R S V :
*R*eady for *S*ome *V*accines ?

Stephen C. Eppes, MD

ChristianaCare

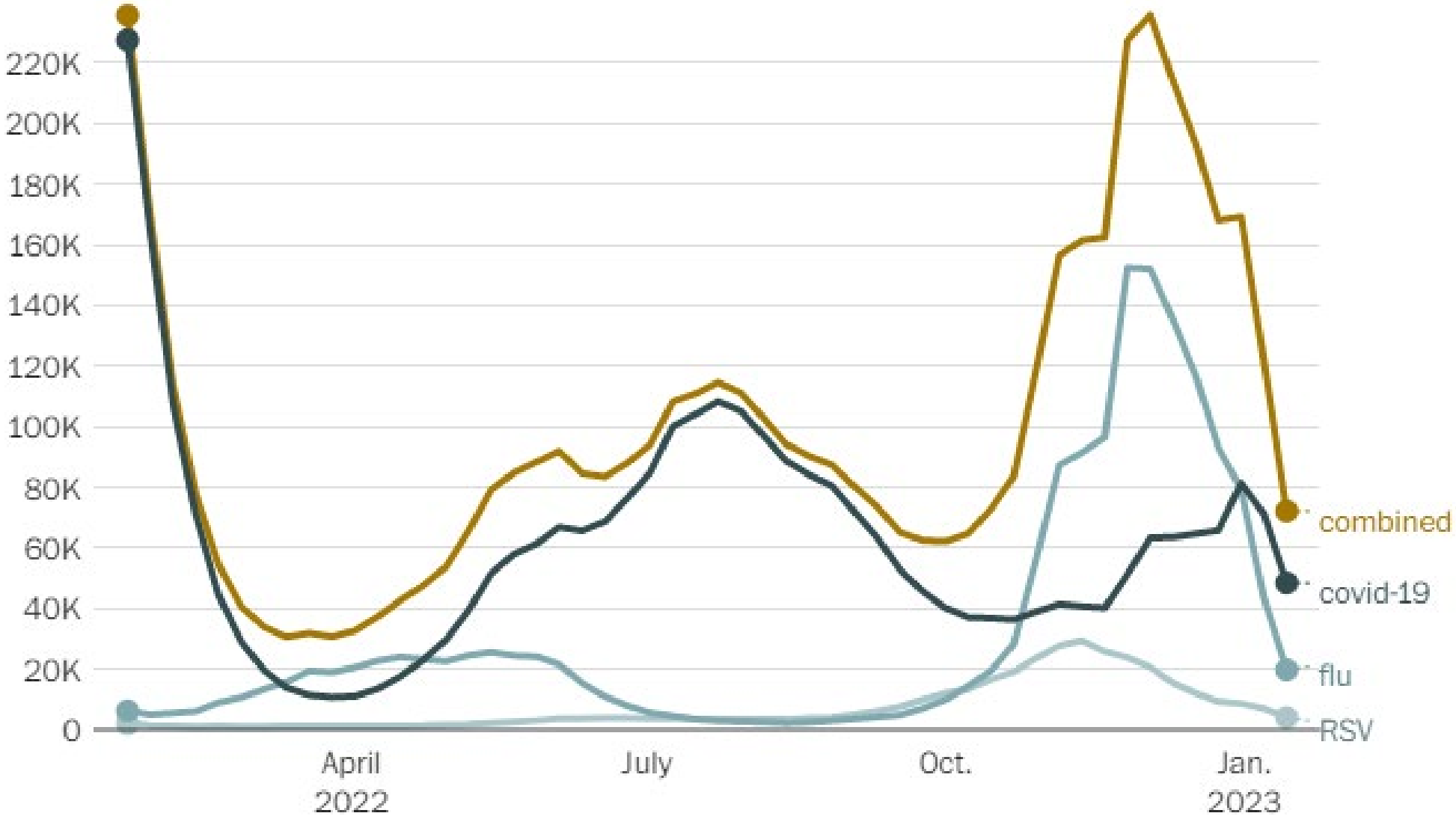
Delaware Immunization Summit

Dec. 7, 2023

Disclosures

Objectives

- Describe the epidemiology of RSV infection.
- Define the characteristics of RSV respiratory tract infection in children and adults.
- Explore efforts to prevent RSV infection – past, present and future.

