# Journey Towards Respiratory Syncytial Virus (RSV) Vaccine Development

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National Institute of Allergy and Infectious Diseases

# Objectives

- Overview of RSV
- What we know about RSV
- History of RSV Vaccine Development
- Where are we now?
- Where are we going?


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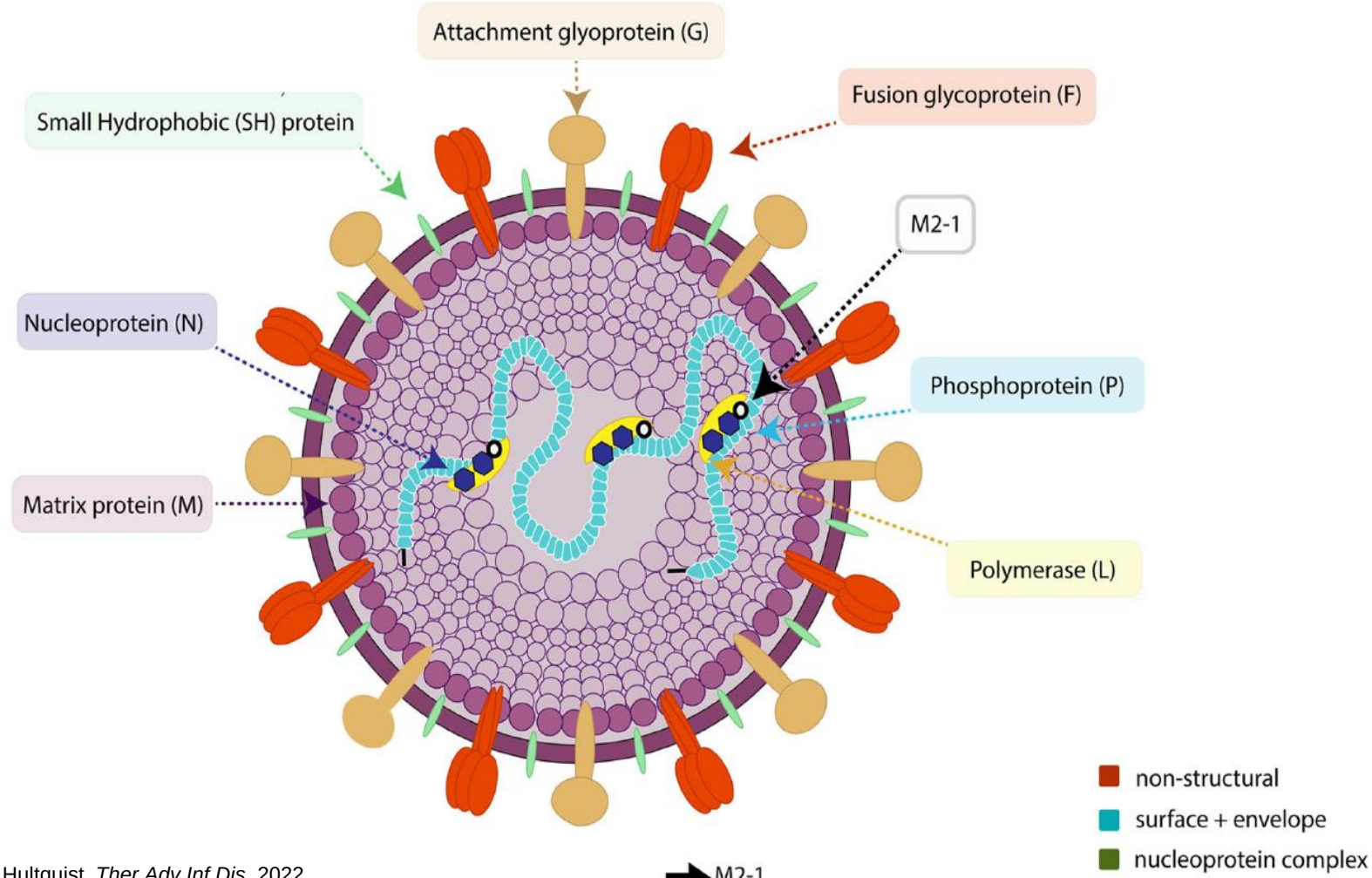
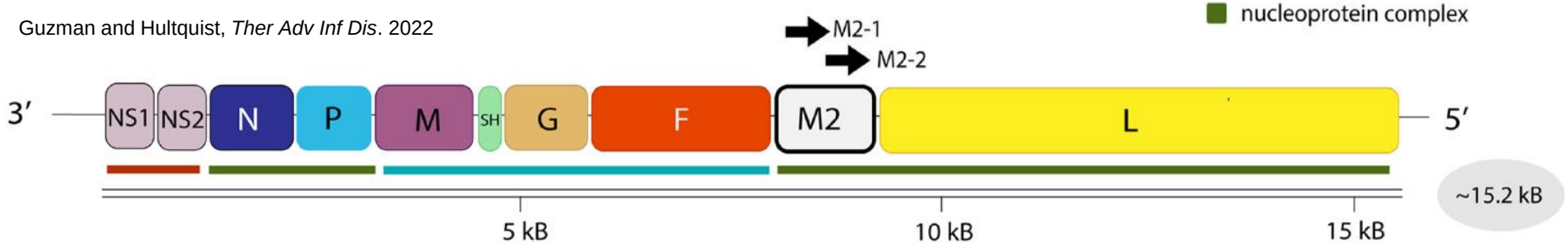
# RSV Virion




