Maternal & Pediatric RSV Work Group Interpretations and Next Steps

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Safety and efficacy of clesrovimab

Policy question being considered by the work group

- **Should clesrovimab be recommended for all infants <8 months of age entering their first RSV season or born during the RSV season?**

Evidence reviewed by the work group

- **Safety and efficacy of clesrovimab**
  - Phase 2b/3 placebo-controlled study in healthy preterm infants (≥29 to <35 weeks gestational age) and full-term infants (≥35 weeks gestational age)
  - Phase 3 palivizumab-controlled study in infants at increased risk for severe RSV disease

Work group interpretation of clesrovimab efficacy data

- **Phase 2b/3 trial demonstrated high efficacy for prevention of severe RSV disease through 150 days**

Outcome	n/N, clesrovimab	n/N, placebo	Efficacy % (95% CI)
Hospitalization for RSV-associated lower respiratory tract infection*	5/2,398	27/1,201	90.9 (76.2, 96.5)
Medically-attended RSV-associated lower respiratory tract infection ≥ 1 indicator of lower respiratory infection or severity**	60/2,398	74/1,201	60.4 (44.1, 71.9)

*Defined by the presence of the following: cough or difficulty breathing; AND ≥ 1 indicator of LRI (lower respiratory infection) or severity (wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms); AND hospital admission for respiratory illness; AND RSV positive reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal (NP) sample.
**Defined by the presence of the following seen in an outpatient or inpatient clinical setting: cough or difficulty breathing and ≥ 1 indicator of (lower respiratory infection) or severity (wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms); and RSV positive reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal (NP) sample.

Merck, presented at IDWeek in Los Angeles, California from October 16-19, 2024

Work group interpretation of clesrovimab safety data

- **Serious adverse events appeared balanced between the clesrovimab and placebo arms, however rare adverse events are unlikely to be detected in a trial of this size**

- **Solicited adverse events were balanced between the clesrovimab and placebo arms**
  - In both arms, irritability and sleepiness was the most commonly observed solicited adverse event

Merck, presented at IDWeek in Los Angeles, California from October 16-19, 2024

Work group considerations regarding clesrovimab

- **Initial efficacy and safety data look promising; however, the work group has requested additional pharmacokinetic, efficacy, and safety data from the manufacturer**
- **Work group discussion also highlighted:**
  - Clesrovimab has demonstrated a shorter half-life than nirsevimab (42[1] vs 71[2] days), however efficacy against severe RSV appeared sustained at 150 and 180 days
  - Trial enrollment began in 2021, a period when typical RSV seasonality had been disrupted by the COVID-19 pandemic
  - Clesrovimab and nirsevimab trial outcomes had different definitions
- **Overall, the work group felt that the initial data merited moving forward with the evidence review for the policy question**

1 Maas et al. https://www.sciensano.be/sites/default/files/pk_sna_and_efficacy_against_rsv_malri_from_a_phase_1b2a_study_of_the_monoclonal_antibody_clesrovimab_mk-1654_in_infants.pdf 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761328s000lbl.pdf

Evidence to be reviewed by the work group

- **Additional data on Phase 2b/3 and Phase 3 studies requested by work group**
- **GRADE of evidence**
- **Cost effectiveness analysis**
- **Evidence to Recommendation Framework (EtR)**
  - Public health problem
  - Benefits and harms
  - Values
  - Acceptability
  - Feasibility
  - Resource use
  - Equity

Proposed timeline

- **February 2025**
  - Summary of GRADE
  - Evidence to Recommendation Framework
  - Cost effectiveness analysis

- **ACIP vote timing dependent on FDA licensure**

Maternal RSV vaccine safety

Imbalance of preterm birth was observed in clinical trials for the Pfizer maternal RSV vaccine (Abrysvo)

- In clinical trials, maternal RSV vaccine was administered at 24–36 weeks' gestation, and more preterm births and hypertensive disorders of pregnancy were observed among pregnant people who received maternal RSV vaccine (Abrysvo) vs. placebo, but the **differences were not statistically significant**
  - Data were insufficient to establish or exclude a causal relationship

- FDA approved maternal RSV vaccine (Abrysvo) for use in pregnant persons at 32–36 weeks’ gestation to avoid the potential risk for preterm birth at <32 weeks’ gestation

- ACIP judged the benefits of maternal RSV vaccine (Abrysvo) at 32–36 weeks’ gestation to outweigh the potential risks for preterm birth and hypertensive disorders of pregnancy

Maternal RSV vaccine safety: first season analysis of preterm birth and small for gestational age

- **Preliminary findings from the first season of maternal RSV vaccine in a Vaccine Safety Datalink (VSD) study found that maternal RSV vaccine during 32–36 weeks' gestation was not associated with an increased risk of preterm birth or small for gestational age[1]**
  - **The work group felt that these data were very reassuring.**

	Matched pairs, N	RSV vaccinated		Unvaccinated match		Risk Ratio (95% CI)
		N events*	Percent %	N events*	Percent %	
Preterm birth[a]	13,965	563	4.0	628	4.5	0.90 (0.80–1.00)
Small for gestational age[b]	11,819	799	6.8	774	6.5	1.03 (0.94–1.14)

[a]Preterm birth = birth <37 weeks gestational age [b]SGA at birth = "Small for Gestational Age"; birthweight <10th percentile for gestational age compared with a U.S. reference population[2]

*Events only included through date of censoring when unvaccinated pair crosses over to vaccinated

1. DeSilva, M. *RSVpreF Vaccine, Preterm Birth, and Small for Gestational Age at Birth Preliminary Results from The Vaccine Safety Datalink.* Presented at ACIP October 23, 2024 2. Talge NM, Mudd LM, Sikorskii A, Basso O. United States birth weight reference corrected for implausible gestational age estimates. Pediatrics 2014;133:84453. PMID:24777216

Work group interpretation of maternal RSV vaccine safety data

- **The work group felt that messaging about potential risks for hypertensive disorder of pregnancy should be separated from preterm birth**
  - Little post-licensure data available for risk of hypertensive disorder of pregnancy
  - One study conducted a secondary analysis of 2,973 pregnant individuals (1,011 vaccinated and 1,962 unvaccinated) found an association of maternal RSV vaccine and hypertensive disorder of pregnancy[1]
- **Some WG members felt that when counseling pregnant people on maternal RSV vaccination at 32–36 weeks, messaging on potential risks of preterm birth could be softened or counselling no longer needed to include discussion regarding a potential risk of preterm birth**
- **CDC and FDA should continue to monitor safety data for maternal RSV vaccine, including further VSD analyses for hypertensive disorders of pregnancy**

1. Son M, Riley LE, Staniczenko AP, et al. Nonadjuvanted Bivalent Respiratory Syncytial Virus Vaccination and Perinatal Outcomes. *JAMA Netw Open.* 2024;7(7):e2419268. doi:10.1001/jamanetworkopen.2024.19268

For more information, contact CDC
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