5% CI, 0.94–1.1)
- SARS-CoV-2 (XBB.1.5) (GMR 1.3; 98% CI, 1.2–1.4)

Secondary Outcome –

- In adults 50–64 years old, the mRNA-1083 vaccine generated superior immune responses to all four influenza strains and SARS-CoV-2 compared with licensed vaccines:
  - A/H1N1 (GMR 1.2; 97.5% CI, 1.2–1.3)
  - A/H3N2 (GMR 1.2; 97.5% CI, 1.1–1.3)
  - B/Victoria (GMR 1.3; 97.5% CI, 1.2–1.4)
  - B/Yamagata (GMR 1.1; 97.5% CI, 1.1–1.2)
  - SARS-CoV-2 (GMR 1.4; 97.5% CI, 1.3–1.5)
- In adults ≥65 years old, mRNA-1083 produced superior immune responses for three influenza strains and SARS-CoV-2:
  - A/H1N1 (GMR 1.1; 97.5% CI, 1.0–1.2)
  - A/H3N2 (GMR 1.1; 97.5% CI, 1.1–1.2)
  - B/Victoria (GMR 1.2; 97.5% CI, 1.1–1.3)
  - SARS-CoV-2 (GMR 1.3; 97.5% CI, 1.2–1.4)
- In adults ≥65 years, immune responses to B/Yamagata did not meet superiority criteria.
- Local and systemic reactions were more frequent with mRNA-1083 but were mostly mild or moderate and short-lived.
- Rates of unsolicited adverse events, serious adverse events, and adverse events of special interest were low and similar between the groups.

LIMITATIONS:

- The trial was funded by the manufacturer of the investigational vaccine (Moderna), creating a potential conflict of interest.
- Interim analysis only; full six-month outcomes pending.
- The study was conducted only in the United States, which may limit generalizability to other populations.
- Immunogenicity used as a surrogate marker instead of vaccine efficacy (prevention of clinical disease).

Santosh Raja, DO
St. Louis University Southwest Illinois FMRP
O'Fallon, IL

The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Air Force, Defense Health Agency, Department of Defense, or the U.S. Government.

Mental Roadblocks in Recovery: Factors Associated with Persistent Symptoms After a Concussion

Factors Associated with Persisting Symptoms After Concussion in Adults with Mild TBI: A Systematic Review and Meta-Analysis

McIntosh SJ, Vergeer MH, Galarneau JM, Eliason PH, Debert CT. Factors Associated With Persisting Symptoms After Concussion in Adults With Mild TBI: A Systematic Review and Meta-Analysis. *JAMA Netw Open*. 2025;8(6):e2516619. Published 2025 Jun 2. doi:10.1001/jamanetworkopen.2025.16619

KEY TAKEAWAY: Pre-injury mental health conditions and a higher occurrence of post-injury symptoms are the factors most consistently associated with persistent symptoms after a concussion (PSAC).

STUDY DESIGN: Systematic review and meta-analysis of 15 prospective cohort and prospective case-control studies (N=592,406)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to low to moderate quality of evidence and significant heterogeneity)

BRIEF BACKGROUND INFORMATION: Most people recover from a concussion within four weeks, but up to 30% may experience PSAC. Understanding the factors that predict PSAC is crucial for identifying at-risk patients and guiding clinical management.

PATIENTS: Adults with a concussion

INTERVENTION: Presence of patient-specific risk factors

CONTROL: Absence of risk factors

PRIMARY OUTCOME: Risk of PSAC

METHODS (BRIEF DESCRIPTION):

- Researchers searched multiple databases for studies published from 1970–2024 using the search terms "mild traumatic brain injury (mTBI), concussion, prognostic variables, predictors, and PSAC."
- Included studies (10 prospective cohorts, 3 prospective case-control, 2 retrospective medical record review, 1 randomized control trial, 1 prospective cross-validation) investigated the association between any patient-specific risk factors and PSAC that occurred within one month and persisted for >1 month after the concussion.
- Studies were excluded if they examined symptom severity, posttraumatic stress disorder (PTSD), or activity levels.
- Patients had an average participant age of 29 years old (42% female, 58% male) and the most common study setting being the Emergency Department (11 of 15 studies).
- Patient-specific risk factors included difficulty concentrating, amnesia or loss of consciousness, history of anxiety/depression or sleep disorders, and mechanism of injury.
- PSAC was most commonly defined as ≥1 symptom on the Post-Concussion Symptom Checklist (PCSS) or Rivermead Post-Concussion Symptoms Questionnaire (RPQ) taken at one, three, or six months after the concussion.
    - Scores on the PCSS range from 0–132, with higher scores indicating greater symptom severity.
    - Scores on the RPQ range from 0–64, with higher scores indicating more severe symptoms.
- The quality of evidence for each study was performed by two independent reviewers, while bias risk was assessed using the Quality in Prognostic Studies tool.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Up to six months

RESULTS:

Primary Outcome –

- At one month, the following patient-specific factors were associated with the greatest risk of developing PSAC:
    - Difficulty concentrating (7 studies, n=4,121; adjusted odds ratio [aOR] 3.1; 95% CI, 1.4–6.8)
    - History of anxiety and/or depression (7 studies, n=4,121; aOR 2.6; 95% CI, 1.3–5.0)
    - Motor vehicle collisions (7 studies, n=4,121; aOR 2.0; 95% CI, 1.3–3.3)
- At three months, the following patient-specific factors were associated with the greatest risk of developing PSAC:
    - History of anxiety and/or depression or sleep disorders (7 studies, n=793; aOR 2.9; 95% CI, 1.4–6.1)
    - Female sex (7 studies, n=793; aOR 2.1; 95% CI, 1.3–3.6)

