

In Focus, RSV infection In Children

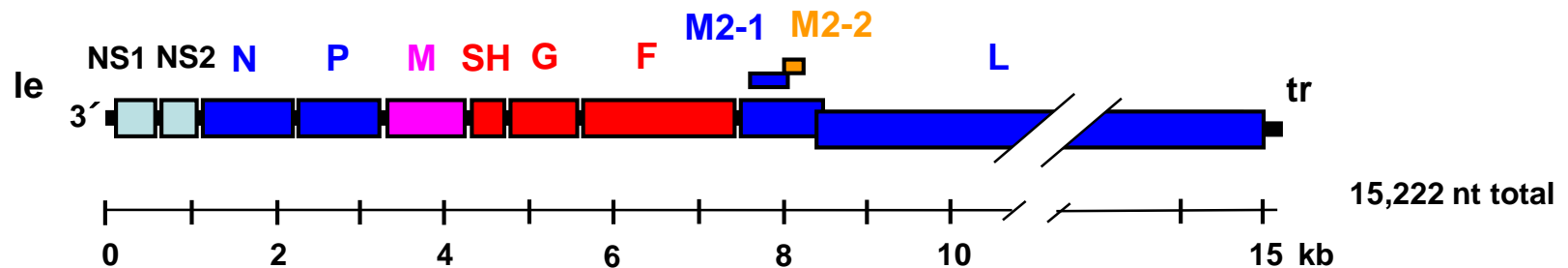
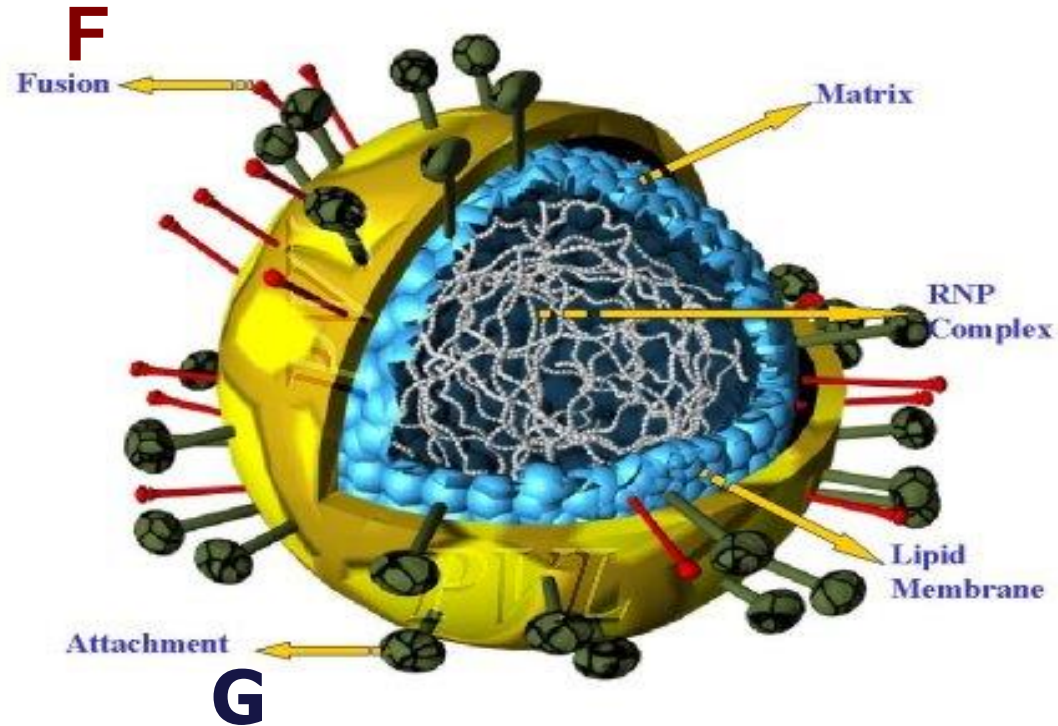
Octavio Ramilo



Outline

1. Importance of RSV disease in children
2. Current therapies for RSV bronchiolitis
3. Immune profiling and disease severity
4. New antivirals for RSV
5. Importance of RSV F protein
6. Preventive strategies for RSV disease

RSV: The Virus

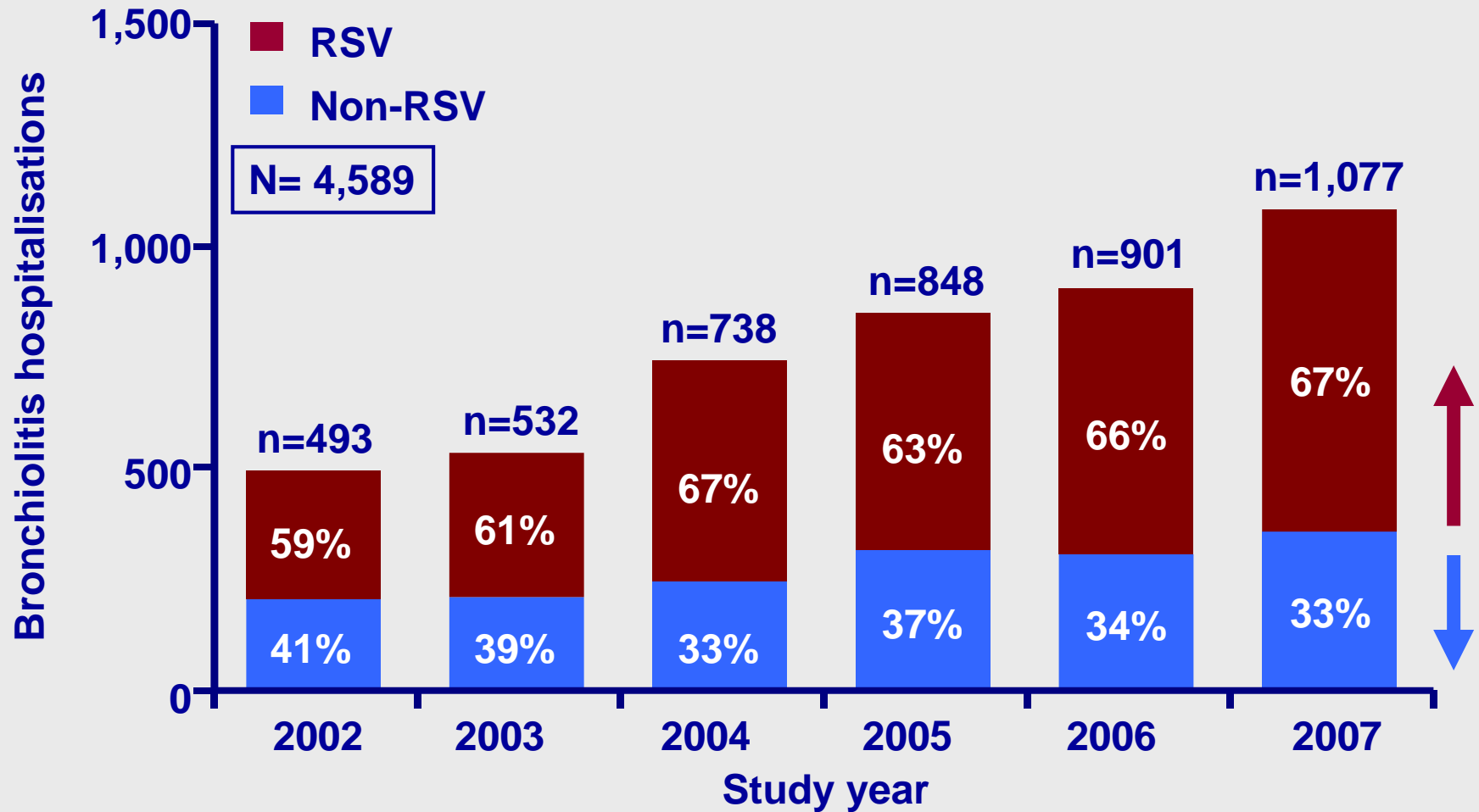


Young infant with RSV bronchiolitis



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.™

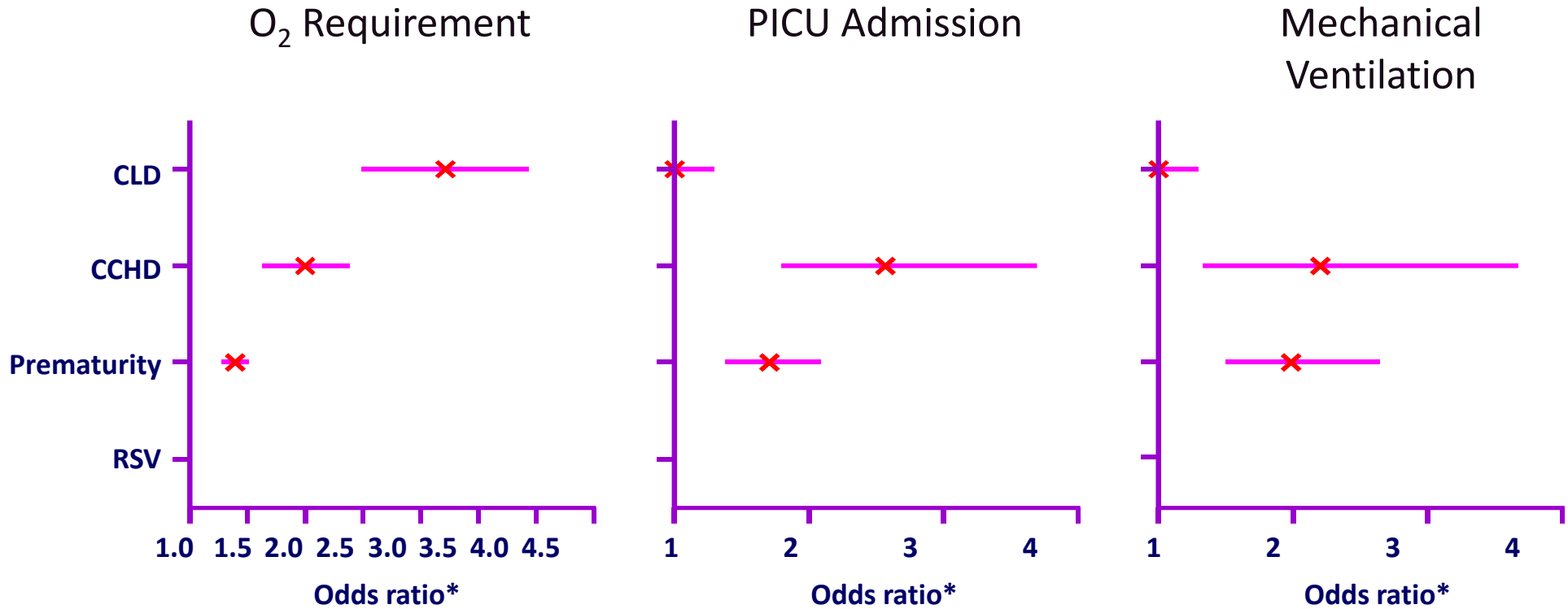
Increase in RSV bronchiolitis hospitalizations



*p<0.01; Chi-square test for trend

Predictors of bronchiolitis disease severity

Logistic regression analyses



*Odds ratios: 95% confidence intervals; p<0.0001

CCHD: complex congenital heart disease

Garcia CG, et al. Pediatrics 2010

Viral etiology of children hospitalized for bronchiolitis in the era of molecular diagnosis

| Country | N (%) pos | Single virus | Multiple viruses | RSV single | RSV co-inf | RV single | hMPV single | PIV single |
|--------------------------|-----------|--------------|------------------|------------|------------|-----------|-------------|------------|
| Israel ¹ | 490 (91%) | 61% | 30% | 49% | 22% | 7% | 2% | 0% |
| France ² | 209 (95%) | 86% | 9% | 46% | 16% | 7% | 4% | NA |
| Spain ³ | 318 (86%) | 62% | 24% | 43% | 18% | 12% | 6% | 1.5% |
| USA ⁴ | 180 (93%) | 70% | 23% | 43% | 18% | NA | 7% | 3% |
| France ⁵ | 180 (96%) | 72% | 24% | 53% | 20% | 12% | 4% | 3% |
| Netherlands ⁶ | 142 (97%) | 56% | 41% | 43% | 30% | 7% | 3% | 0.7% |

1. Miron D, et al. *Pediatr Infect Dis J* 2010;29:e7

2. Marguet C, et al. *PLoS One* 2009;4:e4596

3. Calvo C, et al. *Acta Paediatr* 2010;99:883

4. Stempel HE, et al. *Acta Paediatr* 2009;98:123

5. Richard N, et al. *Pediatr Infect Dis J* 2008;27:213

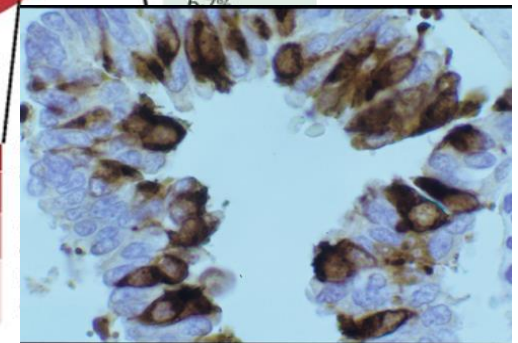
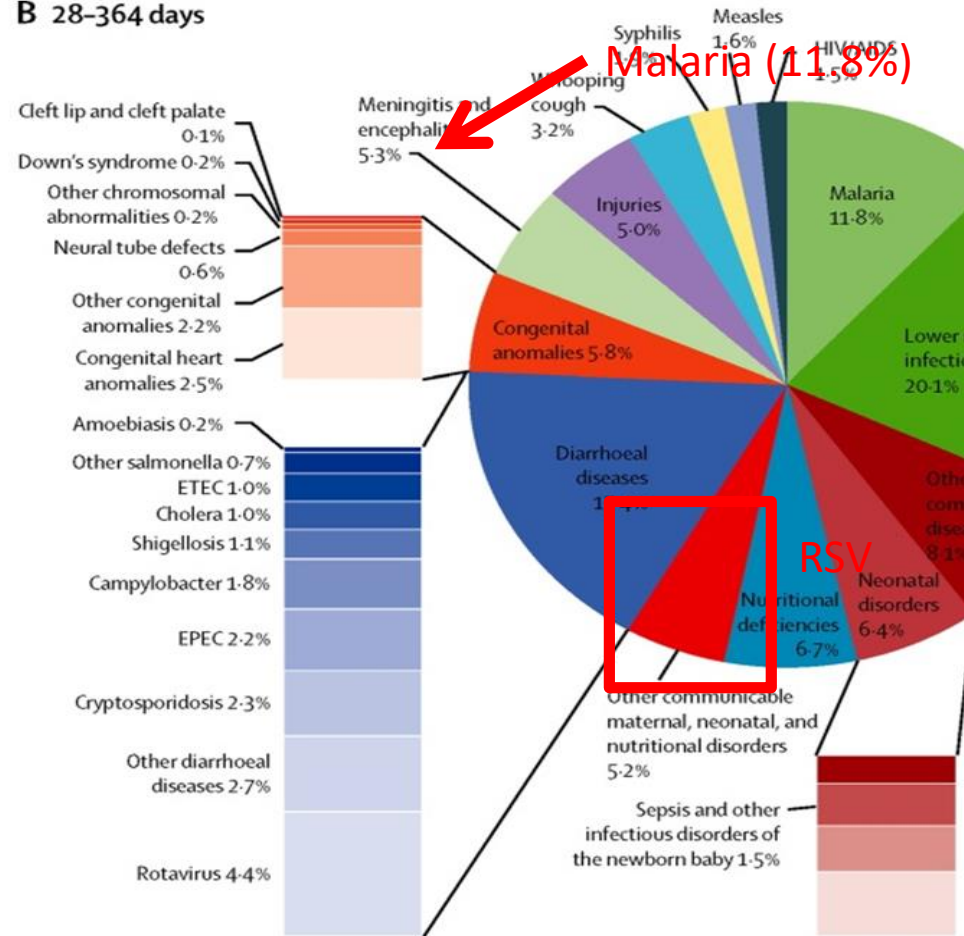
6. Brand H, et al. *Pediatr Pulmonol*, 2011 (ahead of print)

