

GSK's Pediatric RSV vaccine program

**FDA VRBPAC
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Ilse Dieussaert

Overview of GSK's Pediatric RSV vaccine candidate



Global intent	<ul style="list-style-type: none">• Active immunization of infants for the prevention of RSV LRTI
Vaccination regimen	<ul style="list-style-type: none">• Two-dose regimen from 2 months onwards• Co-administration with routine pediatric vaccines
Vaccine composition	<ul style="list-style-type: none">• Adenovector coding for 3 antigens (F; N and M2.1)
Stage of development	<ul style="list-style-type: none">• Phase I: completed• Phase I/II: dose-escalation in seropositive infants ongoing

Key challenges linked to RSV pediatric vaccine development

- **The early burden of disease requires vaccination early in life:**
 - Immature immune system & presence of maternal antibodies
 - Crowded pediatric schedule:
 - Implementation hurdles
 - Possible interference with other pediatric vaccines
- **History of enhanced disease after vaccination with FI-RSV impacts key elements of the program:**
 1. Vaccine candidate selection
 2. Preclinical assessment
 3. Clinical development

Stages impacted by ERD:

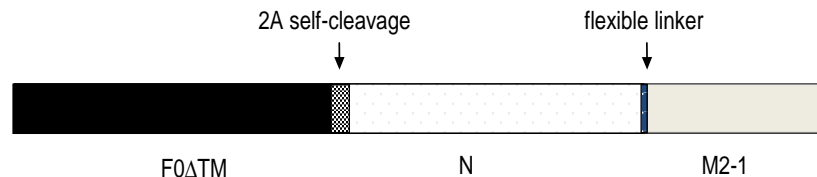
1. Vaccine candidate selection
2. Preclinical assessment
3. Clinical development

GSK selected a Chimpanzee Adenovirus 155 (ChAd155-RSV) to mitigate the risk of ERD



- **ChAd155-RSV vaccine candidate:**

- Codes for 3 RSV antigens: F, N, M2.1



- **Appropriate immune response induced by the adenovector:**
 - Intra-cellular expression of the RSV antigens, as with live RSV virus
 - Induction of a Th1 or balanced Th2/Th1 immune response
- **Control of viral replication by:**
 - Neutralizing antibodies (F antigen)
 - CD8 T cells to clear infected cells (F, N and M2.1 antigens)

Stages impacted by ERD:

1. Vaccine candidate selection
2. Preclinical assessment
3. Clinical development

GSK has generated a comprehensive data set in small and large animal species



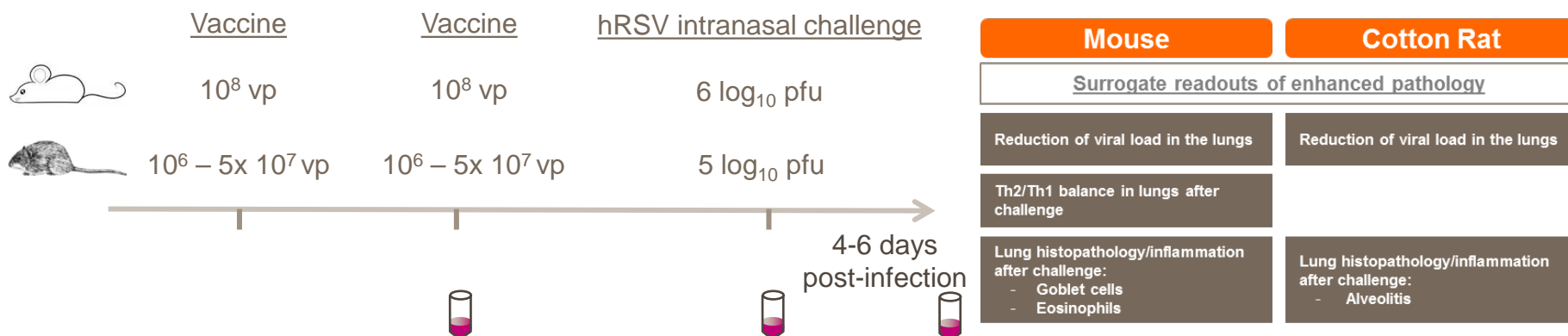
- No single animal model can adequately predict the risk of vaccine-related ERD in humans
- Several models bring complementary information

