

# RSV Research: A Snapshot

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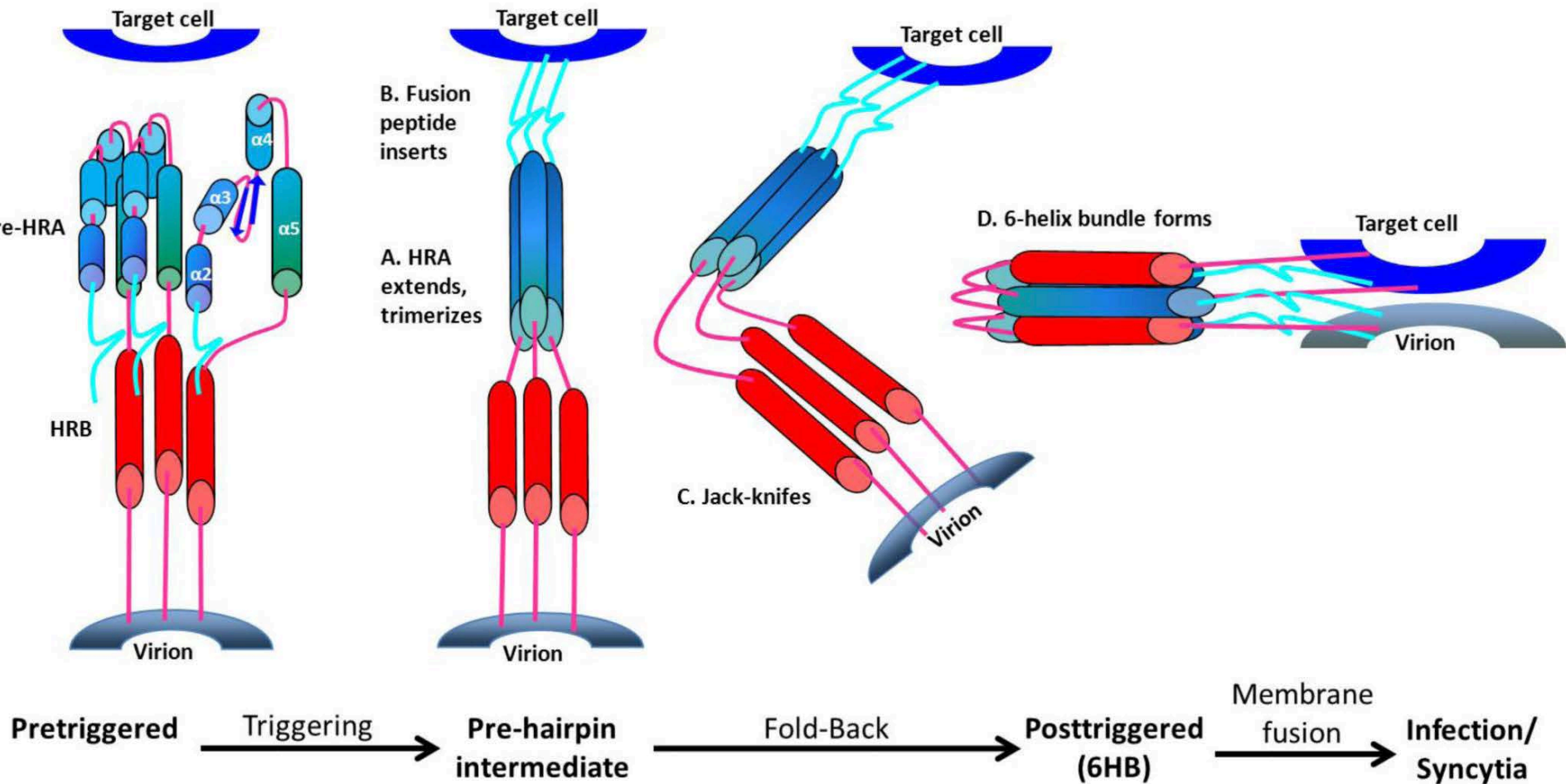
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# Areas to be reviewed

