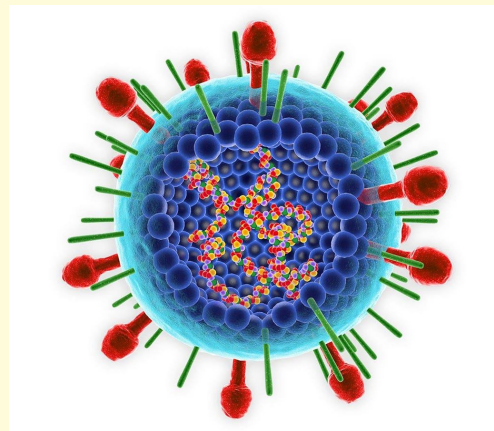




RSV: Progress & Possibility



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Tulane University & Children's Hospital New Orleans
New Orleans, LA

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answer MOC questions
at

slido.com

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#CENLApotpourri



Speaker Disclosure

I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.

I do not intend to discuss unapproved/investigative use of a commercial product/device in my presentation.

I have not used artificial intelligence in the development of this presentation

Objectives

- At the conclusion of this activity, learners will be able to:
 - Understand the impact of RSV on US and Global Child Health
 - Recall the history of our battle with this virus
 - Identify current & potential tools in this fight

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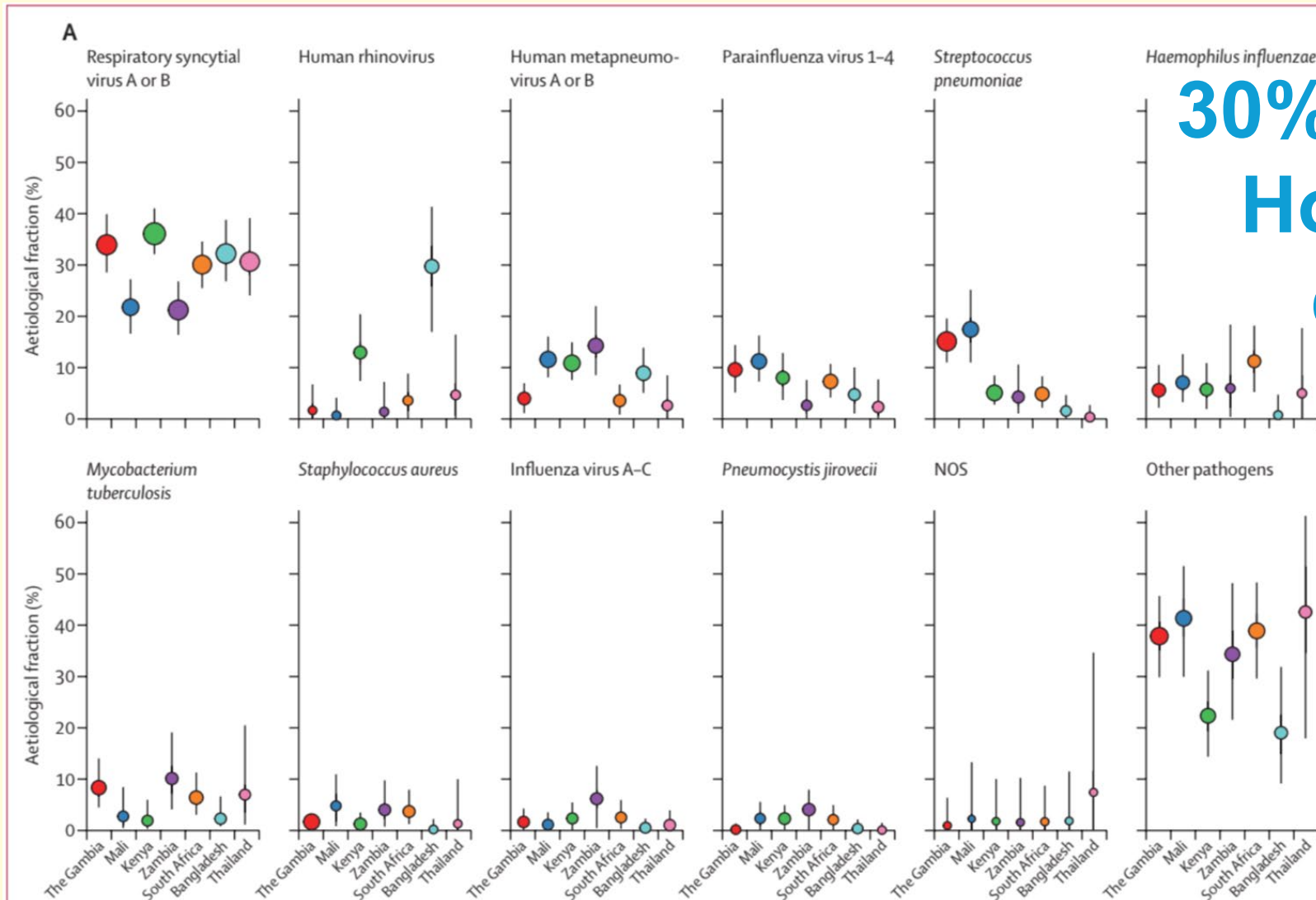
In the United States

- RSV has a very high morbidity and cost
- 1.5 million outpatient visits
- 500,000 ED visits
- 50-80,000 hospitalizations

**~2% of all infants <1 year
are hospitalized with
RSV!**

Ramilo et al (2020) "Measuring the burden of RSV in children to precisely assess the impact of preventive strategies" **Pediatrics**

In Low/Middle Income Countries



30% of respiratory Hospitalization due to RSV

O'Brian et al (2019) "Causes of severe pneumonia requiring hospital admission in children with HIV disease in Africa and Asia: the PERCH multi-country case control study" **Lancet**

Top 10 causes of death in children <5

Location	Deaths, No. (Rate/100,000 Children and Adolescents)										
	All Causes	Lower Respiratory Tract Infections	Preterm Birth Complications	Neonatal Encephalopathy	Malaria	Diarrheal Diseases	Congenital Anomalies	Neonatal Sepsis	Other Neonatal Disorders	Protein-Energy Malnutrition	Meningitis
Global	6 279 920 (951.5)	905 059 (137.1)	742 381 (112.5)	643 765 (97.5)	586 844 (88.9)	519 666 (78.7)	495 319 (75.1)	366 041 (55.5)	276 231 (41.9)	225 906 (34.2)	141 952 (21.5)
Developing	6 193 574 (1 055.7)	900 384 (153.5)	726 053 (123.8)	637 629 (108.7)	586 844 (100.0)	518 963 (88.5)	472 671 (80.6)	363 566 (62.0)	268 355 (45.7)	225 796 (38.5)	140 814 (24.0)
Developed	86 346 (117.8)	4675 (6.4)	16 328 (22.3)	6136 (8.4)	0	703 (1.0)	22 648 (30.9)	2476 (3.4)	7876 (10.7)	110 (0.2)	1138 (1.6)
United States	28 013 (133.1)	627 (3.0)	6822 (32.4)	1650 (7.8)	0	150 (0.7)	6350 (30.2)	806 (3.8)	2399 (11.4)	14 (0.1)	238 (1.1)