Mouse	Cotton Rat	Calf
<u>Surrogate readouts of enhanced pathology</u>		
Induction of RSV-specific T cells		Induction of RSV-specific T cells
Induction of functional antibodies	Induction of functional antibodies	Induction of functional antibodies
Reduction of viral load in the lungs	Reduction of viral load in the lungs	Reduction of viral load in the lungs and nose
Th2/Th1 balance in lungs after challenge		
Lung histopathology/inflammation after challenge: <ul style="list-style-type: none">- Goblet cells- Eosinophils	Lung histopathology/inflammation after challenge: <ul style="list-style-type: none">- Alveolitis	Lung histopathology/inflammation after challenge: <ul style="list-style-type: none">- Alveolitis- Lung consolidation
		<u>Clinical readouts</u>
		Clinical manifestations of lower respiratory tract disease (LRTD)

Rodent models of RSV challenge (mouse-cotton rat)



- Semi-permissive models requiring high challenge doses (10^5 - 10^6 pfu)
- No clinical signs of lower respiratory tract disease
- Commonly used for evaluation of ERD through surrogate markers



Study design:

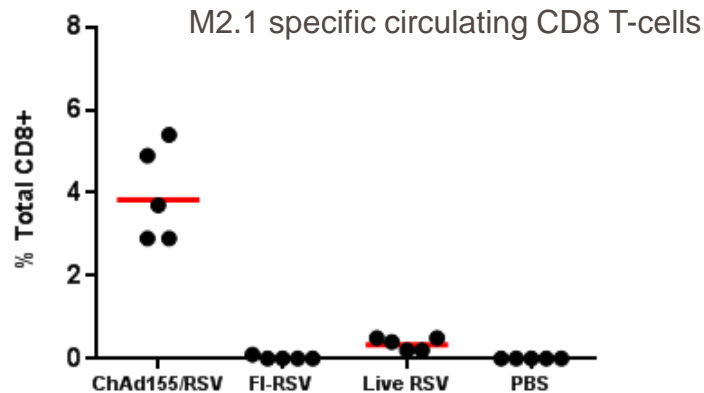
- Vaccinated (2 doses) 3 - 4 weeks apart
- Homologous challenge with hRSV 14 – 21 days post last vaccine dose
- Groups evaluated:
 - GSK's candidate vaccine (ChAd155-RSV)
 - FI-RSV
 - Live RSV
 - Placebo

In mice the ChAd155-RSV vaccine is immunogenic and fully protects from RSV challenge (Balb/c model)



A

ChAd155-RSV induces CD8 T-cells



Mouse

RSV T cells

Functional Abs

Viral load

Th2/1 balance

Lung histopath

Cotton Rat

Viral load

Lung histopath

Calf

Clinical manifestations

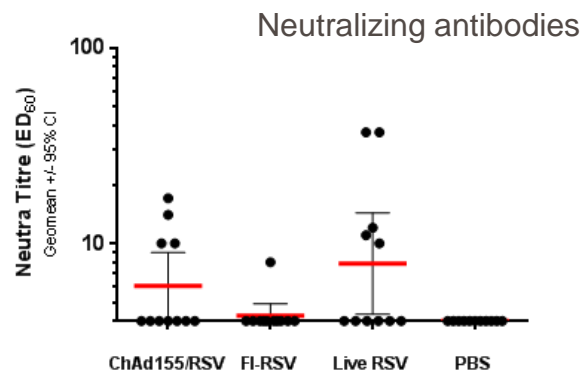
Viral load

Lung histopath

Functional Abs

B

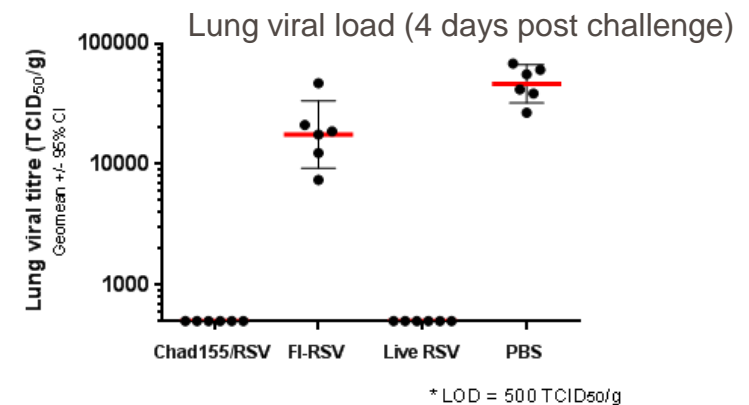
ChAd155-RSV induces neutralizing antibodies comparable to live RSV



