

# Treatment of Normal and Immune Suppressed Cotton Rats with IVIG Containing High Neutralizing Titer Anti-RSV Antibody

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## Introduction

Respiratory syncytial virus (RSV) is recognized as a significant problem in both pediatric and adult immunocompromised hosts and is associated with significant morbidity and mortality. The severity of clinical manifestations and the incidence of mortality depends on the magnitude of the immune suppression. The group at highest risk for severe RSV infection is bone marrow transplant recipients. We have previously demonstrated that our product, RI-002 which is an IVIG containing standardized, high levels of neutralizing anti-RSV antibody titers prevents pulmonary infection in a cotton rat model of RSV, an animal model regarded as the ideal surrogate for RSV infection in humans. RI-002 is nearing completion of its phase three clinical trial designed to prevent serious infections in patients with primary immune deficiency disease (PIDD).

The studies described were designed to determine whether RI-002:

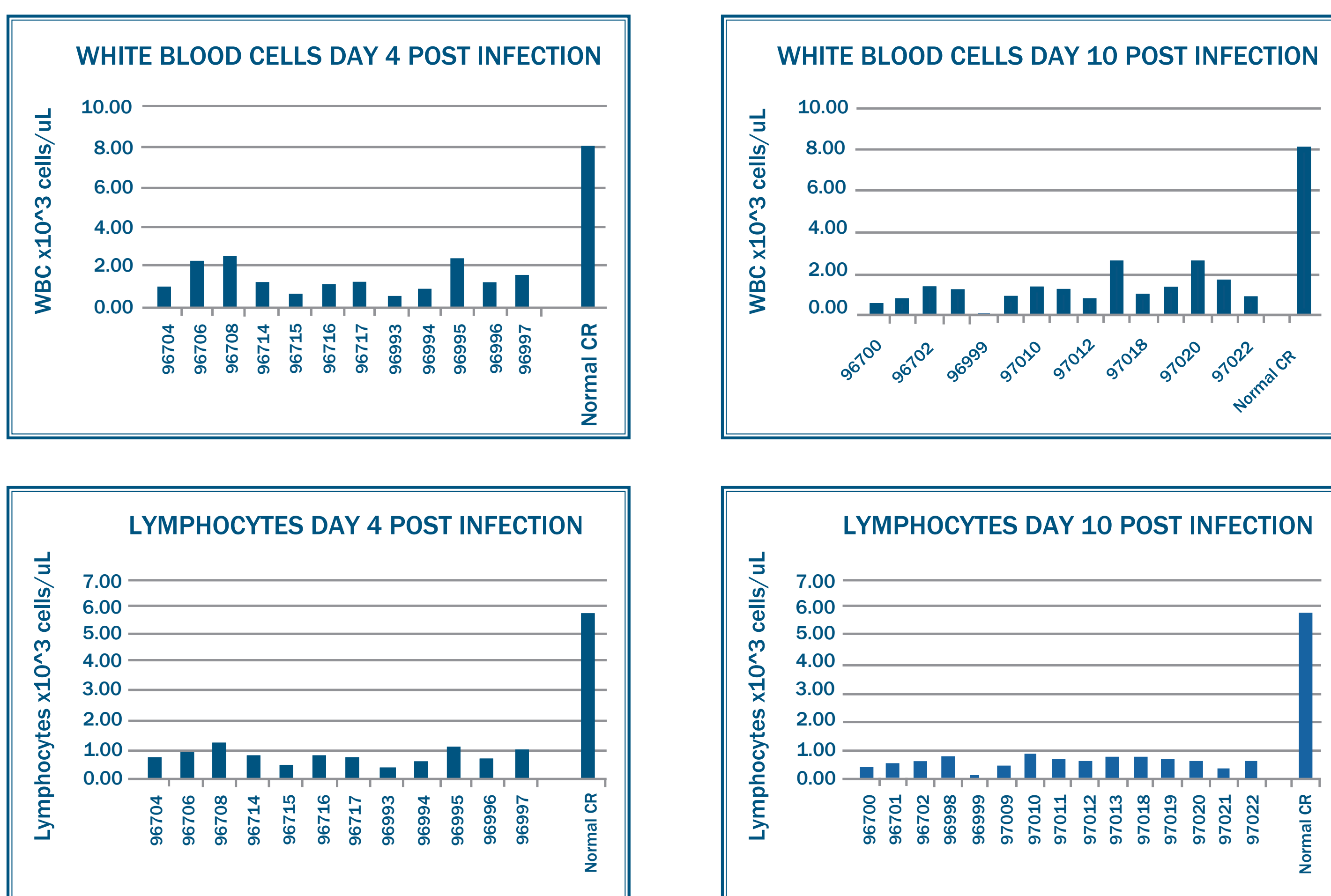
1. Contains elevated levels of antibodies to respiratory viruses other than RSV
2. Could treat normal and immune suppressed RSV infected animals
3. Could prevent systemic dissemination of the virus

