

# Placental Transfer of anti-RSV F Maternal Antibody in Rabbits and Guinea Pigs Immunized with an RSV F Nanoparticle Vaccine Co-administered with Aluminum Phosphate

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## ABSTRACT

### Background:

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract viral infection (LRTI) during infancy and early childhood worldwide. High titers of maternally derived RSV neutralizing antibodies have been shown to be inversely associated with the incidence of RSV acute LRTI during the first 6 months of life indicating that RSV-maternal antibody play's an important role in protection against severe RSV-associated illness. We have evaluated the transplacental transfer of anti-RSV F maternal antibody generated by immunization with a recombinant RSV F protein nanoparticle vaccine in two animal models.

### Methods:

Study 1, rabbits were immunized with 120 µg RSV F + 1200 µg aluminum-phosphate two times prior to mating and twice during fetal development. Maternal antibody was assessed in dam and fetuses obtained by caesarian sectioning on gestation day 29.

A pilot study was also performed in guinea pigs as in this model the morphology and physiology of the hemochorial placenta, the relative length of pregnancy and the development of the young at the time of delivery most closely resembles that of humans. Guinea pigs were immunized gestation day 25 and 46 with 30 µg RSV F + 400 µg aluminum phosphate. Sera were obtained at birth from mothers and pups for serological analysis

### Results:

In the rabbit study, anti-RSV F IgG was present in all maternal serum samples and maternal anti-RSV F antibody was present in 100% of the F1 generation. Geometric mean titer (GMT) anti-RSV F IgG were 30% higher in fetal samples (GMT=2.21x10<sup>6</sup>) compared to maternal samples (GMT=1.65x10<sup>6</sup>) indicating a transplacental concentration effect.

In the guinea pigs pilot study, maternal anti-RSV F IgG was present in 100% of the F1 generation. Analysis of sera from F1 animals indicated anti-RSV F IgG (GMT=9.55x10<sup>5</sup>), neutralizing antibody (GMT=452), and palivizumab competing antibody (GMT=3,830) levels were comparable to levels in maternal serum.

### Conclusions:

Maternal immunization using the RSV F nanoparticle vaccine appears safe and immunogenic and may be beneficial in protecting newborns against RSV via maternal transfer of specific antibody. No adverse effects of immunization with the RSF F protein nanoparticle on the F1 generation were observed.

## INTRODUCTION

Respiratory syncytial virus (RSV) infects nearly all infants under 2 years of age. Most severe RSV infection occurs in infants between two to seven months of age. The humanized monoclonal antibody, Synagis® (palivizumab), is an effective prophylactic immunotherapy which is currently being used to treat high-risk infants; supporting the concept that passive immunization is effective against respiratory infection. These observations support a maternal immunization strategy as an approach to protecting high-risk infants against severe respiratory infection.

## MATERNAL ANTIBODY TRANSFER IN RABBITS

Female New Zealand White Rabbits (NZW) were immunized by intramuscular injection (IM) with placebo control article or with 120 µg of RSV F adjuvanted with 800 µg aluminum phosphate. Rabbits received two doses prior to mating and two doses during the gestation period. On Day 29 of presumed gestation, serum was collected from dams and fetuses obtained by caesarean-sectioning for analysis of anti-RSV F IgG.