challenge

C

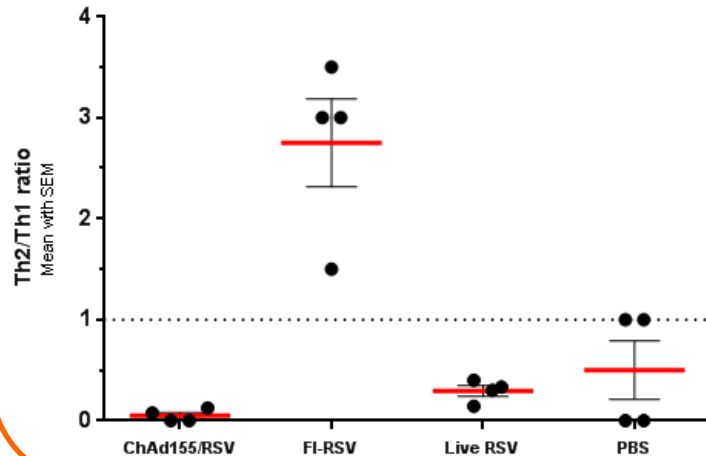
ChAd155-RSV confers full protection post challenge



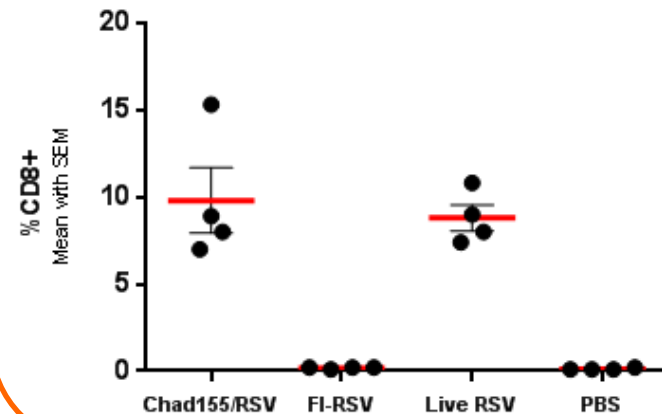
In mice ChAd155-RSV does not induce signs of enhanced pathology post challenge in the lungs



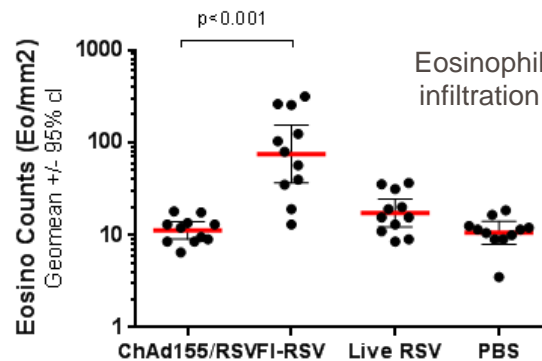
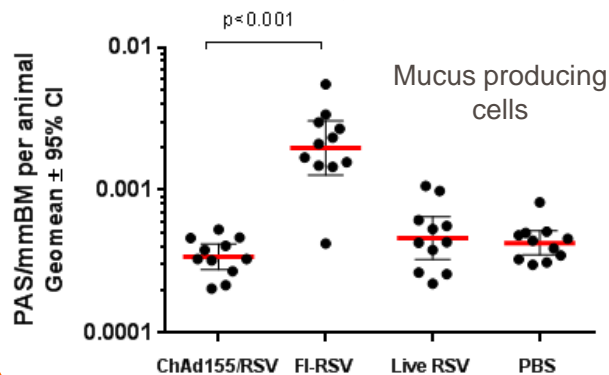
A ChAd155-RSV induces CD4 Th1-bias*



B ChAd155-RSV induces IFN γ ⁺ CD8 T-cells



C Levels of mucus producing cells and eosinophils are increased by FI-RSV but not by ChAd155-RSV



Mouse	Cotton Rat	Calf
RSV T cells	Viral load	Clinical manifestations
Functional Abs	Lung histopath	Viral load
Viral load		Lung histopath
Th2/1 balance		Functional Abs
Lung histopath		

*Th2 marker: IL-13

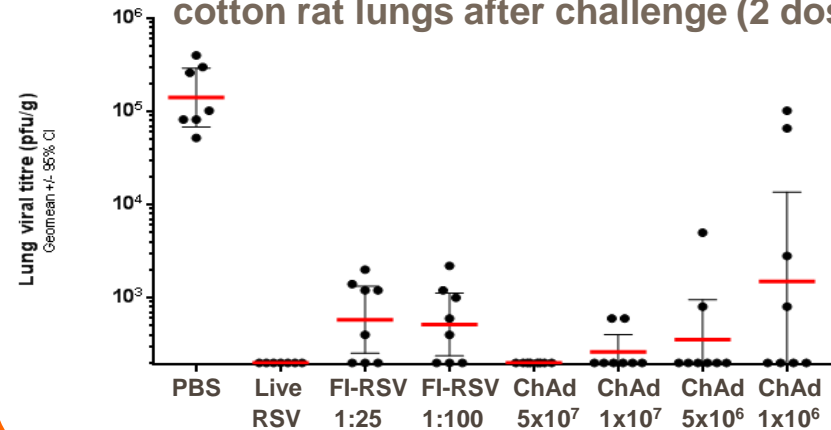
*Th1 marker: IFN γ

In cotton rats the ChAd155-RSV vaccine protects from RSV challenge and does not cause alveolitis