## Methods

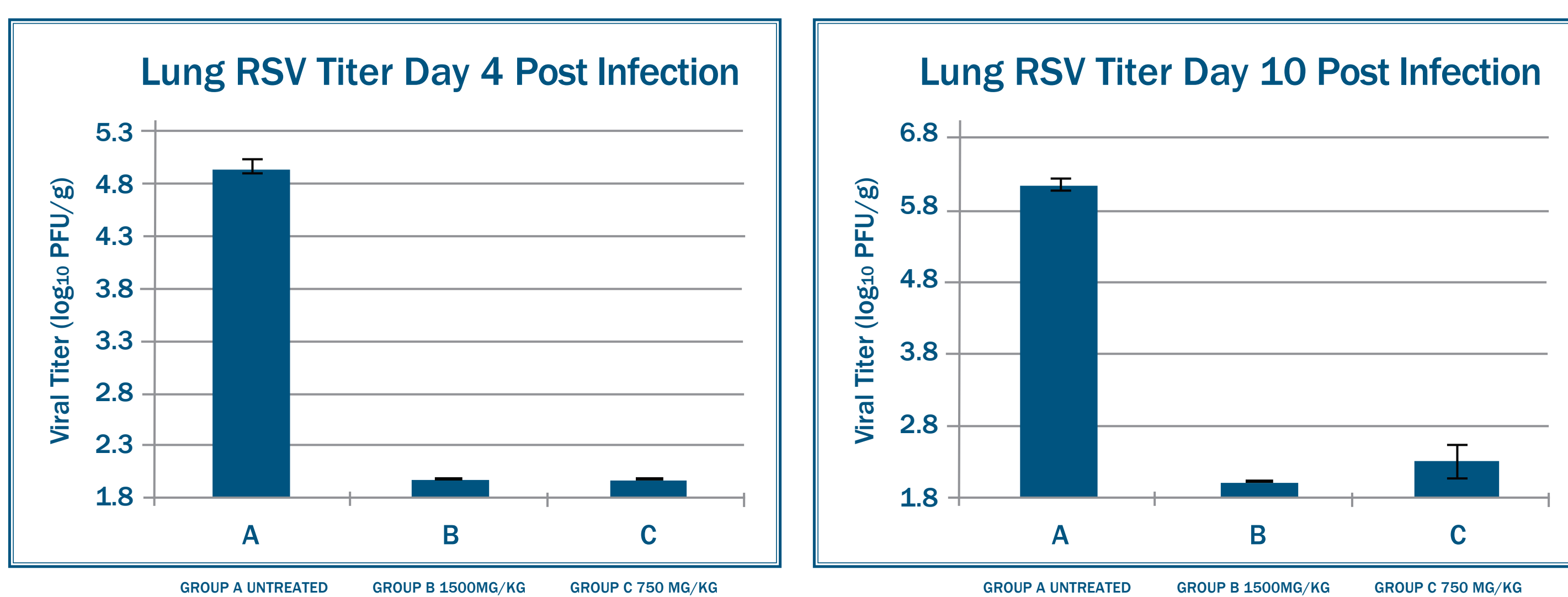
Animal studies: cotton rats chronically suppressed with Cytoxin showed a 90% reduction of lymphocytes and circulating immunoglobulin. Animals were infected with  $10^5$  PFU RSV A/Long and injected intraperitoneally on day 1 (normal animals) and days 1, 4 and 7 (immune suppressed animals) with RI-002 and sacrificed on days 4 and 10 post-infection.

Standard ELISA tests were performed for quantitation of antibodies to other non RSV respiratory viruses.