Guzman and Hultquist, *Ther Adv Inf Dis*. 2022



# What Do We Know About RSV Infection?

- RSV is the leading cause of acute lower respiratory tract infection (LRTI) in young infants
- Impacts elderly and immunocompromised individuals
- Globally there are 34 million RSV-associated ALRI[1]
  - 10% hospitalization
  - Up to 200,000 deaths
  - 99% in developing countries
- In U.S., there are 2.1 million medically attended RSV (outpatient)[2]
  - 80,000 hospitalizations among children <5 years
  - 120,000 hospitalization among adults >65 years
- No vaccine
- Limited treatment

[1] Nair et al. Global, regional, and national burden of acute lower respiratory infection due to respiratory syncytial virus in young children younger than 5 years in 2019: a systematic review and meta-analysis. *Lancet*. 2020 May 19; 399(10340): 2047-2064.

[2] CB Hall et al., NEJM 2009;360:588

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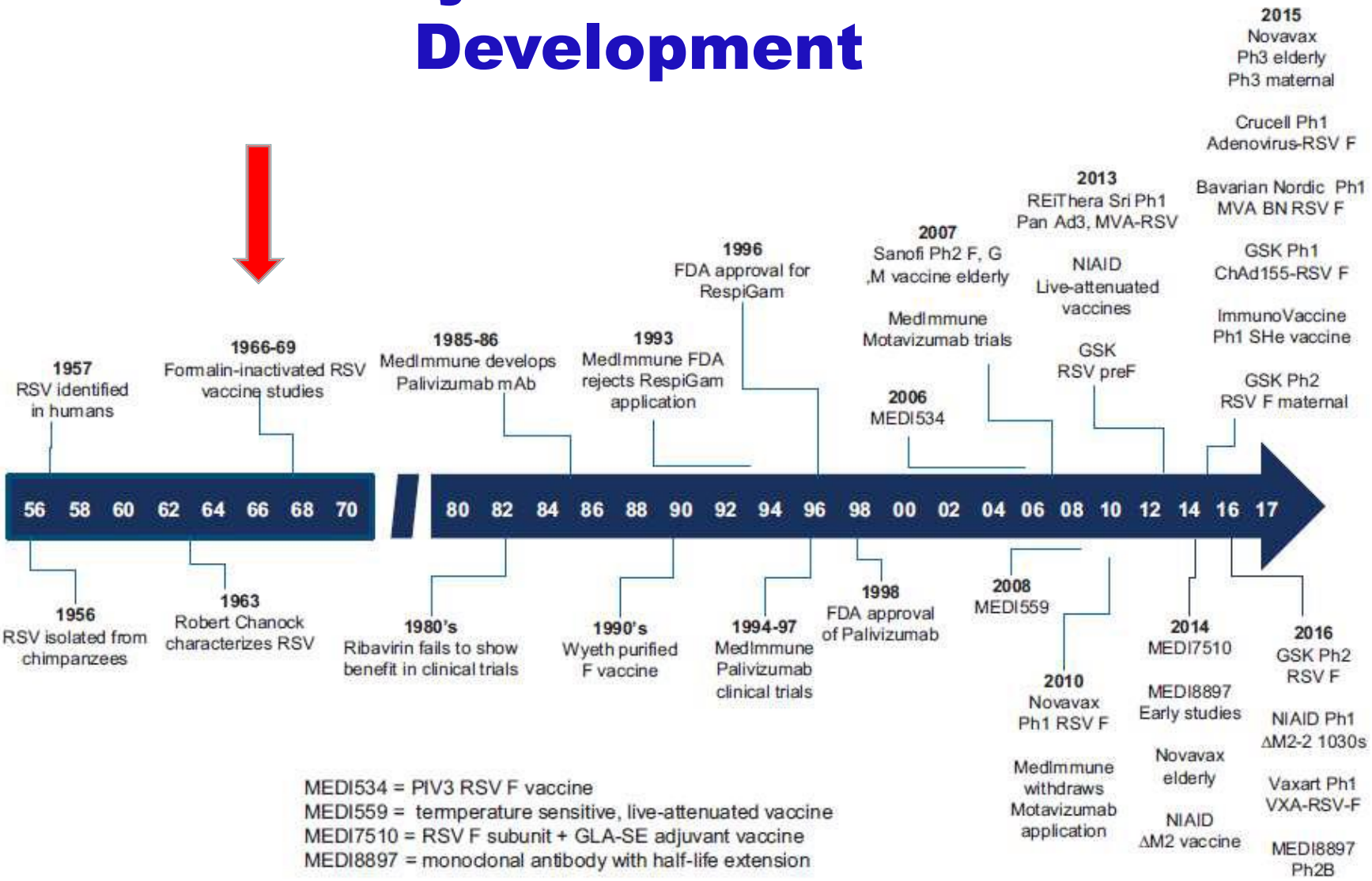
# History of RSV Vaccine Development