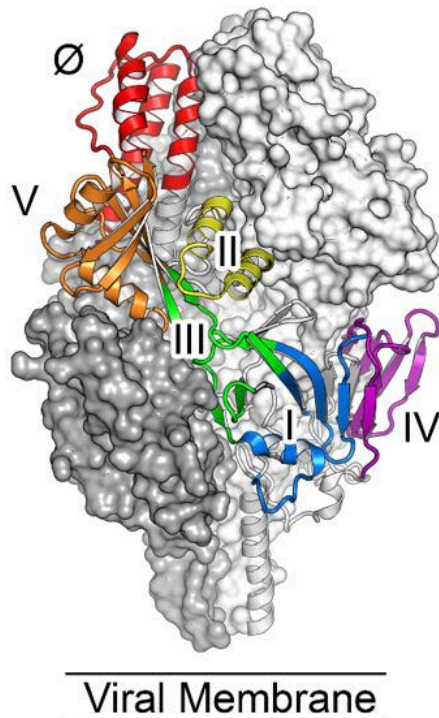
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- Structure of RSV F protein
- Immunological studies of interest
- Epidemiology Studies (Ongoing)
- *Prevention studies (Deb Higgins)*
- Treatment studies
- Long term effects of RSV

# RSV Pre Fusion F- to Post Fusion F

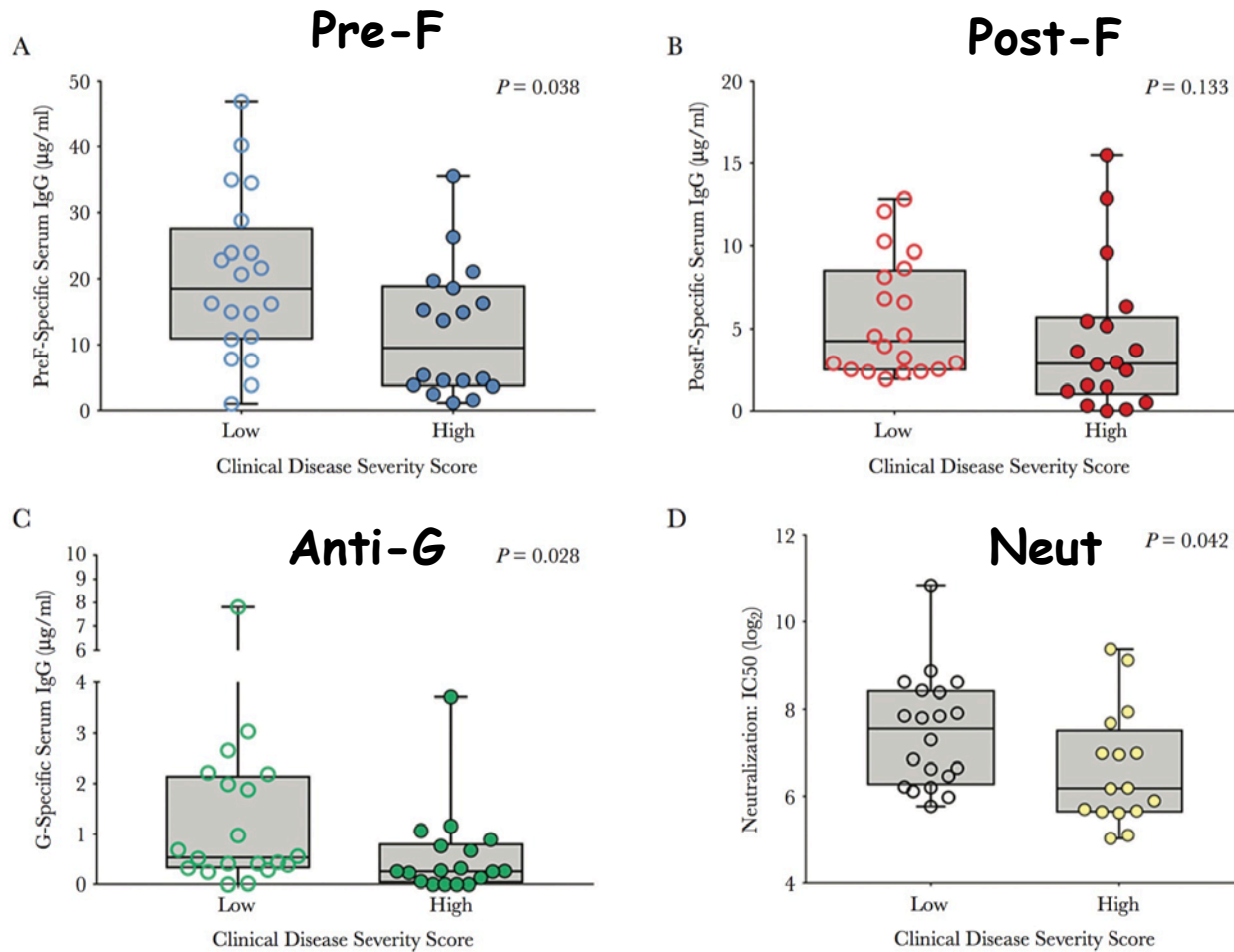


## Antigenic Site Designations



- Site Ø: Pre fusion - D25
- Site I: Post fusion – 131- 2a
- Site II: Pre & Post – Palivizumab
- Site III: Pre fusion – MPE 8
- Site IV: Pre & Post – 101 F
- Site V: Pre fusion – REGN 2222

# Although pre-F is the major viral target for nAbs to RSV, the G protein is also important



# Breast milk antibodies

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- Influenza vaccine trial in Nepal
- Breast milk collected from mothers at 1, 3, 6 months post partum
- Pre F IgA was lower in those without RSV – ARI compared to those with RSV- ARI at 1 month
- In mothers of children with RSV ARI, breast milk RSV Pre F IgA increased over time

# REGAL: 7 Study Questions

- 1. **Epidemiology and disease burden** of severe RSV infection in Western countries.<sup>1</sup>
- 2. Predisposition , morbidity, long-term sequelae and mortality of **preterm infants (<37 wGA) to severe RSV infection** without CLD/BPD or CHD<sup>2</sup>
- 3. Predisposition , morbidity, long-term sequelae and mortality of infants with **underlying CLD/BPD** to severe RSV infection?<sup>3</sup>
- 4. Predisposition , morbidity, long-term sequelae and mortality of infants with **underlying CHD** to severe RSV infection ?
- 5. **Long-term respiratory morbidity** associated with RSVH in infancy, specifically early and late wheeze?<sup>5</sup>
- 6. **Other groups of infants** with underlying medical conditions are at high risk of RSVH and associated morbidity?<sup>6</sup>
- 7. What are the **optimal approaches and strategies for the prevention and treatment** of severe RSV infection and what are the future perspectives in this regard?<sup>7</sup>