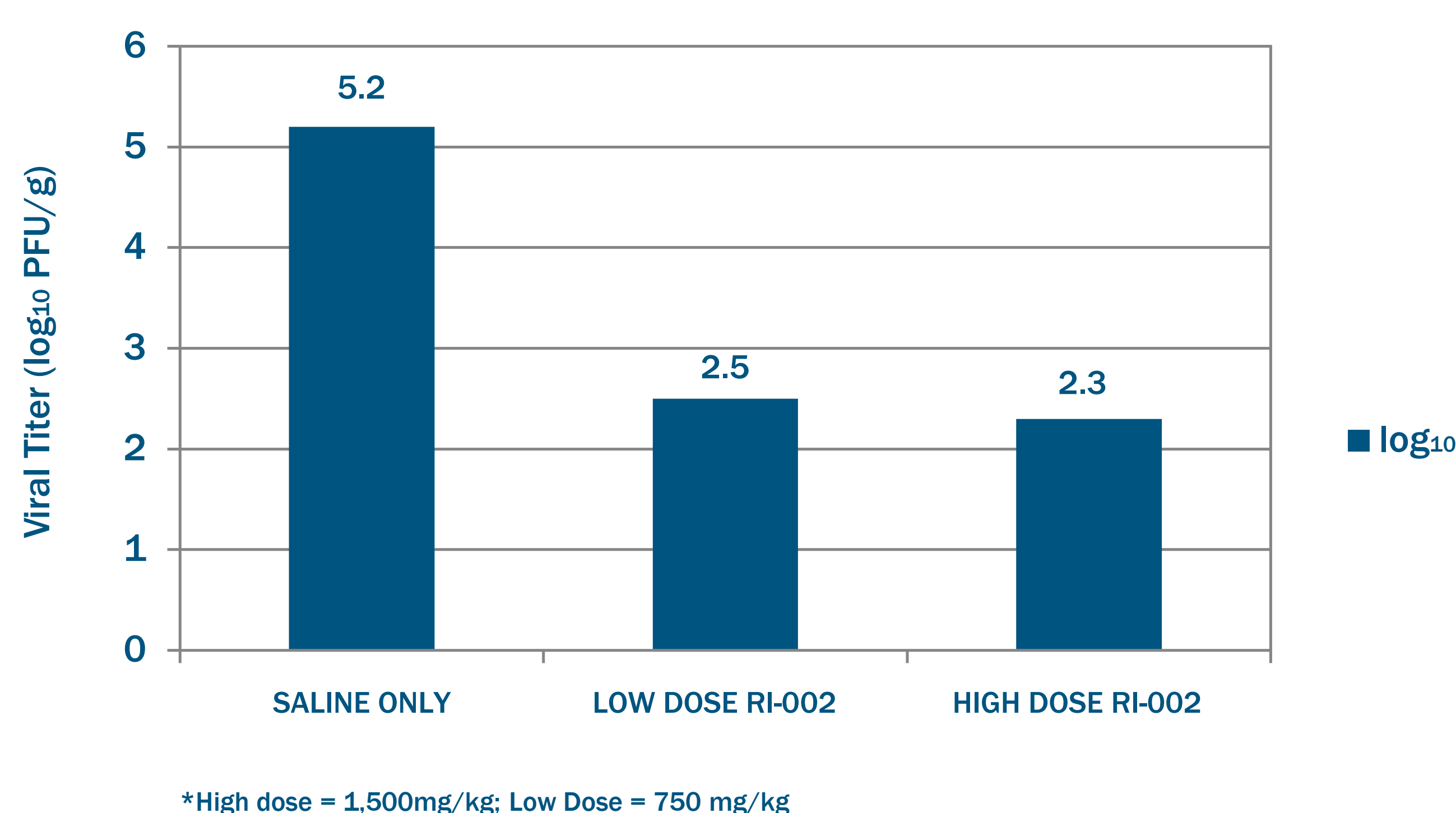
## Whole Blood Analysis Data- Immune Suppressed Cotton Rats



