Review of “Efficacy and safety of mRNA-1273 SARS-CoV-2 vaccine”


One-minute summary

- The authors report interim findings of a phase-3 randomized, stratified, observer-blinded placebo-controlled trial to evaluate the efficacy and safety of the Moderna mRNA-1273 COVID-19 vaccine.
- The trial was conducted at 99 sites in the United States and included adults ≥ 18 years old with no known history of COVID-19, and with locations or circumstances that put them at an appreciable risk of COVID-19 infection and/or its complications. Participants were randomly assigned in a 1:1 ratio and stratified by age and COVID-19 complication risk criteria to receive two doses of intramuscular vaccine or placebo 28 days apart.
- The primary efficacy endpoint was prevention of symptomatic COVID-19 confirmed by RT-PCR on nasopharyngeal or nasal swab, saliva, or respiratory sample if hospitalized; occurring ≥ 14 days after the second dose of vaccine or placebo. The secondary efficacy endpoint was prevention of severe COVID-19.
- Overall vaccine efficacy against confirmed symptomatic COVID-19 after two doses was 94.1% (95% confidence interval, 89.3%–96.8%; P<.001), with a median study follow-up time of 64 days (range 0-92 days) in 28,207 trial participants (per protocol).
- Vaccine efficacy was consistent across racial backgrounds, sex, age groups and presence of risk factors for severe COVID-19.
  - 18–64 years of age, not at risk for severe COVID-19 (n = 16,799): 95.9% (90.0%–98.3%)
  - 18–64 years of age, at risk for severe COVID-19 (n = 4,273): 94.4% (76.9%–98.7%)
  - ≥65 years of age (n = 7,135): 86.4% (61.4%–95.2%)
  - all age groups at risk for severe COVID-19 (n = 6,373): 90.9% (74.7%–96.7%)
  - against severe COVID-19: 100% (with all 30 cases occurring in the placebo group)
- The incidence of COVID-19 in the vaccine and placebo groups began to diverge at 14 days after the first dose.
- Solicited local and systemic reactions were more common in vaccine recipients, than placebo recipients and more common among participants 18–64 years of age, than those ≥ 65 years of age in the 7 days following vaccination.
  - Most local reactions (e.g., pain, erythema, swelling, lymphadenopathy) were mild to moderate.
• Systemic reactions (e.g. fatigue, headache, myalgia, chills, arthralgia, nausea or vomiting, fever) occurred in 54.9% vs. 42.2% after the first dose and 79.4% vs. 36.5% after the second dose in the vaccine vs. placebo groups. The duration of the systemic adverse events after the first and second doses is 2.6 and 3.1 days (mean), respectively; reaction severity increased after the second dose.

• **Serious adverse events were rare in both vaccine and placebo groups (0.6% in both).** Treatment-related severe adverse events were more common in vaccine than placebo recipients (0.5% vs 0.2%) and independent of participants’ age. There were no treatment-related deaths reported in any participants during the 28 days after any injection. However, the authors called for close monitoring of the slight excess of Bell’s palsy that occurred in 3 participants in the vaccine group compared to 1 in the placebo group.

**Additional information**

• The mRNA-1273 vaccine is a lipid-encapsulated mRNA vaccine encoding a perfusion stabilized spike protein of SARS-CoV-2. Each dose contains 100 µg of mRNA-1273.

• A total of 236 participants developed symptomatic COVID-19 starting 14 days after the first dose (11 in vaccine group and 225 in placebo group), corresponding to a **vaccine efficacy of 95.2% (95% CI: 91.2%–97.4%) after the first dose.** However, the trial was not designed to determine efficacy with one dose of vaccine, as 96.4% of the 30,418 randomized participants received two doses.

• Of the 28,207 participants included in the per-protocol efficacy analysis:
  • Median follow-up time = 64 days (range: 0–97 days) after the second dose.
  • Male: 52.6%
  • Mean age = 51.6 years (range: 18–95 years)
    • 18–64 years and not at risk for severe COVID-19: 58.1%
    • 18–64 years and at risk for severe COVID-19: 16.6%
    • ≥ 65 years: 25.3%
  • Racial or ethnic background as reported by participants:
    • white: 79.5%
    • black or African American: 9.7%
    • Asian: 4.6%
    • multiracial or other: 2.1% each
    • American Indian or Alaska Native: 0.8%
    • Native Hawaiian or other Pacific Islander: 0.2%
  • Mean body-mass index (± standard deviation): 29.3 ± 6.7
  • Risk factors for severe COVID-19 infection:
    • diabetes (type 1, type 2, gestational): 9.6%
    • body-mass index ≥ 40: 6.7%
    • significant cardiac disease (e.g., heart failure, congenital coronary artery disease, cardiomyopathies, or pulmonary hypertension): 5.0%
    • chronic lung disease (e.g., emphysema, chronic bronchitis, idiopathic pulmonary fibrosis, cystic fibrosis, or moderate-to-severe asthma): 4.8%
    • liver disease: 0.7%
    • HIV infection: 0.6%

• Severe COVID-19 was defined as the occurrence of COVID-19 as per the primary endpoint AND any of the following:
• Clinical signs indicative of severe systemic illness, including respiratory rate ≥ 30 per minute, heart rate ≥ 125 beat per minute, oxygen saturation ≤ 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mmHg.
• Respiratory failure or acute respiratory distress syndrome.
• Clinically significant acute renal, hepatic or neurologic dysfunction.
• Admission to an intensive care unit or death.

• The authors noted the following limitations in the trial design:
  • It was not intended to evaluate the efficacy of a single dose.
  • Only the short term safety and efficacy of the vaccine was studied.
  • The data were insufficient to assess efficacy against asymptomatic infection or viral transmission.
  • The trial was conducted in the context of implemented nation-wide pandemic preventive measures such as public masking and social distancing.
  • Children, adolescents and pregnant women were excluded.
  • Efficacy evaluation in older adults, ethnic or racial minorities, and persons with prior COVID-19 was not possible due to small numbers.

PHO reviewer’s comments
• Additional studies are needed to assess (1) vaccine effectiveness against infection and/or severe outcomes in vulnerable groups (e.g., persons with social deprivation); (2) vaccine efficacy and safety data in populations excluded from clinical trials (e.g., children, adolescents, pregnant and breastfeeding women, individuals with autoimmune conditions and immunosuppressed states due to disease and/or treatment); (3) duration of vaccine protection; (4) vaccine effectiveness in preventing death, hospitalization, asymptomatic infection and reducing viral transmission.
• As COVID-19 infections with onset within 14 days after the second dose were excluded, vaccine efficacy prior to two weeks after the second dose was not assessed.
• Given the limited evidence on the duration of protection and effectiveness in preventing asymptomatic infection and reducing viral transmission, all layers of public health measures for preventing COVID-19 should still be practised regardless of immunization status until further data are available.

Citation

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