1Bont L et al. Infect Dis Ther. 2016. 2Figueras-Aloy J et al. Infect Dis Ther. 2016.

3Paes B et al. Infect Dis Ther. 2016. 4Checchia PA et al. Infect Dis Ther. 2017.

5Fauroux B et al. Infect Dis Ther. 2017. 6 Manzoni P et al.. Infect Dis Ther. 2017.

7 Simões EAF et al. Infect Dis Ther.2017.

# Major Hospital Based Studies

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- **GABRIEL** (Brazil, Cambodia, China, Haiti, India, Madagascar, Mali, Mongolia, Paraguay):
  - 888 Cases; 870 Controls
  - RSV is the second most important cause of pneumonia 18%
    - Benet T et al *Clin Infect Dis* 2017
- **EPIC** Study (USA)
  - 2358 Cases: 726 Controls
  - RSV Hospitalization 4.6/10,000 children/year
- **PERCH** Study (Gambia, Mali, Kenya, Zambia, South Africa, Bangladesh, Thailand)
  - 4232 Cases: 5325 Controls
  - RSV is the most important pathogen at all sites of radiographic pneumonia



# Hospital Based Studies (Finished /Ongoing)

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- **IRIS**: (Albania, Jordan, Philippines, Nicaragua)
  - Case control Study in Infants
  - RSV is most important pathogen (analysis ongoing)
- **SARI** Studies (Many world wide: CDC, WHO and others)
- **SHERA** (Indonesia Multicenter center ALRI etiology study)
- **RESCEU** (European Study)
- **KEMRI** (Kilifi Kenya)
  - Nokes DJ (Many publications)
- **NICD** (South Africa)
  - Cohen Madhi (Many publications)

# Major Community Based Studies

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- **Drakenstein** Birth Cohort (South Africa)
  - 314 Pneumonia in 967 Children
  - RSV was the most important pathogen aOR (8.05)
    - Zar et al Lancet Resp Med 2016
- **Argentina** Buenos Aires
  - 84,840 Infants, 2588 Severe RSV LRTI, 157 Died with RSV
  - RSV most frequent cause of death in infants post neonatal
    - Geoghegan AJRCCM 2017
- **SHERA** (Indonesia Multicenter center ALRI etiology study)
- **RESCEU** (European Study)
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# RSV Mortality Studies Ongoing

