Safety and Immunogenicity of mRNA-1345, an mRNA-Based RSV Vaccine in Younger and Older Adult Cohorts: Results From a Phase 1, Randomized Clinical Trial

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BACKGROUND

- Human respiratory syncytial virus (RSV) is a negative-sense, single-stranded RNA virus, and is a major cause of respiratory infections worldwide[1,2]
  - RSV can infect people of all ages[3] and typically presents with mild symptoms[4,5]; however, it is a substantial cause of acute respiratory infection and lower respiratory tract disease in older adults and can cause severe disease and complications in infants, young children, older adults, and persons with chronic heart conditions or lung disease and weakened immune systems[1,4,5]
  - RSV is estimated to affect 64 million people of all ages and causes 160,000 deaths each year worldwide[6]
- The burden of RSV disease is high in older adults
  - In the United States, an estimated 177,000 hospitalizations and 14,000 deaths occur each year due to RSV in adults aged ≥65 years[7]
  - RSV also poses a significant economic burden in older adults and other at-risk populations, with the annual cost of RSV hospitalizations in US adults aged ≥50 years estimated to be more than USD $1 billion[8,9]
- Currently, there are no specific treatments for RSV and no vaccines are available to prevent RSV disease in any age group. Therefore, an effective RSV vaccine remains an unmet medical need
  - A lipid nanoparticle-encapsulated mRNA-based RSV vaccine (mRNA-1345) encoding the membrane-anchored RSV prefusion stabilized F (preF) glycoprotein is currently under clinical investigation

OBJECTIVE

- To assess and compare the safety and immunogenicity of mRNA-1345 in younger (aged 18-49 years) and older (aged 65-79 years) adults in a phase 1 study

METHODS

Study Design and Participants

- This phase 1, randomized, observer-blind, placebo-controlled, dose-escalation study enrolled healthy younger adults aged 18-49 years and healthy older adults aged 65-79 years (protocol number mRNA-1345-P101; ClinicalTrials.gov NCT04528719)
  - Interim data through 6 months for a subset of doses that were common between the younger and older adult cohorts are presented
- Healthy younger adults (n = 75) and older adults (n = 203) were randomly assigned to receive 1 dose of mRNA-1345 (50, 100, or 200 µg; n = 19-20 per group for younger adults and n = 47-48 per group for older adults) or placebo (n = 15-59 per group)

Safety and Immunogenicity Assessments

- Safety assessments included graded evaluation (modified version of the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) of the intensity of solicited local and systemic adverse events (AEs) within 7 days of receiving 1 dose of mRNA-1345 or placebo
- Blood samples for immunogenicity assessments (serum RSV-A and RSV-B neutralizing titers and preF and postfusion stabilized F [postF] binding antibody concentrations) were determined prior to injection (baseline), and at Months 1, 2, 3, and 6 in younger and older adults
  - Neutralizing and binding antibody responses were measured using qualified microneutralization assays and multiplex Luminex assays, respectively

Statistical Analyses

- The immunogenicity analyses were performed using the per-protocol set. Neutralizing titers and binding antibody concentrations at each time point are presented as geometric mean titer (GMT) and geometric mean concentration (GMC), respectively, with their corresponding 95% confidence intervals (CIs); geometric mean fold rise (GMFR; the ratio of postbaseline to baseline values) with 95% CI is also shown

