PROTECTION AGAINST HETEROLOGOUS CHALLENGE 1 YEAR AFTER INFANT SARS-CoV-2 IMMUNIZATION

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ABSTRACT

Both the BNT162b2 and the mRNA-1273 SARS-CoV-2 vaccines have been available under emergency-use-authorization to infants, 6 months and older since June of 2022. With the slow rollout of these vaccines and their waning efficacy as new variants of concern emerge, questions of vaccine protection remain.

Infant (2-month old) rhesus macaques (RMs) (n=8/group) were immunized intramuscularly at weeks 0 and 4 with 30μg stabilized prefusion SARS-CoV-2 S-2P spike (S) protein (Washington strain) encoded by mRNA encapsulated in lipid nanoparticles (mRNA-LNP) or 15μg S protein mixed with 3M-052 in stable emulsion (Protein). At 1 year, vaccinated and age-matched unvaccinated RM (n=8) were challenged intranasally (10^6pfu) and intratracheally ($2x10^6$ pfu) with B.1.617.2. Lung radiographs and pathology were blindly assessed, viral N gene RNA (vRNA) copies were measured by qPCR in pharyngeal swabs and lung, and neutralizing antibody and peripheral blood T cell responses were measured.

At the time of challenge, the Protein group had a D614G-specific ID_{50} neutralizing antibody (nAb) titer of 755 (range: 359-1,949) and the mRNA group had an ID_{50} of 73 (range: 41-240). The vaccines also induced cross-neutralizing antibodies to B.1.617.2. Peripheral blood $CD4^+$ T cell responses to the spike protein of the ancestral (wild type [WT]) variant at week 52 did not differ between the groups. However, median $CD8^+$ T cell responses were higher (p=0.002, Mann Whitney) in the mRNA group (2.8%, range: 0.9%-7.1%) compared to the Protein group (0.8%, range: 0.1%-1.6%). Control RMs had significantly higher median vRNA copies/ml ($1.4\pm2.7x10^8$) in day 4 pharyngeal swabs compared to Protein ($3.8\pm6.8x10^3$) or mRNA-LNP ($4.4\pm9.7x10^5$) vaccinated RMs. Severe lung pathology was observed in 7 of 8 controls compared to 1 of 8 or 0 of 8 RMs in the mRNA-LNP or protein group, respectively. Protection against lung inflammation was associated with nAb titers (r=-0.592, p=0.003) and partially with T cell responses.

These results demonstrate that despite lower vaccine doses compared to adults, both vaccines provided comparable protective efficacy against infection with a heterologous variant. Furthermore, these findings add to a growing body of evidence on the durability and cross-reactivity of vaccine-induced antibody and T cell responses.

METHODS

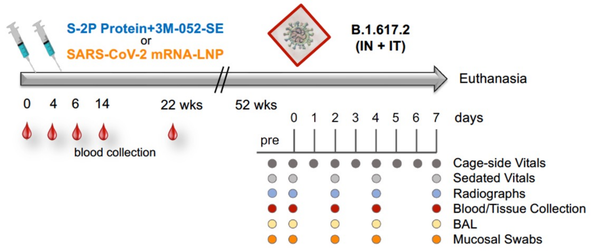


Fig. 1. Experimental Design. Two groups of 2-month-old rhesus macaques (RMs) were immunized intramuscularly at weeks (wks) 0 and 4 with stabilized prefusion SARS-CoV-2 S-2P spike (S) protein of the Washington strain encoded by mRNA encapsulated in lipid nanoparticles (mRNA-LNP; n=8) or purified S protein mixed with 3M-052, a synthetic TLR7/8 agonist, in a squalene emulsion (Protein+3M-052-SE; n=8). RMs were monitored for 1 year post immunization, an additional group of age-matched unvaccinated control RMs were challenged by the intranasal (IN) and intratracheal (IT) route with heterologous B.1.617.2 (Delta). The clinical monitoring and sample collection schedule until euthanasia on day 7 post-challenge is indicated underneath the time bar.