Global RSV Disease Burden

RSV kills more children <1 year than any other pathogen except malaria

28-364 days of life

B 28-364 days



Treatment for RSV Bronchiolitis

◆ Treating the symptoms

- IV Fluids, secretions
- Oxygen

- Bronchodilators

◆ Controlling the inflammatory response

- Corticosteroids
- Antileukotrienes

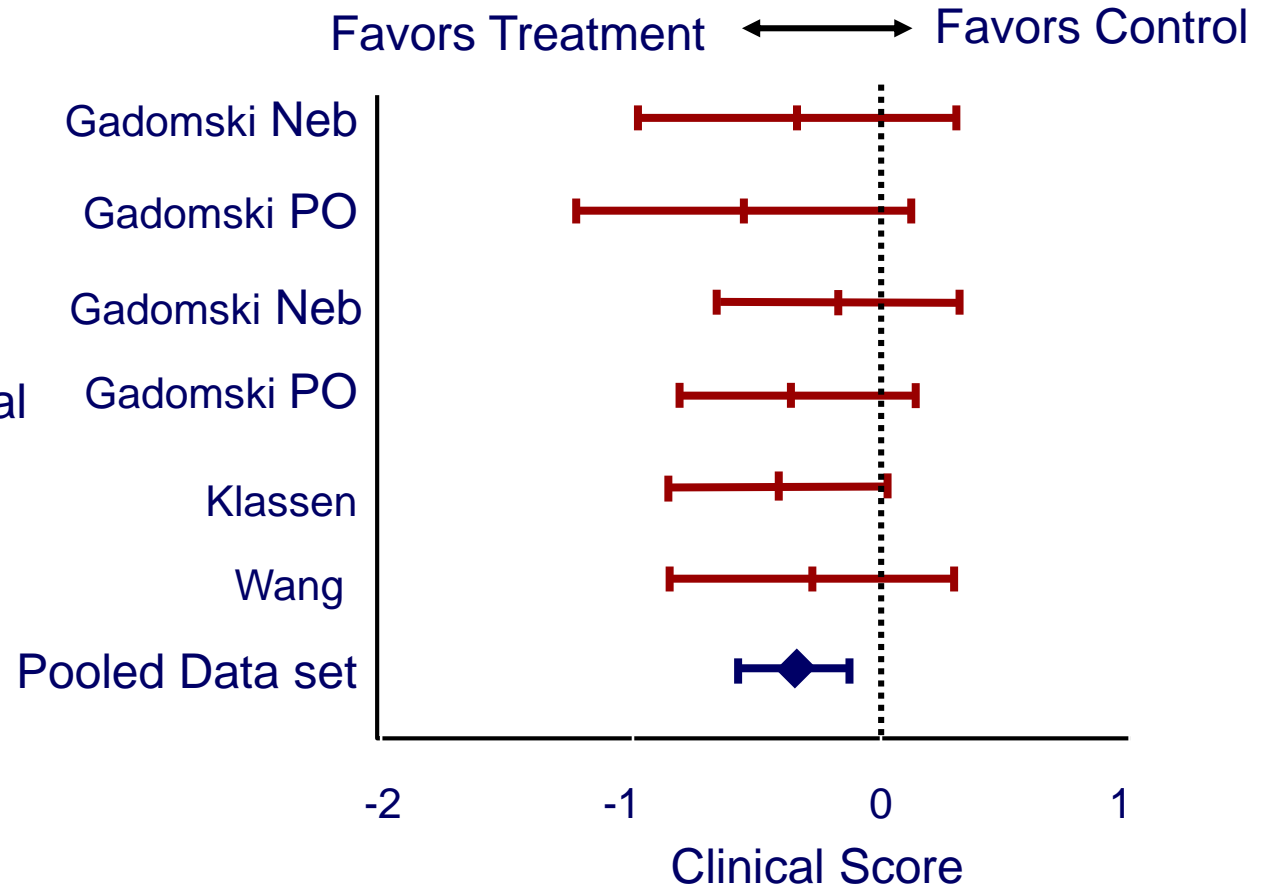
◆ Directed against the virus

- Antivirals: ribavirin

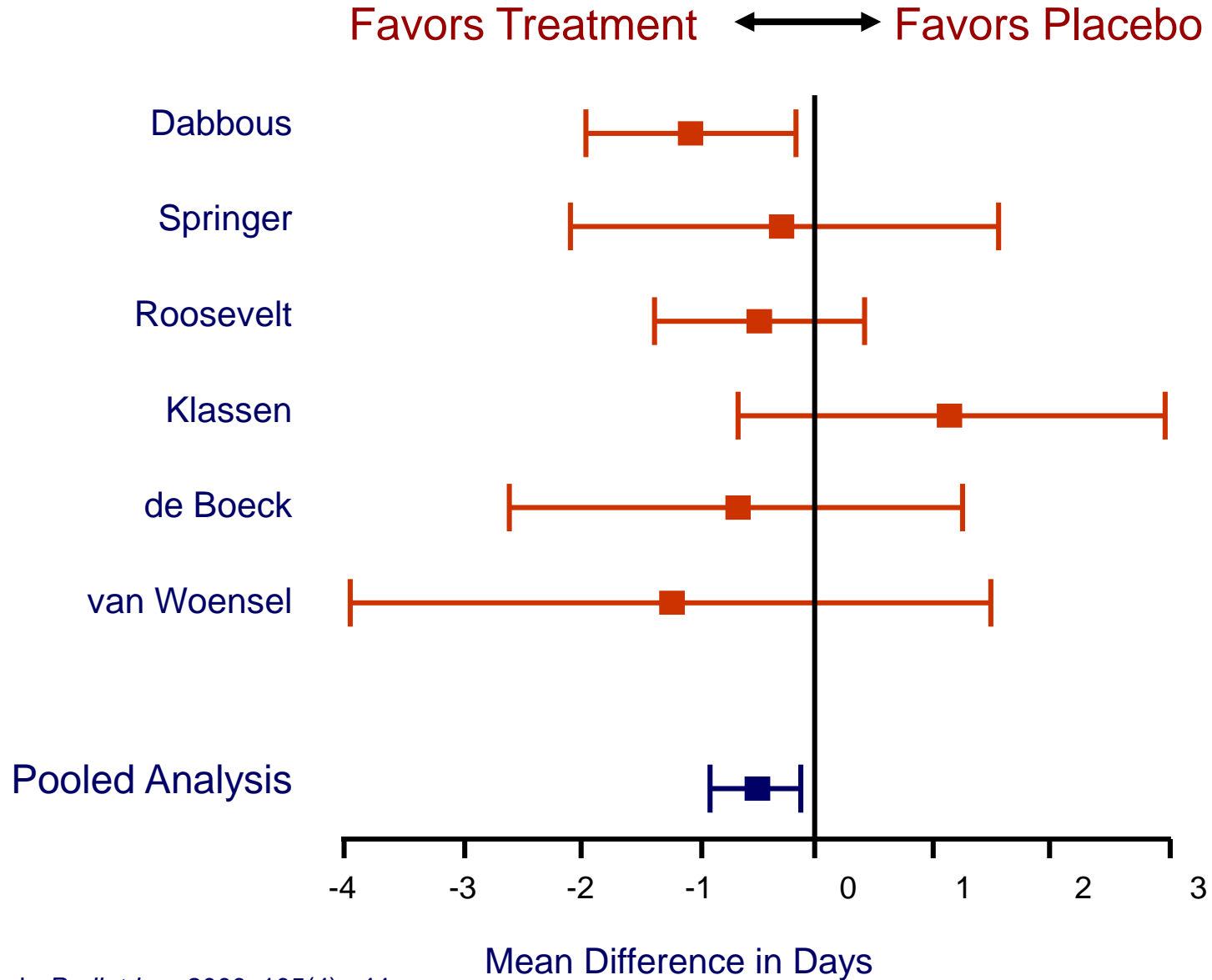
β2 AGONISTS IN BRONCHIOLITIS

Meta-analysis (n=15/89)

- ◆ Only randomized, placebo-controlled trials included
- ◆ Clinical scores, SaO₂ and hospital outcomes
- ◆ CONCLUSIONS: Modest clinical improvement with β2 agonists versus placebo in children with mild to moderate bronchiolitis
- ◆ Estimated cost treat 80% children < 2yr US \$ 37.5 million