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- **Argentina** Buenos Aires
- **India:** Melghat
- **Pakistan:** Karachi
- **Zambia:** Lusaka
- **Global:** RSV GOLD (Hospital based and Community Based)

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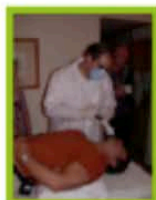
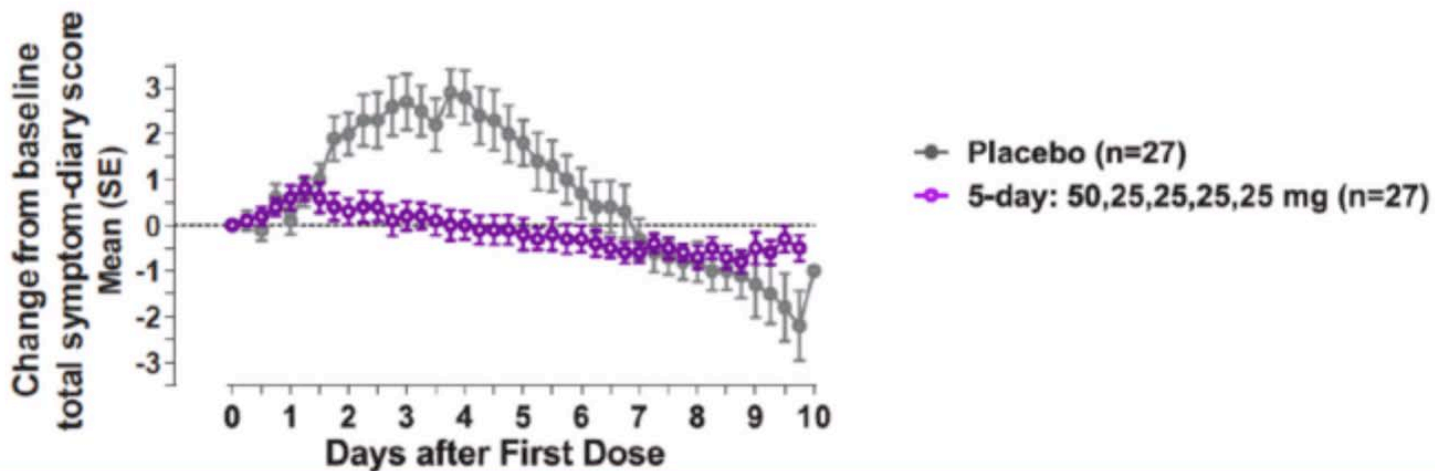
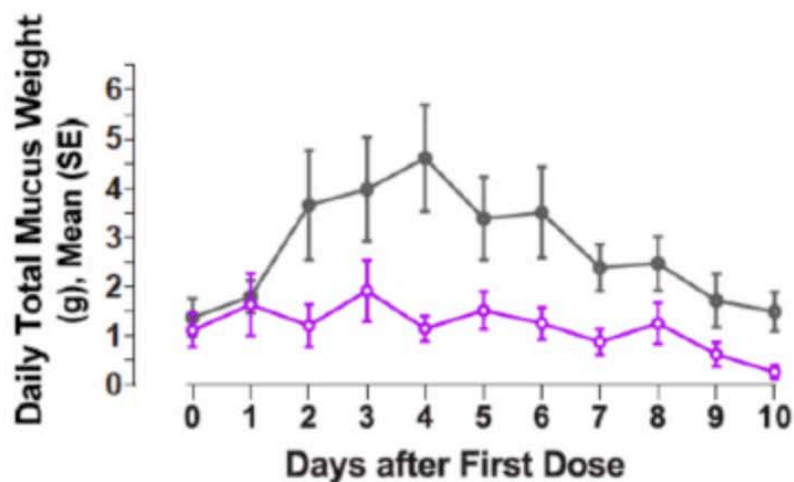
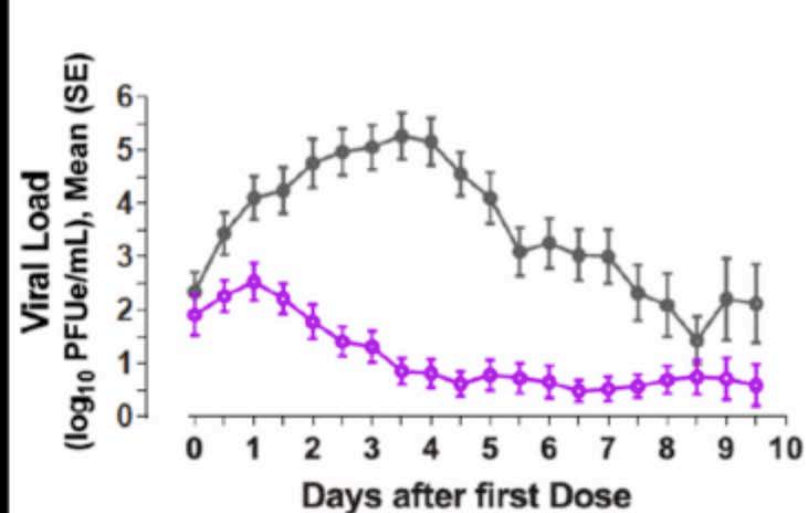
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# Viral and disease dynamics under influence of fusion inhibitor antiviral treatment

