Advances in the Prevention of Respiratory Syncytial Virus Infections

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UAB MEDICINE PEDIATRICS

Children's of Alabama

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Faculty Disclosure

- I do intend to discuss use of commercial products/services – diagnostic tests and antiviral therapies.
- I do intend to discuss non-FDA approved uses of products/services – antiviral therapies, vaccines.
- I do have a relevant financial relationship with the manufacturers of commercial products and/or providers of commercial services discussed in this CME activity.
  - Site PI on two completed Gilead PK/PD studies of remdesivir in pediatric population
  - All monies went directly to my university and not to me

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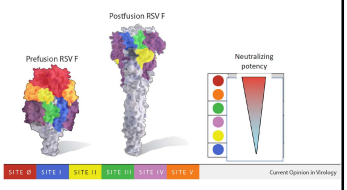
Respiratory Syncytial Virus

- Encodes 11 viral proteins, and is divided into two subgroups/serotypes, A and B
- Two major proteins on the surface of the virus are G (attachment) protein and F (fusion) protein
  - Both are targets of neutralizing antibodies
- The immune system sees the virus in its prefusion state
- Vaccines being developed target F alone or have both F and G
- Monoclonal antibodies available for use target F
  - Palivizumab attaches to Site II of F
  - Nirsevimab attaches to Site 0 of F



Graham B. Current Opinion in Virology. 23:107-112, 2017

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RSV Epidemiology in Children

- The leading cause of hospitalization in infants
  - 50,000 to 80,000 per year among U.S. children under 5 years
  - 68% infected by first birthday; 97% infected by second birthday
- Premature babies < 30 weeks GA are at ~3-fold higher risk of hospitalization
  - But 79% of all RSV hospitalized infants under 2 years have no underlying problems
- 2-3% of U.S. infants are hospitalized annually for RSV
  - No reduction in that statistic in last 2 decades
  - 1 in 5 are admitted to the ICU

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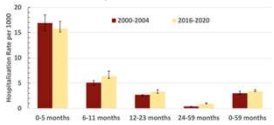
RSV Epidemiology in Children

- Burden of disease in U.S.:
  - ~ 200 U.S. children under 5 years die each year from RSV
  - ~70,000 hospitalizations
  - ~500,000 ED visits
  - ~1.5-2.1 million outpatient visits
- Hospitalization rates are highest in infants under 6 months of age
  - Decrease with each subsequent age bracket



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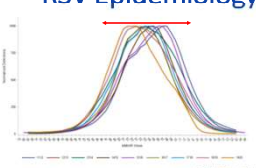
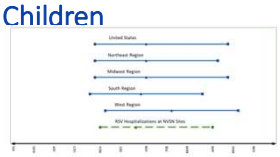
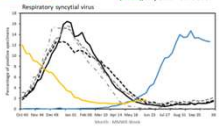
RSV Epidemiology in Children





Median RSV season onset (circle), peak (triangle), and end (square) by census region from NREVSS and pediatric hospitalizations from 7 sites in the New Vaccine Surveillance Network (NVSN), July 2017 – June 2020



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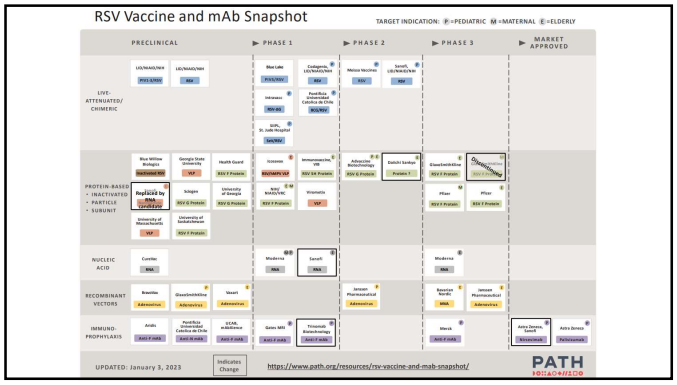