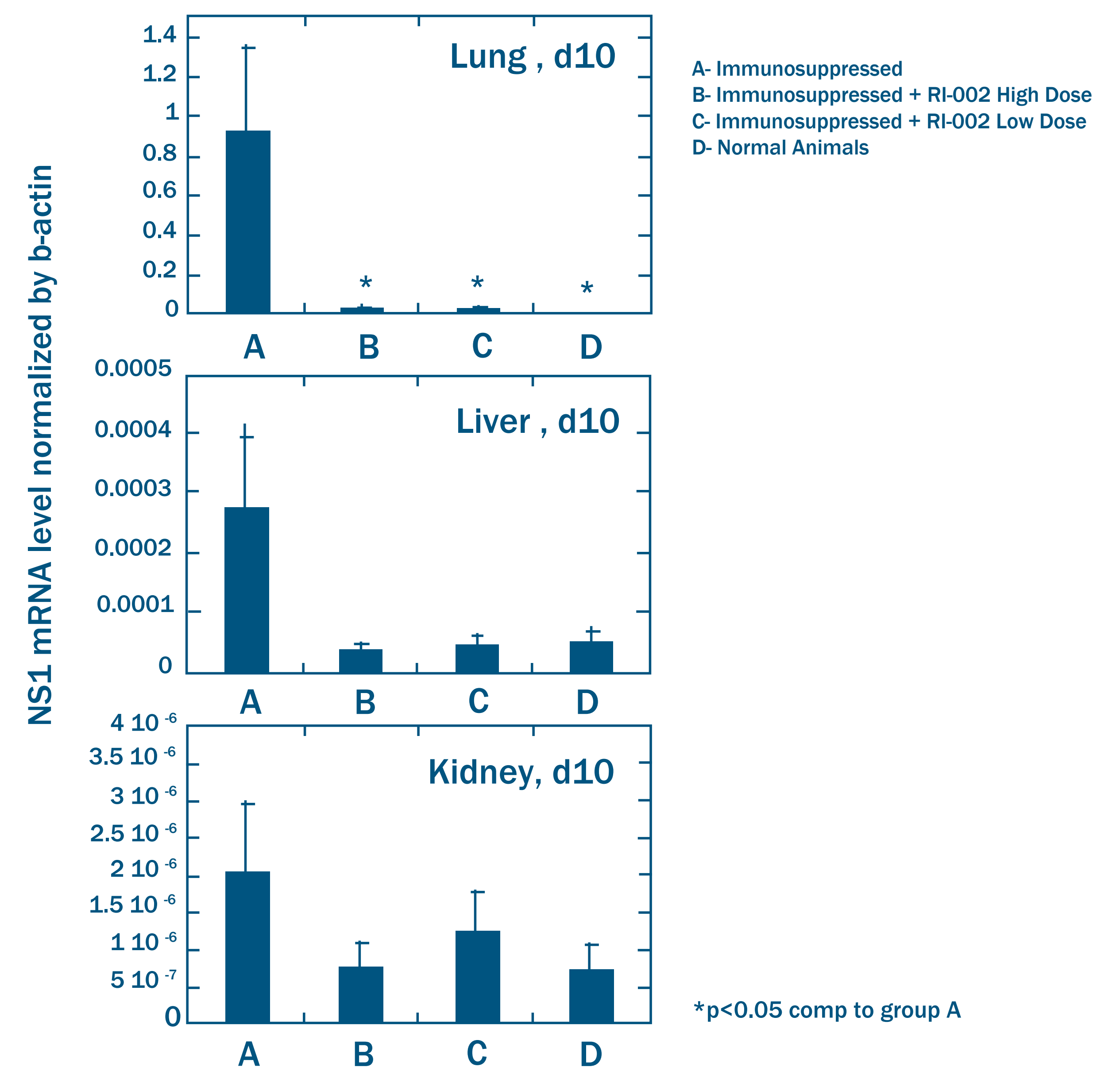
## ADMA IVIG Prevents RSV Infection in the Lungs of Immune-Suppressed Cotton Rats