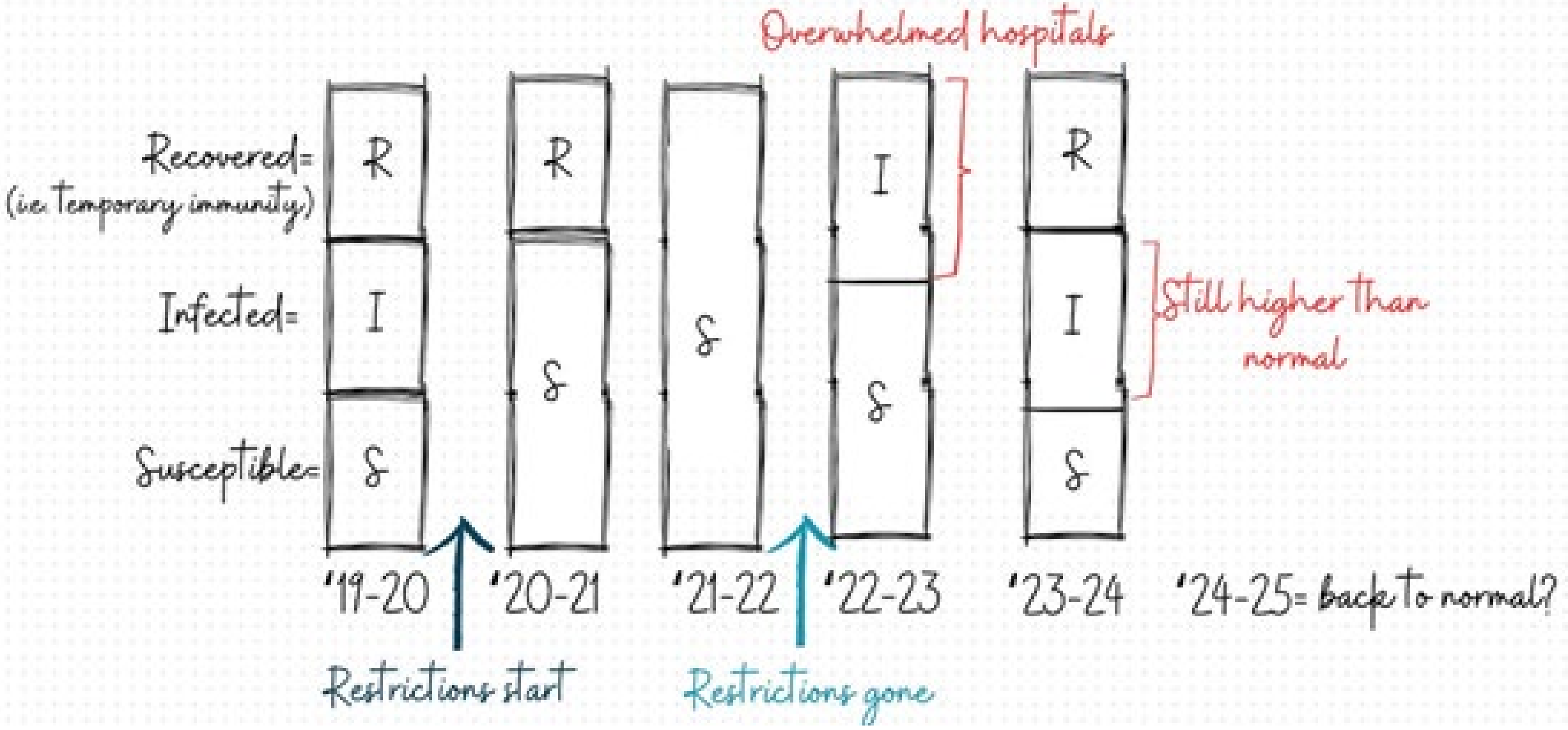


Weekly counts based on the CDC Surveillance national sample of emergency departments

“Triple-demic”