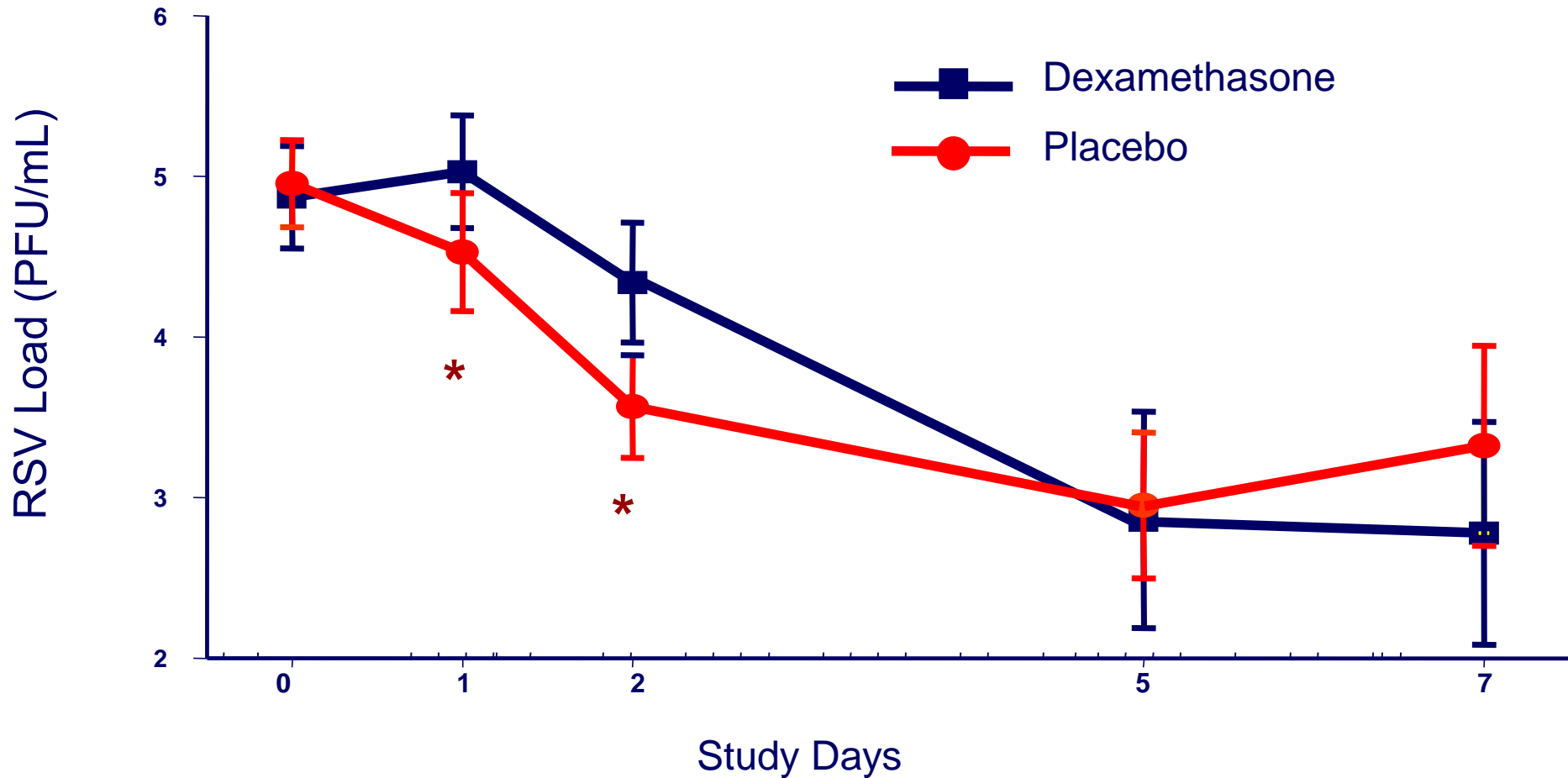


STERIODS AND BRONCHIOLITIS



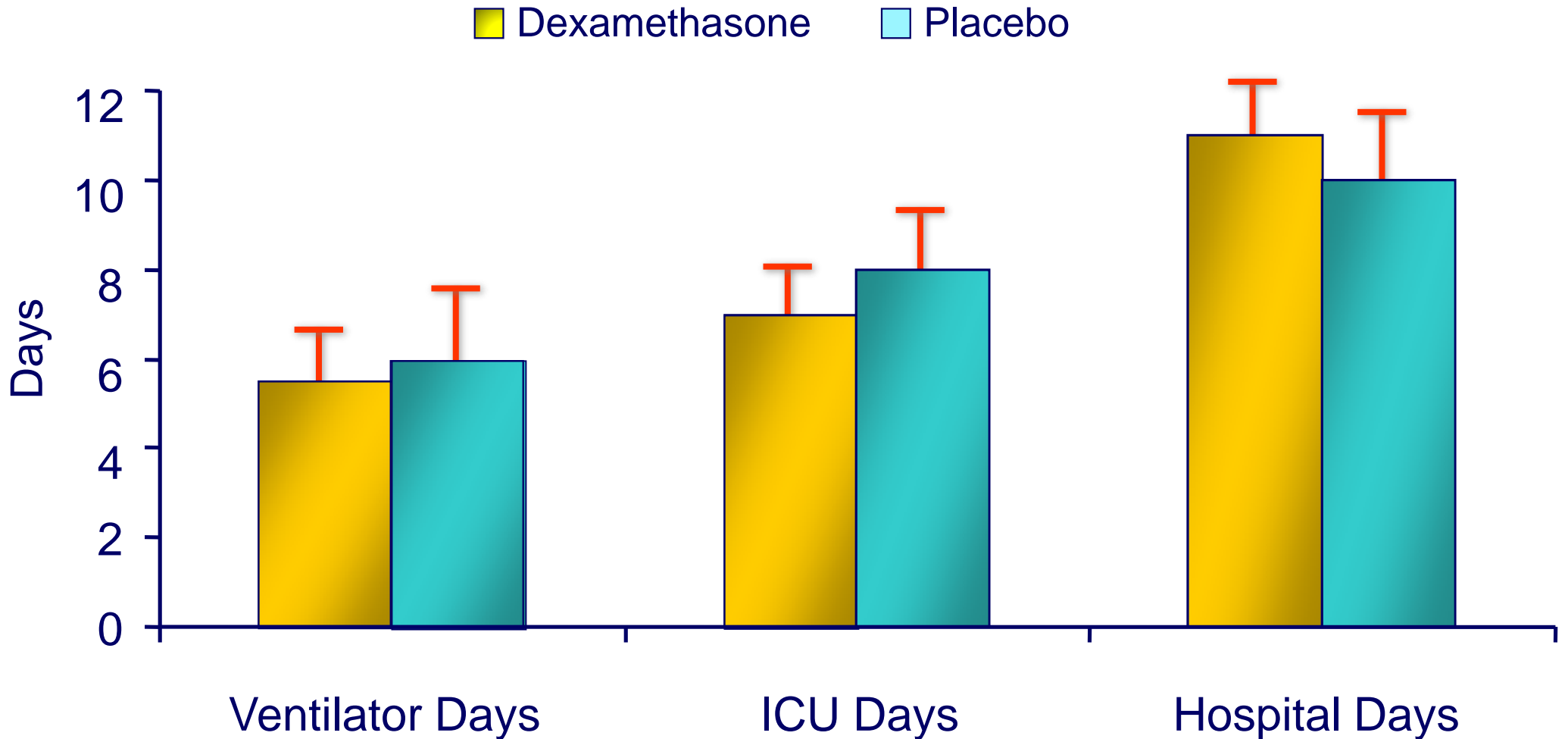
Dexamethasone in intubated RSV patients

RSV loads in tracheal aspirates



* p<0.05, Wilcoxon rank-sum test

Dexamethasone in intubated RSV patients impact on disease severity

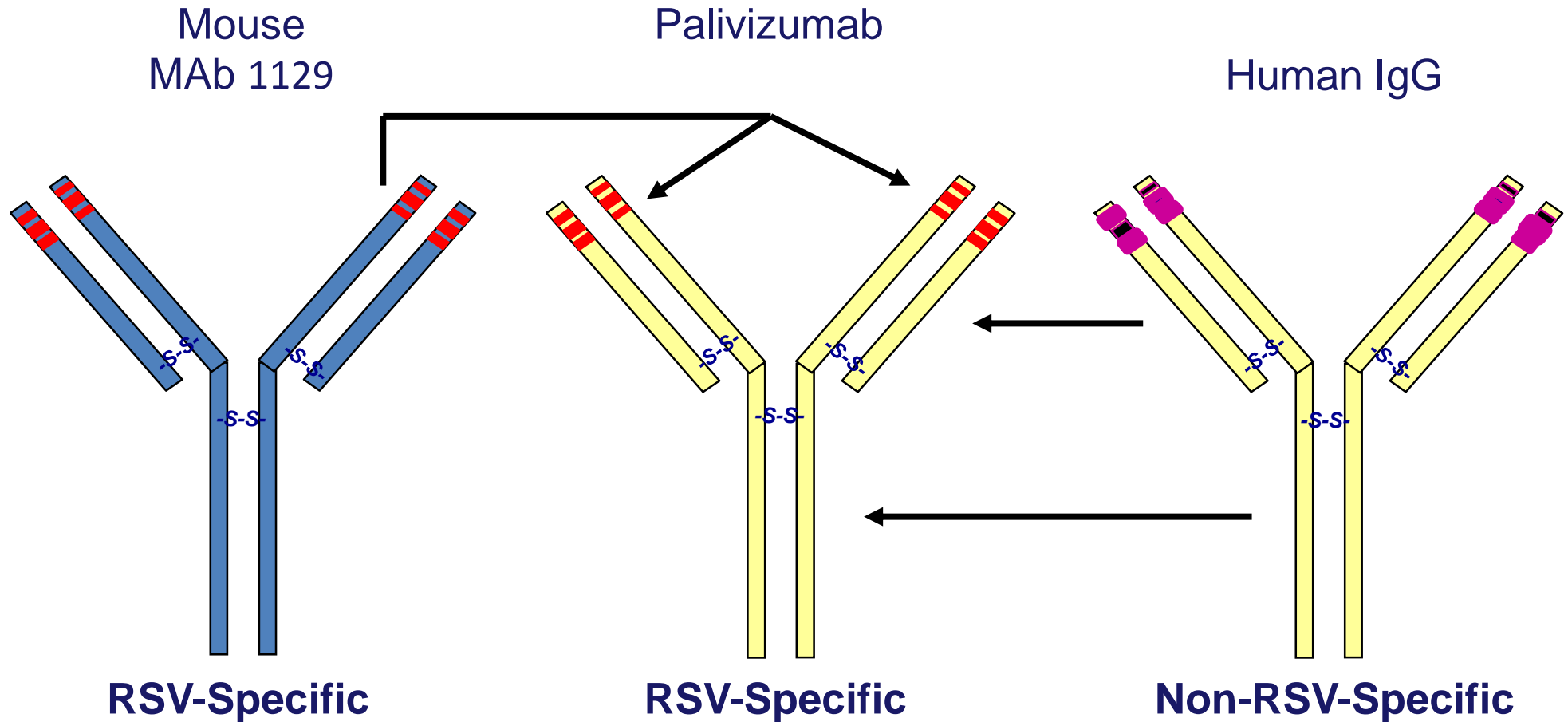


RSV transmission

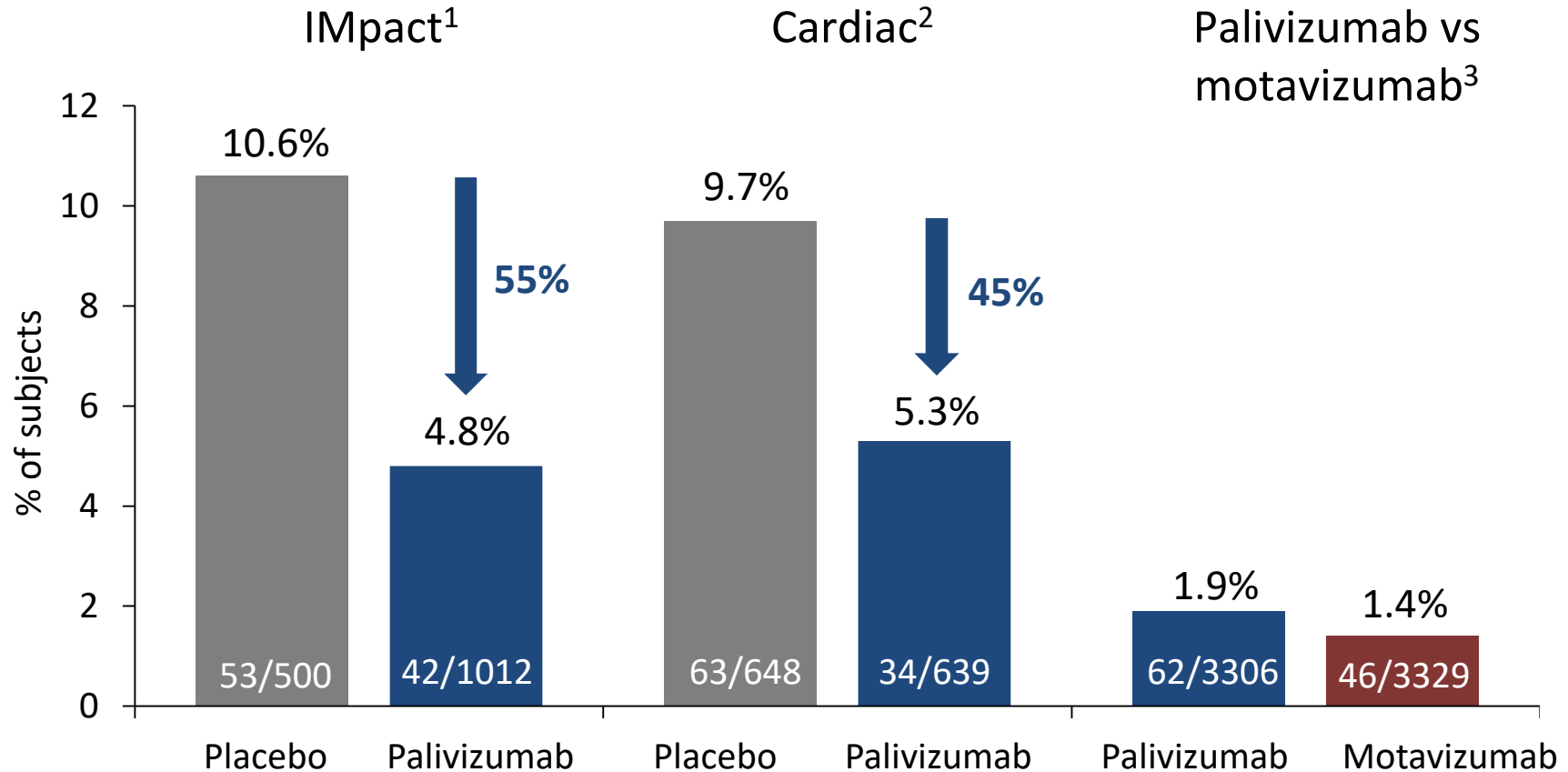
- Transmitted by droplets, large particles, and fomites
- RSV survives up to 6 hours on stethoscopes and up to 12 hours on hard, nonporous surfaces
- Over 50% of medical personnel infected when RSV is prevalent in community
- Nosocomial infection remains a serious problem



Construction of palivizumab: A humanized monoclonal antibody



Randomized studies demonstrate efficacy of palivizumab in reducing RSV hospitalizations

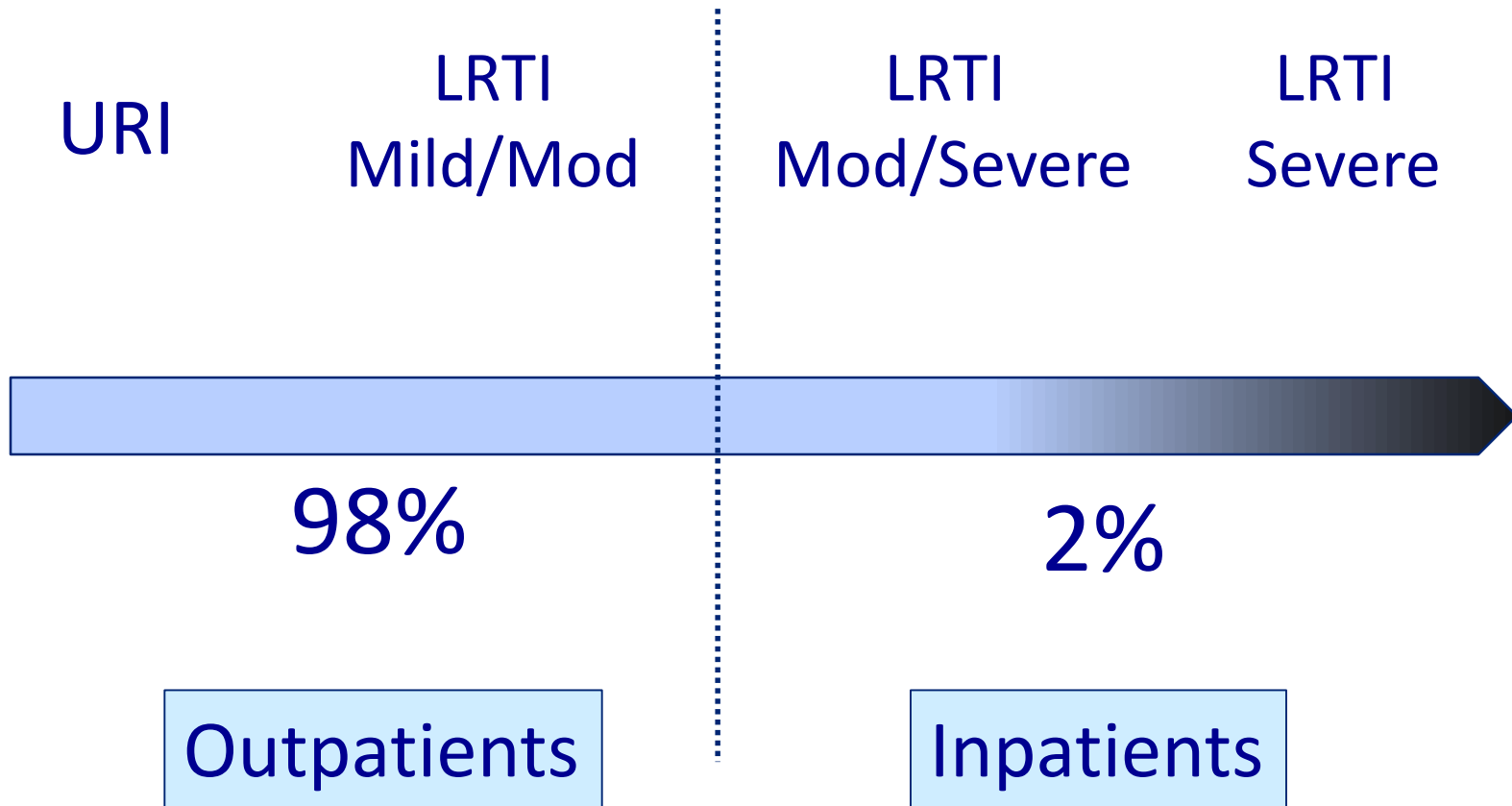


1. The IMpact-RSV Study Group. Pediatrics 1998; 102:531-7;

2. Feltes TF, et al. J Pediatr 2003; 143:532-40;

3. Carbonell-Estrany X, et al. Pediatrics 2010; 125:e35-51

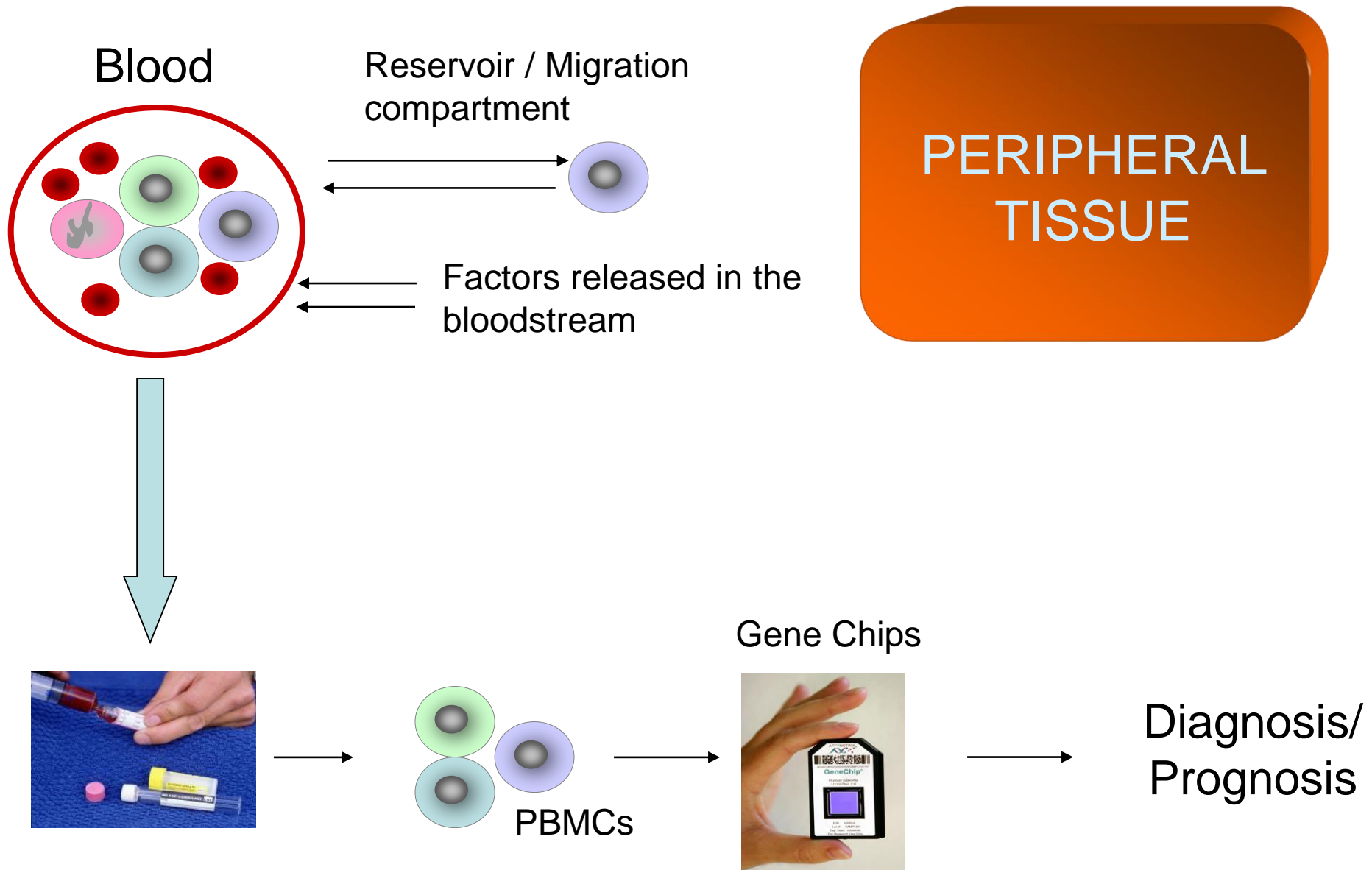
Variability in clinical presentation of RSV infections



How do we explain the variability in clinical presentations?