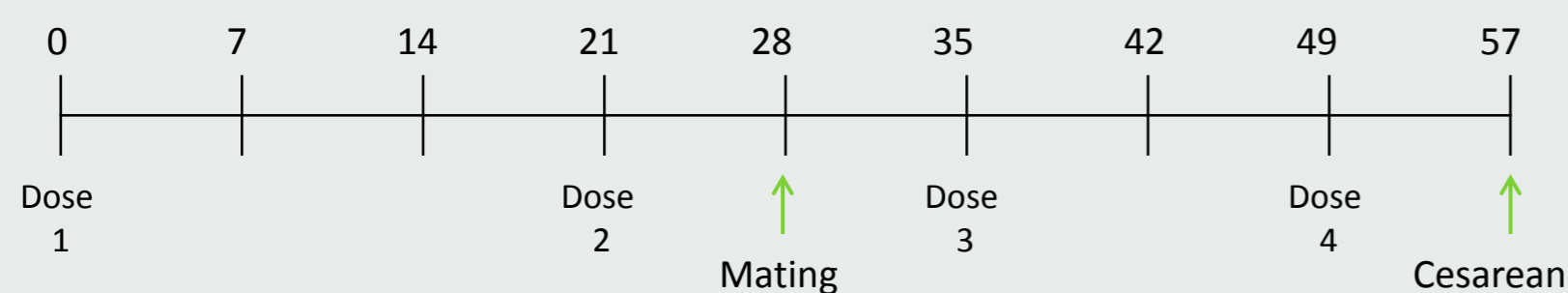
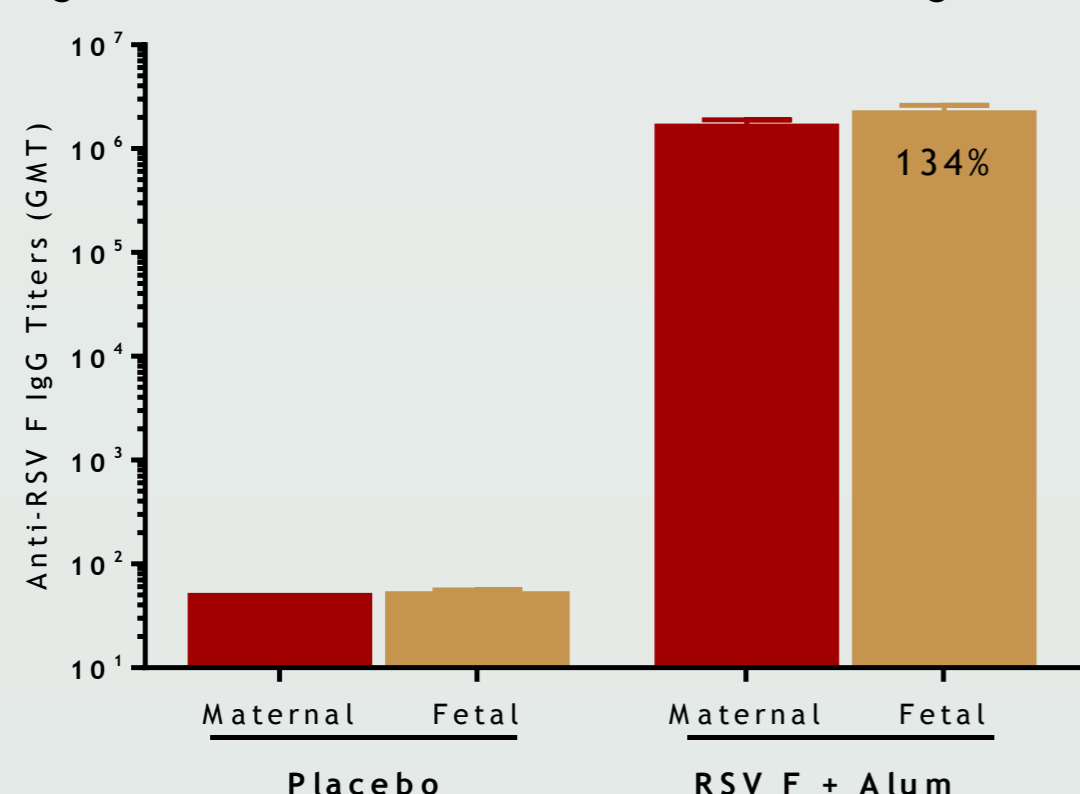


Figure 1: Maternal and Fetal Anti-RSV F IgG Titers



Number on histograms indicate the percent antibody transfer

## MATERNAL ANTIBODY TRANSFER IN GUINEA PIGS

Presumed pregnant female Hartley guinea pigs were obtained on Day 20 of gestation. All sows received two intramuscular (IM) doses as described below pregnancies were allowed to progress to delivery naturally following immunization. Immunogenicity assessments for anti-RSV F IgG, palivizumab competitive antibody (PCA) and RSV neutralizing antibody responses were determined from sera collected on the respective delivery day (DD) for each sow, and for pups on DD and on day 15 and 30 post-delivery for the remaining pups.

## Study Design

Pregnant Guinea Pigs (N)	Vaccine	Immunization (Gestation Day)	Blood Collection	
			Sows	Pups (N)
8	PBS	GD25, GD46	PND0	PND0, PND15, 30 (N=33)
8	RSV F (30µg)	GD25, GD46	PND0	PND0, PND15, 30 (N=29)
9	RSV F (30µg) + AlPO <sub>4</sub> (400µg)	GD25, GD46	PND0	PND0, PND15, 30 (N=32)