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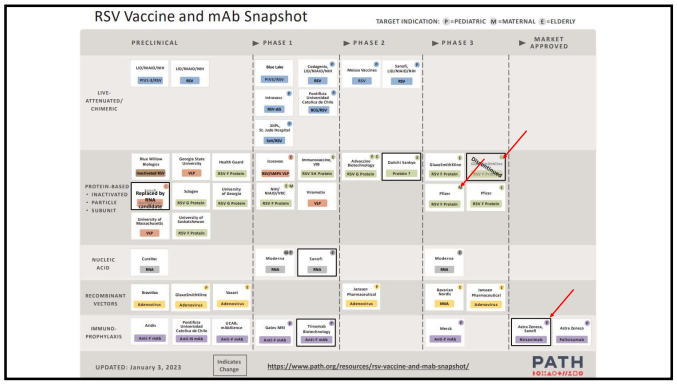

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Nirsevimab

- Highly potent recombinant human IgG1 kappa MAb
- Conserved epitope on prefusion RSV F protein
- Neutralized RSV-A and RSV-B equally
- Prolonged serum half-life
- Single dose per RSV season

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Nirsevimab

- July 2023 – FDA approved nirsevimab
- August 2023 – ACIP recommended its use
  - All infants < 8 months born during or entering first RSV season
  - Infants 8 through 19 months who are at increased risk for severe RSV entering second RSV season
- Anticipated that most regions in U.S. would administer October through March

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Nirsevimab Phase IIb and III Trials

ACIP Meeting, June 2022

	Term and Preterm Healthy Infants 29+ wGA		Infants Eligible to Receive Palivizumab
	Similar Study Design Across Complementary Populations		
	PHASE 3 Pivotal[1] MELODY STUDY	PHASE 2b POC/Pivotal[2]	PHASE 2/3 Pivotal[3] MEDLEY STUDY
STUDY POPULATION	• Infants ≥35 wGA • Not eligible to receive palivizumab (AAP or other national/local guidelines)	• Infants 29-<35 wGA • Not eligible to receive palivizumab (AAP or other national/local guidelines)	Preterm Infants <35 wGA Infants with CLD/CHD
COMPARATOR	2:1 Nirsevimab: Placebo	2:1 Nirsevimab: Placebo	2:1 Nirsevimab: Palivizumab
	Efficacy, Safety and PK		Safety and PK

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Nirsevimab Phase IIb and III Trials Pooled Efficacy

ACIP Meeting, February 2023

Outcome	Efficacy Estimate
Medically attended RSV LRTI	79.0% (95% CI: 68.5%-86.1%)
RSV LRTI with hospitalization	80.6% (95% CI: 62.3%-90.1%)
RSV LRTI with ICU admission	90.0% (95% CI: 16.4%-98.9%)
Death due to RSV respiratory illness	None recorded
All-cause medically attended LRTI	34.8% (95% CI: 23.0%-44.7%)
All-cause LRTI-associated hospitalization	44.9% (95% CI: 24.9%-59.6%)

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Nirsevimab Phase IIIb Study (Harmonie)

- Nirsevimab approved in EU in October 2022
- Conducted in France, UK, Germany August 2022 through February 2023
- 8,058 infants enrolled
  - Age at enrollment: 49% < 3 mo, 24% 3-5 mo, 28% ≥ 6 mo
  - 85% born at term, 50% born in season
- Randomized to nirsevimab versus no injection
- Primary endpoint: RSV hospitalization
- Preliminary efficacy results released at end of season

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Nirsevimab Phase IIIb Study (Harmonie)

- Efficacy
  - RSV hospitalization: 83% (95% CI: 68%-92%)
  - Severe disease (SaO2 < 90% and oxygen given): 76% (95% CI: 33%-93%)
  - All-cause hospitalization with LRTI during RSV season: 58% (95% CI: 40%-71%)
- Safety
  - Grade 1 AEs: Nirsevimab 29%, no infection 25%
  - Grade 2 and 3 AEs similar between groups

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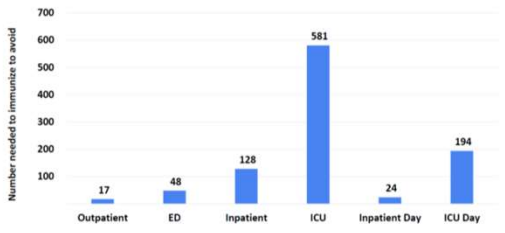
Number Needed to Immunize (NNI) to Prevent One Health Outcome