RESULTS

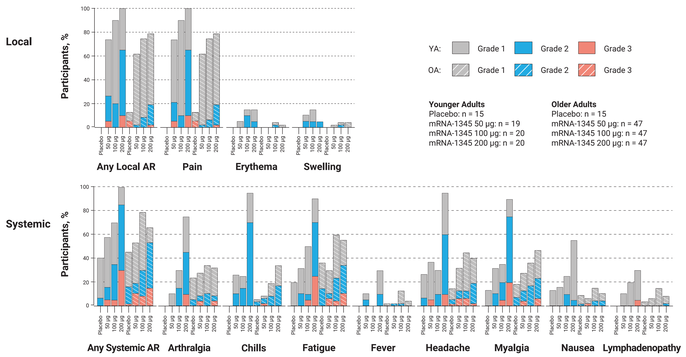
Demographics and Patient Disposition

Younger adults:	Older adults:
• All participants were between 18 and 49 years of age • 79% of participants identified as White, 19% identified as Black or African American, and 3% identified as multiple races • Among the 75 participants randomly assigned to the dose levels assessed here, 70 participants completed the study; 5 participants prematurely discontinued the study for reasons unrelated to an AE or death • Among the dose level cohorts assessed here, 74 younger adults (mRNA-1345 50 µg [n = 19], 100 µg [n = 20], 200 µg [n = 20]; placebo [n = 15]) received study injections	• All participants were between 65 and 79 years of age • 90% identified as White, 7% identified as Black or African American, 1.0% identified as Asian, and 1.0% identified as other • Among the 203 participants randomly assigned to the dose levels assessed here, 197 participants completed the study; 6 participants prematurely discontinued the study for reasons unrelated to death • Among the dose level cohorts assessed here, 202 older adults (mRNA-1345 50 µg [n = 47], 100 µg [n = 48], 200 µg [n = 48]; placebo, n = 59) received study injections

Safety

- mRNA-1345 was well tolerated at all dose levels in both younger and older adults, with lower severity and frequency of solicited adverse reactions observed in older adults vs younger adults at higher doses
- Local solicited adverse reactions (SARs) were reported by 73.7%-100% of younger adults and 61.7%-78.7% of older adults who received mRNA-1345 and 0% of younger adults and 12.7% of older adults who received placebo; the most frequent being injection site pain, which was mostly grade 1, and erythema and swelling being less frequent (**Figure 1A**)
  - Injection site pain
    - » Overall, 73.7%-100% of younger adults and 61.7%-78.7% of older adults who received mRNA-1345 and 0% of younger adults and 12.7% of older adults who received placebo reported injection site pain
- Systemic SARs were reported by 57.9%-100% of younger adults and 53.2%-78.7% of older adults who received mRNA-1345 and 40.0% of younger adults and 45.5% of older adults who received placebo (**Figure 1 B**)
  - The most commonly reported systemic SARs were:
    - » Headache in 30.0%-95.0% younger adults and 31.9%-44.7% older adults who received mRNA1345, and 26.7% younger adults and 14.5% older adults who received placebo
    - » Fatigue in 31.6%-90.0% younger adults and 29.8%-59.6% older adults who received mRNA1345, and 20.0% younger adults and 36.4% older adults who received placebo
    - » Myalgia in 31.6%-90.0% younger adults and 27.7%-46.8% older adults who received mRNA1345, and 13.3% younger adults and 18.2% older adults who received placebo
    - » Arthralgia in 10.5%-75.0% younger adults and 27.7%-34.0% older adults who received mRNA1345, and 0% younger adults and 23.6% older adults who received placebo
- A dose response relationship was observed for both local and systemic adverse reactions, where higher doses were associated with more severe adverse reactions
  - Generally, 5.3% of younger adults and 10.6% of older adults reported grade 3 SARs at the 50-µg mRNA-1345 dose and 30.0% of younger adults and 14.9% of older adults reported grade 3 SARs at the 200-µg dose of mRNA-1345

Figure 1. Solicited Local and Systemic Adverse Reactions in Younger and Older Adults Within 7 Days of Receiving 1 Dose

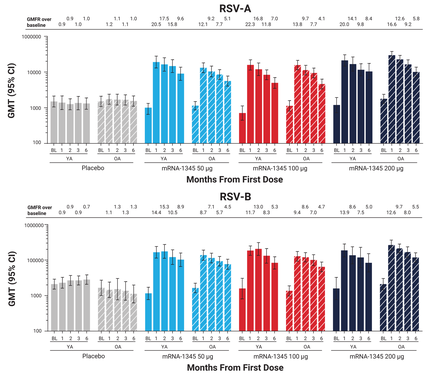


AR, adverse reaction; OA, older adults; YA, younger adults.