GD: Gestation Day

PND: Post Natal Day

## Sows and Pups Immune Responses

Figure 2: Anti-RSV F IgG Titers

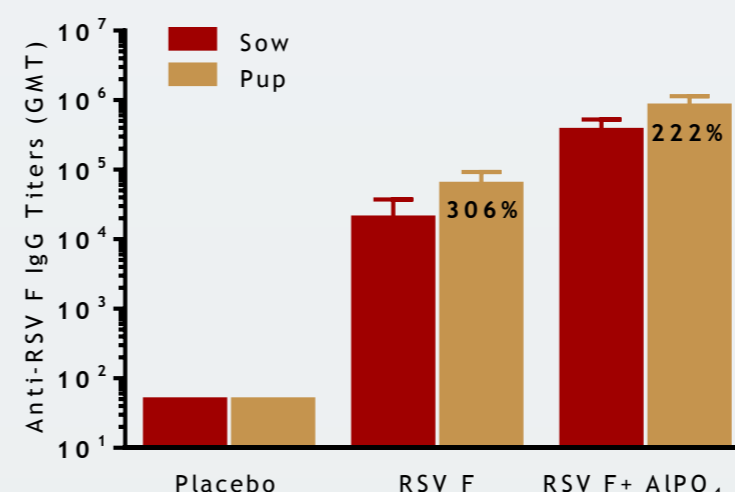


Figure 3: PCA Titers

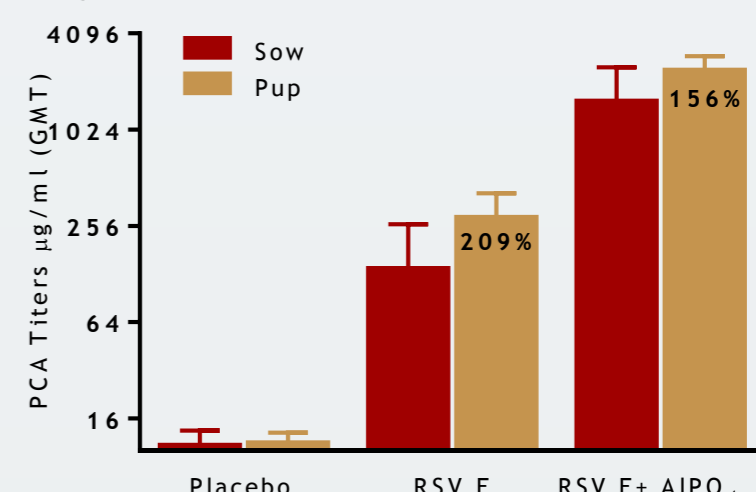
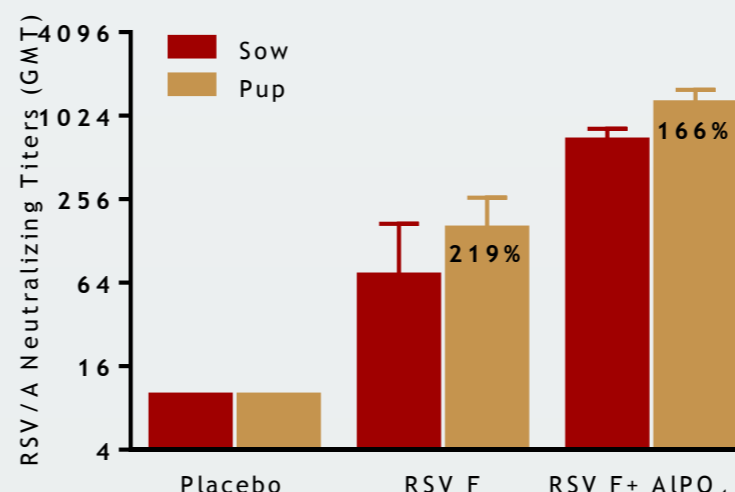


Figure 4: RSV/A Neutralizing Titers



**Immune Responses in Sows (n=8-9) and Pups (n=14-17) on the day of delivery:** Anti-RSV F IgG Titers (Figure 2) and Palivizumab competing antibody (PCA) (Figure 3) were determined by ELISA and reported as GMT with 95% CI. Neutralizing antibody titers against RSV-A2 (Figure 4) were determined by plaque assay and expressed as GMT with 95% CI. Number on histograms indicate the percent antibody transfer.