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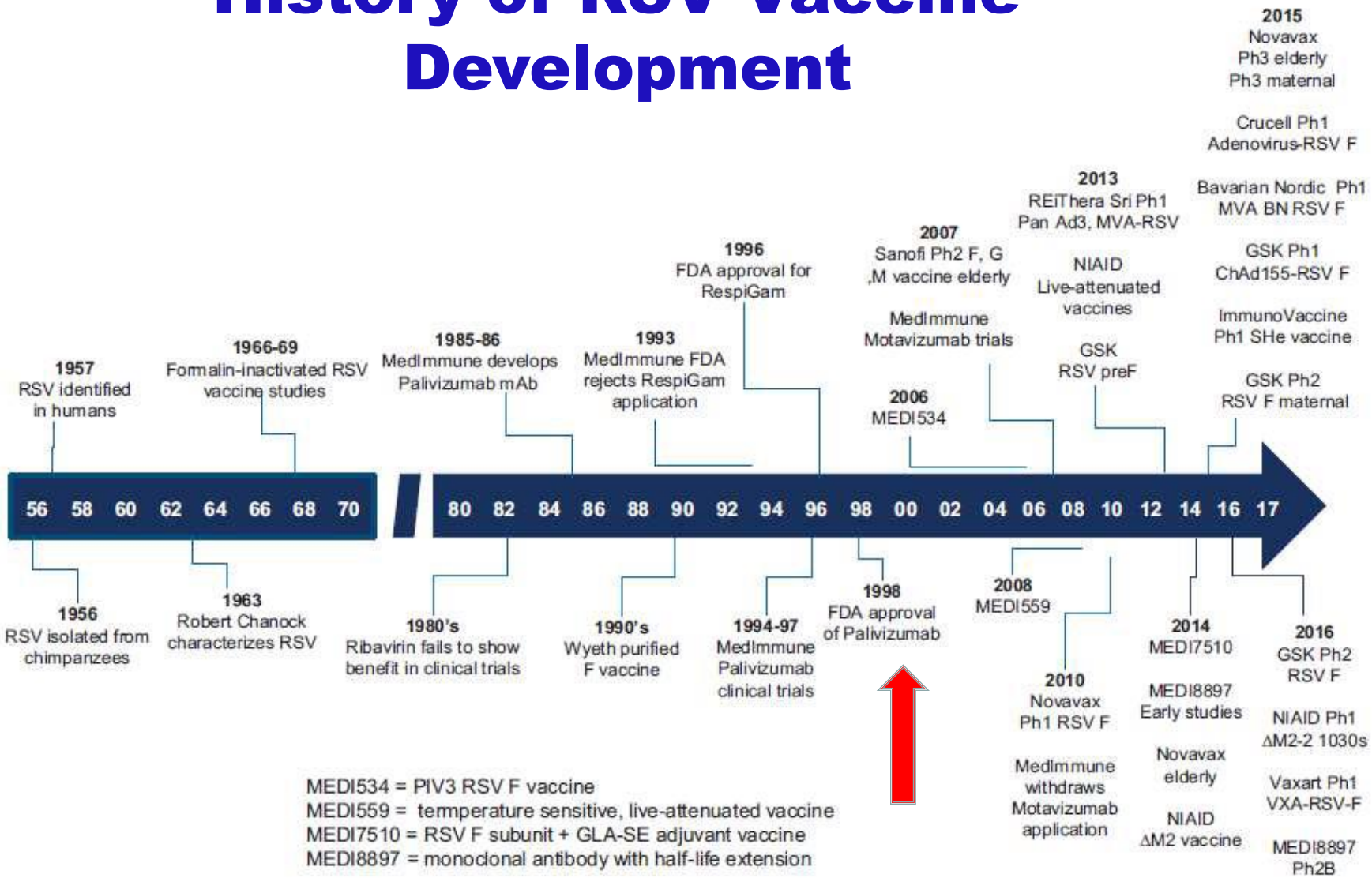
Tonya Villafana, Judith Falloon, M. Pamela Griffin, Qing Zhu & Mark T. Esser
(2017): Passive and active immunization against respiratory syncytial virus for the young and old. Expert Review of Vaccines