Immunogenicity

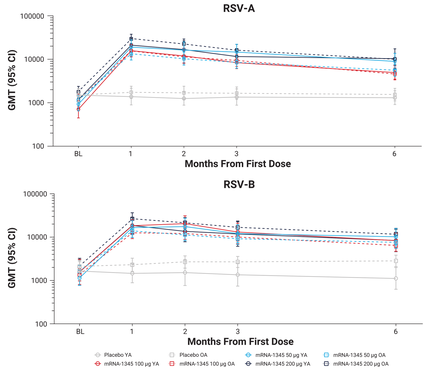
- All younger and older adults had neutralizing antibodies against RSV present at baseline, suggesting prior exposure to RSV (**Figure 2**)
  - Generally, older adults had numerically higher baseline GMTs (**Figure 2**)
  - One dose of mRNA-1345 substantially boosted antibody titers through Month 1 in younger (GMT: 15,776.1-21,093.0) and older (GMT: 12,702.7-29,435.8) adults
  - Comparable immunogenicity was observed across doses, suggesting there was a minimal dose response; of notable exception, at the 200-µg dose, older adults had higher GMTs than younger adults
- Generally, younger adults had higher neutralizing antibody GMFRs than older adults 1 month after the first injection (**Figure 2**)
  - At the mRNA-1345 50-µg dose level, GMFRs were 14.4-20.5 for younger adults and 8.7-12.1 for older adults
  - At the mRNA-1345 100-µg dose level, GMFRs were 11.7-22.3 for younger adults and 9.4-13.8 for older adults
  - At the mRNA-1345 200-µg dose level, GMFRs were 13.9-20.0 for younger adults and 12.6-16.6 for older adults
- Peak antibody titers slightly declined through Month 6, but remained substantially over baseline (**Figure 2**), with comparable rate of decline in titers in both younger and older adults (**Figure 3**)

Figure 2. Serum RSV-A and RSV-B Neutralizing Antibody Titers in Younger and Older Adults



BL, baseline; CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titer; OA, older adults; RSV, respiratory syncytial virus; YA, younger adults.

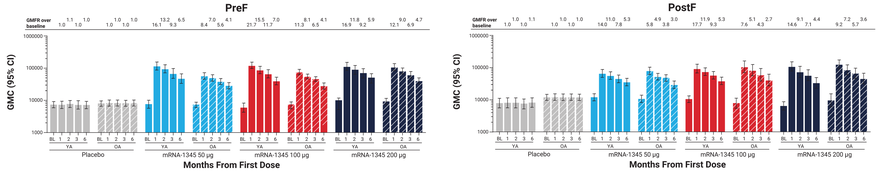
Figure 3. Serum RSV-A and RSV-B Neutralizing Antibody Kinetics in Younger and Older Adults



BL, baseline; CI, confidence interval; GMT, geometric mean titer; OA, older adults; RSV, respiratory syncytial virus; YA, younger adults.

- Month 1 preF binding antibody GMFRs were 16.1-21.7 and 8.4-12.1 for younger and older adults, respectively. Month 6 preF binding antibody GMFRs were 5.9-7.0 and 4.1-4.7 for younger and older adults, respectively (**Figure 4**)
- Month 1 postF GMFRs were 14.0-17.7 and 5.8-9.2 for younger and older adults, respectively. Month 6 postF GMFRs were 4.4-5.3 and 2.7-3.6 for younger and older adults, respectively (**Figure 4**)
- Peak binding antibody concentrations (preF and postF) slightly declined through Month 6 but remained substantially over baseline (**Figure 4**), with comparable decline in both younger and older adults
- The binding antibody response for younger and older adults was preF biased

Figure 4. Serum PreF and PostF Binding Antibody Concentrations in Younger and Older Adults



BL, baseline; CI, confidence interval; GMC, geometric mean concentration; GMFR, geometric mean fold rise; OA, older adults; postF, postfusion stabilized F; preF, prefusion stabilized F; YA, younger adults.

CONCLUSIONS

- Phase 1 data showed that mRNA-1345 is generally well tolerated in younger and older adults
  - In younger adults, more frequent and severe solicited adverse reactions were reported at the 200-µg dose
- Neutralizing and binding antibody levels were boosted substantially above baseline through Month 6 in younger adult and older adult cohorts at all dose levels tested
  - Following 1 dose of mRNA-1345, both younger and older cohorts had comparable GMTs; however, the older adults had lower GMFRs than younger cohorts due to higher baseline GMTs in the older adult cohort
  - The decline in neutralizing antibody response through Month 6 was similar in both younger and older adults
  - The comparable dose response between dose levels in each cohort accompanied by lower reactogenicity at low doses in both younger and older cohorts (particularly in younger adults) suggests that a low-dose vaccine could be sufficient to provide protection from RSV in both younger and older cohorts
  - The binding antibody response was preF biased, suggesting that mRNA-1345 can induce a robust immune response to RSV preF, the main antigenic target of humoral immunity to RSV
- These data support the continued development of mRNA-1345 as an RSV vaccine

ABSTRACT PLAIN LANGUAGE SUMMARY

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Disclosures

All authors are employees of Moderna, Inc., and hold stock/stock options in the company.