100-200,000 deaths/year worldwide
(100-300 deaths in US) from RSV

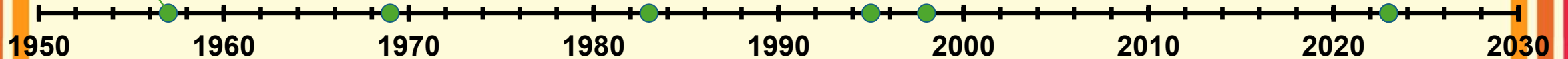
Vos et al (2016) "Global and National Burden of Diseases and Injuries Among Children and Adolescents Between 1990 and 2013" **JAMAPeds**

History of our battle with public enemy #1

1957 - RSV identified

1957

RSV cultured from secretions of infants with “epidemic bronchiolitis”

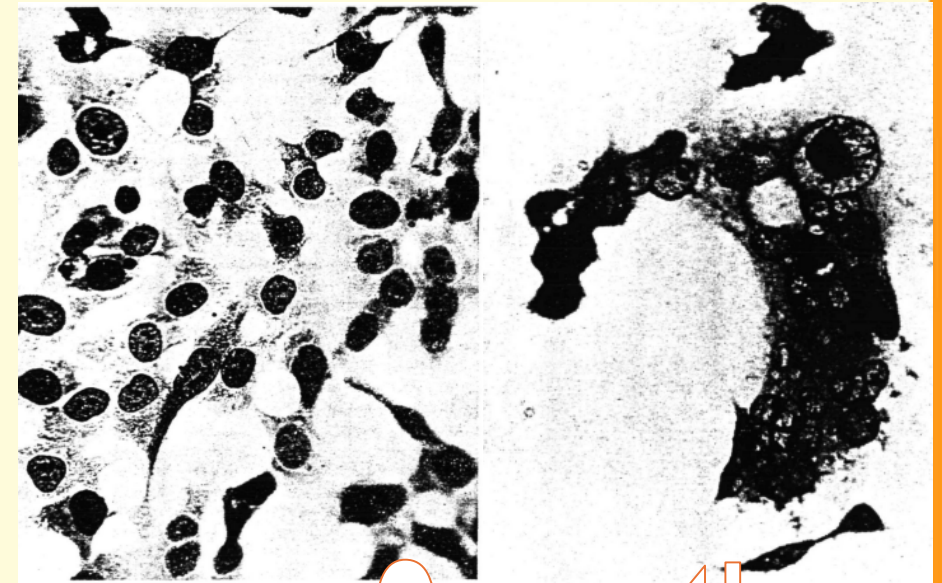


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RSV isolated by viral culture

- CCA (Chimpanzee Coryza Agent) had been isolated in 1955
- Infants with “bronchopneumonia, bronchiolitis, and laryngotracheobronchitis”
- Cultured in epidermoid carcinoma cells, strain KB
- “almost complete destruction of the cell sheet” within 2-8 days of inoculation identical to that seen in the chimpanzees

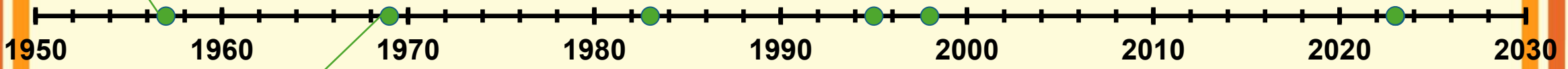


Syncytium

Chanock et al (1957) “Recovery from infants with respiratory illness of a virus related to Chimpanzee Coryza Agent (CCA)” **Am J Hyg**

1969 - First RSV Vaccine 🖱️

1957
RSV cultured from secretions of infants with “epidemic bronchiolitis”



1969
First RSV vaccine trial caused dramatic increase in symptoms after infection

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First RSV Vaccine Trial

Distressing Results!

	31 Infants – RSV Vaccine	40 infants – Control Vaccine
Infected RSV	20 (65%)	21 (53%)
Hospitalized RSV	16 (80%)	1 (5%)
Died RSV	2	0

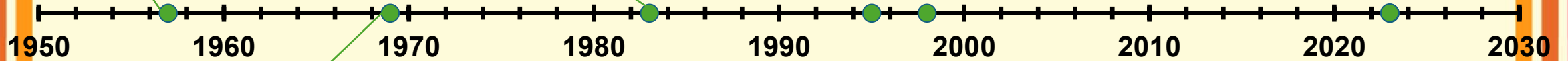
“...the vaccine in some way altered the host response to natural RSV infection...”

Kim et al (1969) “Respiratory Syncytial Virus Disease in infants Despite Prior Administration of Antigenic Inactivated Vaccine” **Am J Epi**

1985 - The First Approved RSV Treatment

1957
RSV cultured from secretions of infants with “epidemic bronchiolitis”

1985
Ribavirin approved for treatment of RSV



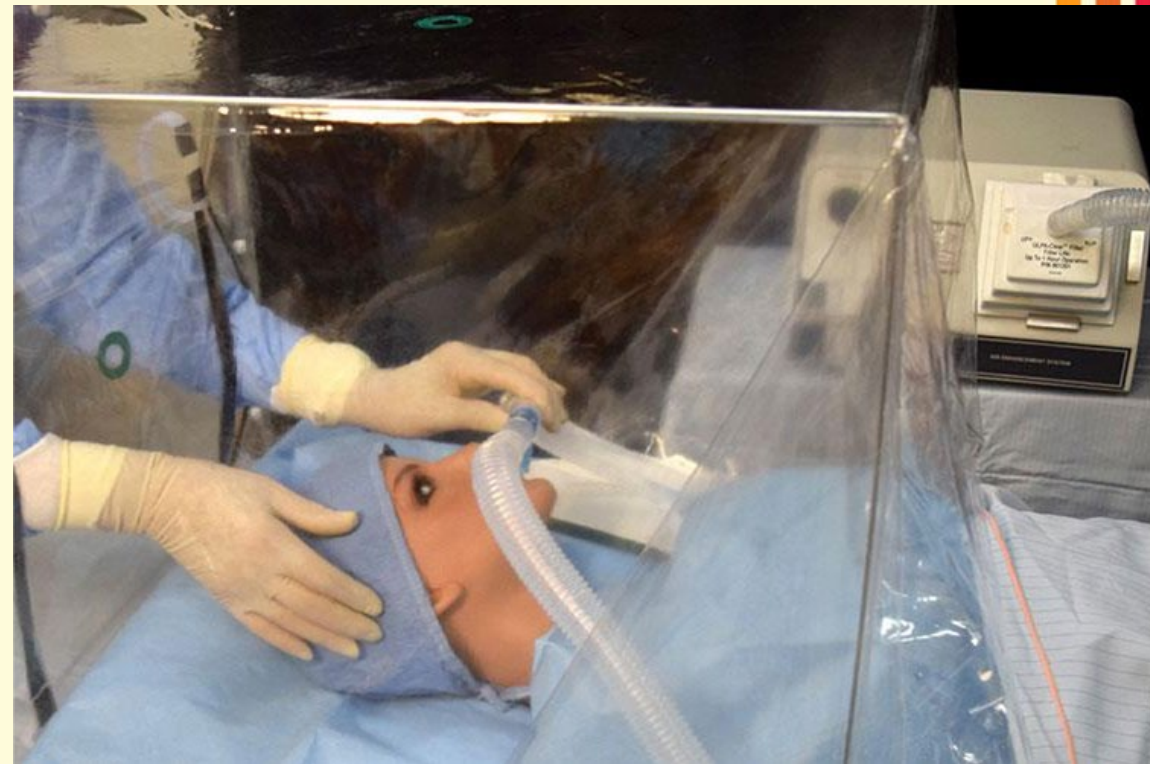
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Challenging Toxicity – Equivocal Benefit