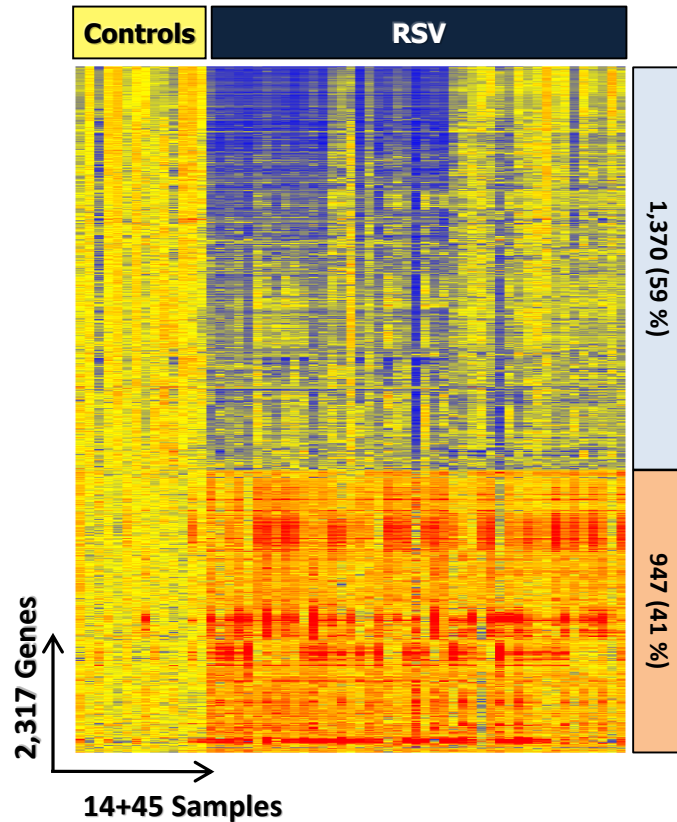


BLOOD IS A SOURCE OF TRANSCRIPTIONAL MARKERS

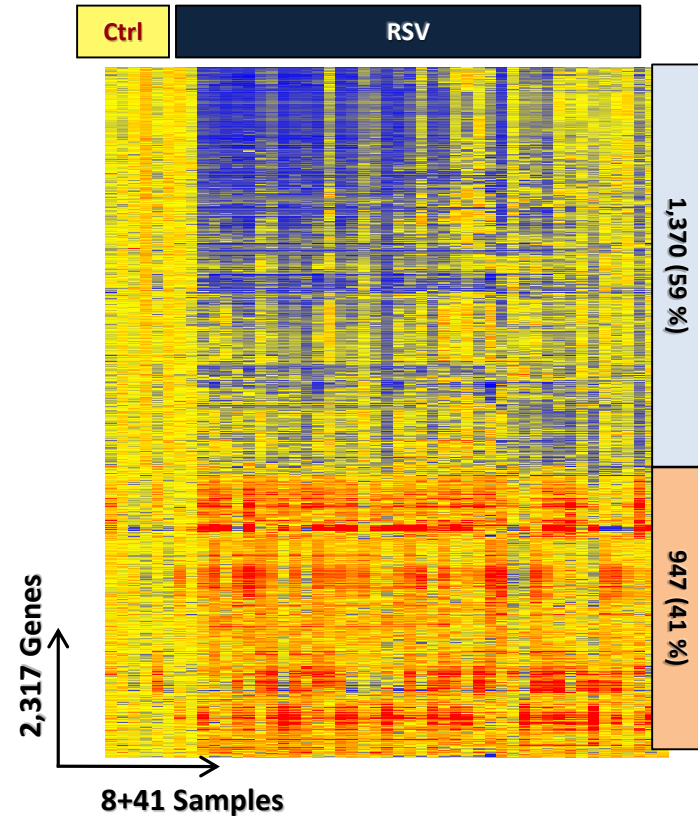


Transcriptional Profile in Children with RSV Bronchiolitis

Training Set
Dallas, TX (n=59)

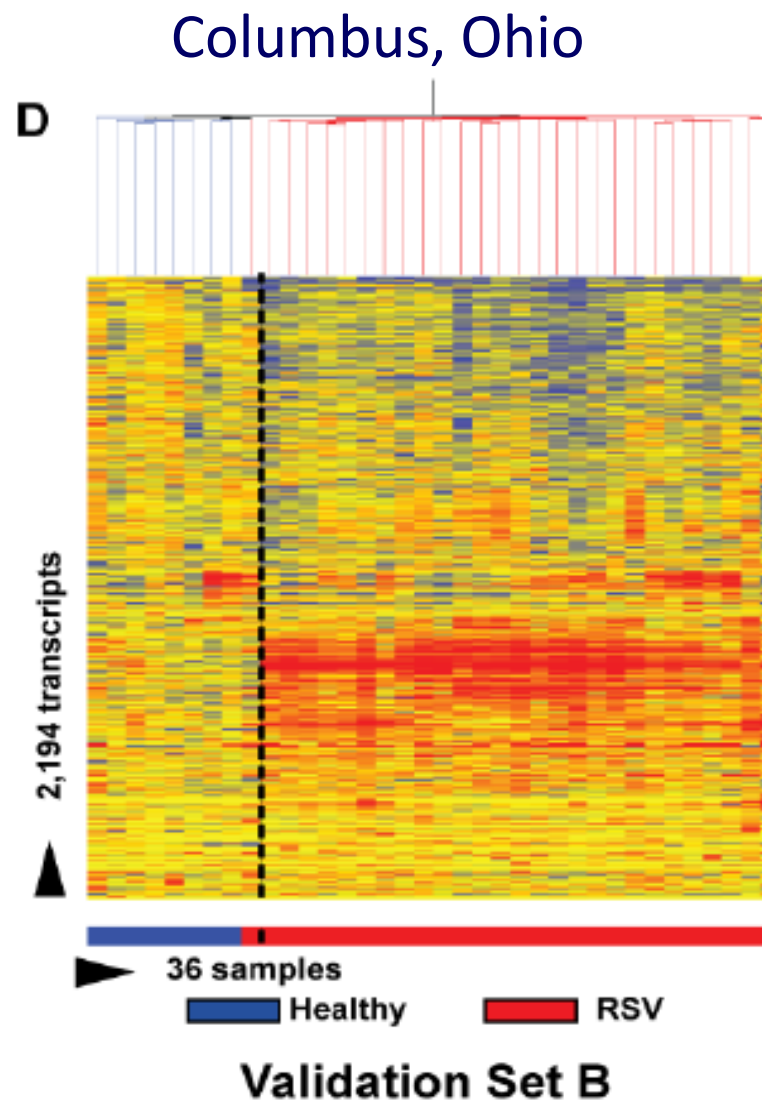
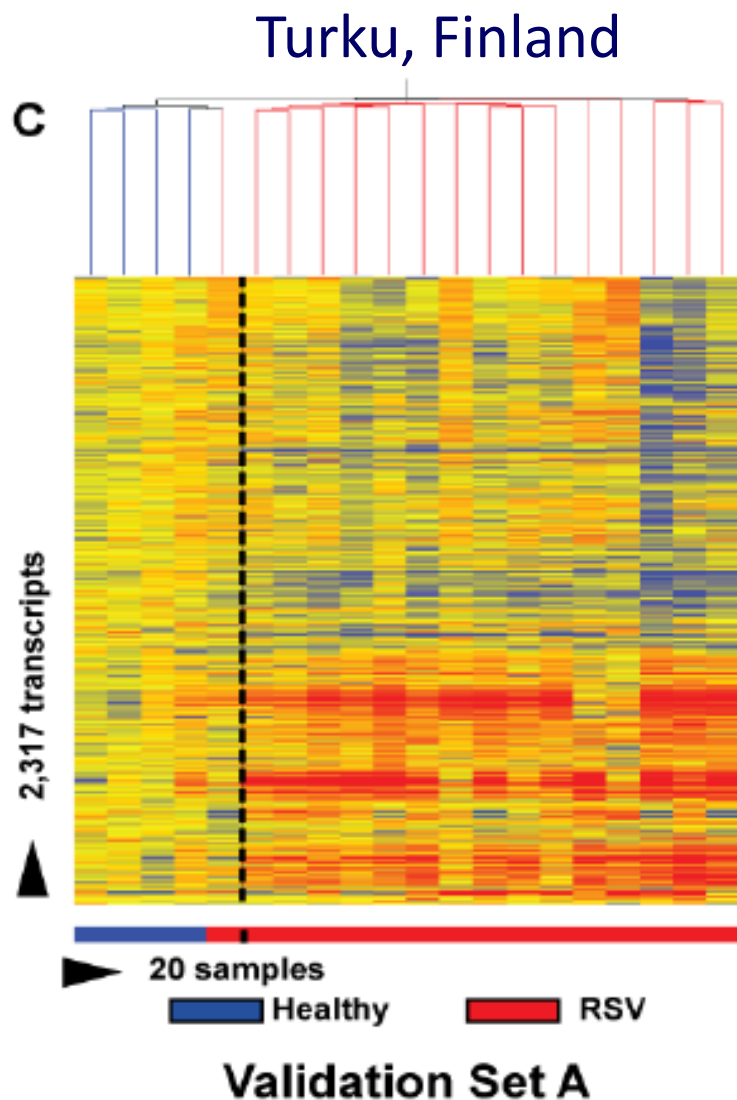


Test Set
Dallas, TX (n=49)



Mann-Whitney <0.01 , Benjamini MTC x1.25 fold change

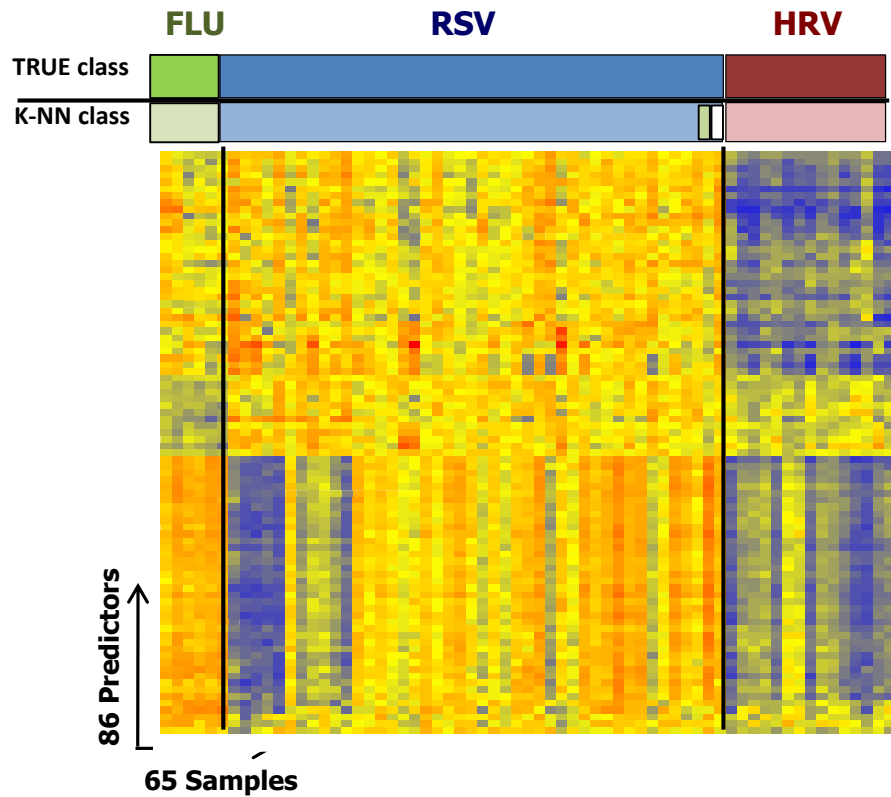
RSV Profile Validated in Two Independent Populations



Is this profile specific for RSV?