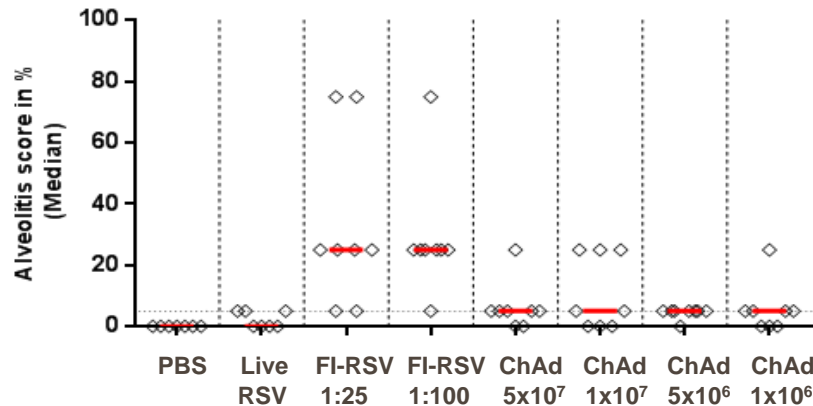
A

Dose-dependent reduction in viral load in cotton rat lungs after challenge (2 doses)



B

Alveolitis scores in animals vaccinated with ChAd155-RSV are significantly lower than in the FI-RSV group



Mouse	Cotton Rat	Calf
RSV T cells	Viral load	Clinical manifestations
Functional Abs	Lung histopath	Viral load
Viral load		Lung histopath
Th2/1 balance		Functional Abs
Lung histopath		

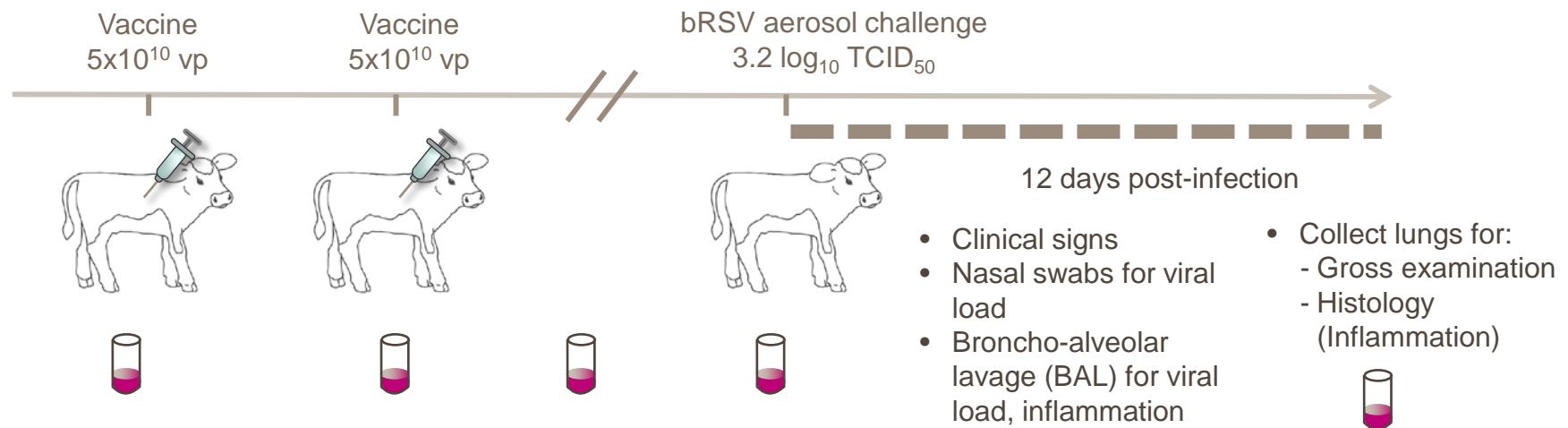
The calf model of RSV challenge



- Similarities in the epidemiology and pathogenesis of bovine RSV (bRSV) in calves and human RSV (hRSV) in infants
- High level of genetic and antigenic similarity between bRSV and hRSV
- Fully permissive to bRSV: only low challenge dose required
- A unique disease model to directly measure clinical signs of disease and does not depend on a surrogate marker for detection of enhanced disease

