

# Maternal Immunization of Pregnant Baboons with the RSV F Nanoparticle Vaccine Leads to Trans-placental Transfer of High Affinity Functional Antibodies in Infants

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Poster 53

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## Abstract

**Maternal immunization of pregnant baboons with the RSV F nanoparticle vaccine leads to trans-placental transfer of high affinity functional, antibodies in infants.**

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**Background:** The infant olive baboon, *Papio cynocephalus anubis* develops RSV disease with replication of virus and clinical symptoms, that closely mimics the findings observed in human infants when challenged with live virus. The RSV F nanoparticle vaccine (F vaccine) is a near-full length recombinant F protein that has been evaluated for safety and immunogenicity in women of childbearing age. In this setting, the vaccine induces high levels of antibodies that compete for F antigenic site II binding (palivizumab competing antibodies, PCA) as well as increases in neutralizing and anti-F IgG antibodies. In active or passively immunized cotton rats, the vaccine has been shown to be safe, immunogenic and protective against challenge in a manner comparable to palivizumab. We immunized pregnant baboons at the onset of third trimester and measured the extent of maternal antibody transferred to the infants.

**Methods:** Seronegative, 5-15 year old pregnant baboons (n=4) were immunized at onset of third trimester 3 times at 21 day intervals with 0.5ml of 60 µg RSV F with 1.2 mg aluminum phosphate adjuvant intramuscularly. Infant baboon sera were evaluated for the presence of anti-F, PCA and RSV A neutralizing antibodies (MN). Antibody binding kinetics were measured using Biacore T200 at birth for both mother and infant.

**Results:** At the time of delivery anti-F (104,396 vs 56,761, 54%), palivizumab competing (169 vs 139 PCA, 85%) and RSV-A MN (226 vs 190 MN, 84%) antibodies were detected in F vaccine immunized mothers and infants, respectively. RSV F antibodies transplacentally transferred to infants had comparable dissociation constants in comparison to their mothers antibodies drawn simultaneously ( $k_{on}$  ( $M^{-1}s^{-1}$ ) 2.5 vs 2.1 x 10<sup>5</sup>,  $k_{off}$  ( $M^{-1}s^{-1}$ ) 2.8 vs 6.6 x 10<sup>-5</sup>).

**Conclusions:** Functional and high avidity antibodies specific to RSV F are transported transplacentally to infant baboons born to RSV F vaccinated mothers in the third trimester. These findings in a non-human primate model indicate that antibodies associated with protection in sero-epidemiology studies (MN) and randomized clinical trials with palivizumab (PCA) can be transmitted to infants and suggests that similar activity may be expected in humans after maternal vaccination.

## Introduction

Approximately 50% of respiratory syncytial virus (RSV) infections requiring hospitalization of human infants occur in their first 3 months of life. Immunization of mothers against RSV might then provide adequate levels of RSV neutralizing antibody to protect young infants, and markedly reduce the burden of RSV infection. We recently established that 28 day old infant baboons challenged with RSV develop illness that is similar to that of human infants, clinically, immunologically and histologically. We therefore determined if immunization of maternal baboons would protect their infants against an RSV challenge.

## Methods

Seronegative, 5-15 year old pregnant baboons (n=5) were immunized at onset of third trimester 3 times at 21 day intervals with 0.5ml of 60 µg RSV F with 1.2 mg aluminum phosphate adjuvant intramuscularly. Infant baboon sera were evaluated for the presence of anti-F, antibody competing for the same antigenic site as palivizumab (PCA) and RSV A neutralizing antibodies (MN). Antibody binding kinetics were measured using Biacore T200 at birth for both mother and infant. Five additional mothers were included as controls.

We infected their infant baboons at 4 weeks of age with 4 x 10<sup>8</sup> units with a human A2 strain of RSV intratracheally. Respiratory rate was determined at baseline and over the next ten days after infection. Bronchoalveolar lavage (BAL) was performed at baseline and at intervals following infection to determine the titer of RSV in BAL fluids.