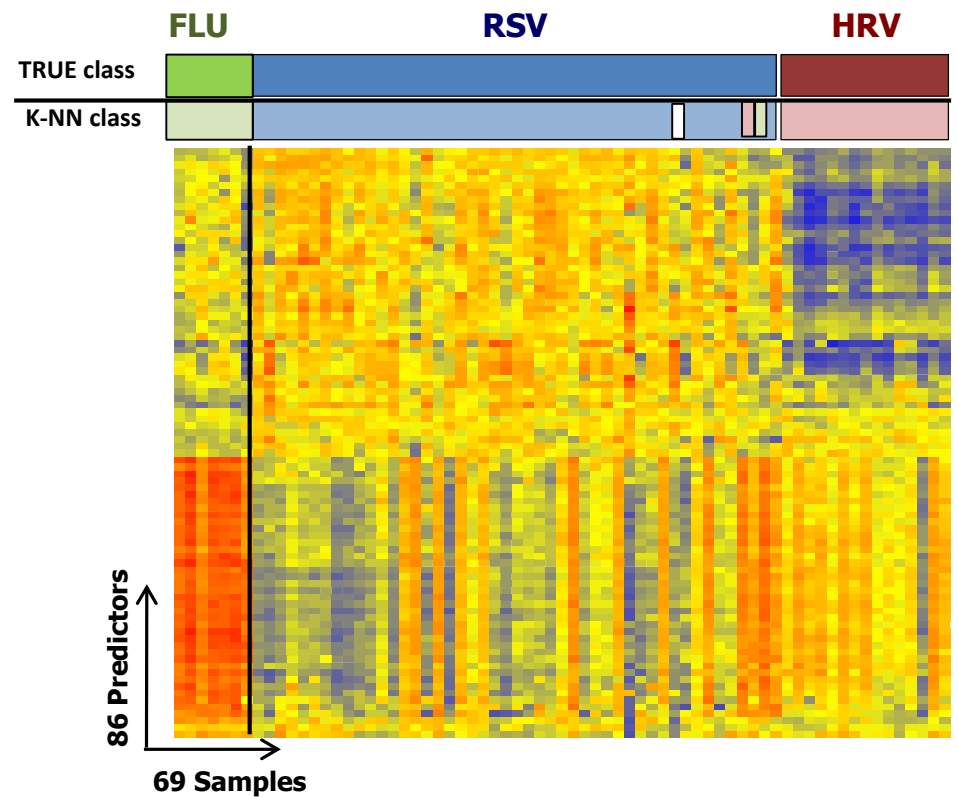
Class Prediction Among Different Respiratory Viruses (86 Genes)

Training Set



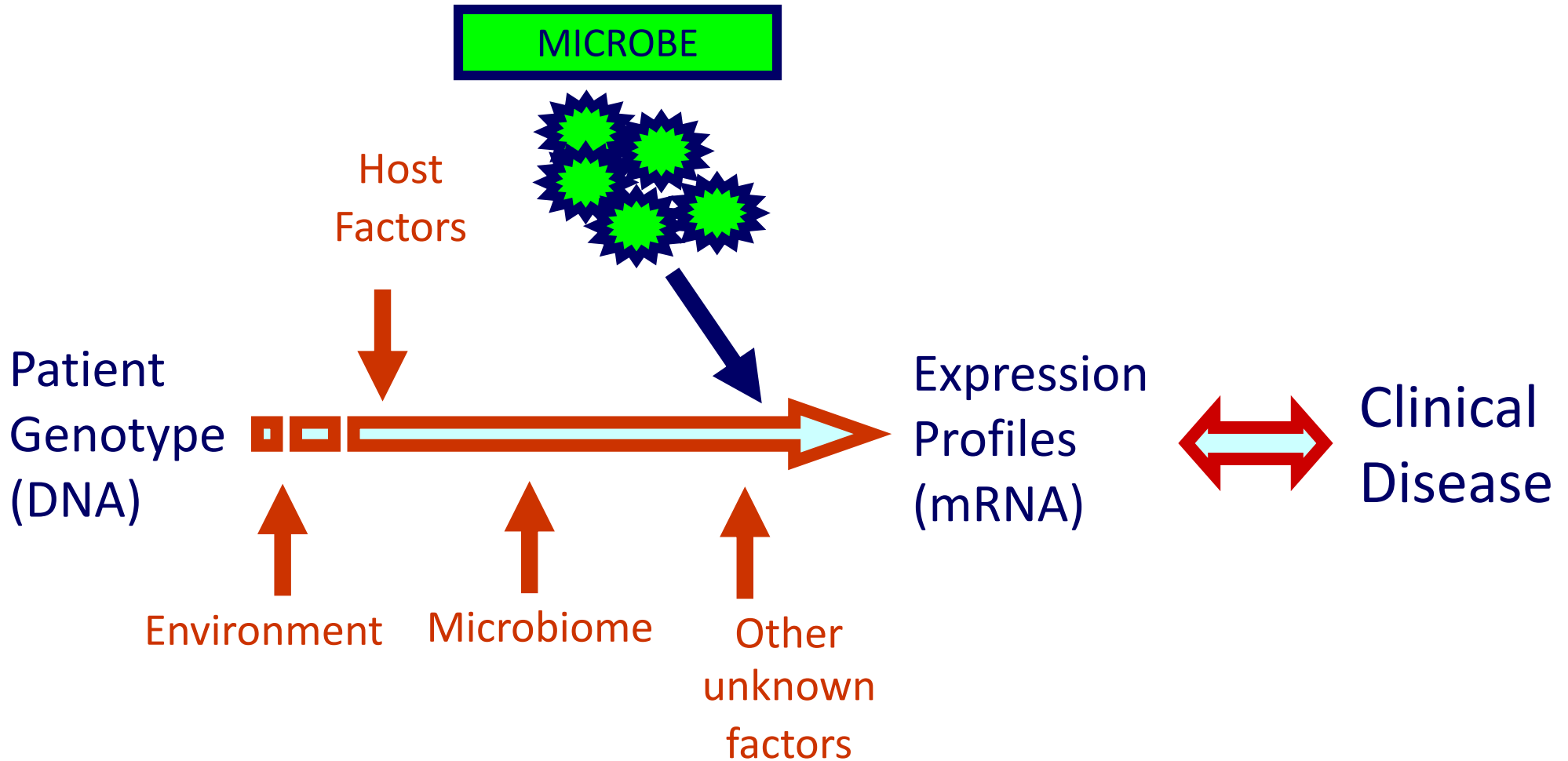
63/65: 96%

Test Set



66/69: 95%

Transcriptomics linking pathogenesis and clinical findings



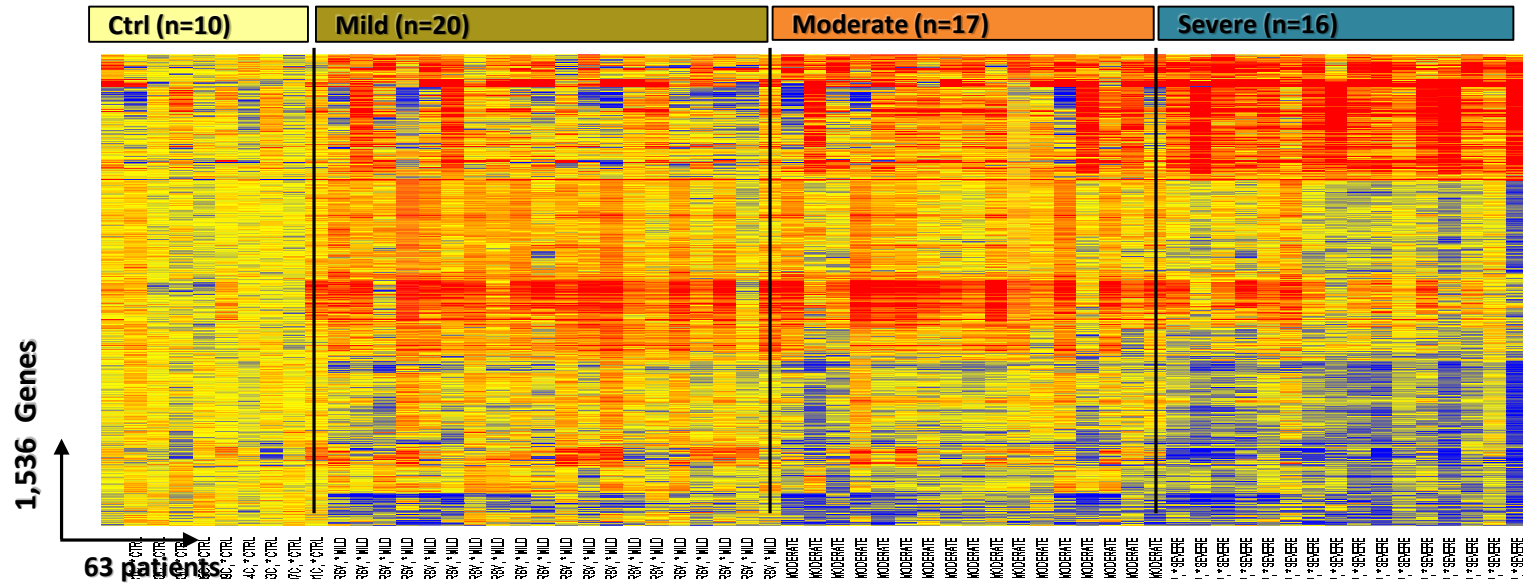
Can we measure disease activity
at the molecular level ?



Molecular Distance to Health (MDTH):

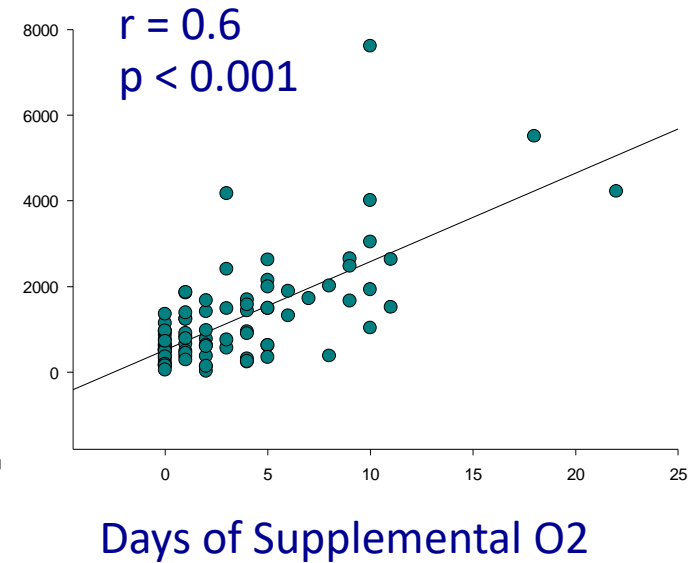
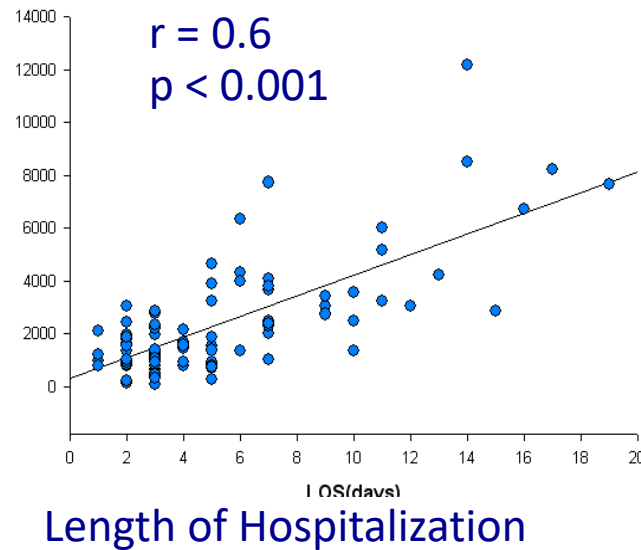
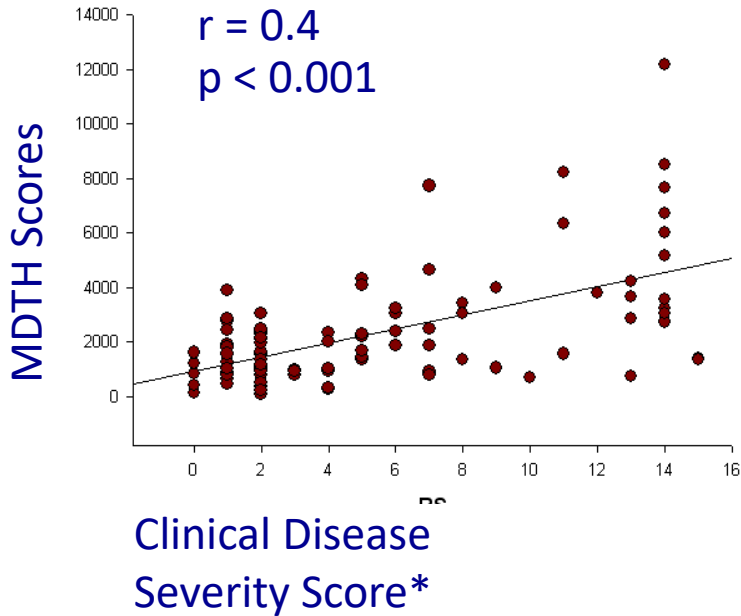
Score summarizes the global transcriptional
perturbation in a way that can be applied in the
clinical context

RSV-induced immune dysregulation correlates with disease severity



Is this clinically relevant?

MDTH Score Correlates with RSV Disease Severity



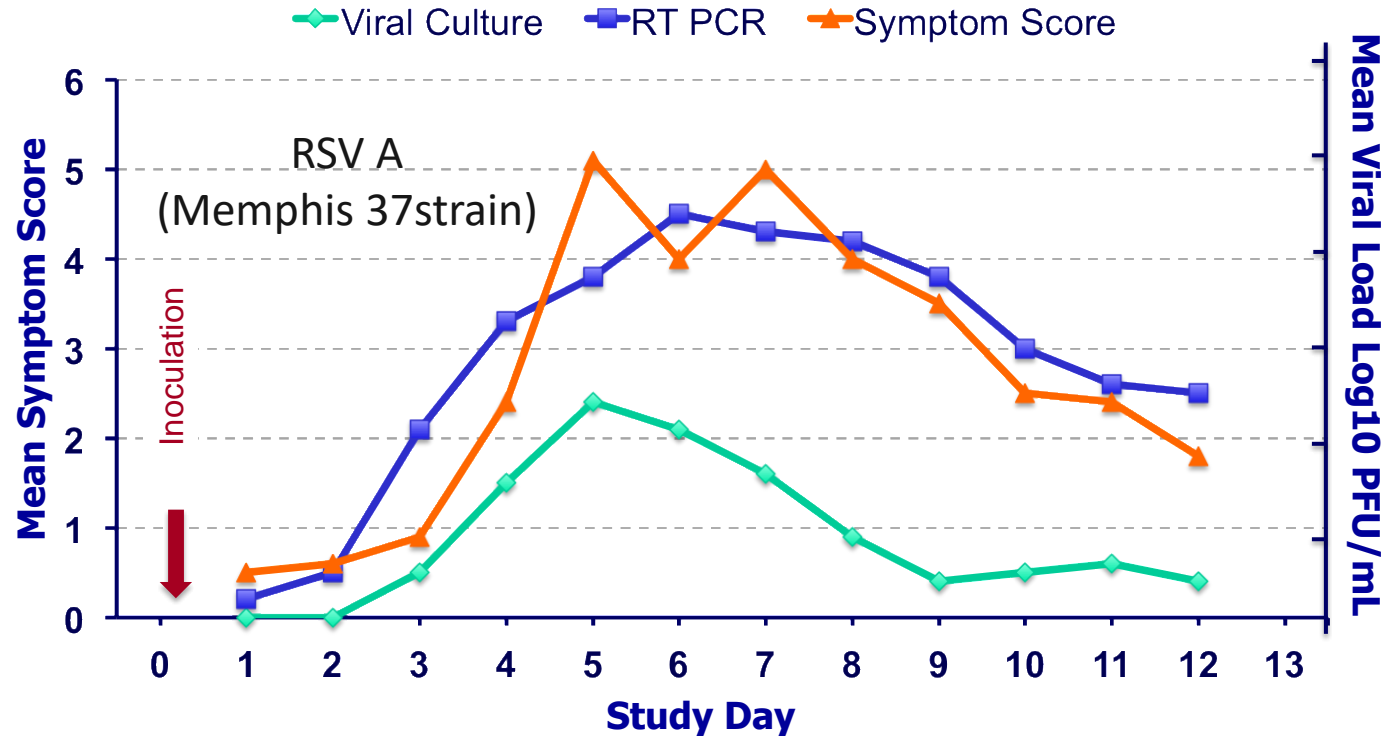
* Disease Severity Score: % Sp O₂, respiratory rate, IVF, retractions, auscultation

Antivirals for RSV infection

Experimental RSV infection in humans



Healthy adult volunteers
(N=35; aged 18–45 years)



- Outcomes:
- a) Virologic: viral loads (culture/PCR)
 - b) Clinical: score, mucus production
 - c) Host responses: cytokines