ACKNOWLEDGEMENTS

1 P01 AI117915:
Early Life to Prevent HIV Acquisition in Adolescence

1 P01 AI 117915 Supplement:
Efficacy of SARS-CoV-2 Spike Protein Vaccines in Infant Rhesus Macaques

S-SPECIFIC CROSS-REACTIVE ANTIBODY and T CELL RESPONSES

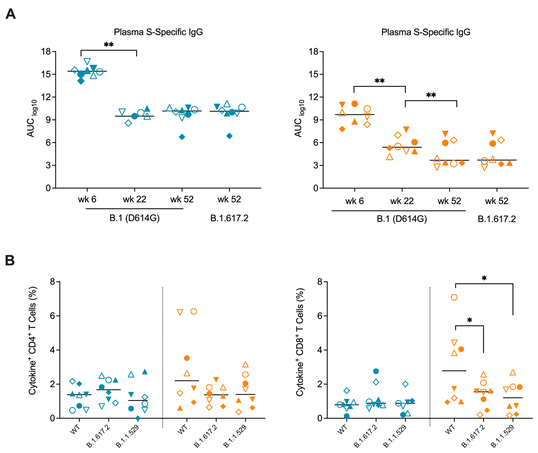


Fig. 2. Vaccine-elicited spike-specific antibody and T cell responses. (A) Plasma B.1 (D614G) S-specific IgG responses peaked at week 6 and then stabilized by week 22 after a decline in the Protein group. In the mRNA group, plasma D614G S-specific IgG responses also persisted, but declined further until week 52. **(B)** Peripheral blood $CD4^+$ and $CD8^+$ T cell responses were assessed after stimulation with a peptide pool spanning the wildtype, B.1.617.2, or B.1.1.529 S protein and measuring the percentage of IL-2, IFN- γ, IL-17, and TNF-α producing by flow cytometry. At week 52, the mRNA group had greater $CD8^+$ T cell responses compared to the Protein group.

NEUTRALIZING ANTIBODIES

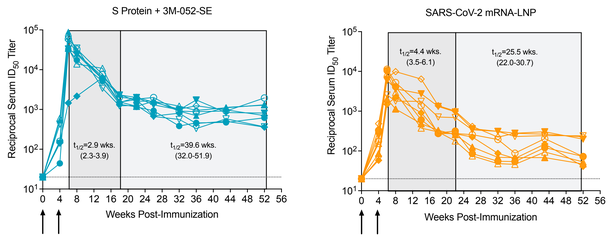


Fig. 3. Vaccine-elicited plasma antibodies exhibit distinct degrees of effector functions. The ID_{50} titers of D614G-specific neutralizing antibodies peaked for both groups at week 6 then declined until week 52. By week 52 the ID_{50} titer for the Protein group (left) declined by 59-fold, whereas for the mRNA group (right) the ID_{50} titer declined by 89-fold. The decay kinetics of nAb are similar to those observed in human adults.

RESULTS

VIRAL OUTCOME

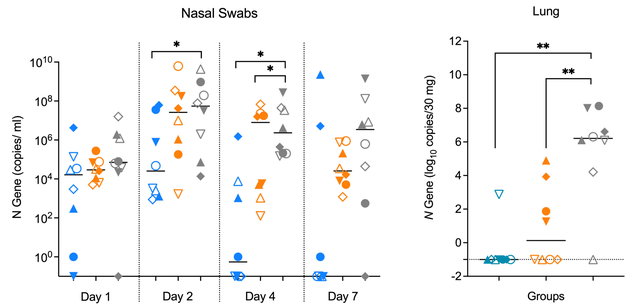


Fig. 4. SARS-CoV-2 RNA concentrations are lower in mucosal secretions and tissues isolated from vaccinated RMs. On day 1 viral replication is observed regardless of vaccine group. By days 2 and 4, vRNA levels significantly decreased in vaccinated animals compared to controls. On day 7, vRNA levels in the lung are significantly lower for the Protein vaccinated animals compared to the mRNA and control animals.