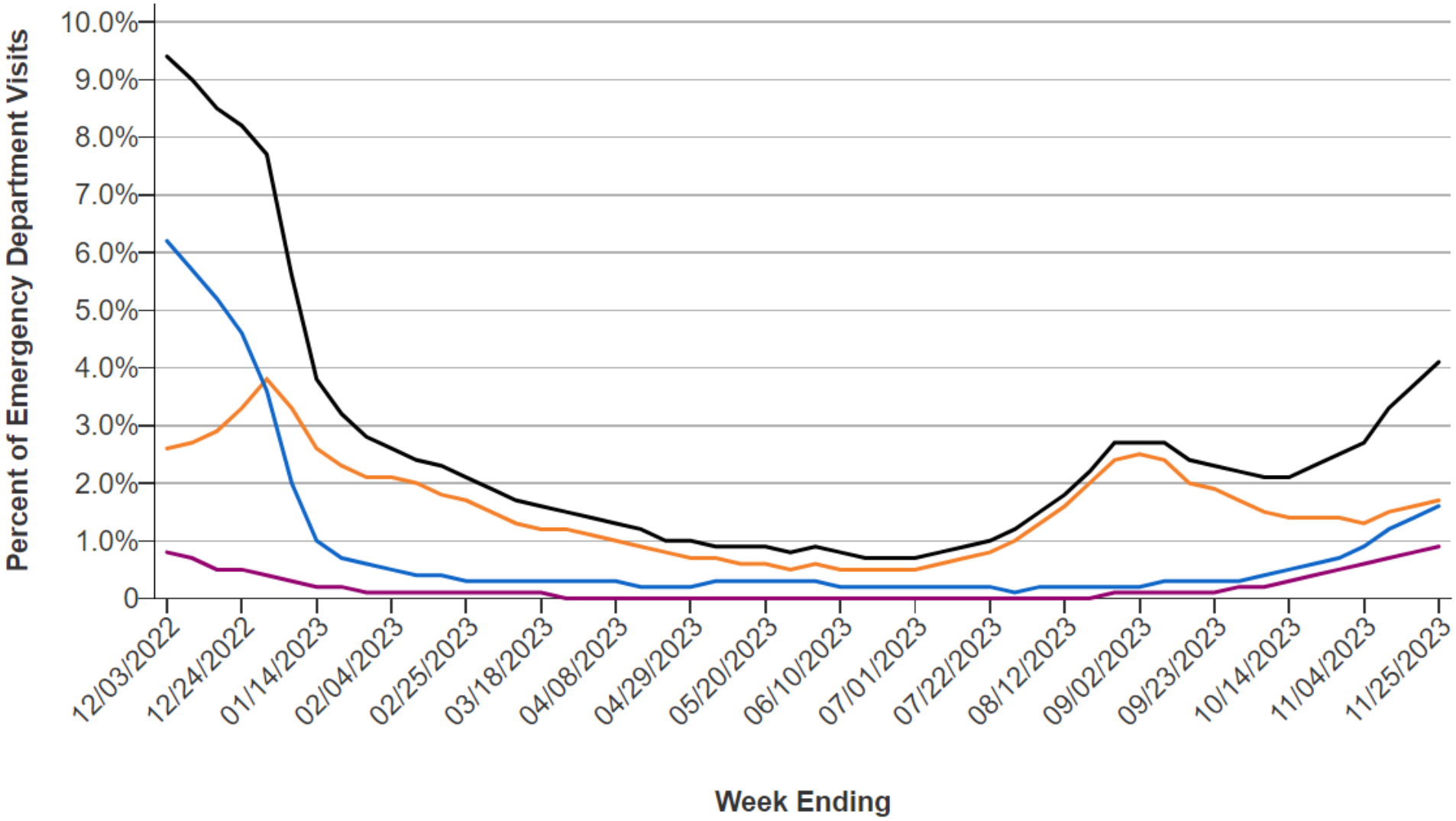
“RSV Immunity Debt”

- COVID-19 mitigation efforts resulted in fewer RSV exposures of young children
  - School and childcare closures / at home learning
  - Masking, hand hygiene, other non-pharmacologic interventions
- Reduced natural infections through winter of 2020-21