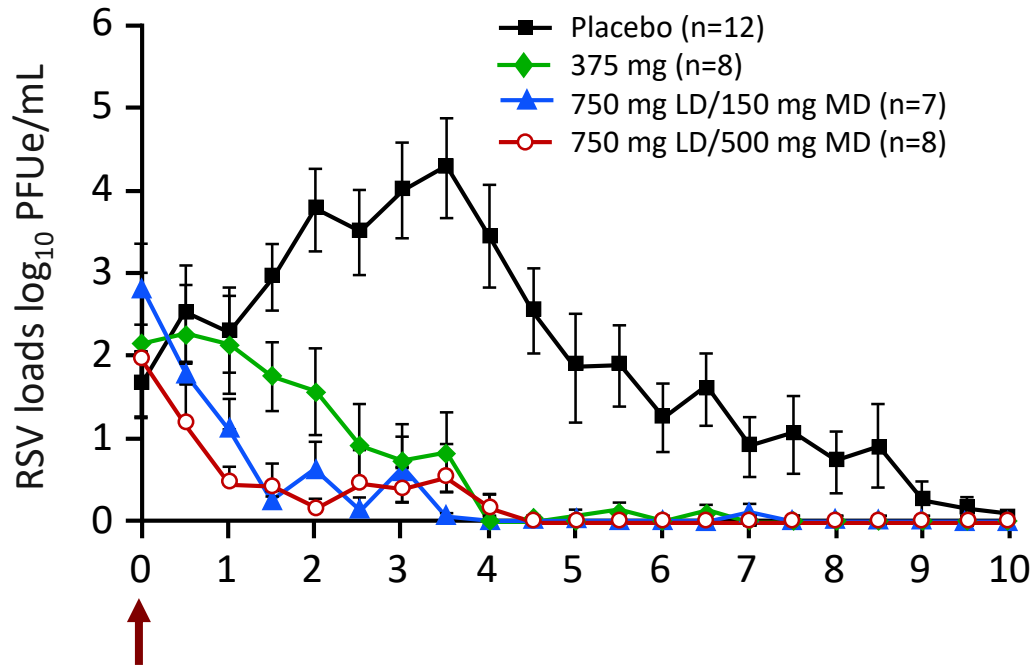
PFU, plaque-forming units

Modified from DeVincenzo JP, et al. Am J Respir Crit Care Med 2010; 182:1305–14

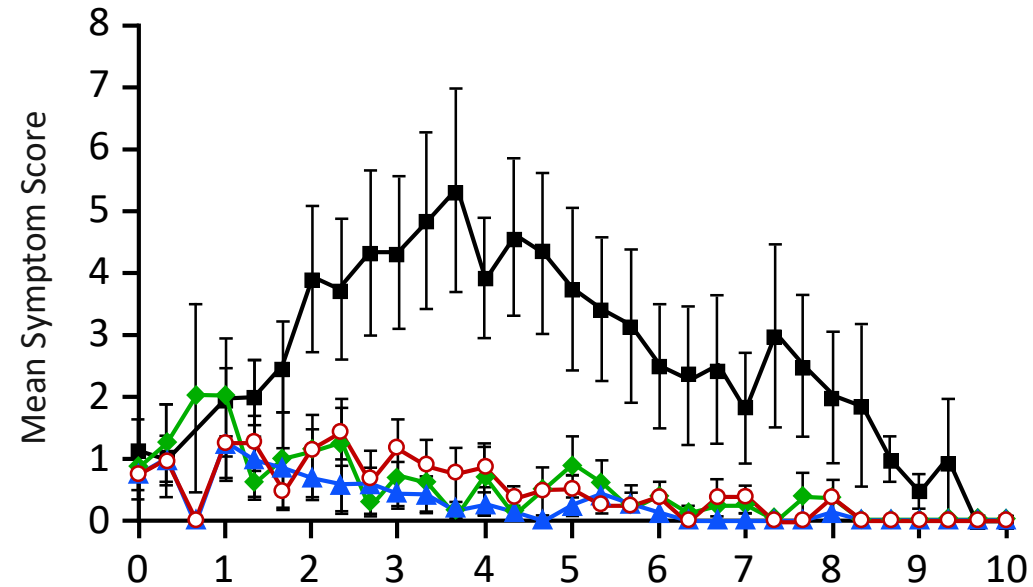
ALS-008176 (nucleoside analog) rapidly reduces RSV viral load and clinical disease severity in healthy adult volunteers

Viral load

N total=62 subjects



Symptom Score



MD, maintenance dose

DeVincenzo JP, et al. N Engl J Med 2015; 373:2048–58

New preventive strategies for RSV

RSV Vaccine and mAb Snapshot

TARGET INDICATION: P = PEDIATRIC M = MATERNAL E = ELDERLY

| | PRECLINICAL | | | | PHASE 1 | | | PHASE 2 | | PHASE 3 | MARKET APPROVED |
|------------------------------------|---|---|--|-------------------------------|---|---|---|-----------------------------------|--|---------------------------------|-----------------|
| LIVE-ATTENUATED/ CHIMERIC | Codagenix, LID/NIAID/NIH RSV | LID/NIAID/NIH RSV | | | Intravacc P Delta-G RSV | Sanofi, LID/NIAID/NIH RSV ΔNS2/Δ1313/11314L P | Sanofi, LID/NIAID/NIH RSV 6120/ΔNS2/1030s P | | | | |
| | LID/NIAID/NIH PIV1-3/RSV | Meissa Vaccines RSV | | | Pontificia Universidad Catolica de Chile BCG/RSV P | Sanofi, LID/NIAID/NIH RSV D46/NS2/N/ΔM2-2-HindIII P | SIPL, St. Jude Hospital SeV/RSV P | | | | |
| WHOLE-INACTIVATED | Blue Willow Biologics RSV | | | | | | | | | | |
| PARTICLE-BASED | AgilVax VLP | Fraunhofer VLP | TechnoVax VLP | VBI Vaccines VLP | Novavax P RSV F Nanoparticle | | | Novavax E RSV F Nanoparticle | | Novavax M RSV F Nanoparticle | |
| | Artificial Cell Technologies Peptide microparticle | Georgia State University VLP | University of Massachusetts VLP | Virometix VLP | | | | | | | |
| SUBUNIT | Instituto de Salud Carlos III RSV F Protein | University of Georgia RSV G Protein | | | Beijing Advaccine Biotechnology RSV G Protein P E | Immunovaccine, VIB DPX-RSV-SH Protein E | NIH/NIAID/VRC RSV F Protein E M | Pfizer E M RSV F Protein | | | |
| | Sciogen RSV G Protein | University of Saskatchewan RSV F Protein | | | GlaxoSmithKline E M RSV F Protein | Janssen Pharmaceutical E RSV F Protein | | | | | |
| NUCLEIC ACID | CureVac RNA | Inovio Pharmaceuticals DNA | | | | | | | | | |
| RECOMBINANT VECTORS | BravoVax Adenovirus | | | Vaxart E Adenovirus | | | Bavarian Nordic E MVA | | Janssen Pharmaceutical P E Adenovirus | | |
| | | | | | | | GlaxoSmithKline P Adenovirus | | | | |
| IMMUNO-PROPHYLAXIS/ COMBINATION | Arsanis Anti-F mAb | Biomedical Research Models DNA prime, Particle boost | Pontificia Universidad Catolica de Chile Anti-N mAb | UCAB, mAbXience Anti-F mAb | Merck P Anti-F mAb | | | MedImmune, Sanofi P Anti-F mAb | | MedImmune P Synaxis | |