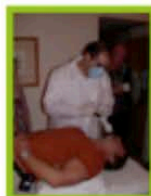
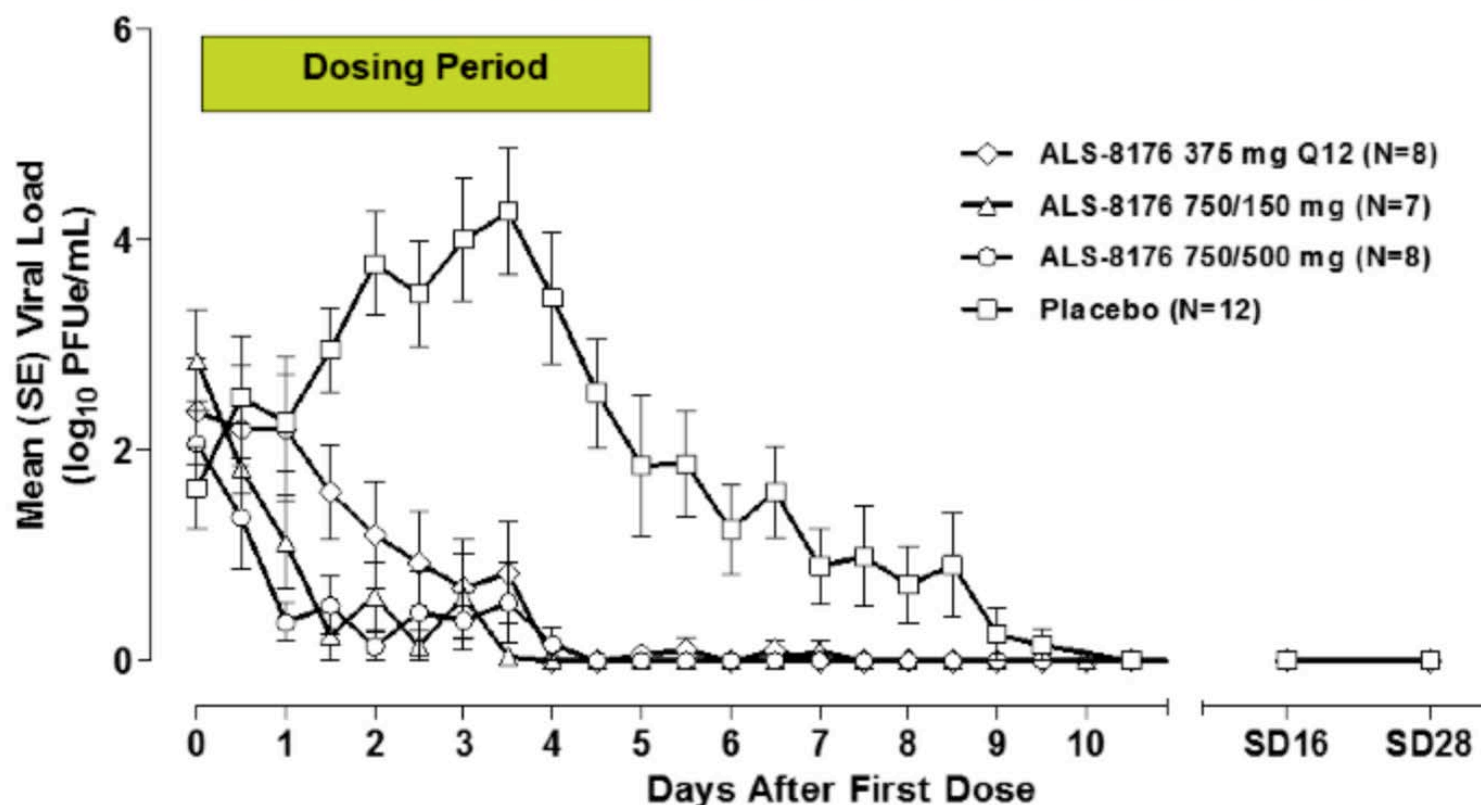
DeVincenzo et al. N Engl J Med 2014;371:711-22