- Reduced immunity of children < 2 years
- In summer of 2021, with *relaxation of COVID measures* an “out of season” RSV epidemic occurred
- In fall of 2022 – “triple-demic”
  - RSV, influenza and COVID-19



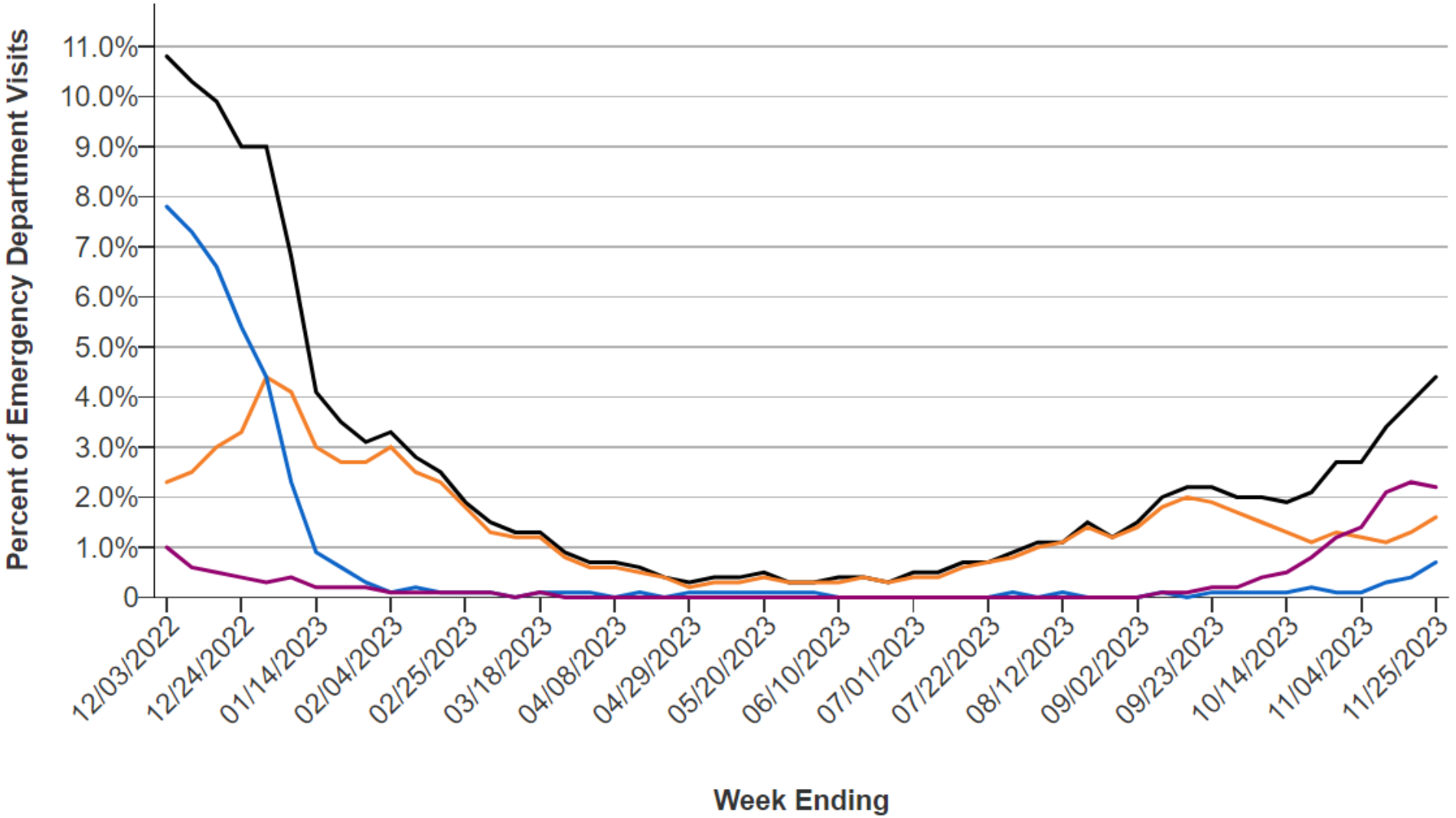
Your Local Epidemiologist, Nov. 30, 2023