# Formalin Inactivated RSV Vaccine and Enhanced Disease

- Clinical trials in seronegative infants resulted in severe lung inflammatory response upon natural infection
  - 80% hospitalized
  - Two deaths

# History of RSV Vaccine Development

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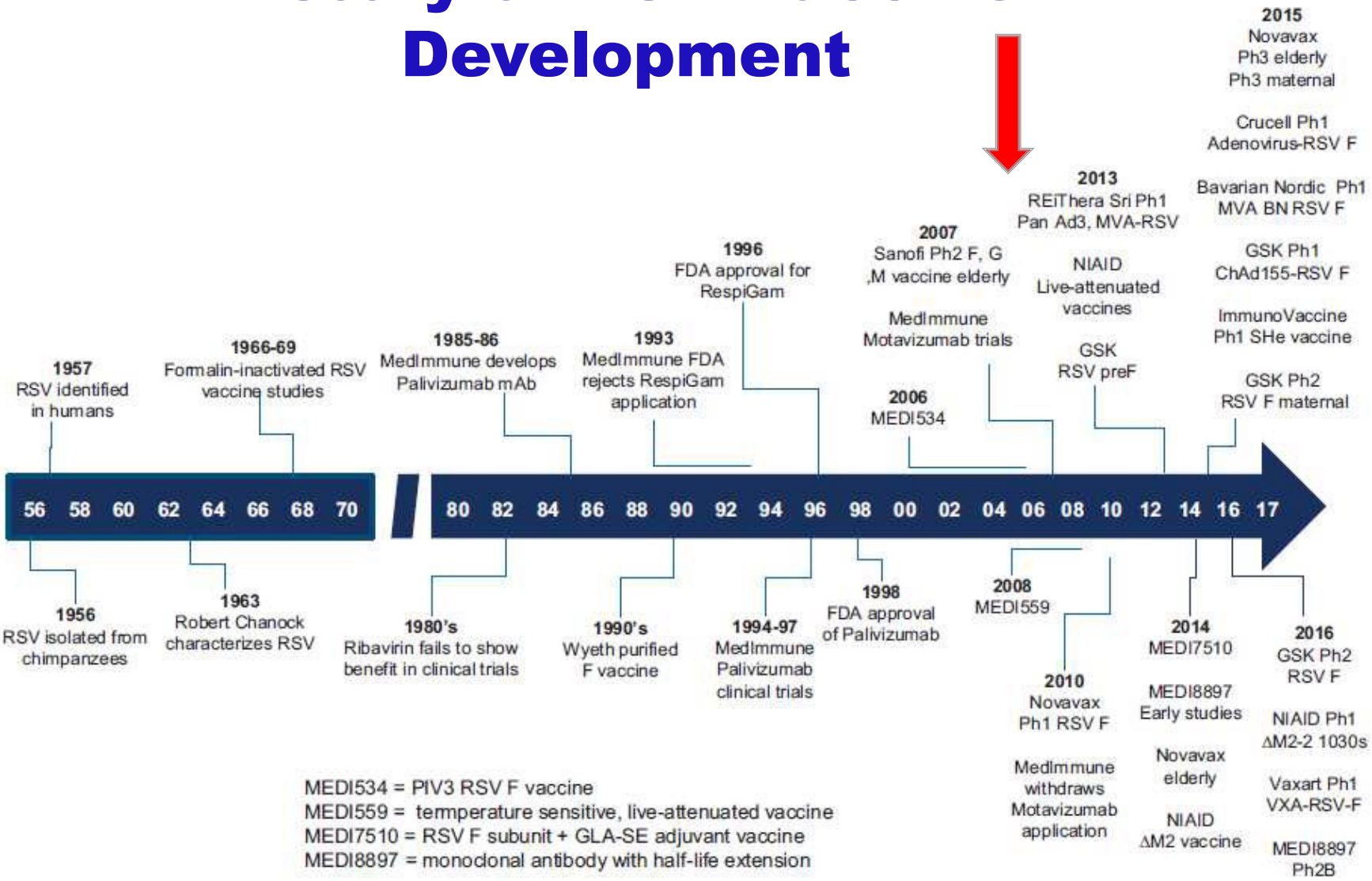


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# Challenges to Vaccine Development

- Mechanism of enhanced disease is unknown
- Multiple target population
  - Affects infants, elderly and immunocompromised
- Immune status
- Recurrent infection
- Pre-existing immunity