- Trialed in healthy adults inoculated with RSV
- Nebulization for 12 hours/day showed measurable decrease in fever, but not mucus production or PFTs
- IV ribavirin toxic to patient
- PO ribavirin ineffective



We need something better!

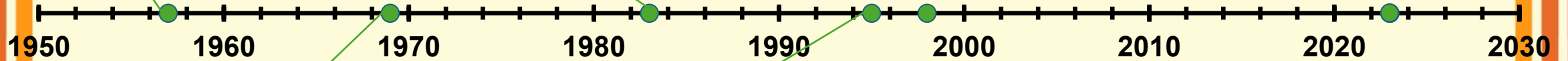
Hall et al (1983) "Ribavirin Treatment of Experimental Respiratory Syncytial Viral Infection" **JAMA**

Committee on Infectious Diseases (2021) "Respiratory Syncytial Virus" **Red Book**

1995 – First Effective Prevention

1957
RSV cultured from secretions of infants with “epidemic bronchiolitis”

1985
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1969
First RSV vaccine trial caused dramatic increase in symptoms after infection

1995
RespiGam approved for use as a preventative in high risk infants

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RespiGam

- Polyclonal RSV-IVIG derived from plasma donors with high titers of neutralizing antibodies to RSV
- Human blood product given by ***IV infusion*** over 2-3 hours every 30 days
- Provided protection from ***hospitalization*** for RSV (about 40% decrease) when given to infants and toddlers at high risk of severe RSV



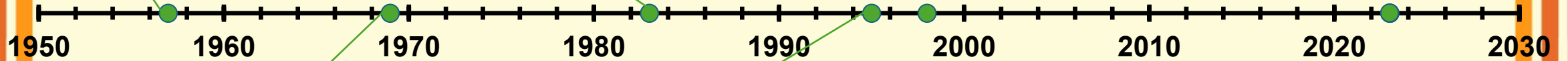
Groothuis et al (1993) "Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children" **NEJM**

1998 – Dominant Biologic for Decades Approved

1957
RSV cultured from secretions of infants with “epidemic bronchiolitis”

1985
Ribavirin approved for treatment of RSV

1998
Palivizumab “Synagis” approved for prevention in high-risk infants



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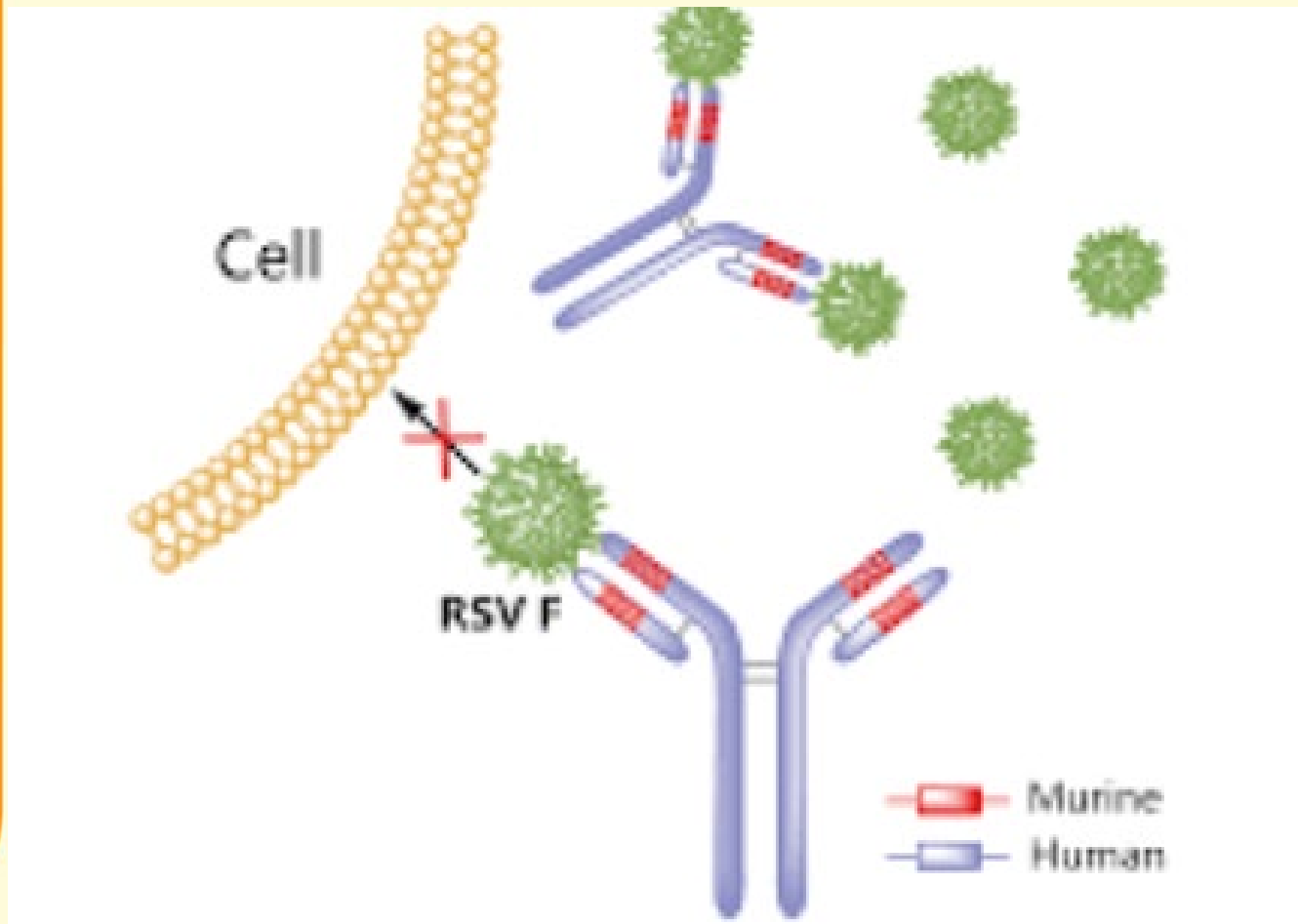
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RespiGam approved for use as a preventative in high risk infants

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Palivizumab “Synagis”

- Humanized monoclonal antibody against RSV



Subramanian et al (1998) “Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia” **PIDJ**

Effective...but cumbersome & costly

- Palivizumab much smaller dose than RespiGam & **given IM**
- Given **monthly** throughout RSV season
- Decreases risk of hospitalization ~ 50%
- Has remained very expensive
 - 1998 AWP \$901/vial ~ **\$2700/child/season**
 - 2006 AWP \$1145/vial ~ **\$6000/child/season**
 - 2023 AWP \$1927/vial ~ **\$9000/child/season**
- Restricted use due to cost



Subramanian et al (1998) "Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia" **PIDJ**

Joffe et al (1999) "Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants" **Pediatrics**

Hampp et al (2011) "Cost-effectiveness of Respiratory Syncytial Virus Prophylaxis in Various Indications" **JAMApediatrics**

To improve cost-effectiveness ... decrease the cost?