United States



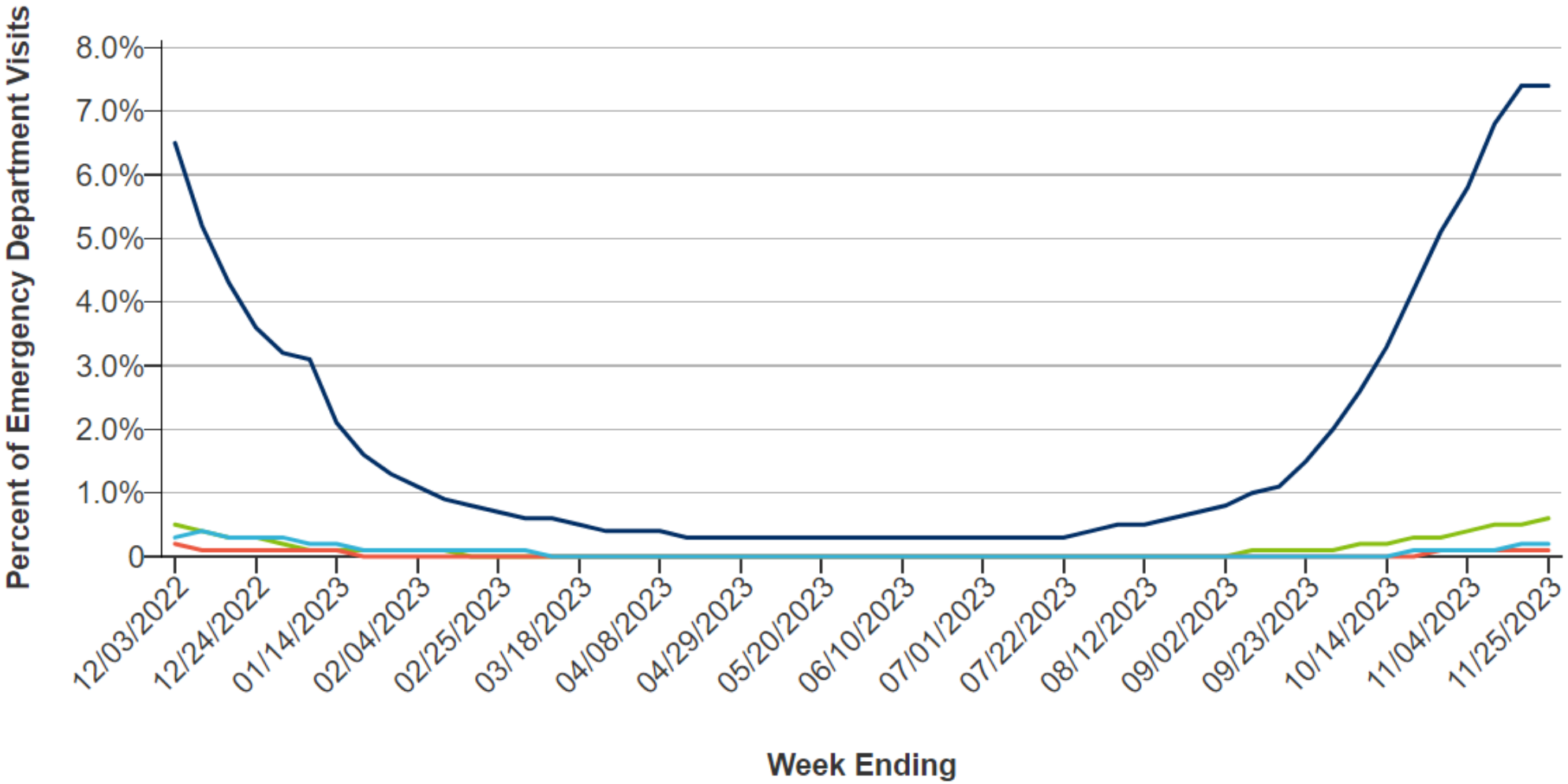
Combined COVID-19 Influenza RSV

Delaware


Percent of Emergency Department Visits
11.0%
10.0%
9.0%
8.0%
7.0%
6.0%
5.0%
4.0%
3.0%
2.0%
1.0%
0
12/03/2022
12/24/2022
01/14/2023
02/04/2023
02/25/2023
03/18/2023
04/08/2023
04/29/2023
05/20/2023
06/10/2023
07/01/2023
07/22/2023
08/12/2023
09/02/2023
09/23/2023
10/14/2023
11/04/2023
11/25/2023
Week Ending
Combined
COVID-19
Influenza
RSV

Respiratory Illness

RSV

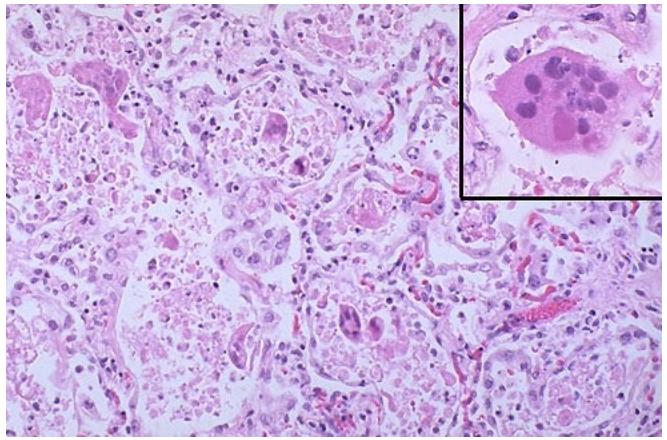


Age Groups

- 0-4 years
- 5-17 years
- 18-64 years
- 65+ years

RSV – History

- 1956 – identified in secretions of chimps with bronchiolitis
- 1957 – found in children with bronchiolitis
- 1957 – noted to form multinucleated giant cells in tissue culture



The New England
Journal of Medicine

Volume 263 SEPTEMBER 15, 1960 Number 11

ASSOCIATION OF THE CHIMPANZEE CORYZA AGENT WITH ACUTE RESPIRATORY DISEASE IN CHILDREN*

MARC BEEM, M.D.,† F. H. WRIGHT, M.D.,‡ DOROTHY HAMRE, PH.D.,§ ROSALIE EGERER, B.S.,¶ AND MAFALDA OEHME, B.S.‖

CHICAGO

IN 1956 Morris, Blount and Savage[1] described the recovery of a cytopathogenic agent that produced acute respiratory illness in chimpanzees and possibly in human beings. They termed this the chimpanzee coryza agent. In 1957 Chanock and his co-workers[2,3] reported two isolations of a similar agent from infants with respiratory illness. They also found serologic evidence of infection of a number of additional children from whom it had not been possible to isolate the virus. On the basis of serologic responses, this infection was shown to occur in a significantly greater portion of outpatients with respiratory infections than in those without respiratory infections. Among hospitalized patients there was a high rate of serologic conversion in the control group as well as those with acute respiratory disease, and a clear relation between infection with this agent and overt respiratory disease could not be demonstrated. The present report describes the isolation of the virus from inpatients and outpatients seen at the Bobs Roberts Memorial Hospital for Children of the University of Chicago during the winter of 1958-1959, and provides additional evidence that this agent is associated with acute respiratory illness in humans.

MATERIAL AND METHODS

Subjects

These observations were made as part of a continuing study of acute respiratory illness being made at this hospital. Physicians working in the Pediatric Out-Patient Clinic referred to the study patients with acute respiratory illness of uncertain etiology, children with illness of known etiology and children who were considered to be well. During the same interval most of the children admitted to the hospital were included in the study if appropriate specimens could be obtained during the first three days in the hospital.

Definition of Clinical Status

Patients were considered to have acute respiratory illness if they had experienced an abrupt change in state of health that was associated with symptoms or signs of inflammation of the respiratory tract. If clinical findings included signs of bronchiolar inflammation such as expiratory dyspnea, emphysema and musical expiratory rales, the child was considered to have bronchiolitis, provided this was the first such episode that he had experienced. If there were signs of consolidation, with or without the findings mentioned above, a diagnosis of bronchopneumonia was made. Patients were considered to be free of respiratory infection if there was no history of abnormal respiratory symptoms within the two weeks before or the two days after sampling.