# Target Population and Vaccine Strategy

**Maternal**

- Placental antibody transfer
- Pre-existing immunity
- Potential adverse events (fetus)

Protein based (no adjuvant)

**Infants < 4-6 mo**

- Protection against severe disease
- Antigen naïve
- Immature immune system

Monoclonal antibodies

**Children > 6 mo**

- Herd protection
- Antigen naïve (< 2 yr)
- Pre-existing immunity

Live attenuated Vector based

**Elderly (> 65 yr)**

- At risk for severe disease
- Pre-existing immunity
- Immunosenescence

Protein based (adjuvanted)

Mejias, A et al. The journal to a respiratory syncytial virus vaccine. *Annals of Allergy, Asthma & Immunology*. July 2020
https://doi.org/10.1016/j.anai.2020.03.017

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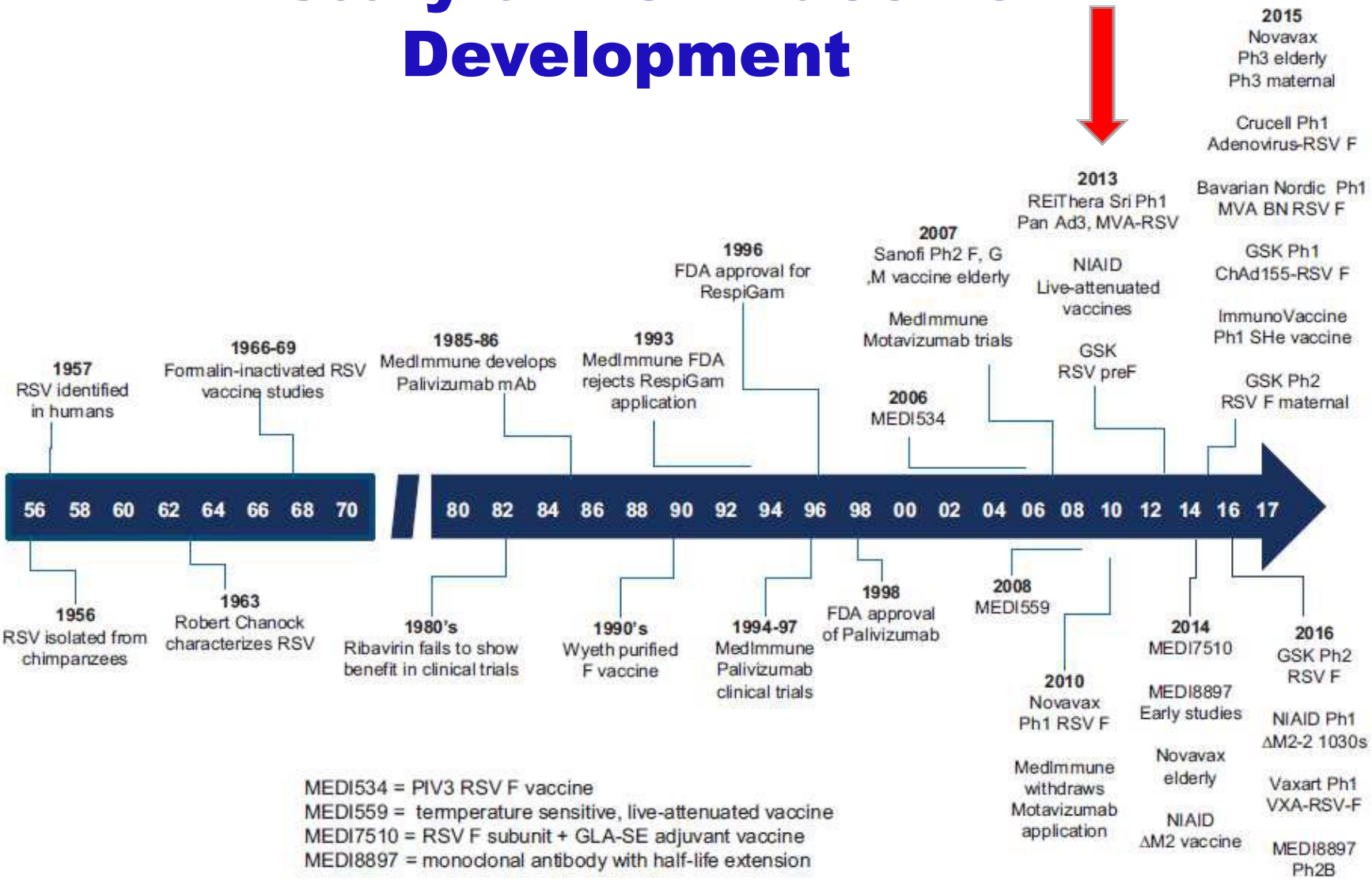