Mouse	Cotton Rat	Calf
<u>Surrogate readouts</u>	<u>Surrogate readouts</u>	<u>Surrogate readouts</u>
Induction of RSV-specific T cells		Induction of RSV-specific T cells
Induction of functional antibodies	Induction of functional antibodies	Induction of functional antibodies
Reduction of viral load in the lungs	Reduction of viral load in the lungs	Reduction of viral load in the lungs and nose
Th2/Th1 balance in lungs after challenge		
Lung histopathology/inflammation after challenge: Goblet cells Eosinophils	Lung histopathology/inflammation after challenge: Alveolitis	Lung histopathology/inflammation after challenge: Alveolitis Lung consolidation
		<u>Clinical readouts</u>
		Clinical manifestations of lower respiratory tract disease (LRTD)

Using the calf model to evaluate efficacy and enhanced disease



- **Study design:**

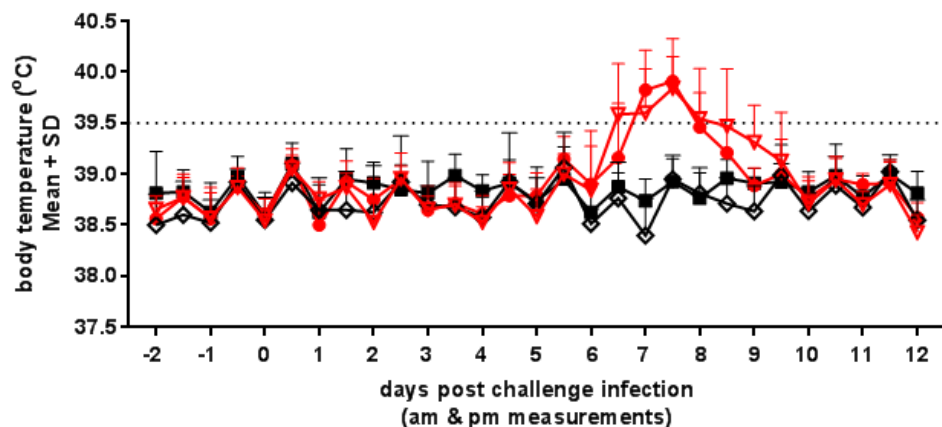
- Vaccinated (2 doses) 4 weeks apart
- Heterologous challenge with bRSV 1 or 4 months post last vaccine dose
- Groups evaluated:
 - GSK's candidate vaccine (ChAd155RSV)
 - Placebo

In calves clinical signs of RSV disease are decreased in vaccinated animals



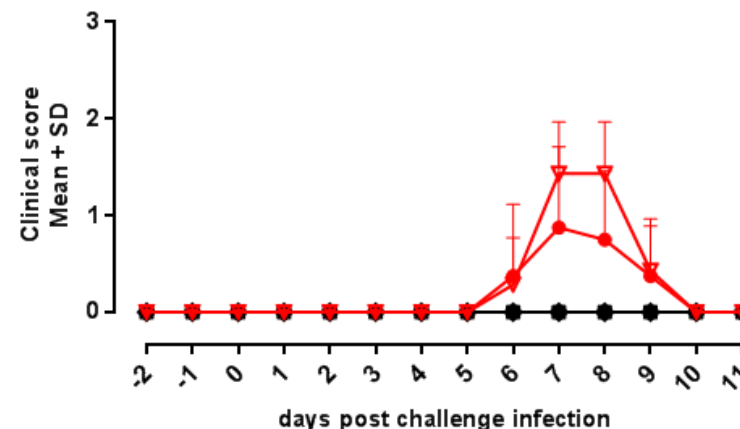
A

Fever

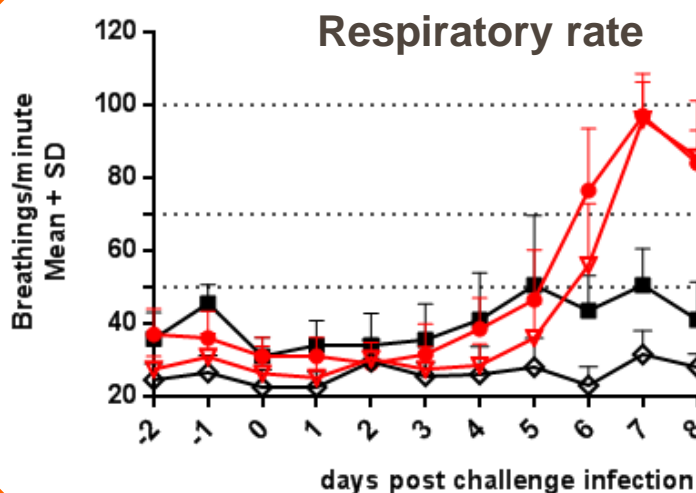


B

General illness



- Ctrl - 1 month
- ChAd155-RSV - 1 month
- ▼ Ctrl - 4 months
- ◆ ChAd155-RSV - 4 months