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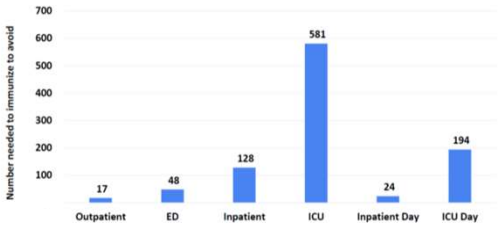
Number Needed to Immunize (NNI) to Prevent One Health Outcome



Inpatient NNI
- RSV 128
- Flu ~2000
- Rota ~200
- PCV ~671 (IPD)

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Nirsevimab Cost Effectiveness Analyses

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Scenario	Michigan-CDC Model ($ / QALY gained)
Base case (Nirsevimab cost $300/dose, 1st season)	$102,805
Nirsevimab, 1st season, $300/dose, all infants, and replacing palivizumab for eligible infants	$59,250
Nirsevimab cost per $500/dose (1st season)	$244,677
Intervention period October through February	$107,963
Prevention of all MA RSV visits (LRTI and URTI)	$45,092
Nirsevimab cost per $200/dose (1st season)	$31,869

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Nirsevimab Recommendations

MMWR Morb Mortal Wkly Rep 2023;72:920-925

- 1 dose of nirsevimab should be given to all infants aged <8 months born during or entering their first RSV season
  - 50 mg for infants <5 kg; 100 mg for infants ≥5 kg
  - Infants and children aged ≥8 months have likely experienced an RSV season and are at decreased risk for severe RSV-associated disease compared with younger infants without previous RSV exposure
- 1 dose of nirsevimab for infants and children aged 8 through 19 months who are at increased risk for severe RSV disease* and entering their second RSV season
  - 200 mg, administered as two 100 mg injections
  - Children aged ≥20 months have likely experienced two RSV seasons and are at decreased risk for severe disease compared with younger children who have experienced only one RSV season

* See next slide for listing

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Children at Increased Risk of Severe RSV Disease

MMWR Morb Mortal Wkly Rep 2023;72:920-925

- Children with chronic lung disease of prematurity who required medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season
- Children with severe immunocompromise
- Children with cystic fibrosis who have either 1) manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest imaging that persist when stable) or 2) weight-for-length <10th percentile
- American Indian or Alaska Native children

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Effectiveness and Post-Marketing Safety Evaluation Plans

- CDC will use current systems to evaluate **effectiveness**
  - Throughout the RSV season
  - At end of season; power depends on uptake and RSV incidence
- NVSN is the New Vaccine Surveillance Network
  - 7 pediatric centers
  - Can evaluate effectiveness v. hospitalization, ED visits, outpatient visits
- VISION (Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network)
  - Multisite, EHR-based
  - Can evaluate effectiveness v ED/urgent care, hospitalization, and critical illness
- FDA and CDC will use current systems to evaluate **safety**
  - FAERS and VAERS reports
  - FDA via literature, safety reports, ongoing studies
  - CDC via VAERs (co-administration) and Vaccine Safety Datalink (VSD)

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RSVPreF Vaccine


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 20, 2023 VOL. 388 NO. 16

Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

- Single dose vaccine against RSV, manufactured by Pfizer
- Approved for use in pregnant women, and in adults ≥60 years of age*
- 60 µg preF-A and 60 µg preF-B, no adjuvant, 0.5 mL IM

* GSK's RSVPreF3 also is approved for use in adults ≥60 years of age

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Infant Neutralizing Titers Following Maternal Bivalent RSV Prefusion F Vaccine

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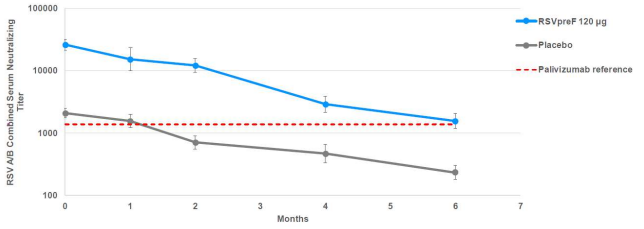

---Palivizumab reference line = 50% A/B neutralizing titer of a 100ug/mL palivizumab dose, demonstrated to be efficacious in preventing infant RSV-associated ICU admission (Forbes ML, Kumar VR, Yogev R, et al. Hum Vaccin Immunother 2014;10:2789-94.)