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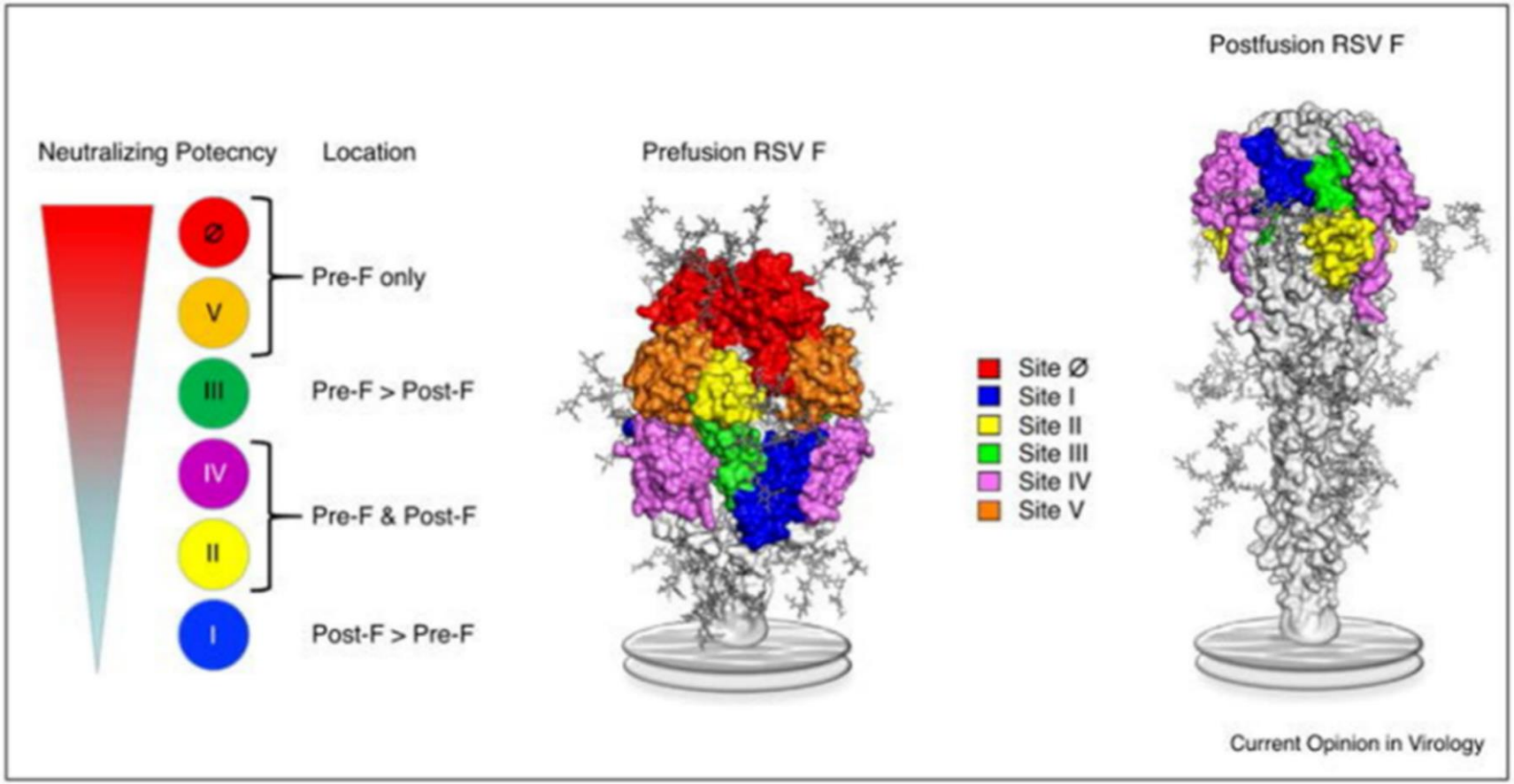
# Structural Forms of RSV F Protein




The fusion (F) protein exists in two or more structural forms, which bind different antibodies
Neutralizing potency Graham B. Current Opinion in Virology. 23: 107-112. 2017.

