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Protective Efficacy of Gastrointestinal SARS-CoV-2 Delivery Against Intranasal and Intratracheal SARS-CoV-2 Challenge in Rhesus Macaques

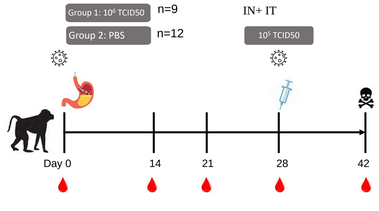
Jingyou Yu[1]*, Natalie D. Collins[2]*, Noe B. Mercado[1], Katherine McMahan[1,] Kayvon Modjarrad[2], Nelson L. Michael [2], Dan H. Barouch[1,3,4]** for the Research Group Barouch lab and WRAIR
[1]Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [2]2Walter Reed National Military Medical Center, Bethesda, MD, USA;
[3]Harvard Medical School, Boston, Massachusetts, USA; [4]Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA, USA

BACKGROUND

- Historically, live oral vaccines have been successfully applied in real world, such as Ad4/Ad7 vaccines in military recruits
- Despite the rapid deployment but limited coverage of multiple SARS-CoV-2 vaccines. Alternative vaccine strategies that have favorable manufacturing timelines, greater ease of distribution and improved coverage may offer significant public health benefits, especially in resource-limited settings
- Live oral vaccines have the potential to address some of these limitations; however, no studies have yet been conducted to assess the immunogenicity and protective efficacy of a live oral vaccine against SARS-CoV-2.

METHODS

- 21 rhesus macaques with 1x106 50% tissue culture infectious dose (TCID50) SARS-CoV-2 from the WA1/2020 strain (NR-52281; BEI Resources) (N=9) or PBS sham controls (N=12) by esophagogastroduodenoscopy (EGD).
- Viral shedding was quantified on study days 1, 2, 4, 7, 14, 21 and 28 by genomic (gRNA) or envelope (E) subgenomic (sgRNA) RT-PCR assays in various anatomic sites, including stool, rectal swab, nasal swab, BAL, etc.
- Four weeks after vaccination, humoral immunity was determined by pseudovirus neutralization assay and ELISA; while cellular immunity was examined by IFN-γ ELISPOT assays and intracellular cytokine staining (ICS) assays
- Upon challenge, viral load in BAL and NS was determined by RT-PCR and the viral pneumonia was assessed by histopathology



GI delivery of live SARS-CoV-2 elicited modest immune responses and provided partial protection against intranasal and intratracheal challenges.

The neutralizing antibody titers correlated with protective efficacy.

It is likely that the poor immune response and protection were due to delivery of an antigenic load in the GI tract.

RESULTS

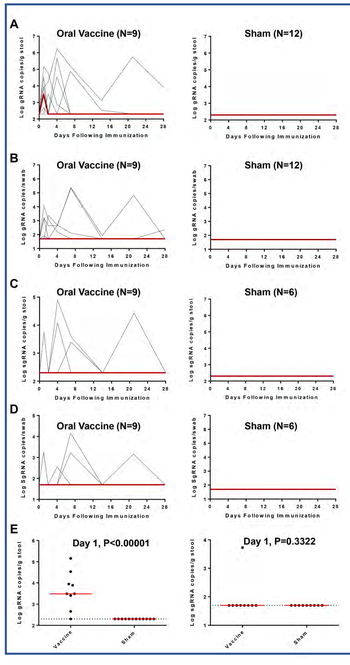


Figure 1. Viral shedding in rhesus macaques following live vaccine EGD administration. Rhesus macaques were administered 10^6 TCID50 SARS-CoV-2GI via EGD. (A) Log10 gRNA copies/g stool (limit 200 copies/ml) or (C) Log10 sgRNA copies/g stool were assessed in stools in sham controls and in vaccinated animals following challenge. (B) Log10 gRNA copies/swab or (D) Log10 sgRNA copies/swab (limit 50 copies/swab) were assessed in rectal swabs (RS) in sham controls and in vaccinated animals following challenge. Red lines reflect median values. (E) Peak viral loads in stool on day 1 following vaccination. Red lines reflect median viral loads. P-values indicate two-sided Mann-Whitney tests.

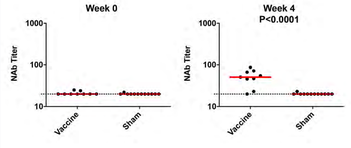


Figure 2. Humoral immune responses in vaccinated rhesus macaques. Humoral immune responses were assessed at weeks 0 and 4 by pseudovirus neutralization assays. Red bars reflect median responses. Dotted lines reflect assay limit of detection.

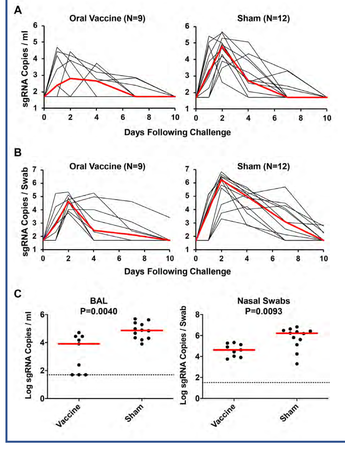


Figure 3. Viral loads in rhesus macaques following SARS-CoV-2 challenge. Rhesus macaques were challenged by the intranasal and intratracheal route with 10^5 TCID50 SARS-CoV-2. (A) Log10 sgRNA copies/ml (limit 50 copies/ml) were assessed in bronchoalveolar lavage (BAL) in sham controls and in vaccinated animals following challenge. (B) Log10 sgRNA copies/swab (limit 50 copies/swab) were assessed in nasal swabs (NS) in sham controls and in vaccinated animals following challenge. Red lines reflect median values. (C) Peak viral loads in BAL and NS following challenge. Peak viral loads occurred on day 2 following challenge. Red lines reflect median viral loads. P-values indicate two-sided Mann-Whitney tests.

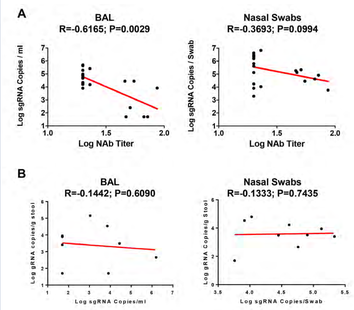


Figure 4. Histopathologic examination following SARS-CoV-2 challenge. Lung tissues were collected at necropsy on day 14 post-challenge, fixed with neutral buffered formalin, and stained with hematoxylin and eosin (H&E) for standard microscopic examination. Representative lung tissue sections from the PBS control (A), high-dose (10^6 TCID50) vaccinated (B) low-dose (10^4 TCID50) vaccinated (C) SARS-CoV-2 challenged rhesus macaques. Minimal to mild interstitial pneumonia is characterized by inflammatory cellular infiltrates and type II pneumocyte hyperplasia. Scale bars: 100 µm.

Figure 5. Immune correlates of protection. (A) Correlations of pseudovirus NAb titers at week 4 with log peak sgRNA copies/ml in BAL and NS following challenge. (B) Correlations of log peak sgRNA copies/ml in BAL and NS with log peak gRNA copies/g stool. Red lines reflect the best-fit relationship between these variables. P and R values reflect two-sided Spearman rank-correlation tests.

CONCLUSIONS

- A single post-pyloric administration of live SARS-CoV-2 by EGD elicited detectable serum NAb titers and partially protected against respiratory SARS-CoV-2 challenge in rhesus macaques.
- Optimization of the current strategy, with encapsulation and extended delivery systems, as well as improvements in dosage and schedule will be required for a live, oral, SARS-CoV2 vaccine.

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