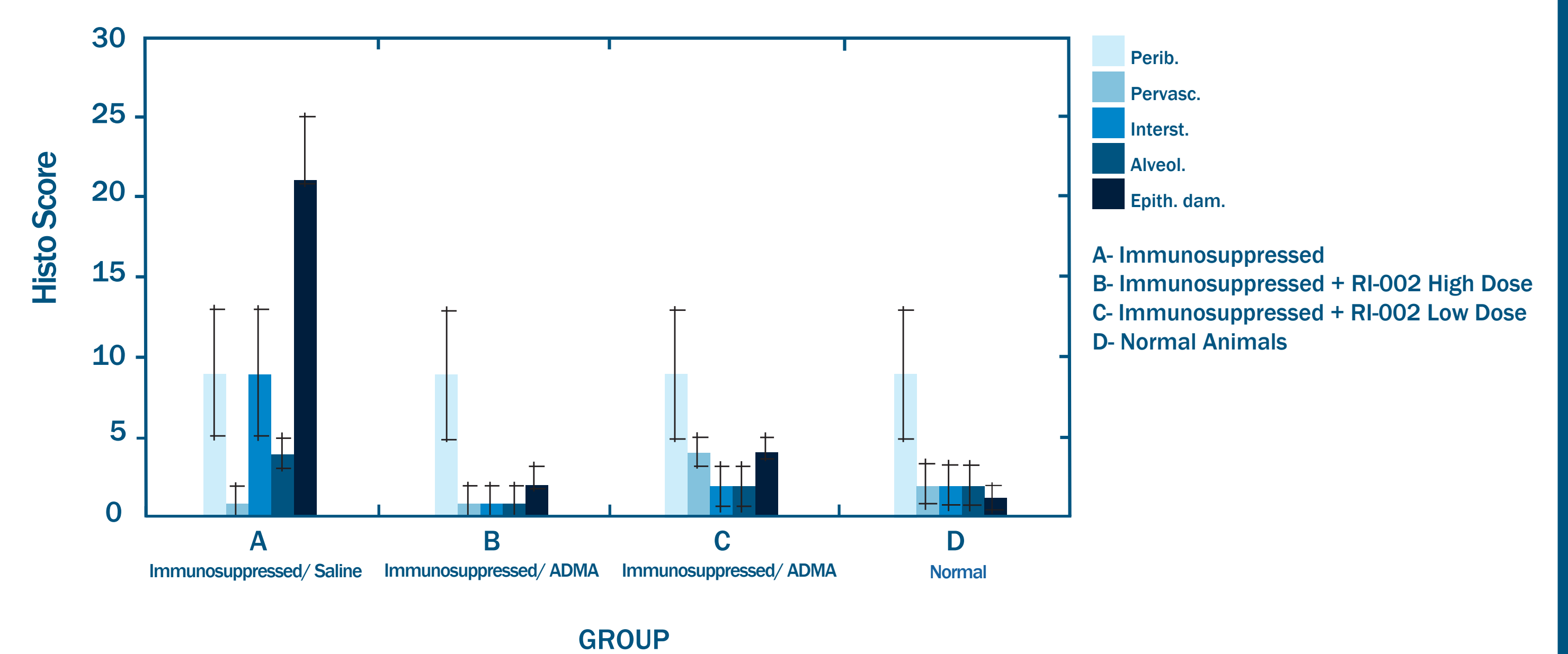
## Reduction of Viral Load in the Lungs of Normal Cotton Rats Treated with RI-002 ( $\log_{10}$ PFU\*)