## Results

**Table 1: Transplacental transfer of antibodies**

Assay	N	Mom	Infant	% Transfer
Anti F	4	104,396	77,620	74%
PCA	4	168	139	83%
MN	4	226	190	84%

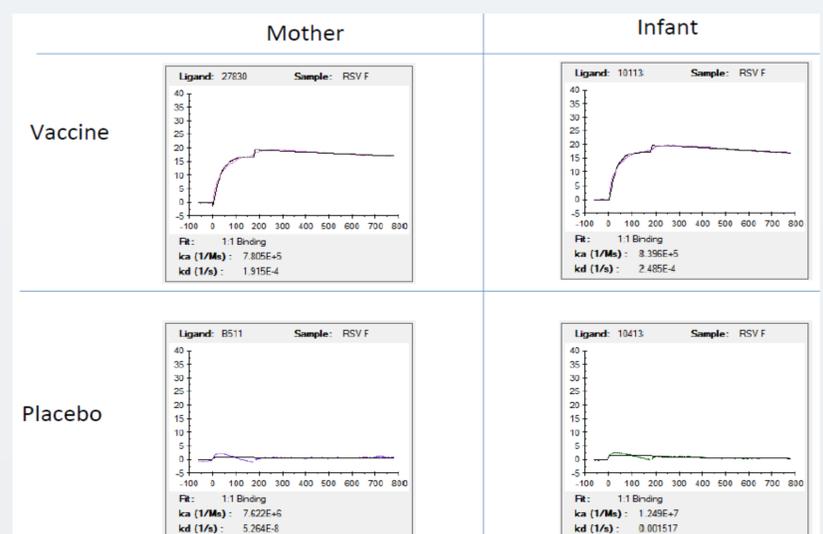
**Transplacental transfer of maternal antibodies from RSV-vaccinated mothers to their infants.** Transfer of antibodies was measured in mothers and infants one day after delivery. Efficiency of transfer of antibodies ranged from 74-84%

**Table 2 : RSV antibodies in mothers and infants**

Group (n=5)	PCA		Neut		Anti F		Lung Viral Load	
	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
Maternal	171	<20	381	<20	115,535	191	-	-
Infant	53	<20	113	<20	31,815	97	*25,634	*103,465

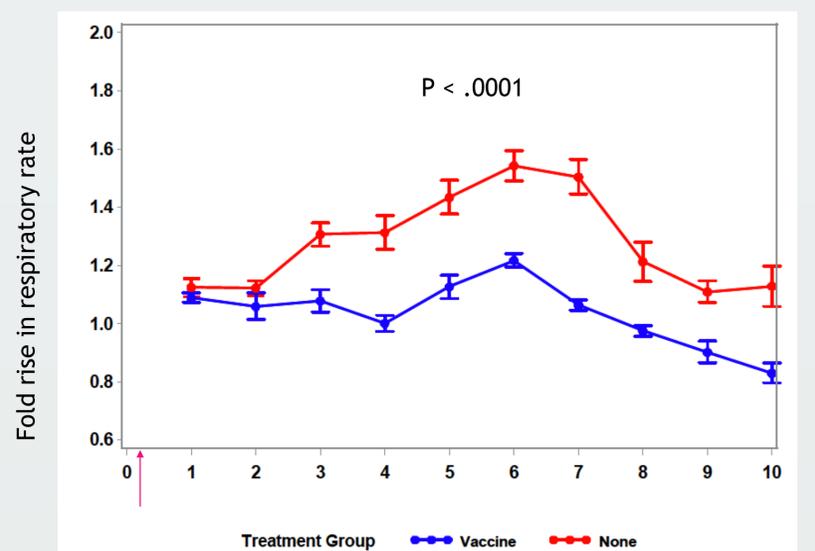
**RSV-specific antibodies in sera of immunized mothers and infants.** Maternal titers were measured on the day of delivery. Infant titers were drawn at 28 days of age, just before RSV infection. Viral load was measured in BAL fluid obtained on Day 5 after infection (peak).

**Figure 1 : Binding affinity of RSV antibodies**



**Binding affinities of RSV antibodies.** High affinity antibodies crossed the placenta from mother to infant. The  $K_{on}$  and  $K_{off}$  were similar for mother and infant

**Figure 2 : Protection of infants by maternal immunization**



**Fold rise in respiratory rates above baseline rate (Day 0) after RSV challenge in infants of vaccinated and unvaccinated mother baboons (n = 5 per group).** Maternal immunization resulted in reduced respiratory rates in infants after RSV challenge, in comparison to infants of control mothers. Oxygenation was also improved in infants of vaccinated mothers (not shown). Arrow indicates time of challenge.

## Conclusions

**Antibodies induced in mother baboons vaccinated with with RSV F nanoparticle vaccine crossed efficiently to the infant**

**The presence of maternally-acquired antibody was associated with lower viral titers in the infant following challenge**

**Binding affinity of antibodies was similar in mother and infant**

**Maternal immunization resulted in reduced respiratory rates after RSV challenge of infants**

**Maternal immunization may prove effective in protecting human infants against RSV infection**

## Funding

Novavax. No other conflicts to declare