## Cohorts 1-4



# ALS-008176 RSV Challenge Study: Efficacy - RSV Viral Load Over Time (ITT-I Population)

DeVincenzo J, McClure et al. N Engl J Med. 2015; 373(21):2048-2058

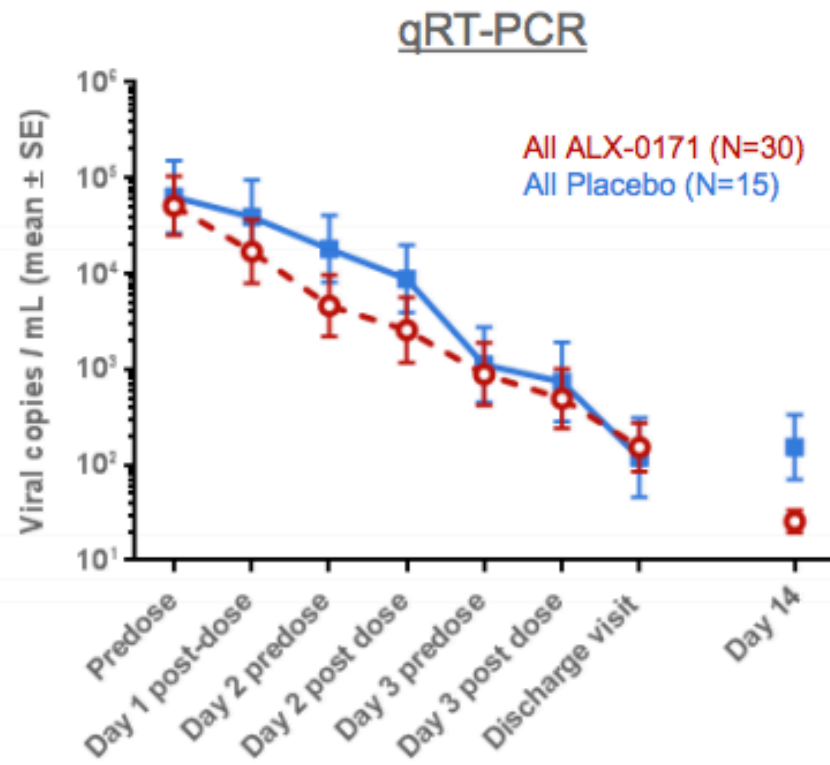
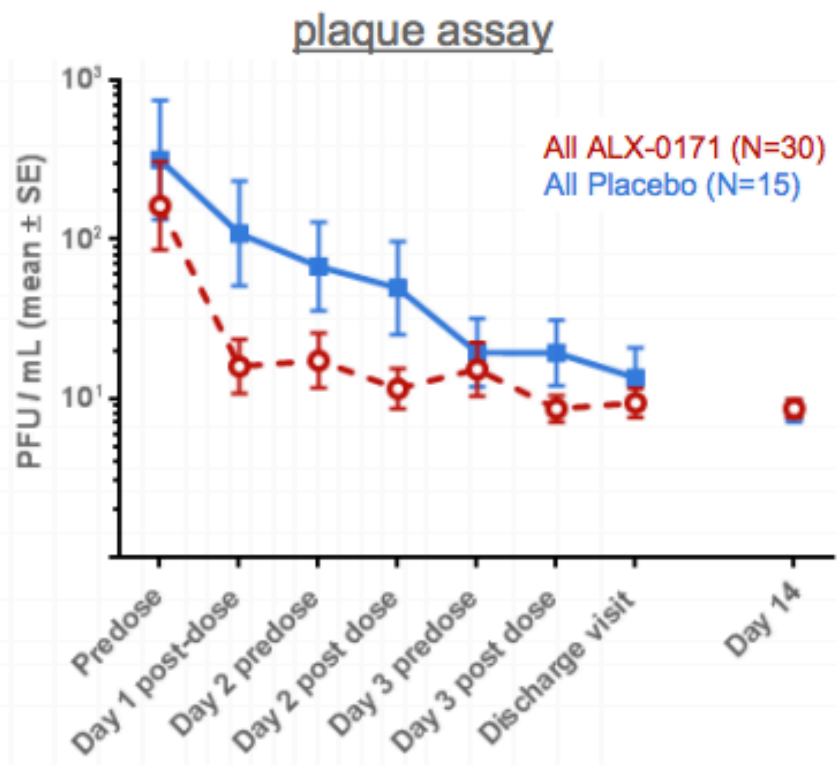