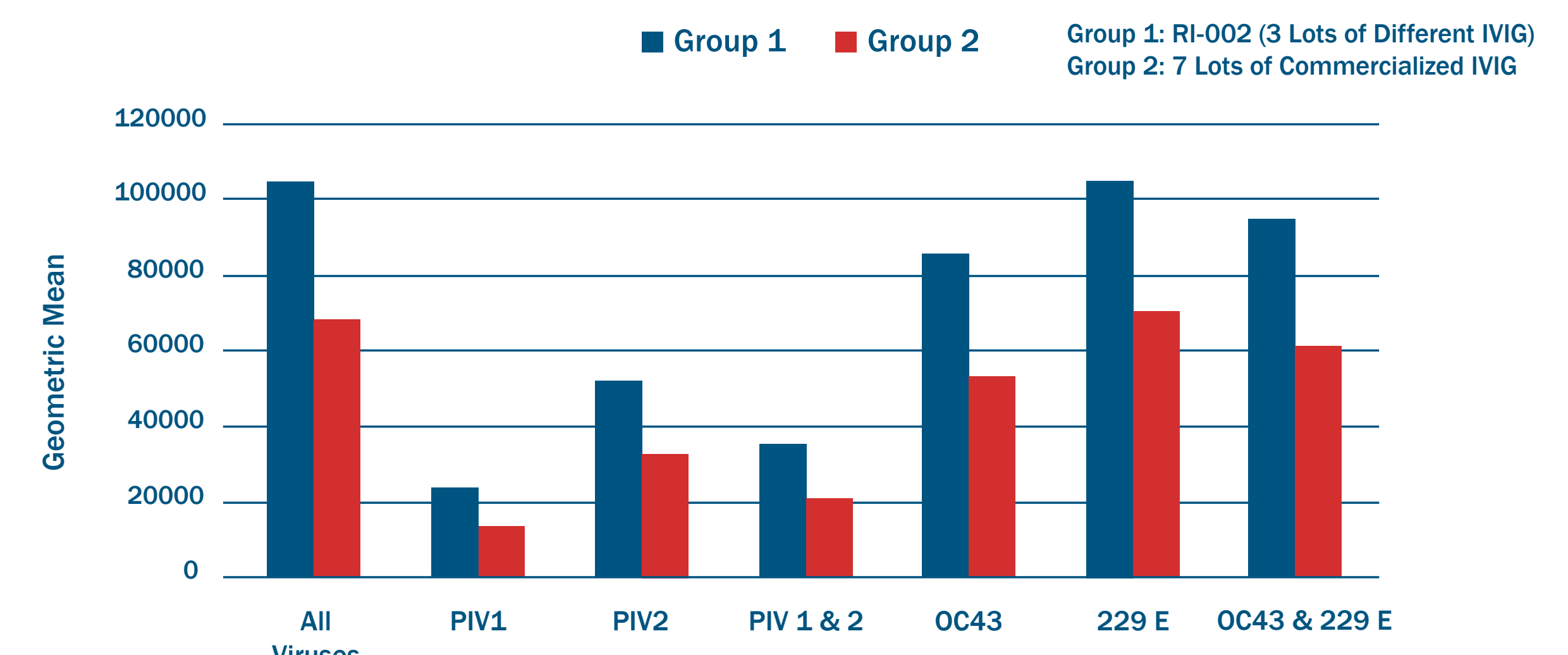
## RSV qPCR Detection



## Pulmonary Histopathology



## Antibody Titers; Comparison of RI-002 to Standard IVIG for Other Respiratory Viruses



| Analysis    | Ratio of Geometric Means (95% CI)<br>(Group 1 ÷ Group 2) | P-Value* |
|-------------|--|----------|
| All Viruses | 1.529 (1.227, 1.907)                                     | 0.0002   |
| PIV1        | 1.792 (1.282, 2.505)                                     | 0.0010   |
| PIV2        | 1.601 (1.160, 2.210)                                     | 0.0050   |
| PIV 1 & 2   | 1.694 (1.250, 2.296)                                     | 0.0009   |
| OC43        | 1.610 (1.127, 2.301)                                     | 0.0099   |
| 229E        | 1.494 (1.144, 1.950)                                     | 0.0039   |
| OC43 & 229E | 1.551 (1.237, 1.945)                                     | 0.0002   |

\* 2-group t-test for null hypothesis of no difference between the groups in geometric means (i.e., ratio of geometric means =1).

PIV1 & 2: Parainfluenza  
OC43 & 229E: Coronavirus

## Summary

- Selection of plasma donors with high titer antibodies to RSV also selected for plasma which contained high titer antibodies to other respiratory viruses.
- There was a 99.9% ( $3 \log_{10}$ ) reduction in viral load in both lung and nasal tissue of normal and immune suppressed cotton rats with the reduction being slightly greater in the tissues of normal animals. Histopathology of the lungs in the immune suppressed cotton rats showed perivascular, interstitial and alveolar inflammation and epithelial death with striking improvement in all of these parameters in the animals treated with RI-002. Notably, in the peripheral organs of immune suppressed animals there was evidence of systemic dissemination of the virus by PCR and this was reduced after treatment with RI-002.

## Conclusions

IVIG containing standardized, high levels of neutralizing RSV antibody titers also contains elevated levels of antibodies to other respiratory viruses. This product may be an effective treatment to suppress RSV induced viral load and viral induced inflammation in the lungs, suppress systemic dissemination of RSV and may also provide some level of protection to other respiratory viruses. Whether the standardized, high-titer antibody to RSV or other polyclonal antibodies against other respiratory and infectious pathogens will provide added clinical benefit requires further study.