Mouse

- RSV T cells
- Functional Abs
- Viral load
- Th2/1 balance
- Lung histopath

Cotton Rat

- Viral load
- Lung histopath

Calf

- Clinical manifestations
- Viral load
- Lung histopath
- Functional Abs

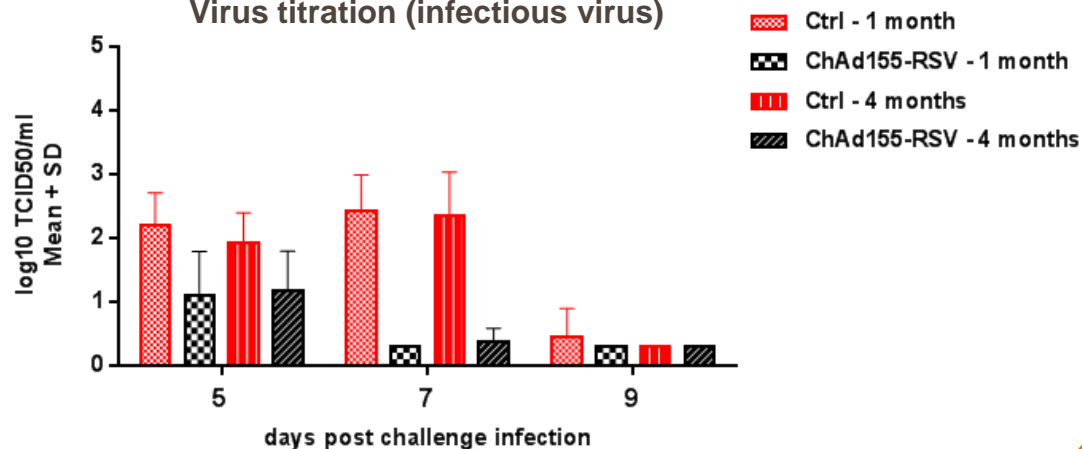
In calves viral load is decreased in vaccinated animals



A

Broncho-alveolar lavage fluid

Virus titration (infectious virus)

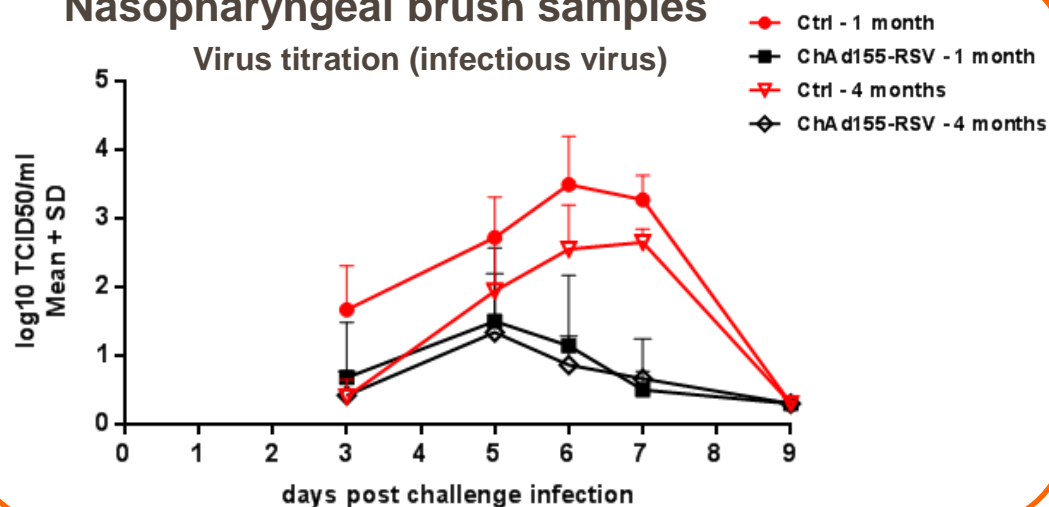


Mouse	Cotton Rat	Calf
RSV T cells	Viral load	Clinical manifestations
Functional Abs	Lung histopath	Viral load
Viral load		Lung histopath
Th2/1 balance		Functional Abs
Lung histopath		

B

Nasopharyngeal brush samples

Virus titration (infectious virus)

