Intranasal and intrapulmonary vaccination with an M protein-deficient respiratory syncytial virus (RSV) vaccine provides protection to infant baboons against an RSV infection

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INTRODUCTION

- Respiratory syncytial virus (RSV) is a major respiratory pathogen in infancy, yet there is no licensed RSV vaccine. This is because :
- Use of Injectable RSV vaccines may result in enhanced illness at the time of subsequent RSV infection, and...
- Live, replicating vaccines may cause unacceptable respiratory illness.
- We have developed a live RSV vaccine ("Mnull RSV") by deleting the gene for the M protein from a human RSV strain (A2)
- After RSV infects a cell and synthesizes its proteins, the RSV M protein is responsible for reassembling other viral proteins into intact virus
- In the absence of M, RSV infects a cell, expresses all its proteins (except M) and induces immune responses. However, it cannot reassemble and replicate further.
- Mnull RSV should therefore avoid problems of immunogenicity and reactogenicity associated with earlier vaccines
- We studied the effectiveness of Mnull RSV given by intranasal (IN) and intrapulmonary (IP) routes of vaccination in an infant baboon model

STUDY DESIGN

Infant (2 week) baboons were vaccinated as follows:

-IN: Mnull RSV (4 x 10e7 vaccine units) was introduced by nasal spray at age 2 weeks, and a booster dose was repeated in 4 weeks.

-IP: Mnull RSV (8 x 10e7units) was introduced once through an endotracheal tube in sedated, intubated animals at age 2 weeks. No booster dose was administered.

- A sham vaccine was administered (IN or IP) to similar animals in the same fashion as described for Mnull RSV vaccinees

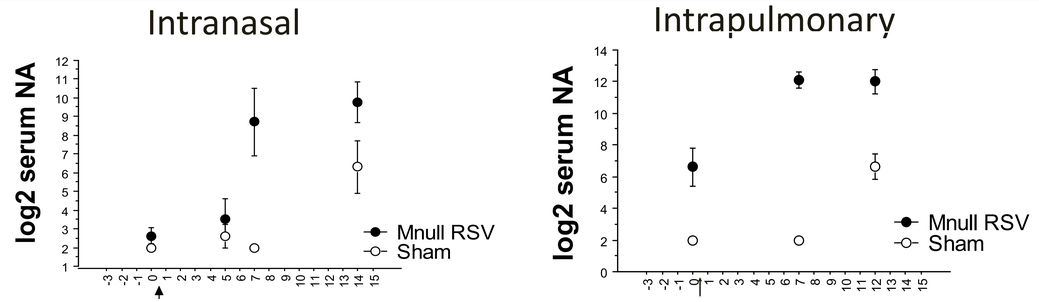
All animals were challenged with 8 x 10e7 pfu of live RSV delivered intratracheally 4 weeks after IN vaccination, and 4-6 months after IP vaccination

- Animals were followed continuously daily for respiratory rates both before and after RSV challenge

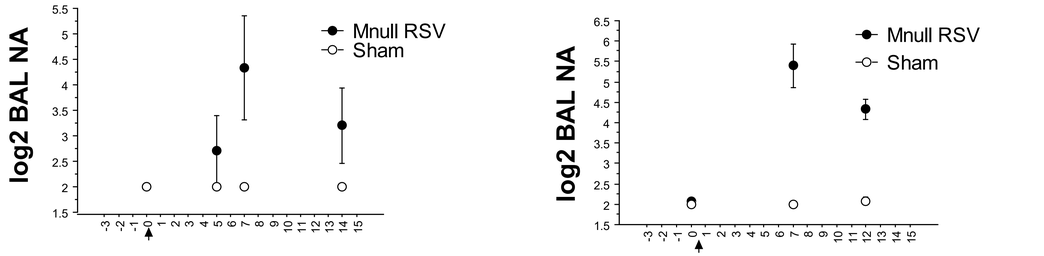
- On days 0, 5, 7 and 12-14 after challenge, serum and BAL fluid were obtained for RSV neutralizing antibody (RSV NA), and BAL fluid was cultured for RSV. In addition, work of breathing was assessed using software intrinsic to the ventilator