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# RSV Vaccine Snapshot

PATH

| | Preclinical | Phase 1 | Phase 2 | Phase 3 | Market Approved |
|---|---|---|---|---|---|
| Live-Attenuated | MedImmune NIH/NIAID/LID — RSV cpx2<br>St. Jude's Children's Research Hospital — SeV/RSV<br>NIH/NIAID/LID — RSV ΔNS2 Δ1313 | MedImmune NIH/NIAID/LID — Medi-RSV ΔM2-2 | MedImmune NIH/NIAID/LID — Medi-559, RSV<br>MedImmune — Medi-534, RSV/PIV3 | | |
| Whole-Inactivated | NanoBio — RSV | | | | |
| Particle-based | Agilvax — VLP<br>LIGOCYTE — VLP<br>pevion — Virosome<br>University of Massachusetts — VLP<br>Artificial Cell Technologies, Inc. — Peptide microparticle<br>Mucosis — BLP<br>RUB — VLP<br>Zetra Biologicals — VLP<br>Fraunhofer — VLP<br>MYMETICS — Virosome<br>TechnoVax — VLP | | | | |
| Subunit | gsk GlaxoSmithKline — RSV F protein<br>IMV — DPX-RSV<br>NOVARTIS — RSV F protein<br>University of Georgia — RSV G protein<br>YTB — SH protein<br>RSV F protein<br>PeptiVir — RSV peptides<br>University of Saskatchewan — RSV F protein | | NOVAVAX — RSV F protein | | |
| Nucleic Acid | BRM — Vector prime/ subunit boost<br>INOVIO — DNA<br>NOVARTIS — RNA<br>RUB — DNA | | | | |
| Gene-based Vectors | ALPHAVAX — Alphavirus<br>BAVARIAN NORDIC — MVA<br>okairos — Adenovirus/MVA<br>TWI Biotech — Adenovirus<br>AMVAC — Sendai virus<br>GENVEC — Adenovirus<br>RUB — Adenovirus<br>Vanderbilt University Medical Center — Alphavirus | | | | |
| Undisclosed | Crucell — Universal<br>Georgia State University — Particulate<br>Merck — Undisclosed<br>Sanofi Pasteur — Undisclosed | | | | |

Updated: 12/5/2012

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# 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 | LID/NIAID/NIH<br>PIV1-3/RSV | LID/NIAID/NIH<br>RSV | | Blue Lake<br>PIV5/RSV | Codagenix, LID/NIAID/NIH (P)<br>RSV | Meissa Vaccines (P)<br>RSV | Sanofi, LID/NIAID/NIH (P)<br>RSV | | | | |
| | | | | Intravacc (P)<br>RSV-ΔG | Pontificia Universidad Catolica de Chile (P)<br>BCG/RSV | | | | | | |
| | | | | SIIPL, St. Jude Hospital (P)<br>SeV/RSV | | | | | | | |
| PROTEIN-BASED • INACTIVATED • PARTICLE • SUBUNIT | Blue Willow Biologics<br>Inactivated RSV | Georgia State University<br>VLP | Health Guard<br>RSV F Protein | Icosavax (E)<br>RSV/hMPV VLP | Immunovaccine, VIB (E)<br>RSV SH Protein | Advaccine Biotechnology (P E)<br>RSV G Protein | Daiichi Sankyo (E)<br>Protein ? | GlaxoSmithKline (E)<br>RSV F Protein | GlaxoSmithKline (M)<br>RSV F Protein<br>Discontinued | | |
| | Sanofi (E)<br>Nanoparticle<br>Replaced by RNA candidate | Sciogen<br>RSV G Protein | University of Georgia<br>RSV G Protein | NIH/ NIAID/VRC (E M)<br>RSV F Protein | Virometix<br>VLP | | | Pfizer (M)<br>RSV F Protein | Pfizer (E)<br>RSV F Protein | | |
| | University of Massachusetts<br>VLP | University of Saskatchewan<br>RSV F Protein | | | | | | | | | |
| NUCLEIC ACID | CureVac<br>RNA | | | Moderna (M P)<br>RNA | Sanofi (E)<br>RNA | | | Moderna (E)<br>RNA | | | |
| RECOMBINANT VECTORS | BravoVax<br>Adenovirus | GlaxoSmithKline (P)<br>Adenovirus | Vaxart (E)<br>Adenovirus | | | Janssen Pharmaceutical (P)<br>Adenovirus | | Bavarian Nordic (E)<br>MVA | Janssen Pharmaceutical (E)<br>Adenovirus | | |
| IMMUNO-PROPHYLAXIS | Aridis<br>Anti-F mAb | Pontificia Universidad Catolica de Chile<br>Anti-N mAb | UCAB, mAbXience<br>Anti-F mAb | Gates MRI (P)<br>Anti-F mAb | Trinomab Biotechnology (P)<br>Anti-F mAb | | | Merck (P)<br>Anti-F mAb | | Astra Zeneca, Sanofi (P)<br>Nirsevimab | Astra Zeneca (P)<br>Palivizumab |

UPDATED: January 3, 2023

Indicates Change

https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/

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# Where are we now?