**Rapid clearance of RSV RNA without rebound in all ALS-008176 treatment arms**

PFUe: plaque-forming unit equivalents; SD: Study Day

# First-in-infant Phase I/IIa study

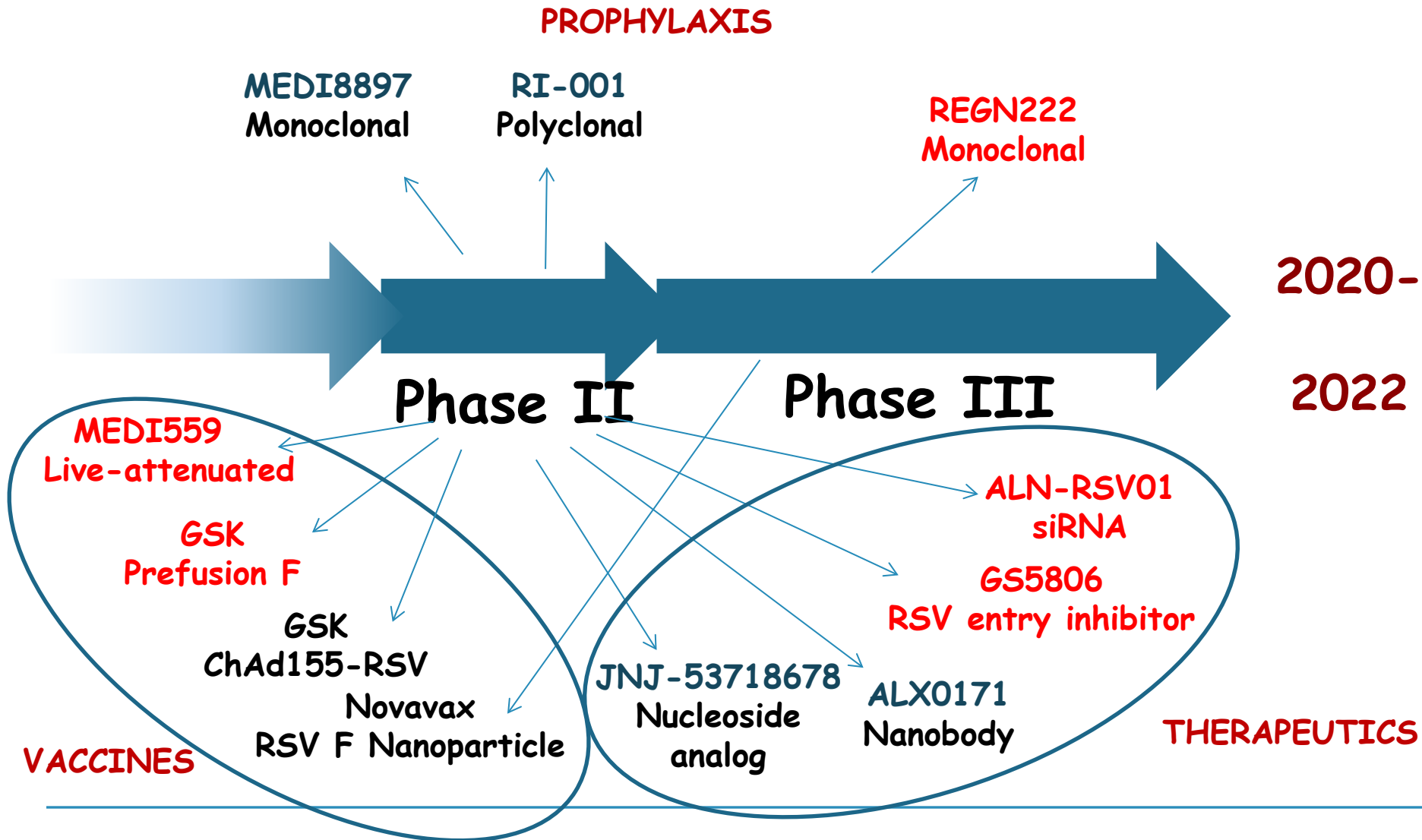
## Anti-viral effect – viral load over time