Table 3 Vaccine prices required to achieve cost-effectiveness ^a

Risk group	Cost per DALY (excluding asthma)	Cost per DALY (including asthma)	Palivizumab price to achieve cost-Effectiveness (including asthma)		% decrease in Palivizumab Price
			50 mg Vial ^b	100 mg Vial ^c	
CHD	\$266,020	\$218,968	\$278	\$512	46.5%
CLD	\$472,139	\$287,057	\$270	\$497	48.1%
<29	\$585,537	\$226,900	\$329	\$605	36.8%
29-32	\$685,961	\$347,593	\$237	\$436	54.5%
33-36	\$2,092,809	\$1,149,584	\$87	\$160	83.3%
No risk	\$7,503,953	\$3,023,294	\$31	\$57	94.0%

^a based on threshold of \$105,986 per averted DALY and 2945 annual hospitalizations in children under two

^b current price (excluding VAT) of \$520 per vial

^c current price (excluding VAT) of \$959 per vial

Vaccines for Adults & Pregnant Women

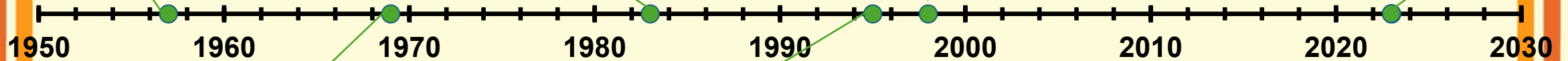
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Palivizumab “Synagis” approved for prevention in high-risk infants

2023
RSVpreF “Abrysvo” approved for adults 60+ and pregnant women

2023
RSVPreF3 antigen-ASO1E (PF) “Arexvy” approved for adults 60+



1969
First RSV vaccine trial caused dramatic increase in symptoms after infection

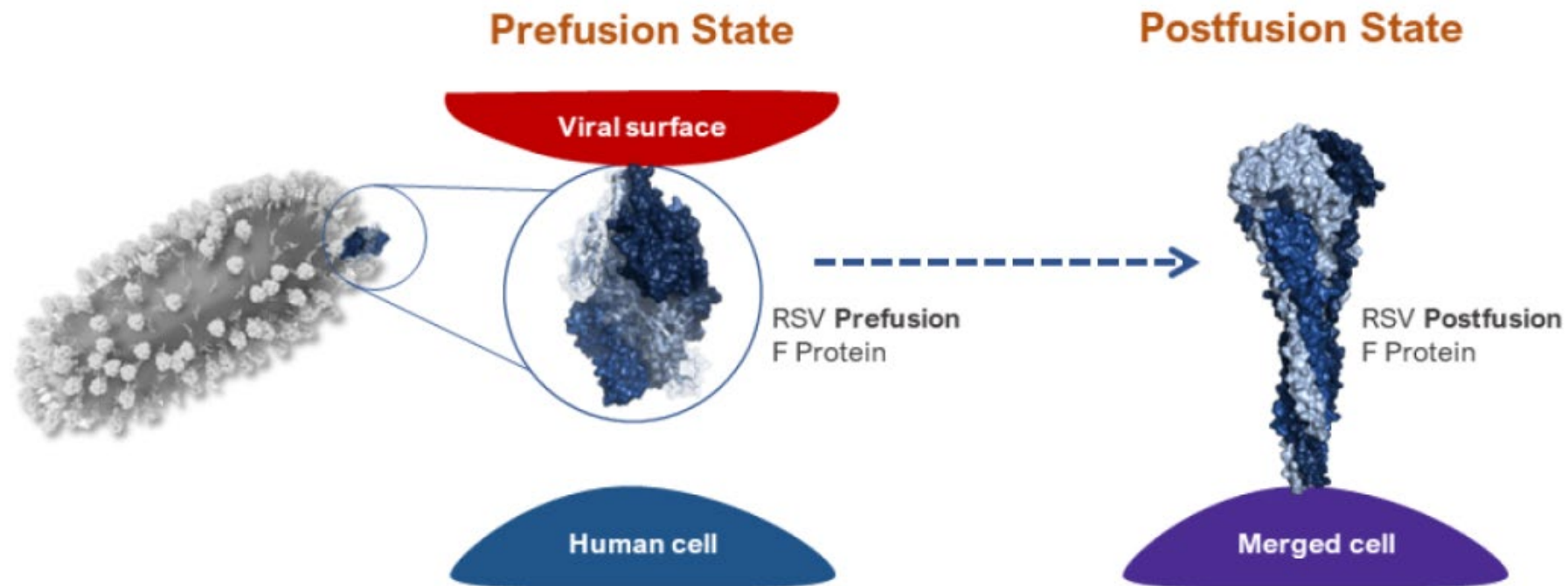
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RespiGam approved for use as a preventative in high risk infants

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Key discovery leads to similar vaccines

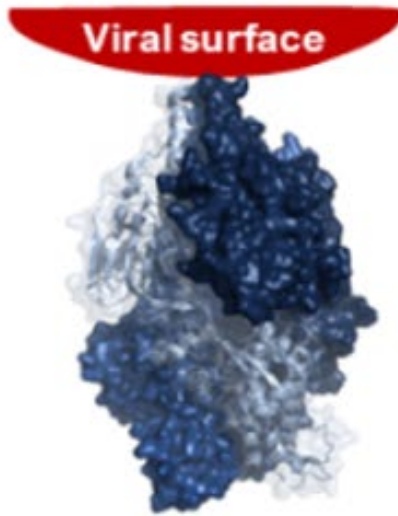
Two States of the RSV F Protein



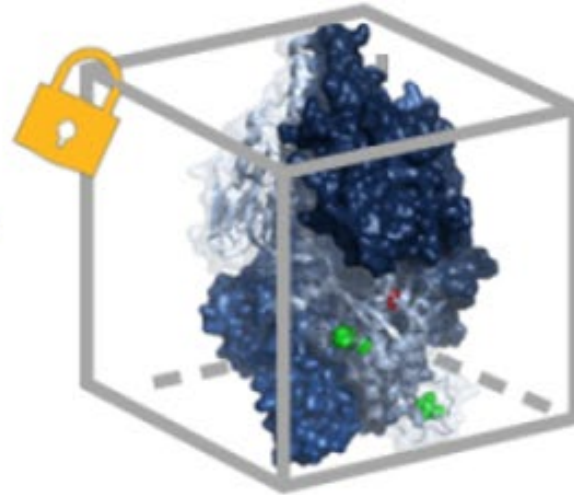
McLellan et al (2013) "Structure of RSV Fusion Glycoprotein Trimer Bound to a Prefusion-Specific Neutralizing Antibody"
Science

Anti-pre fusion F is highly protective!