## Anti-RSF F Antibody Half-Life in Pups

Figure 5: Anti-RSV F IgG Titers

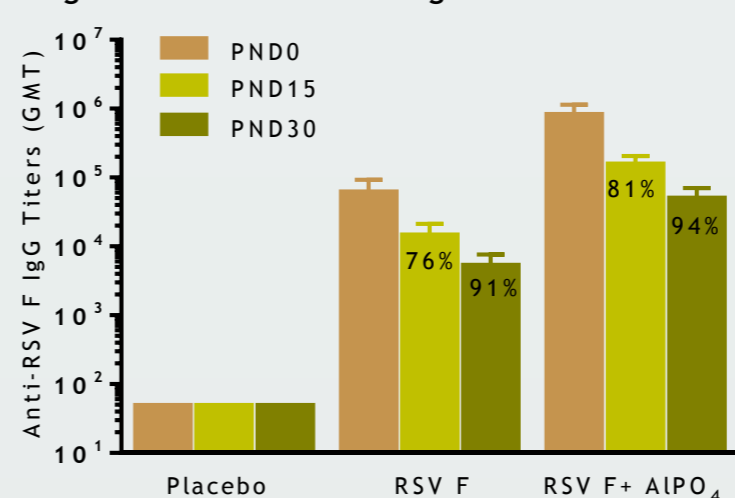


Figure 6: PCA Titers

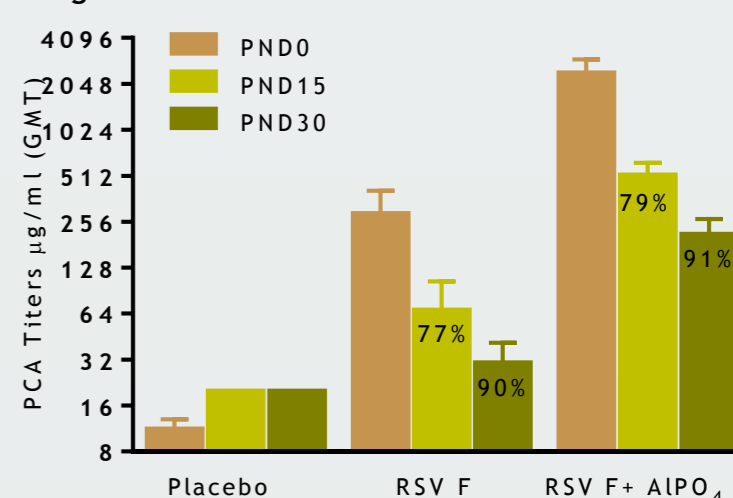
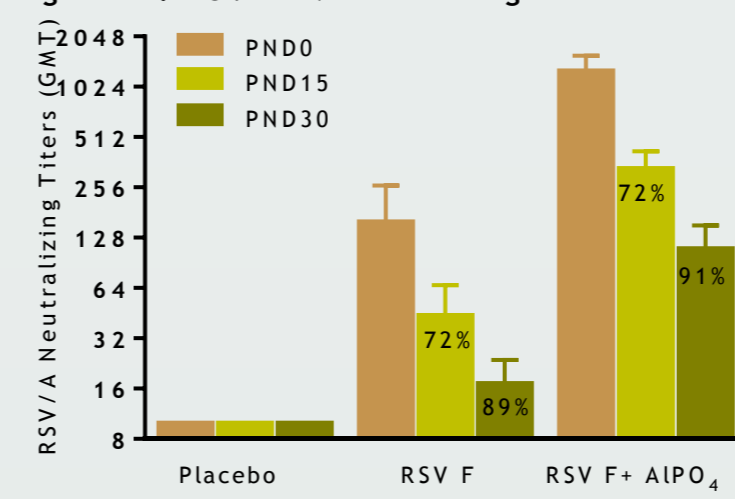


Figure 7: RSV/A Neutralizing Titers



**Immune Responses in Pups on PND0, PND15 and 30:** Anti-RSV F IgG Titers (Figure 5) and PCA (Figure 6) were determined by ELISA and reported as GMT with 95% CI. Neutralizing antibody titers against RSV-A2 (Figure 7) were determined by plaque assay and expressed as GMT with 95% CI. The numbers on histograms represent the percent of antibody decay. Number on histograms indicate the percent antibody reduction from birth.

## CONCLUSIONS

- 100% of pups born from RSV F vaccinated sows had vigorous anti-RSV F IgG, PCA and RSV/A neutralizing titers on the day of delivery.
- Anti-RSV F IgG, PCA and RSV neutralizing antibody titers were higher in pups than those observed in their birth mothers, consistent with a concentration of these antibodies in the sera of newborn pups as well.
- Anti-RSV F IgG, PCA and neutralizing antibody responses that were 7- to 15-fold higher with the adjuvanted vaccine.
- Antibody titers declined on Day 15 and Day 30 following birth but the levels remain still high.
- Immunization with RSV F vaccine before and during pregnancy was safe as indicated by similar rate of pregnancy and litter size observed in placebo and vaccine groups.

Maternal immunization with RSV F Vaccine has the potential to treat/prevent serious RSV disease in infants.