None of the authors have conflicts to declare Robert-Welliver@OUHSC.edu

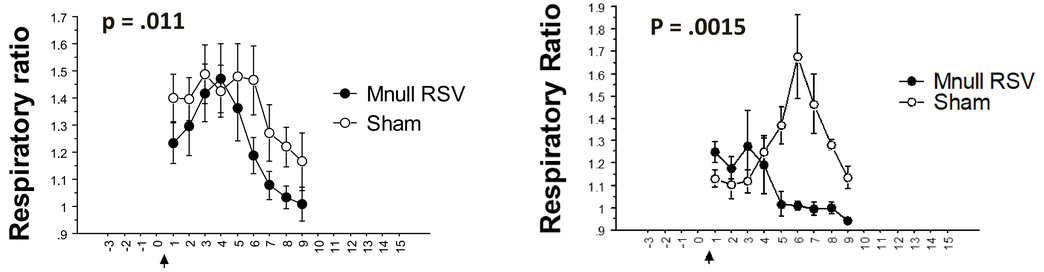
RESULTS



Figures 1 and 2. Serum RSV NA responses in animals vaccinated IN or IP or Sham. Horizontal axis depicts time before and after RSV challenge (day 0). Animals vaccinated IP 4-6 months previously with Mnull RSV had higher RSV NA titers on the day of RSV challenge (day 0) than Sham vaccinees, indicating persistent RSV NA responses following IP vaccination. Mnull RSV vaccination also accelerated RSV NA responses following RSV challenge.

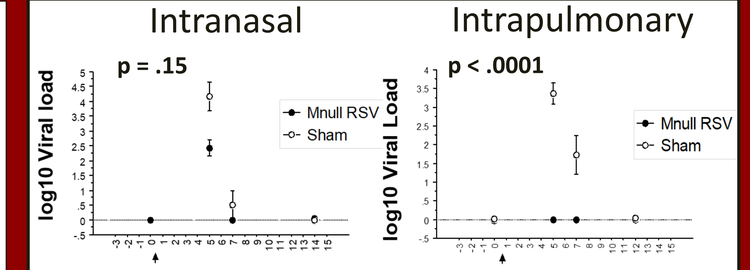


Figures 3 and 4. BAL RSV NA responses in animals vaccinated IN or IP or Sham. Neither animals vaccinated IN or IP had detectable antibody on the day of RSV challenge. Previous Mnull RSV vaccination accelerated BAL RSV NA responses following RSV challenge.

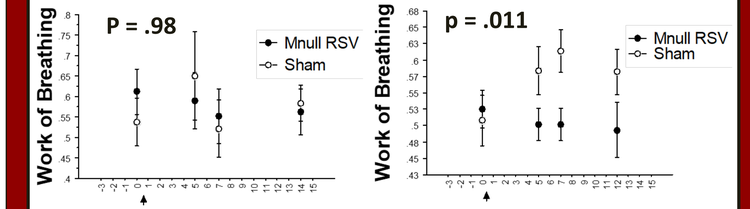


Figures 5 and 6. Respiratory rates following RSV challenge in animals previously vaccinated with Mnull RSV IN or IP. Previous IN vaccination reduced tachypnea moderately following RSV challenge. However. previous IP vaccination completely prevented tachypnea following RSV challenge.

Results (con't)



Figures 7 and 8. Viral growth at peak replication (day 5) following RSV challenge in animals previously vaccinated with Mnull RSV IN or IP. Previous IN vaccination resulted in moderately reduced viral replication in BAL fluid. However, previous IP vaccination completely eliminated replication of RSV in BAL fluid.



Figures 9 and 10. Work of breathing (WOB) following RSV challenge in animals previously vaccinated with Mnull RSV IN or IP. WOB was not affected by previous Mnull RSV vaccination IN. Previous IP vaccination reduced WOB following RSV challenge.

CONCLUSIONS

- IN vaccination with Mnull RSV induced inconsistent antibody responses, but still moderately reduced tachypnea and viral replication following RSV challenge

- A single IP vaccination at 2 weeks of age induced RSV NA responses persisting at least 6 months, and reduced tachypnea, viral replication, and WOB 4-6 months following RSV challenge, suggesting a novel method of preventing RSV infection.

- We are investigating Mnull RSV immunization of the lung using nebulizer delivery.