Characteristics of Study Group

A total of 291 patients were studied. The sex, race and age characteristics of the clinic and hospital patients studied are presented in Table 1. The subjects are divided into four groups: the hospital group with acute respiratory illness, which includes approximately 90 per cent of the patients admitted to Bobs Roberts Hospital with acute respiratory illness from late December, 1958, through June, 1959; the hospital control group, which is a sampling of children hospitalized during the same period who had no evidence of respiratory illness (in comparison to the hospital group with acute respiratory illness, this control group contained a higher percentage of white children and the average age was greater); the clinic group with acute respiratory illness, which is a sampling of the outpatients with acute respiratory

*From the Pediatric Virus Laboratory, Bobs Roberts Memorial Hospital for Children, University of Chicago School of Medicine.
Aided by a grant from the National Institutes of Health E 1800 (c-2), the United Fund of Harvey, Illinois, and the United Fund of Downers Grove, Illinois.
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‡Professor of pediatrics and chairman, Department of Pediatrics, University of Chicago School of Medicine.
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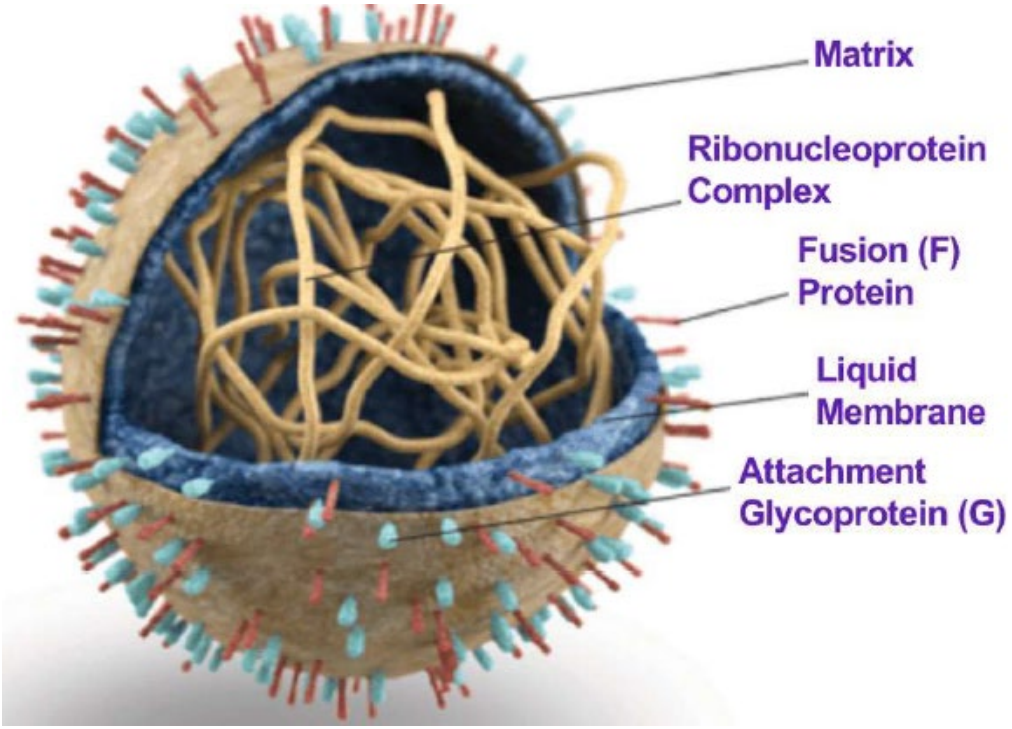
¶Epidemiologic nurse, Department of Pediatrics, University of Chicago School of Medicine.
‖Research assistant, Department of Pediatrics, University of Chicago School of Medicine.

Respiratory Syncytial Virus

- Mainly a pathogen for humans
- Negative strand RNA genome
- 2 major subtypes (A and B)
- 2 surface glycoproteins
  - G – attaches to host cells and determines subtype
  - F – fusion protein facilitates entry into host cell
    - Better conserved than G
    - Target for vaccines and mono-clonal antibodies