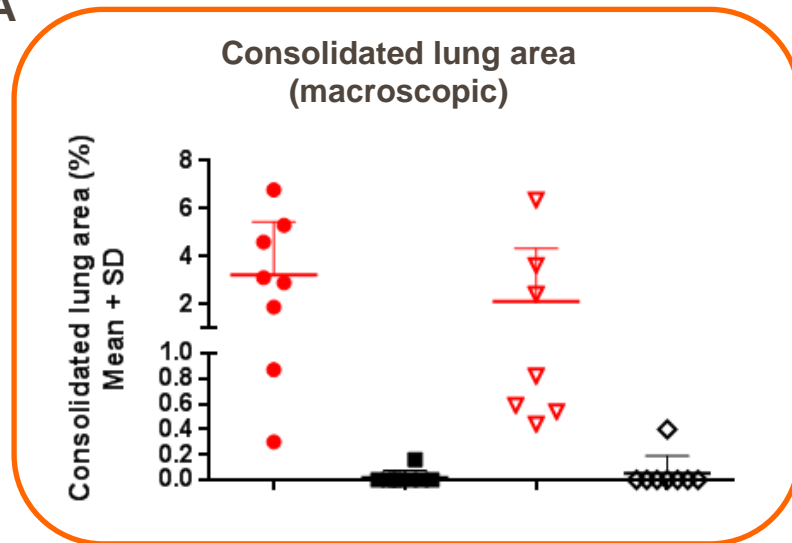


In calves lung pathology is decreased in vaccinated animals

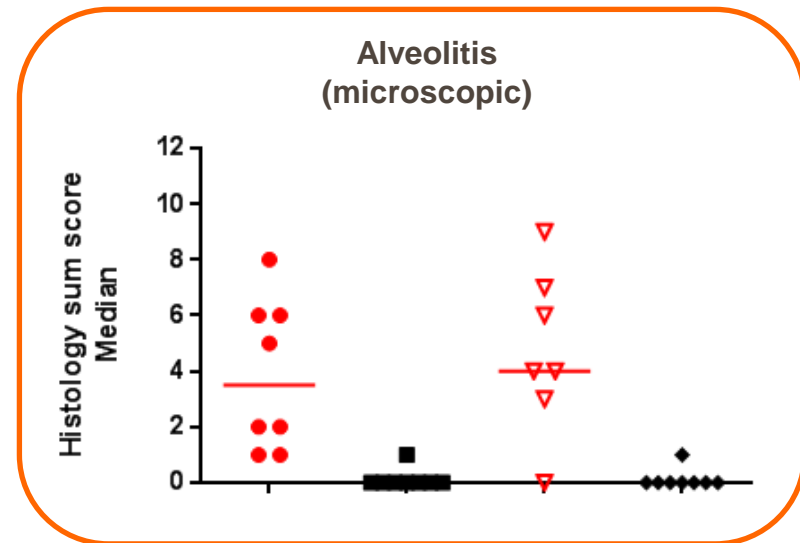


- Ctrl - 1 month
- ChAd155-RSV - 1 month
- ▼ Ctrl - 4 months
- ◇ ChAd155-RSV - 4 months

A



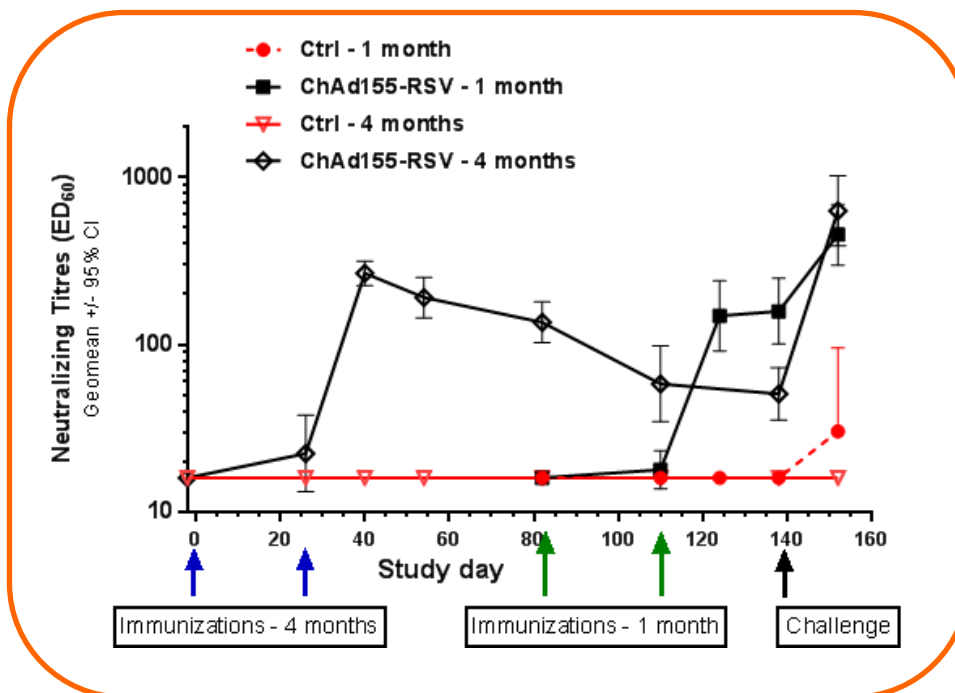
B



Other lung parameters (bronchitis, peribronchitis, interstitial pneumonia) show the same trend