**Treatment with ALX-0171 had an immediate impact on viral replication in RSV-infected infants**



# RSV: New therapies under investigation

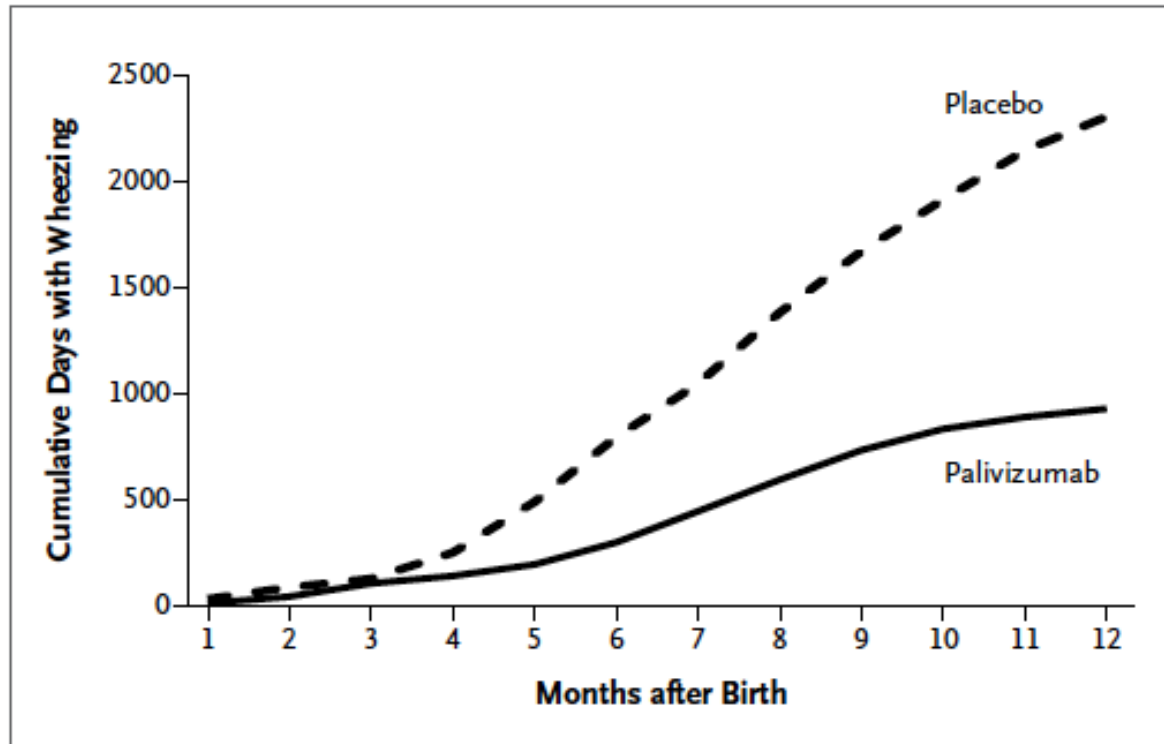


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# RSV and Recurrent Wheeze in Healthy Preterm Infants: Dutch RSV Neonatal Network



**Figure 2.** Cumulative Wheezing Days for 429 Preterm Infants during the First Year of Life.

$P < 0.001$  for the comparison between palivizumab and placebo with the use of Poisson regression.

# Conclusion:

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RSV F protein structure definition is leading to new vaccines  
MAB's and therapeutic possibilities

Antibodies to Prefusion F are probably important in protection

Several large scale studies identify RSV as the single most important cause of hospitalization in LMIC and industrialized countries

Several small molecule therapies are in clinical trials in children and adults.

RSV appears to cause a significant proportion of recurrent wheezing in preterm infants

RSV probably does not cause atopic asthma in preterm infants

RSV has significant long term impact on medical outcomes