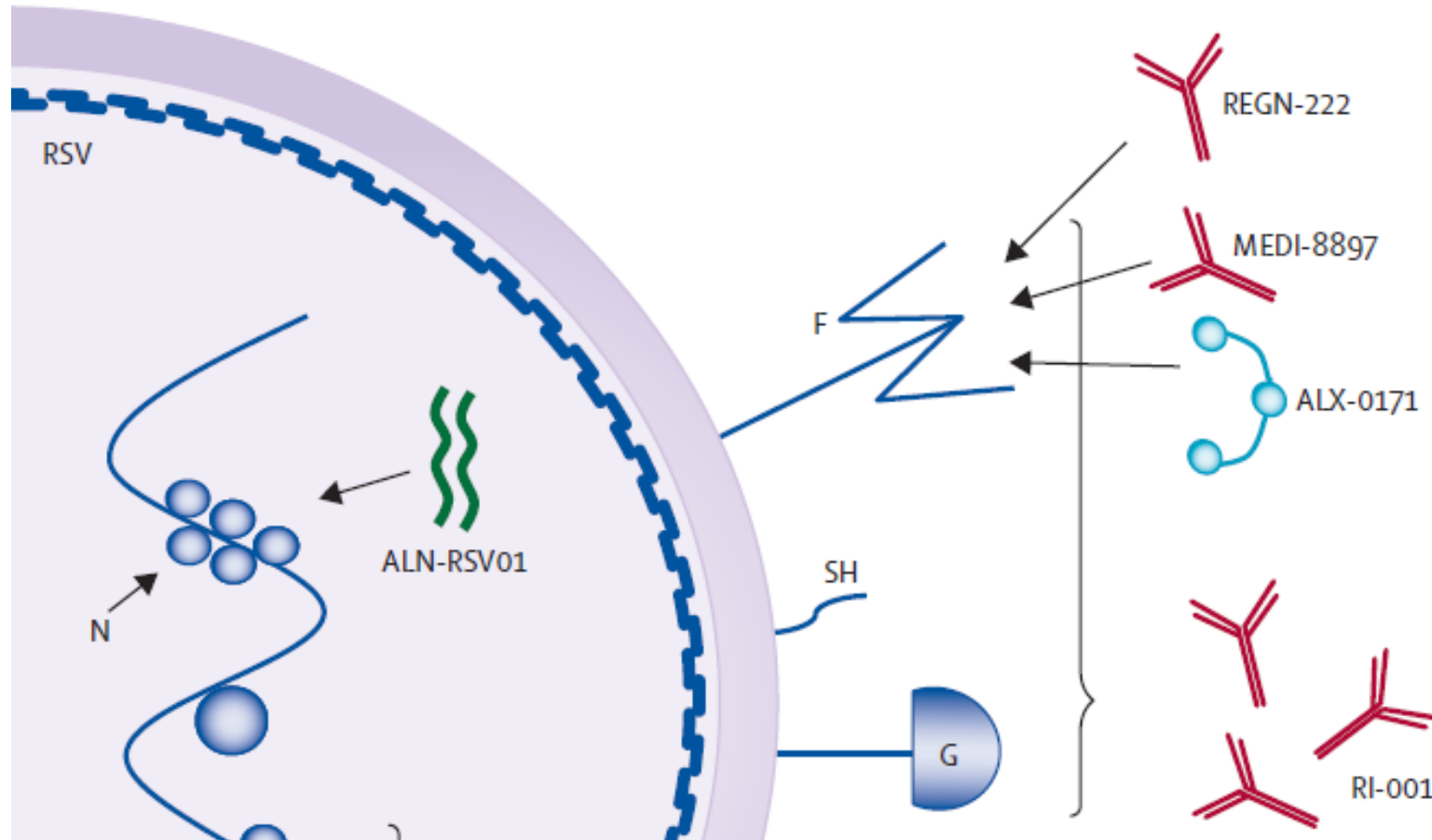
UPDATED: December 10, 2018

Indicates Change

<http://vaccineresources.org/details.php?i=1562>

Anti-RSV neutralizing monoclonal antibodies

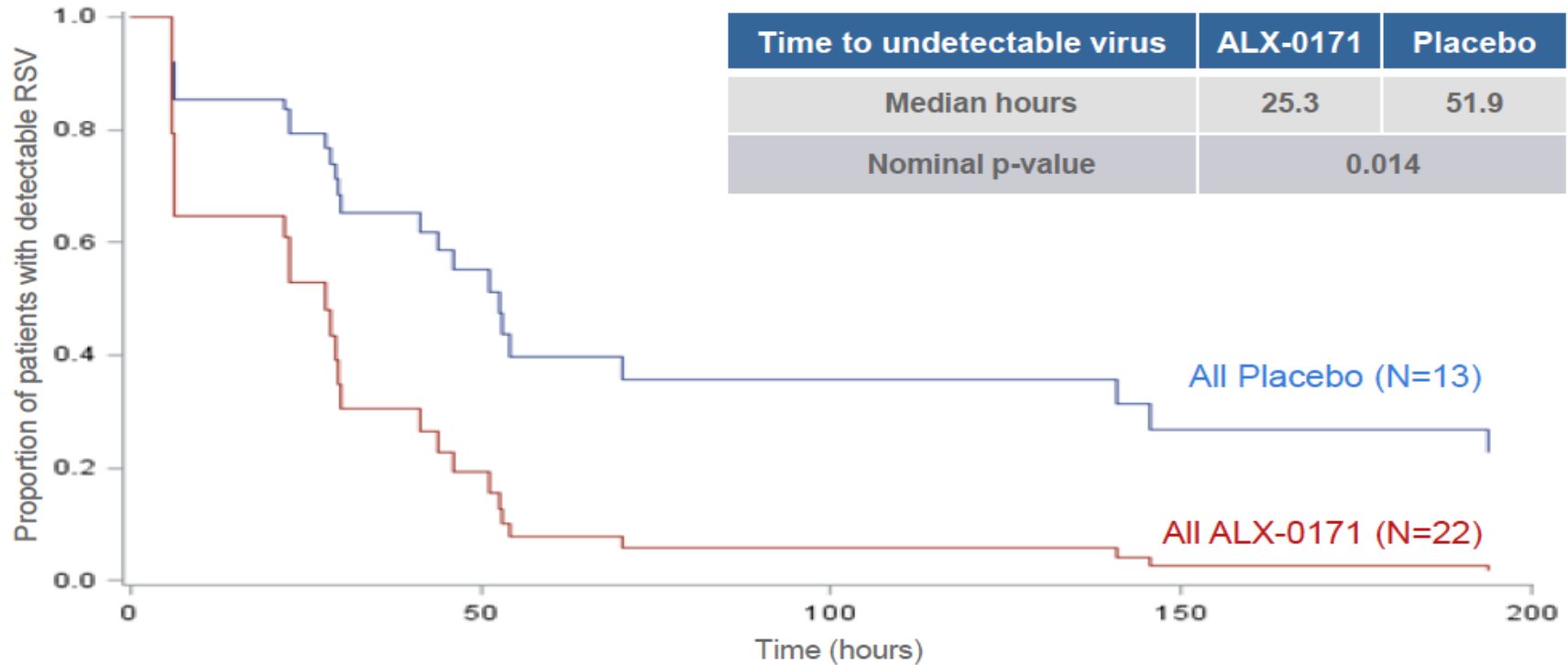
Anti-RSV neutralizing antibodies



Phase I/IIa study of ALX-0171 in infants

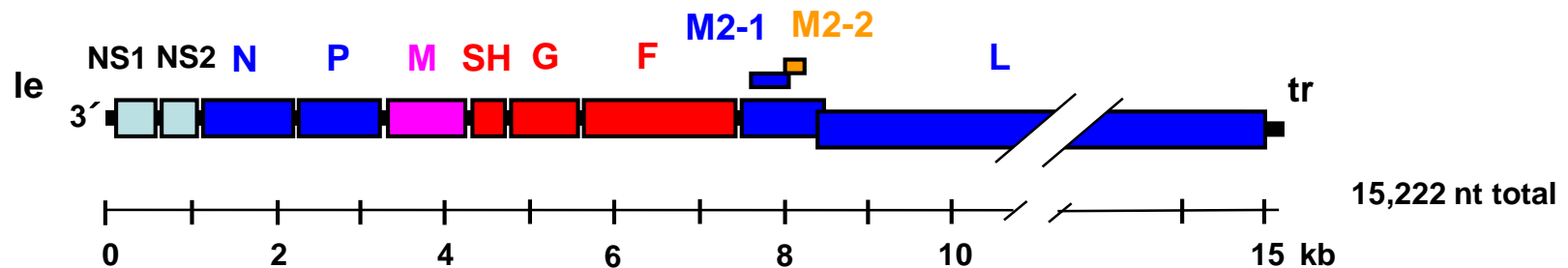
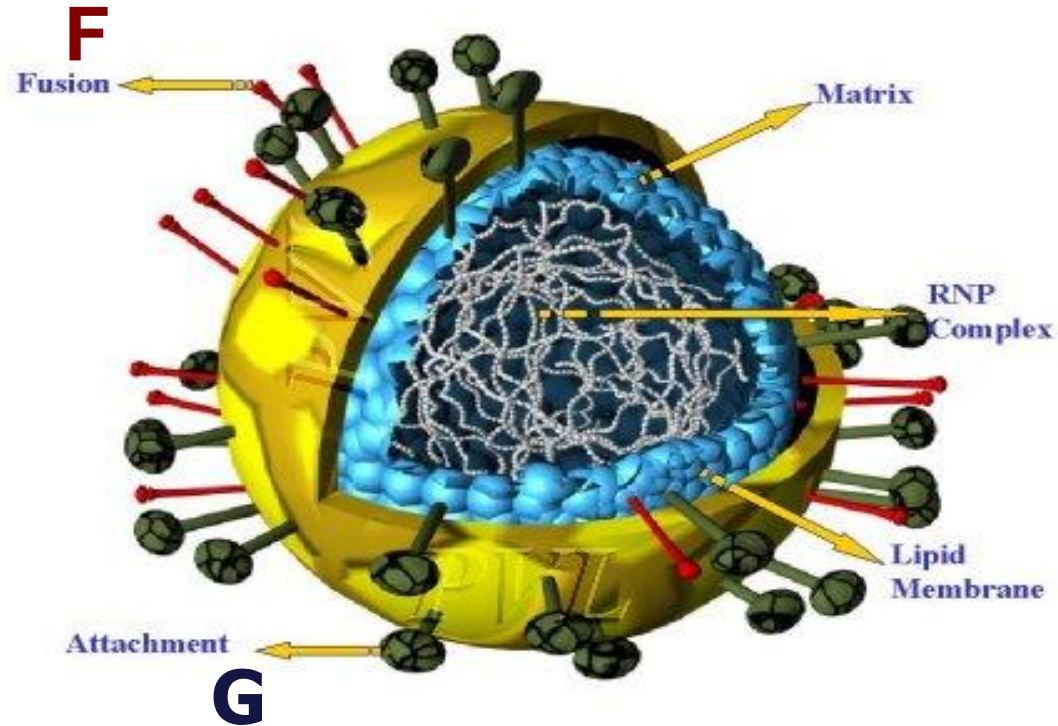


Antiviral effect: time to undetectable virus in culture

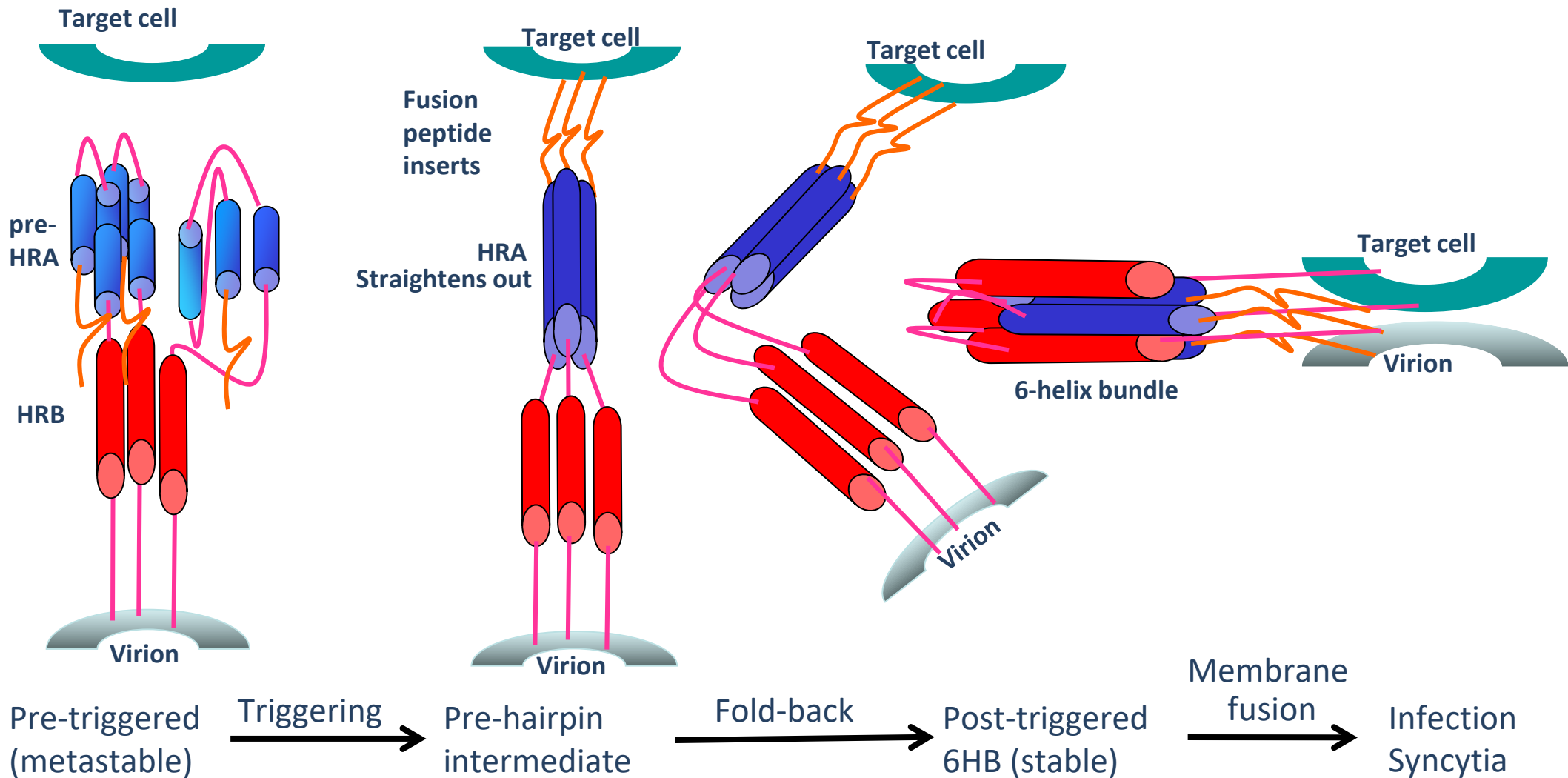


Cox model to compare ALX-0171 and placebo with respect to time to first undetectable virus in culture (undetectable at 2 consecutive time points) from time of start of treatment

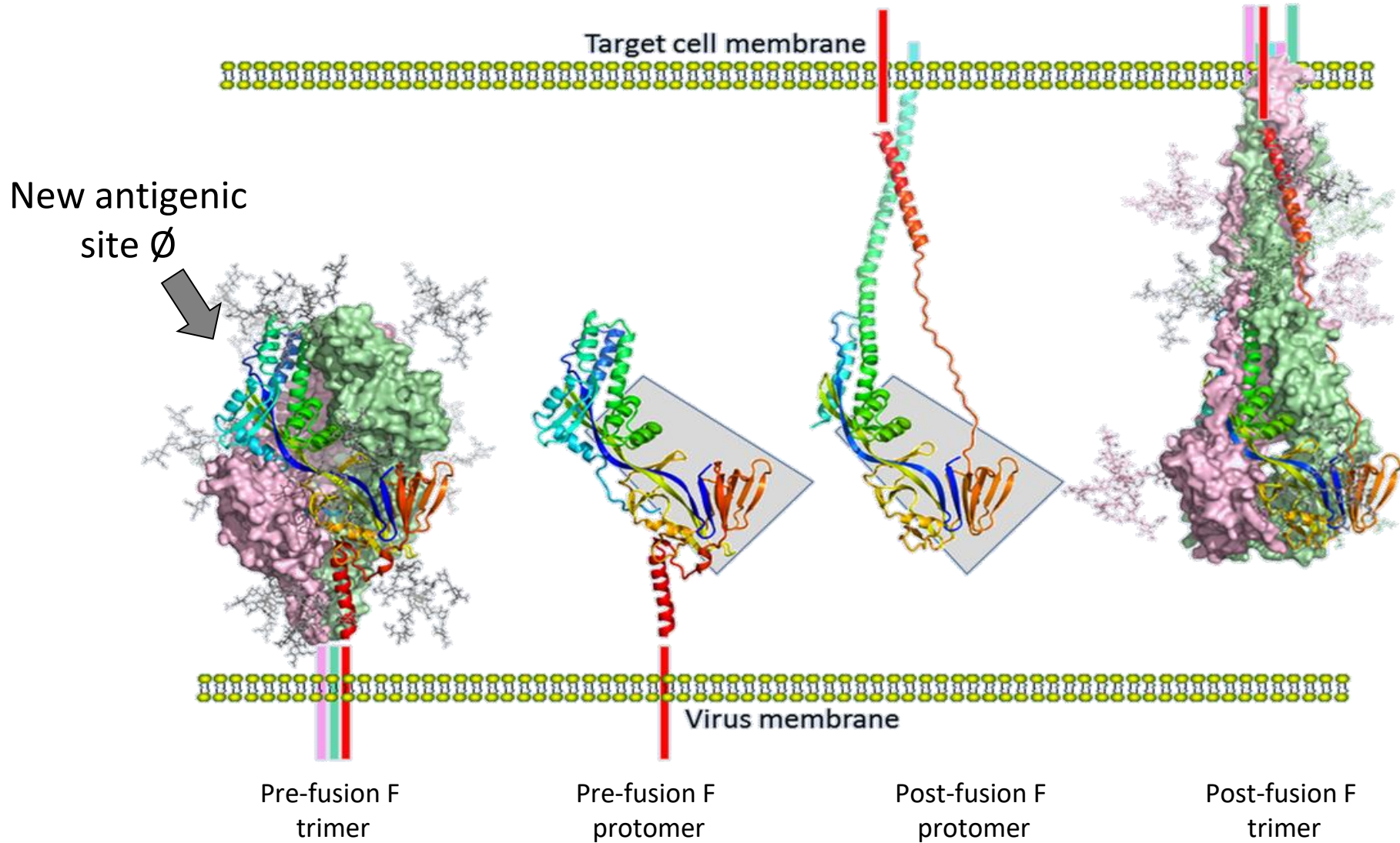
RSV: The Virus



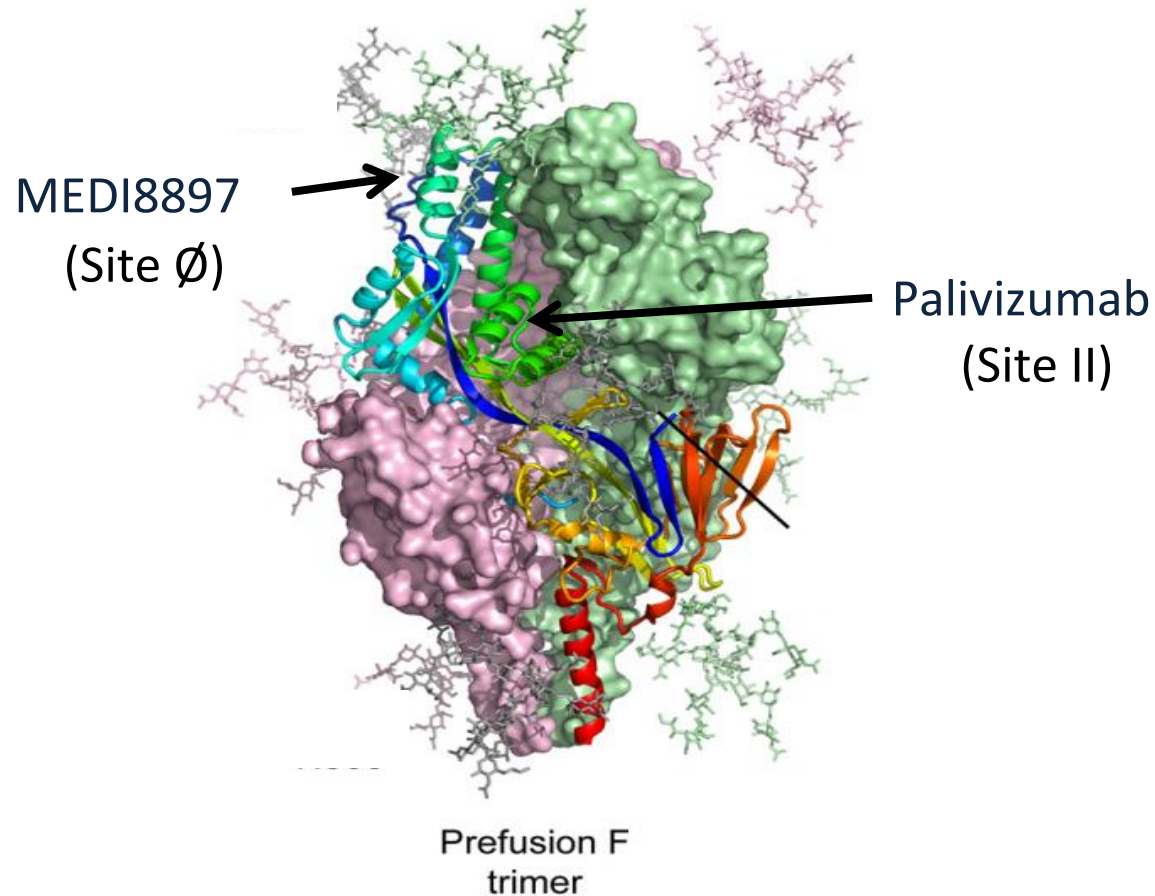
F protein trimer-mediated fusion



RSV F protein: Pre-fusion vs post-fusion



MEDI8897 blocks RSV F protein-mediated fusion



- Fully human IgG1 mAb derived from human B-cells
- Targets a unique antigenic site on pre-fusion RSV F (distinct from palivizumab)