- Pfizer's RSV vaccine in older adults >60 years was safe and well tolerated with 85.7% vaccine efficacy

- GSK's RSV vaccine in older adults >60 years was safe and well tolerated with 82.6% vaccine efficacy

# Where are we now?

- AstraZeneca's (in collaboration with Sanofi) mAb nirsevimab for prophylactic treatment was approved by EMA

- Pfizer's RSV maternal vaccine show a vaccine efficacy of 81.8% against severe RSV in infants from birth through the first 90 days of life and 69.4% efficacy through the first six months of life

# RSV Vaccine and mAb Snapshot

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| | | | | Intravacc (P)<br>RSV-ΔG | Pontificia Universidad Catolica de Chile (P)<br>BCG/RSV | | | | | | |
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# Overview of RSV Vaccine Development

## Questions ???

# Overview of RSV Vaccine Development

## Back up slide

# NIAID Supported Achievements in RSV Research and Product Development

- Studies under cotton rat model task order supported Novavax's RSV nanoparticle vaccine for maternal immunization
- PIV5 platform technology (Blue Lake Technology and CyanoVax)
- Codon optimization platform technology (Meissa)
- GLP tox MVA-RSV vaccine
- GLP tox for rSeV-RSV vaccine and phase 1 trial
- Advanced Codagenix's codon deoptimization platform for RSV, flu and COVID vaccine development
- Define the role of viral defective genome used as predictor of severe disease
- Identified RSV variant associated with prolonged infection in healthy infants using GWAS

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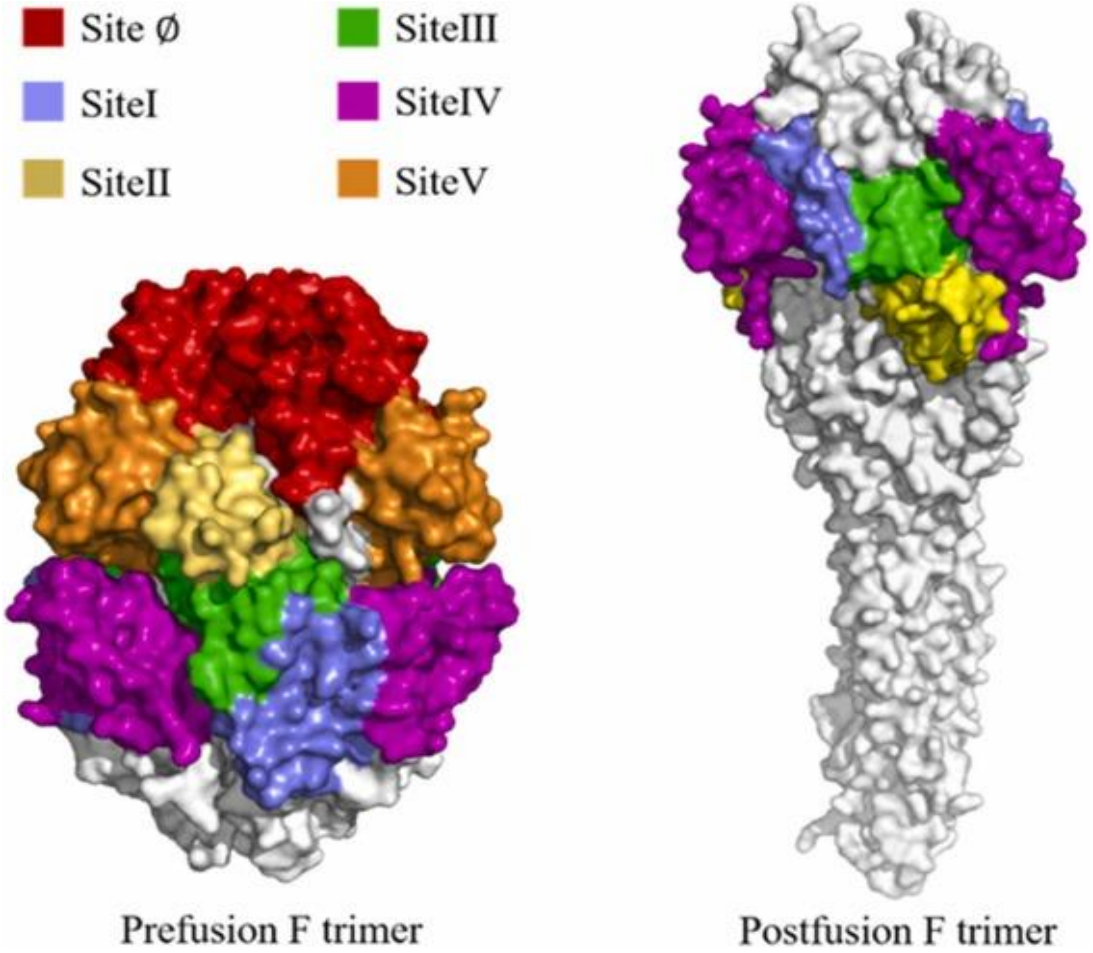
# Structural Forms of RSV F Protein

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