Mouse	Cotton Rat	Calf
RSV T cells	Viral load	Clinical manifestations
Functional Abs	Lung histopath	Viral load
Viral load		Lung histopath
Th2/1 balance		Functional Abs
Lung histopath		

In calves two doses of ChAd155-RSV induce RSV neutralizing antibodies



Mouse	Cotton Rat	Calf
RSV T cells	Viral load	Clinical manifestations
Functional Abs	Lung histopath	Viral load
Viral load		Lung histopath
Th2/1 balance		Functional Abs
Lung histopath		

Pre-clinical key messages



GSK has generated a comprehensive data set in small and large animal species

- No single animal model can adequately predict the risk of vaccine-related ERD in humans
- Several models bring complementary information

Endpoint	Mouse	Cotton Rat	Calf
<u>Clinical readouts</u>			
Clinical manifestations of lower respiratory tract disease (LRTD)	NA	NA	✓
<u>Surrogate readouts of enhanced pathology</u>			
Induction of functional antibodies	✓	✓	✓
Induction of RSV-specific T cells	✓	ND	ND
Reduction of viral load in the lungs	✓	✓	✓
Th2/Th1 balance in lungs after challenge	✓	ND	ND
Lung histopathology/inflammation after challenge	✓ (eosinophils, goblet cells)	✓ (alveolitis)	✓

NA: Not Applicable ND: Not Determined

Stages impacted by ERD:

1. Vaccine candidate selection
2. Preclinical assessment
3. Clinical development

GSK's clinical development plan



Increased confidence in the safety profile of the vaccine

Sequential age de-escalation



All trials in infants are monitored by an IDMC

Clinical development steps prior to RSV naïve infants

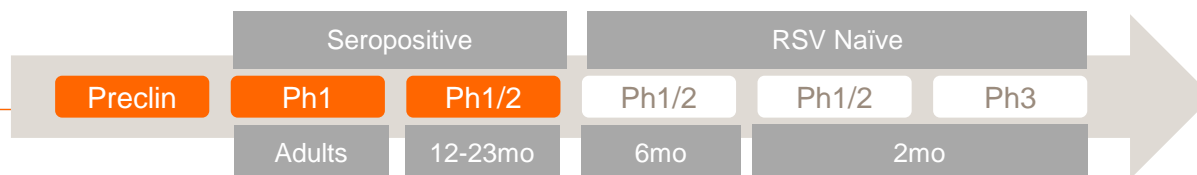


A comprehensive set of experiments in small and large animal species

Phase 1: adults → Phase 1/2: seropositive infants (>12Mo):

- Healthy adult population → infants screened for seropositivity
- Low risk of enhanced respiratory disease in the seropositive population
- Test the highest dose levels for safety and tolerability in adults and toddlers
- Immunogenicity not truly representative of the target population

IDMC/DSMB oversight as from the first trial in children



Further age de-escalation in RSV naïve infants



Age de-escalate in two stages in healthy full term RSV naïve infants :

- First in 6 months old infants, who are less vulnerable to severe RSV disease
- Then in 2 months old, the target population

Clinical studies will be conducted with maximum care :

- In settings with availability of advanced medical care
- Active surveillance for RSV infection and progression to disease in first study
- Document clinical parameters of RSV disease to detect pattern of increased severity
- 1:1 randomization ratio throughout the development
- 2 years follow up of all infants in Phase 2
- Use WHO case definition to compare disease incidence/group
- Measure the immune response

De-risking of ERD in RSV naïve infants prior to Ph III



- GSK's primary goal is to ensure the maximum safety of subjects at each step, and before moving into a Phase 3 study → Patient safety first
 - GSK development plan addresses the key challenges linked to prior history of ERD
 1. Vaccine candidate selection → designed to elicit the appropriate immune response
 2. Preclinical assessment → extensive data package in relevant animal models
 3. Clinical development → careful age de-escalation; intensive disease monitoring
- The current preclinical data package shows no evidence of ERD following administration of the ChAd155-RSV vaccine
 - The proposed stepwise age de-escalation will provide increasing confidence in the safety profile of the vaccine at each step

→ **Together, these data support the proposed approach to evaluate the ChAd155-RSV vaccine in RSV naïve children**

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Thank you