Anti-RSV neutralizing mAbs

Palivizumab

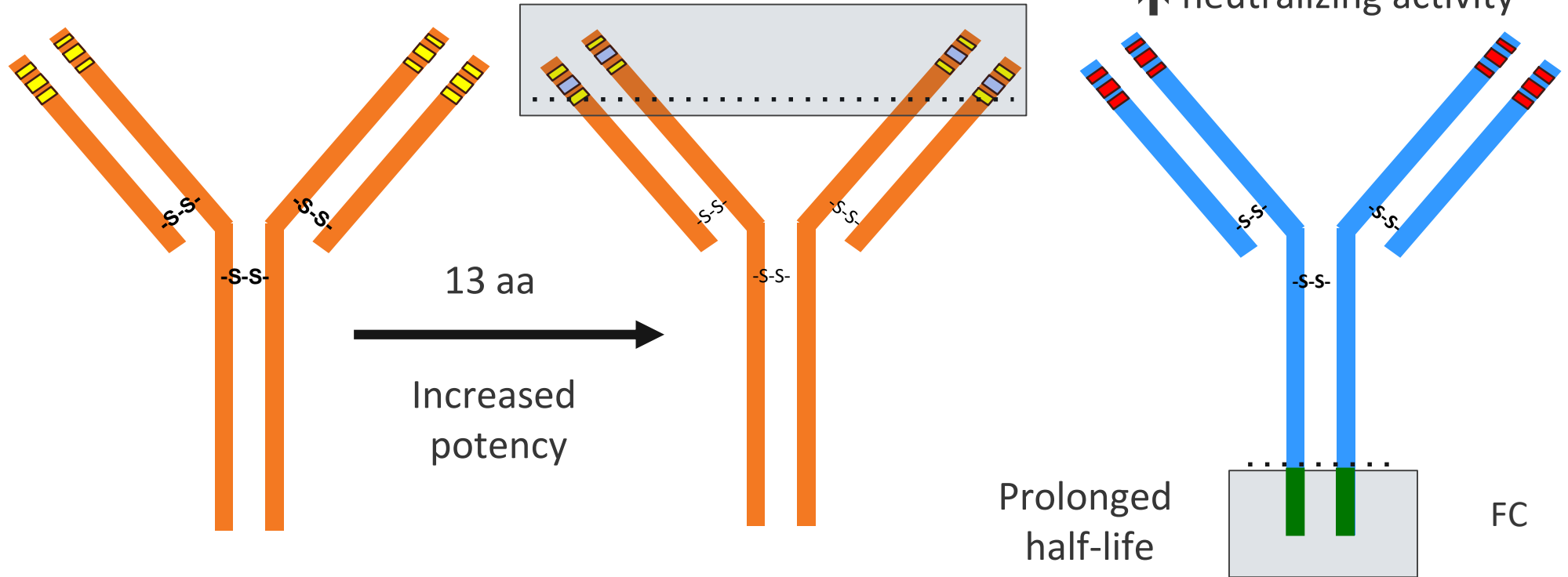


Motavizumab

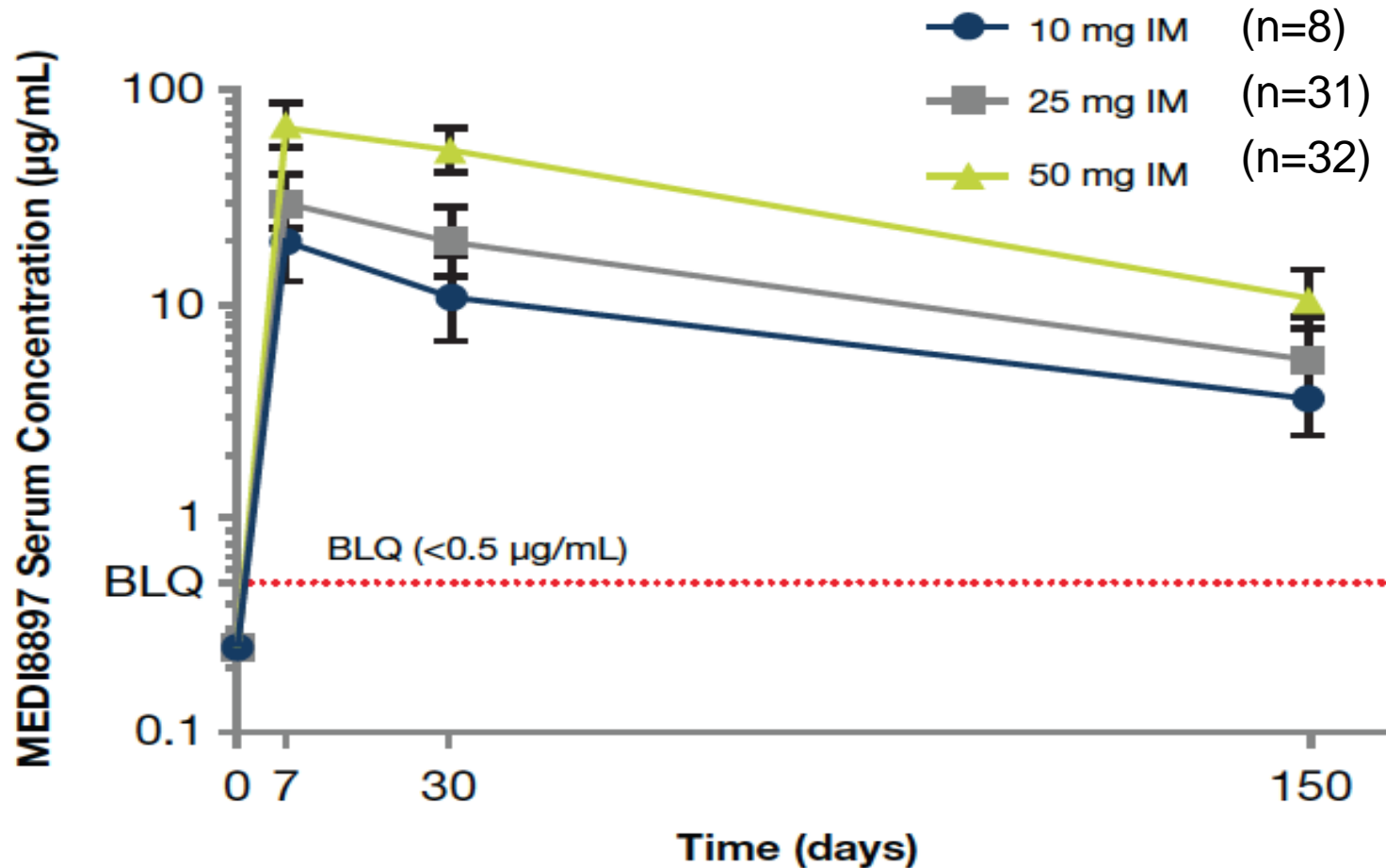
MEDI8897 (D25)

Binds PreF

↑ neutralizing activity

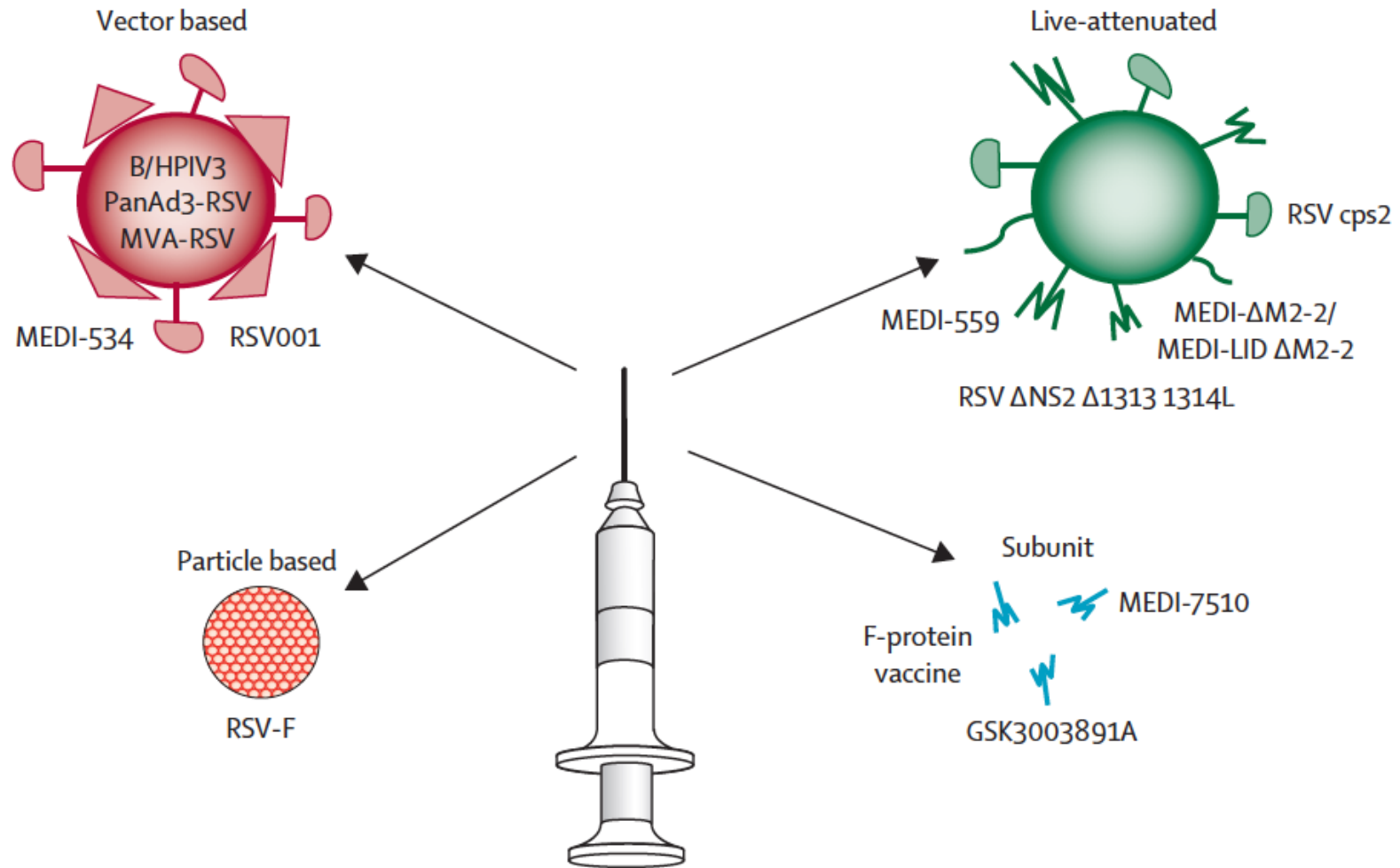


MEDI8897 mean serum concentration-time profiles

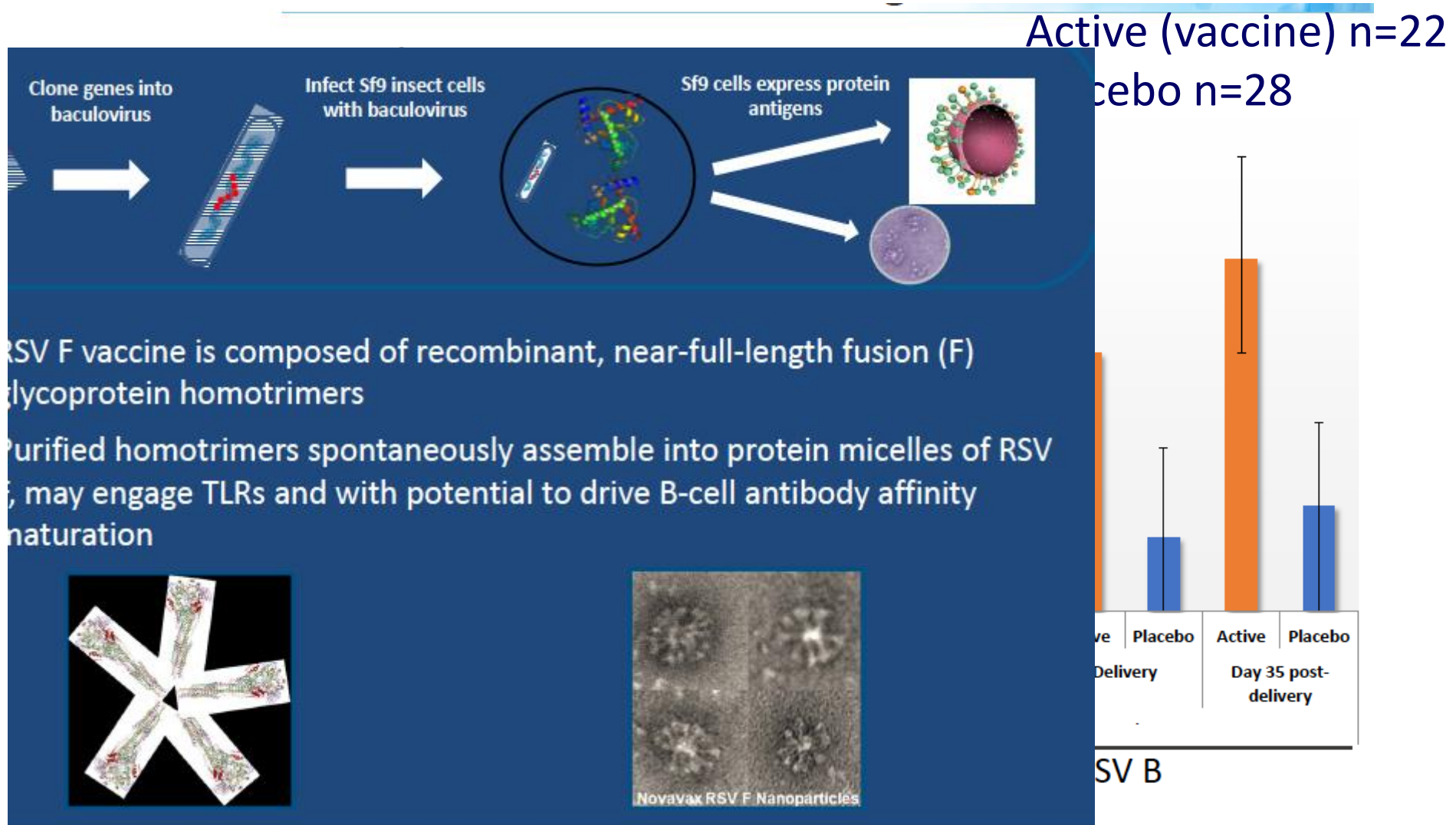


87% infants in 50 mg group had serum concentrations > 6.8 µg/mL target concentration for clinical efficacy on Day 150

RSV vaccines in clinical development



Maternal immunization RSV F nanoparticle vaccine (Phase 2: Maternal microneutralizing antibodies)



August A. RSV F Vaccine: Phase 2 Clinical Trial to Protect Infants via Maternal Immunization. XXI FIGO World Congress of Gynaecology and Obstetrics, 4–9 October 2015, Vancouver, Canada; oral presentation available at <http://novavax.com>

Time from vaccination impacts placental antibody transfer (Phase 2 infants)

| Assay | Source | Delivery <30d post-vacc (n=7) | Delivery >30d post-vacc (n=12) | All n=21 |
|--|------------------|-------------------------------|--------------------------------|------------|
| Anti-F IgG | Cord | 7,227 | 8,659 | 8,153 |
| | Mother | 12,979 | 6,993 | 8,594 |
| | Ratio C/M | 0.6 | 1.2 | 0.9 |
| Palivizumab competing antibodies (PCA) | Cord | 177 | 195 | 189 |
| | Mother | 303 | 178 | 213 |
| | Ratio C/M | 0.6 | 1.1 | 0.9 |

- Maternal antibody peaks at 14 d after vaccination
- Period of placental transfer > 30 d maximizes Ab titers in infants

Summary

1. RSV is a major pathogen for young children worldwide
2. Current therapies for RSV are suboptimal
3. RSV induces a robust and specific RNA immune profile
4. Genomic score (MDTH) offers new objective tool to assess disease severity in respiratory infections
5. Antivirals for RSV with different mechanisms of action are in clinical development
6. Pipeline: new monoclonal Abs and several vaccines strategies

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