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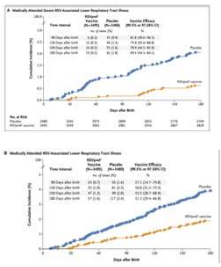
RSVPreF Vaccine in Pregnant Women

- Maternal Immunization Study for Safety and Efficacy [MATISSE]
  - Phase 3, double-blind, randomized, placebo-controlled
  - 18 countries over four RSV seasons
  - Pregnant women 24-36 weeks GA
  - MA-severe/all-RSV LRTI at 90-180d
  - About 7000 enrolled
    - ~3500 active vaccine
    - ~3500 placebo



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Infant Efficacy Primary Endpoints

ACIP Meeting, February 2023

	Maternal Vaccine Group (as Randomized)		
RSV-Positive Severe MA-LRTI	RSVpreF 120 µg (N[a]=3495)	Placebo (N[a]=3480)	
Time Interval	**Number of Cases (%)**	**Number of Cases (%)**	**Vaccine Efficacy[b] (%) (CI[c])**
90 Days after birth	6 (0.2)	33 (0.9)	81.8 (40.6, 96.3)
120 Days after birth	12 (0.3)	46 (1.3)	73.9 (45.6, 88.8)
150 Days after birth	16 (0.5)	55 (1.6)	70.9 (44.5, 85.9)
180 Days after birth	19 (0.5)	62 (1.8)	69.4 (44.3, 84.1)
RSV-Positive MA-LRTI			
Time Interval	**Number of Cases (%)**	**Number of Cases (%)**	**Vaccine Efficacy[b] (%) (CI[c])**
90 Days after birth	24 (0.7)	56 (1.6)	57.1 (14.7, 79.8)
120 Days after birth	35 (1.0)	81 (2.3)	56.8 (31.2, 73.5)
150 Days after birth	47 (1.3)	99 (2.8)	52.5 (28.7, 68.9)
180 Days after birth	57 (1.6)	117 (3.4)	51.3 (29.4, 66.8)

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RSVPreF Vaccine in Pregnant Women

- **August 2023**: FDA approved RSVPreF
  - 32-36 weeks gestation (narrower than range in the clinical trial)
  - Preterm birth in study: 5.7% v 4.7%, a "numerical imbalance", not statistically significant, driven by data from South Africa, nearly all were >30 days after vaccine, led to tight FDA GA window
- **September 22, 2023**: ACIP recommended use
  - "Maternal RSV vaccine is recommended for pregnant people during 32 through 36 weeks gestation, using seasonal administration, to prevent RSV lower respiratory tract infection in infants."
  - September through January in most of the continental U.S.
  - Healthcare providers of pregnant women should provide information on both products and consider patient preferences when determining whether to vaccinate the pregnant patient or to not vaccinate and rely on administration of nirsevimab to the infant after birth

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RSVPreF Vaccine Preterm Birth

- Most were late preterm (34 through 36 weeks)
- Most occurred > 30 days after vaccination
- Did not reach statistical significance
- Difference driven by South African data
- "Imbalance" plus GSK statistically significant difference led to concern

	Trial dosing interval (24-36 weeks gestation)				Approved dosing interval (32-36 weeks gestation)			
	RSVpreF recipients N=3568		Placebo recipients N=3558		RSVpreF recipients N=1628		Placebo recipients N=1604	
Country	No. births	% preterm	No. births	% preterm	No. births	% preterm	No. births	% preterm
Argentina	423	6.4%	416	4.1%	230	4.8%	230	4.3%
Australia	11	0.0%	13	7.7%	8	0.0%	8	12.5%
Brazil	35	8.6%	37	2.7%	22	9.1%	23	4.3%
Canada	27	0.0%	28	3.6%	20	0.0%	27	3.7%
Chile	86	8.1%	85	7.1%	47	6.4%	50	2.0%
Denmark	30	3.3%	31	0.0%	21	4.8%	17	0.0%
Finland	75	2.7%	73	1.4%	44	0.0%	40	2.5%
Gambia	78	2.6%	79	2.5%	32	3.1%	24	0.0%
Japan	218	3.2%	216	6.0%	111	2.7%	94	2.1%
Korea	7	0.0%	4	25.0%	6	0.0%	1	100.0%
Mexico	37	8.1%	37	5.4%	13	7.7%	13	0.0%
Netherlands	97	3.1%	95	3.2%	43	2.3%	44	0.0%
New Zealand	49	4.1%	47	6.4%	29	3.4%	28	3.6%
Philippines	32	3.1%	34	5.9%	0	0.0%	1	0.0%
South Africa	469	8.3%	471	4.0%	150	6.7%	127	2.4%
Spain	117	3.4%	123	2.4%	73	2.7%	88	3.4%
Taiwan	123	4.9%	125	5.6%	58	5.2%	57	3.5%
United States	**1654**	**5.7%**	**1644**	**5.3%**	**721**	**4.0%**	**732**	**4.4%**