CORRELATES OF PROTECTION

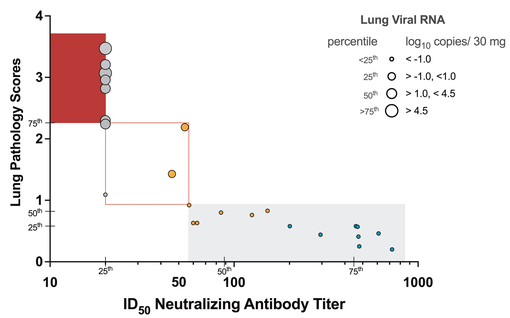
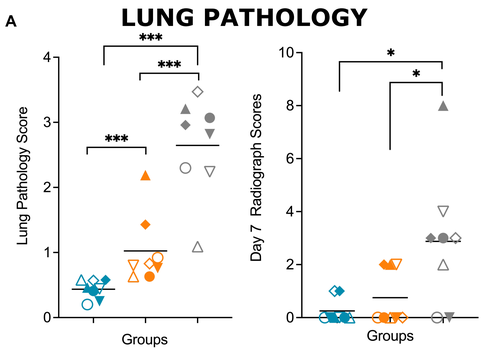
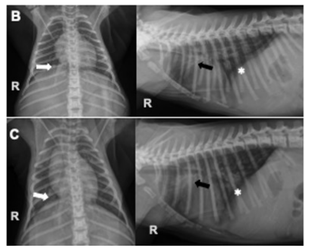


Fig. 5. Neutralizing ID_{50} antibody titers are a correlate of protection in infant RMs challenged with SARS-CoV-2. ID_{50} titers of B.1.617.2-specific nAbs at the time of challenge are plotted against lung pathology scores. The symbol size for each RM is based on the degree of virus replication in the lung of the same RM. RMs in the Protein or mRNA vaccine groups are indicated by blue and orange circles, respectively, and control RMs by gray circles. Vertical ticks indicate the 25th, 50th and 75th percentile of all ID_{50} titers across all groups and horizontal ticks indicate the 25th, 50th and 75th percentile of lung pathology scores. Red-filled, red-outlined, and light gray shaded areas indicate severe, intermediate and no or mild lung pathology, respectively.

LUNG PATHOLOGY





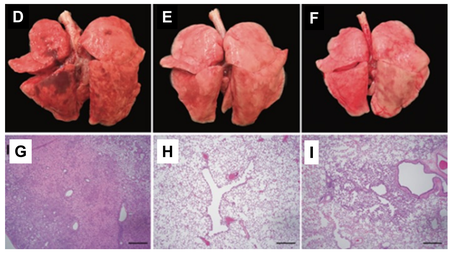


Fig. 6. Lung pathology is reduced in vaccinated RMs compared to controls. (A) Each vaccine protected animals better from severe lung pathology compared to controls; however, the Protein vaccine provided better protection compared to the mRNA vaccine. **(B and C)** Representative radiograph images of a control animal pre (B) and post (C) challenge. **(D-F)** Whole lung images of control (D), Protein (E), and mRNA animals (F). The image of the control lung shows areas of severe lung damage. **(G-I)** H&E staining at 4x magnification of different control animals indicating varying degrees of interstitial pneumonia.

CONCLUSIONS

- mRNA-LNP and Protein+3M-052-SE vaccines were well tolerated and immunogenic in infant rhesus macaques.
- Both vaccines induced Spike-specific cross-variant reactive antibodies with neutralizing function that provided protection up to one year after vaccination.
- Despite a range of pathology scores in the mRNA-LNP vaccinated animals, pathology scores indicate that both vaccinated groups were protected against severe lung disease compared to controls.
- The Protein+3M-052-SE vaccine induced higher titers of nAbs and provided better protection against severe lung pathology.
- In mRNA-LNP vaccinated animals, greater Spike-specific T cell responses compared to the Protein-3M-052-SE vaccinated animals likely contributed to protection.