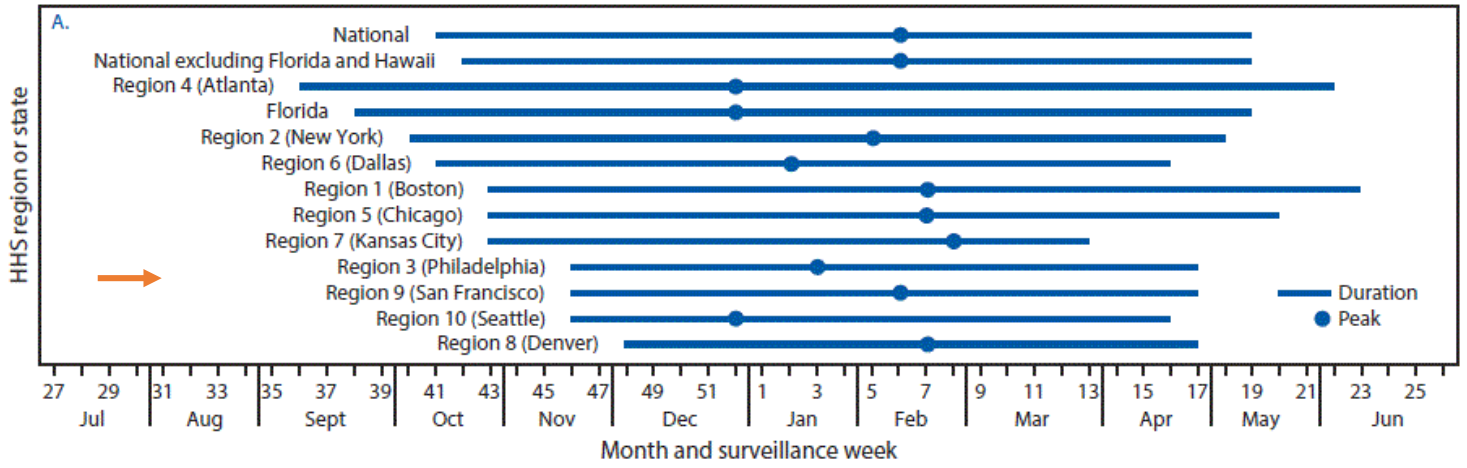
Immunity to RSV

- Cellular and humoral immune response
- Young infants have ~ 20% antibody response compared with older children
  - One reason for recurrences
  - Challenge for vaccine development
- Cell-mediated immunity vitally important
  - RSV causes severe disease in SCID and transplant patients
- Secretory and serum antibodies
  - Secretory Ab (IgA) protects upper respiratory tract
  - Serum neutralizing Ab protects lower respiratory tract
  - Maternal IgG provides some protection in young infants

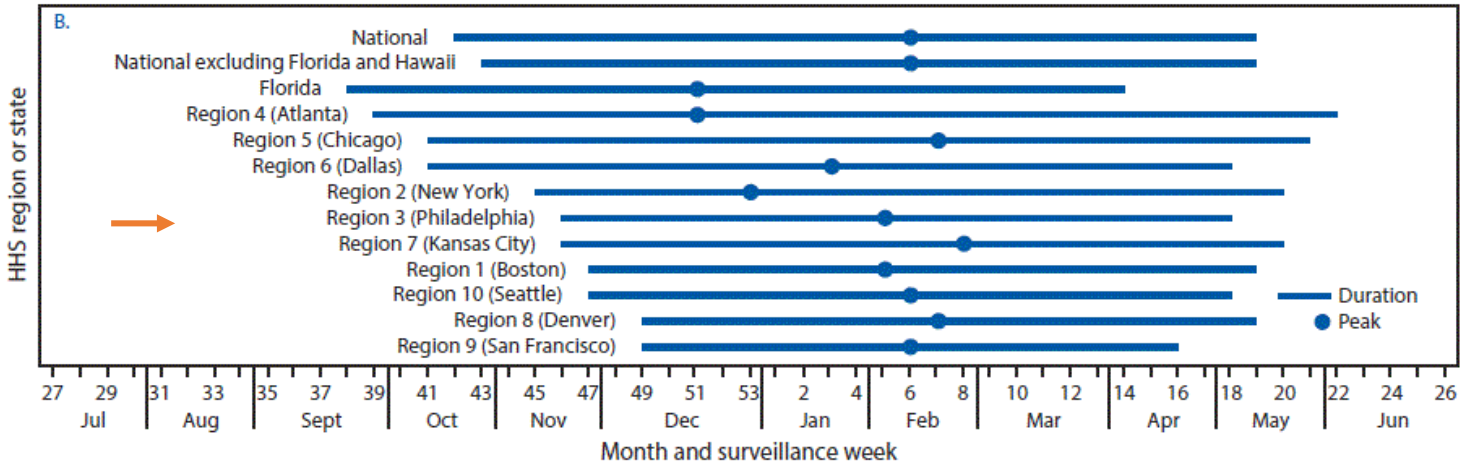
RSV – Epidemiology

- Transmission is via large particle droplets
  - Travel a distance up to 6 feet
  - Viral shedding after infection lasts 3-8 days
- Can persist on surfaces, objects (fomites), and hands
- Once infection acquired, typical incubation period before symptom onset is 4-6 days
- Spread within households and child care facilities
  - Also within hospitals / healthcare settings
  - OFID paper April 19, 2023 – more likely to be transmitted in hospitals than influenza