    - Physical symptoms, including headache, dizziness, light, and noise sensitivity (7 studies, n=793; aOR 2.0; 95% CI, 1.4–2.9)
- At six months, the following patient-specific factors were associated with the greatest risk of developing PSAC:
    - Difficulty concentrating (3 studies, n=587,237; aOR 27; 95% CI, 3.4–210)
    - Emotional symptoms (3 studies, n=587,237; aOR 1.6; 95% CI, 1.2–2.2)
    - History of anxiety/depression or sleep disorders (3 studies, n=587,237; aOR 1.5; 95% CI, 1.01–2.4)
- The following patient-specific factors were associated with the greatest risk of developing PSAC across all time points:
    - Difficulty concentrating (15 studies, n=592,406; aOR 3.4; 95% CI, 1.9–6.4)
    - History of anxiety and/or depression or sleep disorders (15 studies, n=592,406; aOR 2.5; 95% CI, 1.6–3.8)
    - Clinical symptoms of amnesia and loss of consciousness (15 studies, n=592,406; aOR 1.9; 95% CI, 1.3–2.8)

LIMITATIONS:

- The quality of evidence included in the meta-analyses was generally low to moderate.
- There was significant heterogeneity among the studies, particularly regarding the definitions used for concussion and persistent symptoms.
- 40% of the included studies had a high risk of bias.
- Study participants were predominantly male (58%).

Jacob Hathaway, DO
Naval Medical Center Camp Lejeune FMRP
Camp Lejeune, NC

The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Navy, Defense Health Agency, Department of Defense, or the U.S. Government.

Probiotics Shorten Fever Duration Among Children with URIs

Probiotics and Fever Duration in Children with Upper Respiratory Tract Infections. A Randomized Clinical Trial
Bettocchi S, Comotti A, Elli M, et al. Probiotics and Fever Duration in Children With Upper Respiratory Tract Infections: A Randomized Clinical Trial. *JAMA Netw Open*. 2025;8(3):e250669. Published 2025 Mar 3. doi:10.1001/jamanetworkopen.2025.0669

KEY TAKEAWAY: Probiotics may shorten fever duration in children with upper respiratory tract infection (URI) by two days.

STUDY DESIGN: Triple-blind, single site randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high dropout rate and small sample size)

BRIEF BACKGROUND INFORMATION: URI is very common in the first five years of life. URI resulting in fever can cause significant impact on child's well-being including missing physical and scholastic activities. Studies have shown that probiotics might be associated with reduced occurrence of URIs and symptom severity in children. This study investigated the effects of probiotics in reducing duration of fever in children with URIs.

PATIENTS: Toddlers and preschoolers with URI

INTERVENTION: Daily probiotic

CONTROL: Placebo

PRIMARY OUTCOME: Reduction in fever duration

Secondary Outcome: Development of diarrhea

METHODS (BRIEF DESCRIPTION):

- Investigators conducted a randomized, triple-blinded trial at a single pediatric emergency department (ED).
- Patients were 28 days to four years old from an Italian pediatric emergency department in Milan that presented with fever.
- Patients with diarrhea, history of probiotic use in the last two weeks, chronic autoimmune disease on immunosuppressing therapy and need for hospitalization were excluded.
- The mean age was 1.3 years old, 54% were males, 79% identified as White, and 1–3 % had fever before admission.
- The treatment group received single daily dose 0.5 mL or 1.5 g probiotic mix by mouth (oily drops or stick) for 14 days.
- Probiotic sticks contained maltodextrin, *Bifidobacterium breve*, *Bifidobacterium lactis*, and *Lactobacillus rhomnosus*.
- Probiotic oily drops contained the same bacterial species, vegetal fats, medium-chained triglycerides, and monoglycerides and diglycerides of fatty acids.
- Comparison group received placebo stick (maltodextrin) or oily drops (medium-chain triglycerides, vegetal oil, monoglyceride and diglyceride fatty acids and maltodextrin like replacement) matching in appearance and color.
- Caregivers measured rectal temperature three times daily.
- Reduction in fever duration and adverse effects were measured via a telephone call at seven days.
- Investigators assessed for compliance, fever, and adverse effects.
- If a patient had a persistent fever, follow up calls continued every seven days.

INTERVENTION (# IN THE GROUP): 65

COMPARISON (# IN THE GROUP): 65

FOLLOW-UP PERIOD: Seven days

RESULTS:

Primary Outcome –

- Patients who received probiotics had fewer days of fever compared to placebo (3 vs 5 days, respectively; adjusted risk ratio [RR] 0.64; 95% CI, 0.51–0.80).

Secondary Outcome –

- Patients who received probiotics had similar events of diarrhea compared to placebo.

LIMITATIONS:

- The study did not identify specific infectious diseases.
- Diagnosis of upper respiratory tract was not standardized.
- The antibiotic prescriptions were not standardized.
- The trial setting was limited to one emergency department.

- Although fever was measured more important patient-oriented outcomes may be readmission, ED visits, or symptom assessment.
- The study had a 32% drop out rate.

Sofia Shabbir, MD
Alaska FMRP
Anchorage, AK