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Nirsevimab Shortage

- 50 mg – unchanged recommendations
- 100 mg – prioritize for infants at highest risk of severe RSV disease
  - <6 months
  - AI/AN <8 months
  - 6 through <8 months – higher risk: <29 wks, CLD, hemodynamically significant CHD, severe immunocompromise, severe CF, neuromuscular disease or congenital pulmonary abnormalities that impair the ability to clear secretions
- In palivizumab-eligible children aged 8 through 19 months, use palivizumab
- Continue offering nirsevimab to AI/AN children aged 8 through 19 months
- Follow AAP recommendations for palivizumab-eligible infants aged <8 months when the appropriate dose of nirsevimab is not available
- Do not give two 50 mg doses
- Encourage pregnant women to receive RSVpreF vaccine

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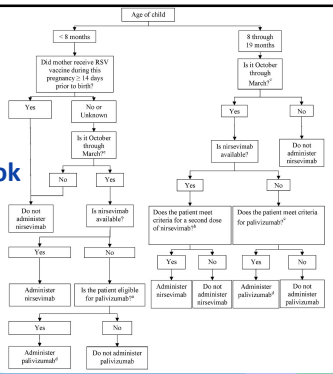
RSV Prevention Figure in 2024 Red Book



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RSV Prevention Figure in 2024 Red Book

a. Preterm infants with CLD; infants with hemodynamically significant CHD; preterm infants without CLD or CHD but born before 29 weeks, 0 days gestation who are younger than 12 months at the start of the RSV season; children with anatomic pulmonary abnormalities or neuromuscular disorder; immunocompromised children; children with cystic fibrosis.

b. Children with CLD who required medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season; severe immunocompromise; cystic fibrosis who have either (1) manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest imaging that persist when stable), or (2) weight-for-length <10th percentile; American Indian or Alaska Native children

c. Preterm infants with CLD requiring require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season; immunocompromised children; children with cystic fibrosis with manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year or abnormalities on chest radiography or chest computed tomography that persist when stable) or weight-for-length less than the 10th percentile.

d. For recommendations on use of palivizumab, see Ralston SL, Lieberthal AL, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5):e1474-e1502; and Caserta MT, O'Leary ST, Munoz FM, Ralston SL, COMMITTEE ON INFECTIOUS DISEASES. Technical Report: Palivizumab Prophylaxis in Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Pediatrics* (2023) 152 (1): e20230618

e. In jurisdictions with seasonality that differs from most of the continental United States (e.g., Alaska, jurisdictions with tropical climates), providers should follow state, local, or territorial guidance on timing of administration

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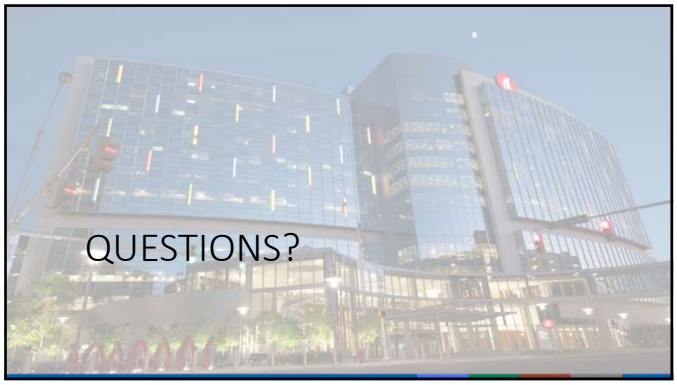

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