Prefusion State



Stabilized Prefusion Protein



Early Vaccine Trials

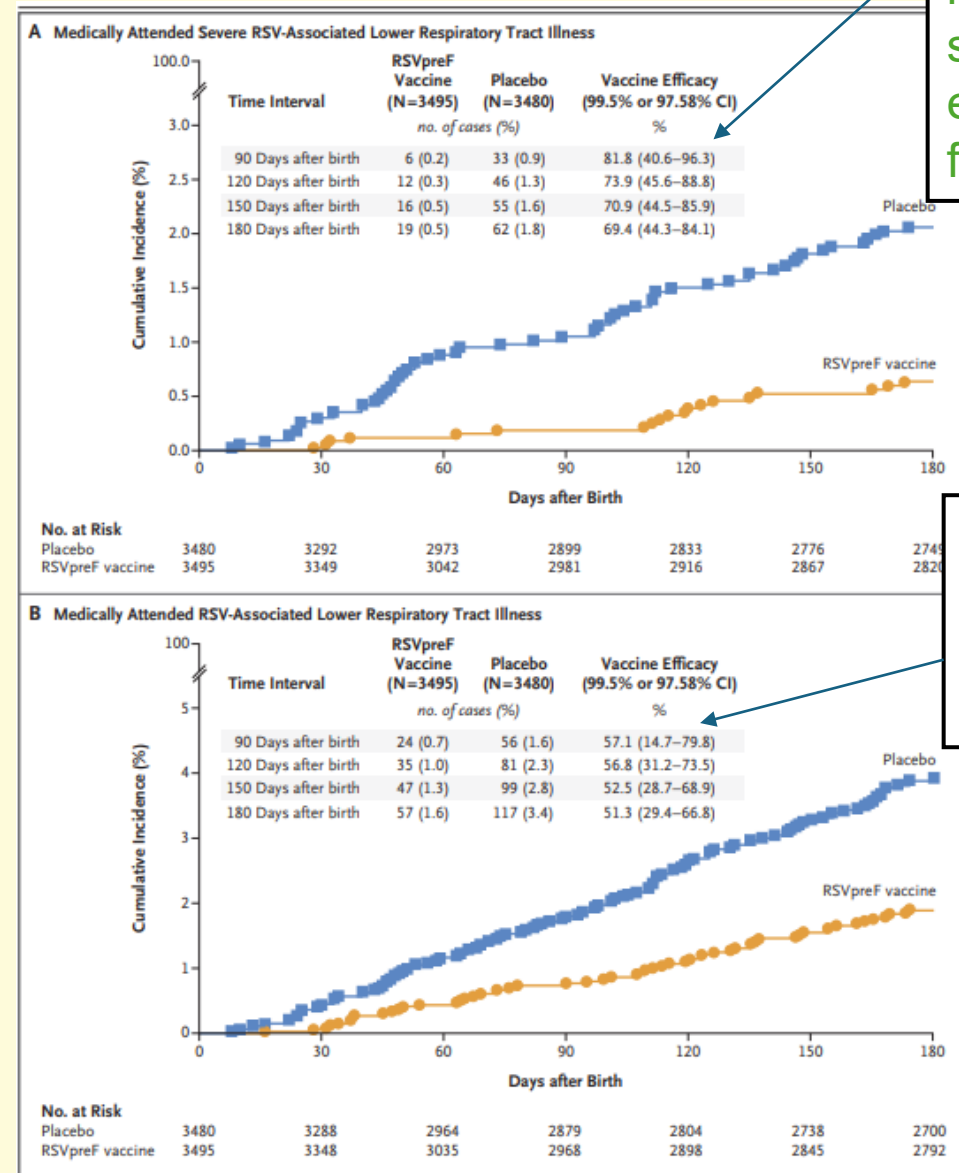


Gordon et al (2016) "Iterative structure-based improvement of a fusion-glycoprotein vaccine against RSV" *Nat Struct & Mol Bio*

Immunization during pregnancy

- >3000 women 32-36 WGA in each group
- Infants followed for 1 year
- Infants tested for RSV every time had resp illness
- Adverse events similar in both groups for mothers and infants

Kampmann et al (2023) "Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants"
NEJM



Efficacy preventing hospitalization strong – especially in first 90 days

Efficacy preventing disease less impressive

*Immunization for people aged 60+

- Moderate to strong efficacy at preventing
 - Symptomatic RSV
 - Doctor visits for RSV
- Studies not powered to detect mortality difference
- No significant increase in AEs
- ACIP accepted 2023
- Most private insurance must pay without copay next season

During 2023-2024:

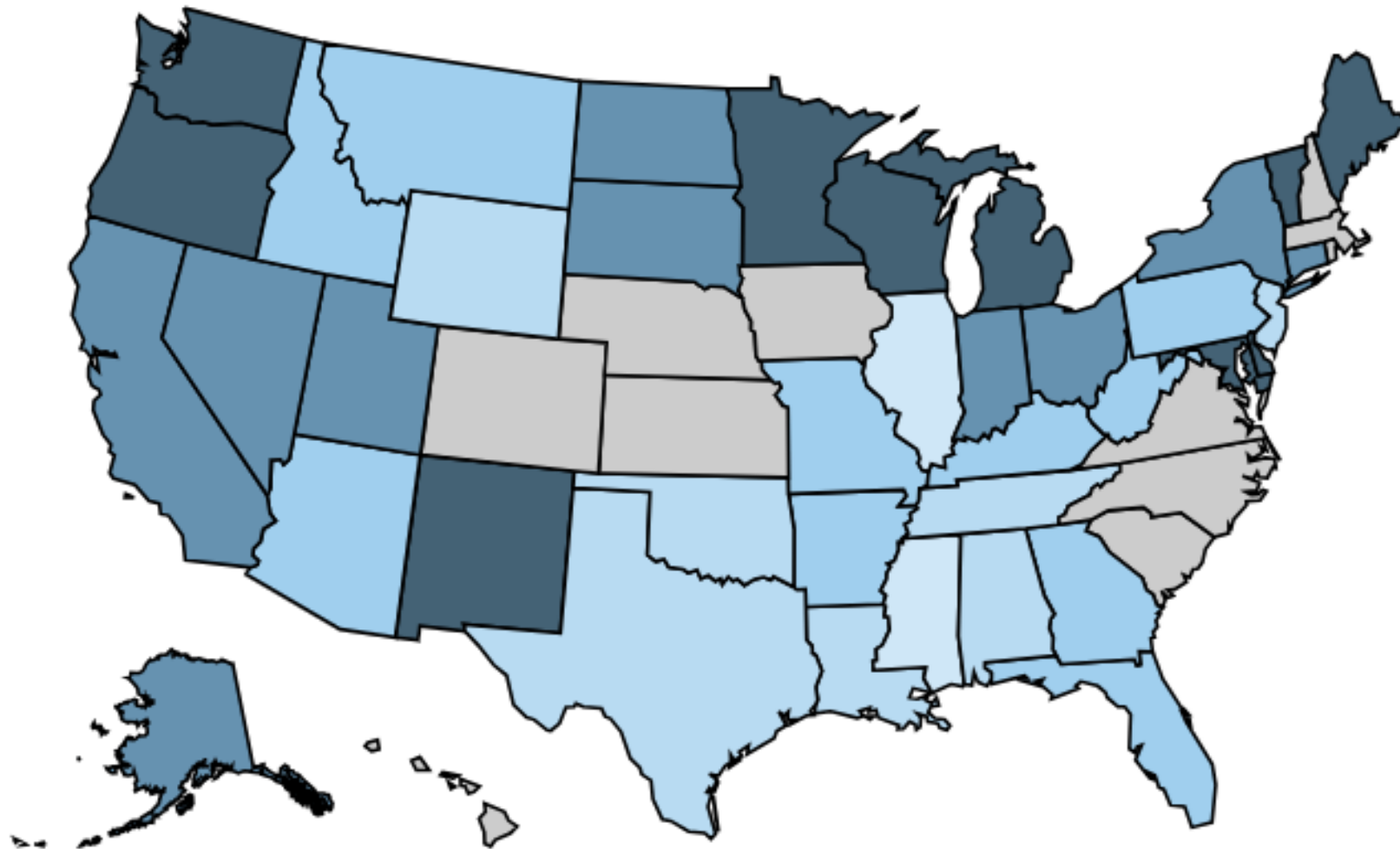
- AREXVY was approximately 77% to 83% effective in preventing RSV-associated hospitalization or emergency department encounters in adults 60 and older.
- ABRYSSVO was approximately 73% to 79% effective in preventing RSV-associated hospitalization or emergency department encounters in adults 60 and older.

**New Moderna mRNA
Vaccine “mRESVIA”
approved in March, ‘24**

***New guideline ‘24-25 season:
Adults 75+
Adults 60-75 with risk factors**

[https://www.cdc.gov/vaccines/vpd/rsv/hcp/older-adults.html#:~:text=Protein%20Subunit%20Vaccines%20\(GSK's%20AREXVY%20and%20Pfizer's%20ABRYSSVO\)&text=CDC%20data%20from%20the%20first,people%20ages%2060%20and%20older. CDC "Vaccines and Preventable Disease" Aug 11,2024](https://www.cdc.gov/vaccines/vpd/rsv/hcp/older-adults.html#:~:text=Protein%20Subunit%20Vaccines%20(GSK's%20AREXVY%20and%20Pfizer's%20ABRYSSVO)&text=CDC%20data%20from%20the%20first,people%20ages%2060%20and%20older. CDC)

In the first season 8.2% of LA residents >60 have received RSV vaccination (USA=24.4%)



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RSV cultured from secretions of infants with “epidemic bronchiolitis”

1985
Ribavirin approved for treatment of RSV

1998
Palivizumab “Synagis” approved for prevention in high-risk infants

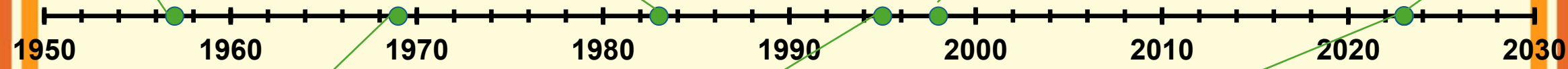
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1969
First RSV vaccine trial caused dramatic increase in symptoms after infection

1995
RespiGam approved for use as a preventative in high risk infants

2023
Nirsevimab “Beyfortus” approved for prevention in all infants <8 mo



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Nirsevimab

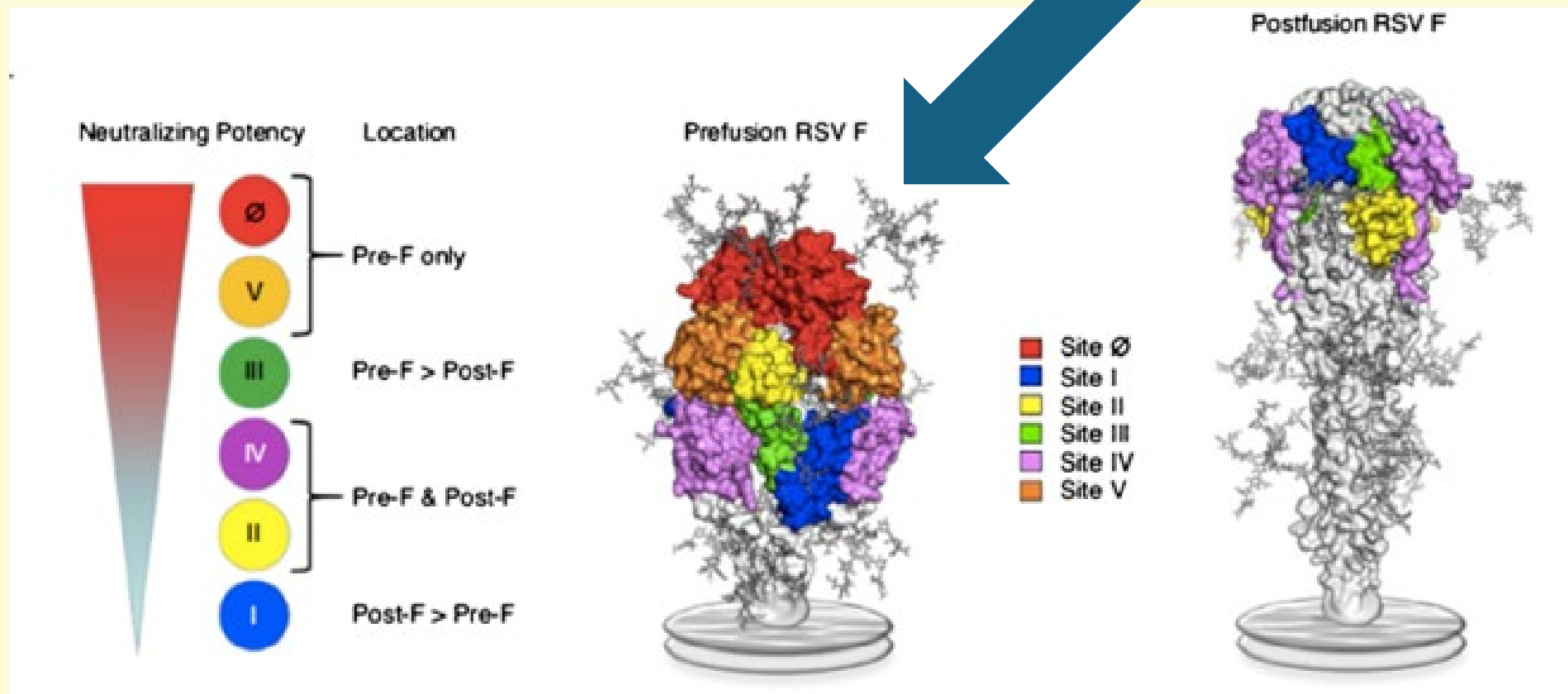
- Like palivizumab
 - Humanized monoclonal antibody
 - Given IM
- Unlike palivizumab
 - Engineered Fc region
 - prolonged $\frac{1}{2}$ life
 - 1 dose per season
 - Targets pre-fusion conformation of F protein
 - Improved protection from disease
 - Single-dose, prefilled syringes

Taleb et al (2018) "Human RSV: pathogenesis, immune responses, and current vaccine approaches"

Eur J Clin Micro Inf Dis

Wilkins et al (2023) "Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants" **Nat Med**

Nirsevimab binding site



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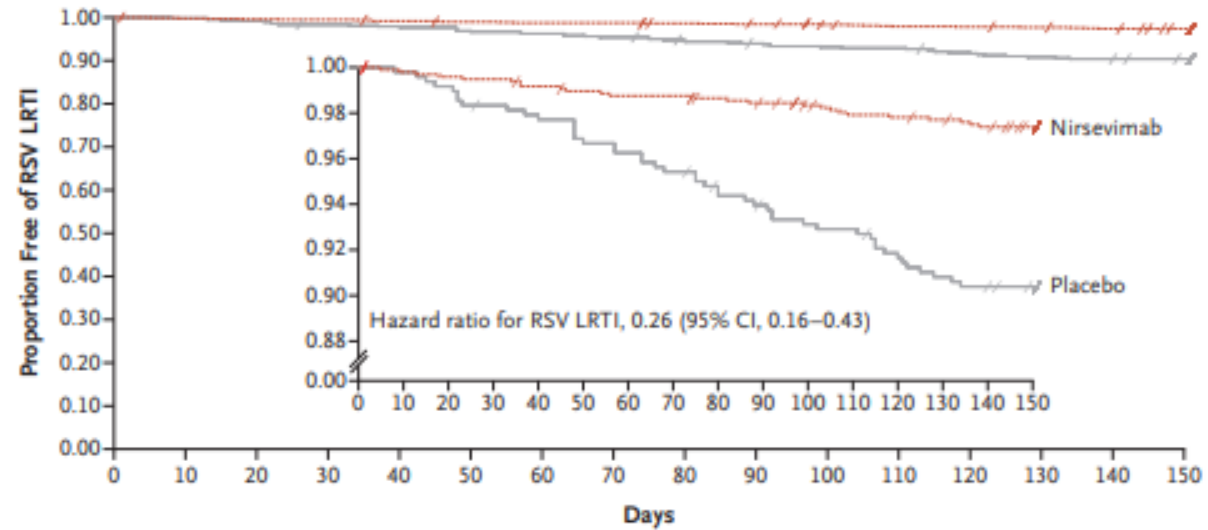
Taleb et al (2018) "Human RSV: pathogenesis, immune responses, and current vaccine approaches" *Eur J Clin Micro Inf Dise*



Nirsevimab (1 dose)

- Reduced doctor visits for RSV by **>75%**
- Reduced hospitalizations for RSV by **~ 80%**
- Reduced PICU admissions for RSV by **~ 90%**
- Effective for 6 months

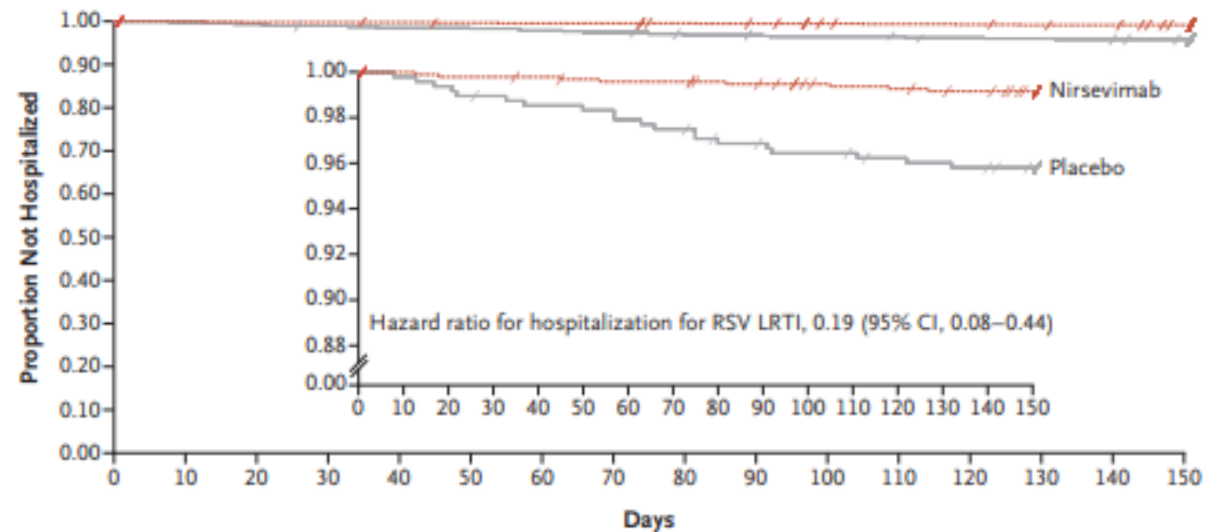
A Time to First Medically Attended RSV Lower Respiratory Tract Infection



No. at Risk

Nirsevimab	969	962	960	959	955	952	950	950	946	943	937	932	931	929	925	920
Placebo	484	480	477	472	469	464	462	458	451	448	444	443	436	432	429	427

B Time to First Hospitalization for RSV Lower Respiratory Tract Infection

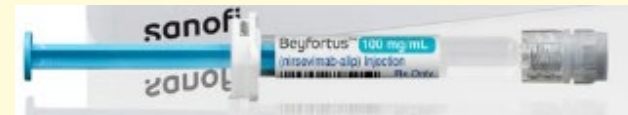
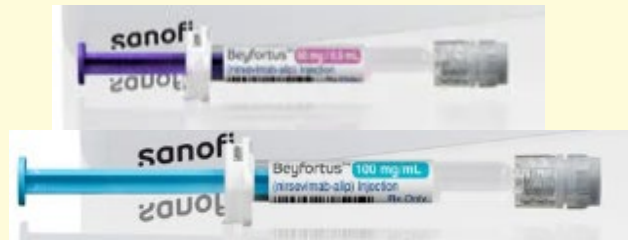


No. at Risk

Nirsevimab	969	964	962	962	961	959	958	958	955	953	948	946	945	943	942	937
Placebo	484	480	478	475	473	472	470	468	463	462	460	459	457	456	454	452

Nirsevimab for healthy infants

- 1 dose at any time just before or during RSV season
 - Infants <8 months
 - 50mg for infants <5kg
 - 100mg for infants \geq 5kg
 - Infants 8-19 months
 - 200mg
- Even in low-risk (healthy) infants cost-effective at current price (<\$400-500)



Hammit et al (2023)
“Nirsevimab for Prevention
of RSV in Healthy Late-
Preterm and Term Infants”
NEJM

Infants born shortly before or during RSV season

(October-March)

- Mother did not receive RSV vaccine or unknown: Nirsevimab
- Mother received RSV vaccine <14 days before delivery: Nirsevimab
- Mother received >14 days before delivery: **NO Nirsevimab** unless:
 - Maternal immunocompromise
 - Infant had cardiopulmonary bypass or ECMO
 - Infant with substantial risk of severe RSV disease (CHD, BPD on O2)

Infants born after the RSV season (April-September)

Starting in October (typically)

- Receive a dose at their next routine visit (2, 4, 6 month)
- If >5kg -100mg vial

High risk infants 8 -19 months

- Starting in October (typically)
 - Preterm birth < 29 WGA
 - CLD
 - CHD (hemodynamically significant)
 - Severe immunocompromise
 - Neuromuscular or pulmonary disease that impairs ability to clear secretions
 - American Indian & Alaska Native
 - (2) 100mg vials (200mg)

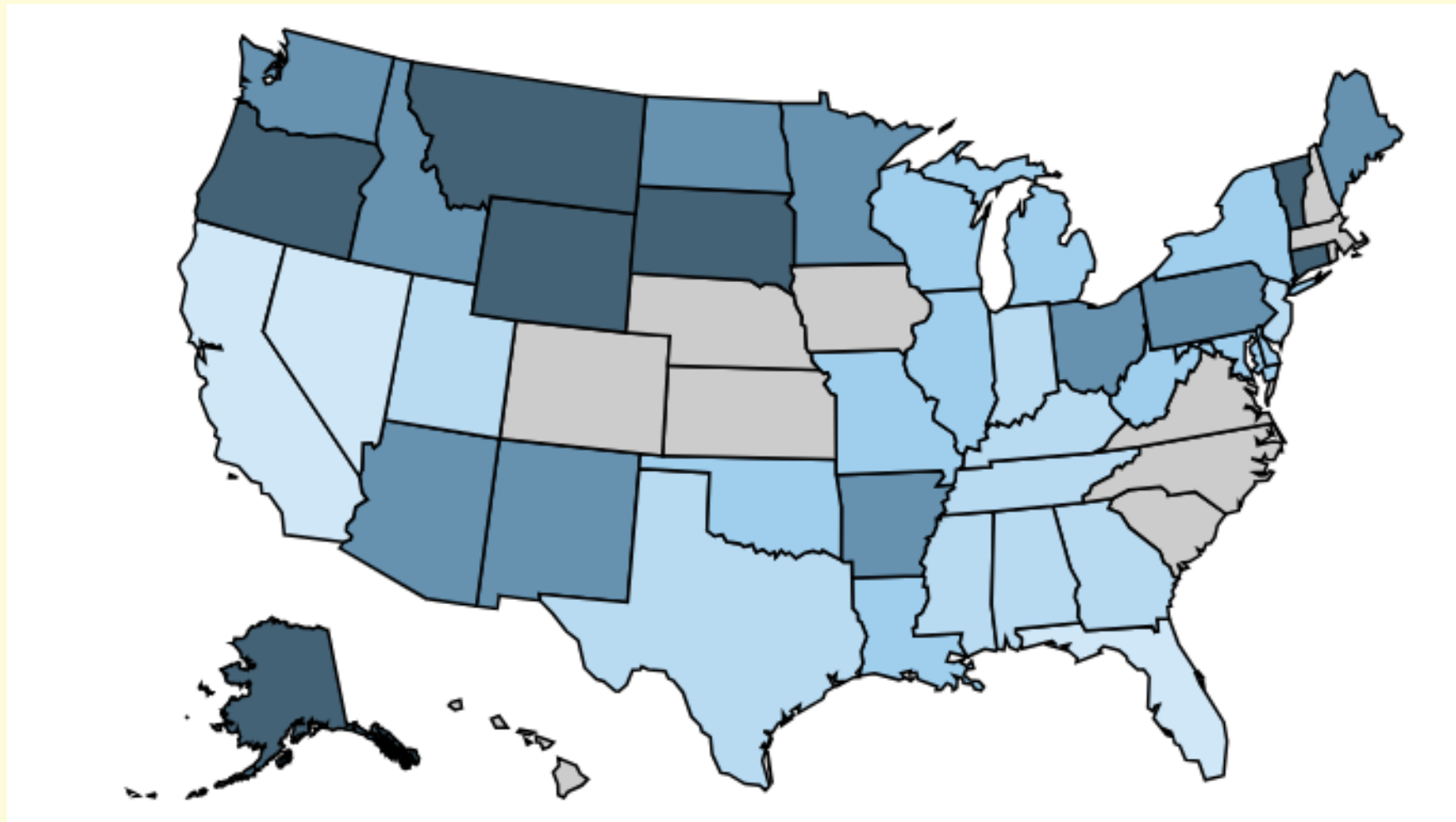
Real World Experience '23-24 season

Nirsevimab efficacy in *preventing RSV Hospitalization*

- France - 83%
- France - 75%
- Italy - 98%
- Luxemburg - 89%
- Spain - 73%
- UK - 81%
- USA - 84%

Ricco et al (2024) "Impact of Nirsevimab Immunization on Pediatric Hospitalization Rates"
Vaccines

In the first season 9.4% of LA infants 0 -6 months have received nirsevima b (USA=41%)



How Does the Price Compare to Other Vaccines?

Fully immunize an infant through VFC:

DTaP-HepB-HiB-IPV	\$97.79 x 3	\$293.37
Rota	\$105.45 x 2	\$210.90
Prevnar 20	\$178.00 x 3	\$534.00
MMR	\$89.87 x 1	\$89.87
Varicella	\$106.36 x 1	\$106.36
		\$1,234.50

To fully immunize an infant in a GAVI country:

BCG	\$0.20 x 1	\$0.20
DTP-HepB-HiB	\$1.14 x 3	\$3.42
Rota	\$0.95 x 2	\$1.90
Prevnar 10	\$3.05 x 3	\$9.15
OPV	\$0.18 x 3	\$0.54
MR x 1	\$0.66 x 1	\$0.66
		\$15.87

Can a low-income country afford \$180-1000/infant for Nirsevimab?

<https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/>

<https://www.unicef.org/supply/media/2471/file/Gavi-product-menu-April2020.pdf>

Future vision: accessible prevention and treatment for RSV

Immunization
during gestation

Monoclonal
Ab for
vulnerable
infants

Effective
vaccines for
infants 3-6
months

Effective
antivirals for
sick infants and
children with
RSV



**Several
candidates
in trials...**

**No very
promising
contenders**

Thank you for your attention...and for your enthusiasm in protecting the health of Louisiana's Future!



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