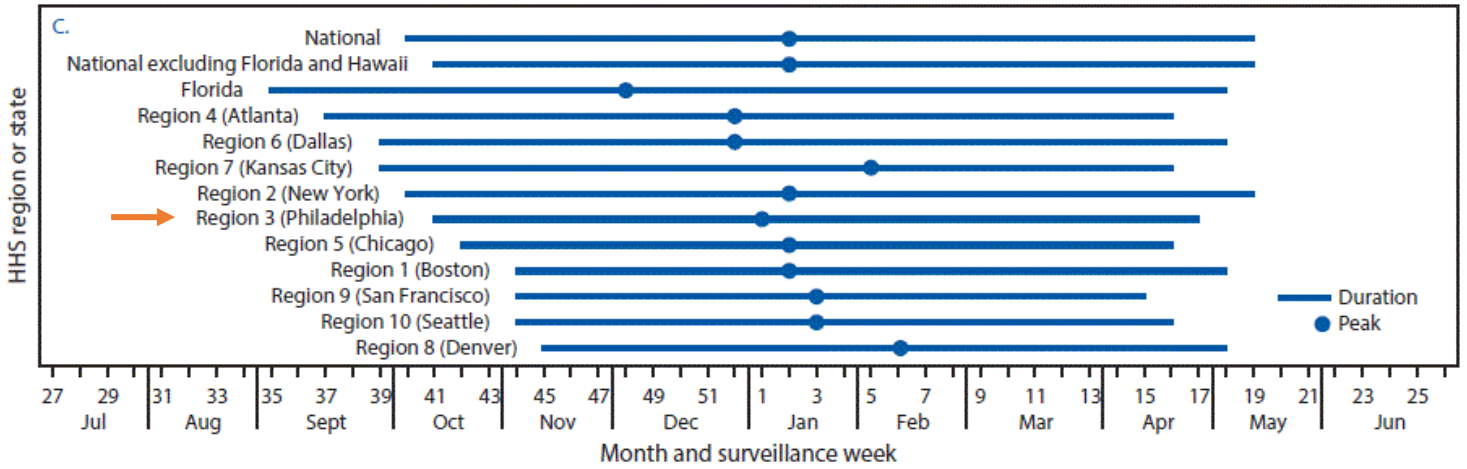
2014-2015



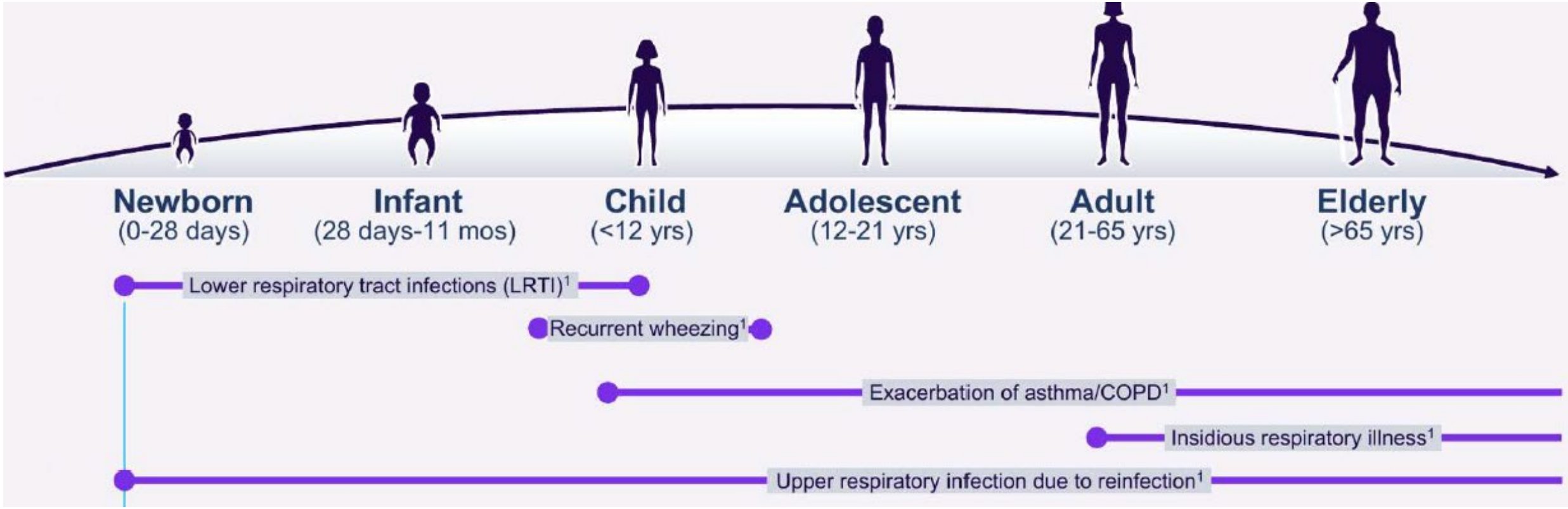
2015-2016



2016-2017

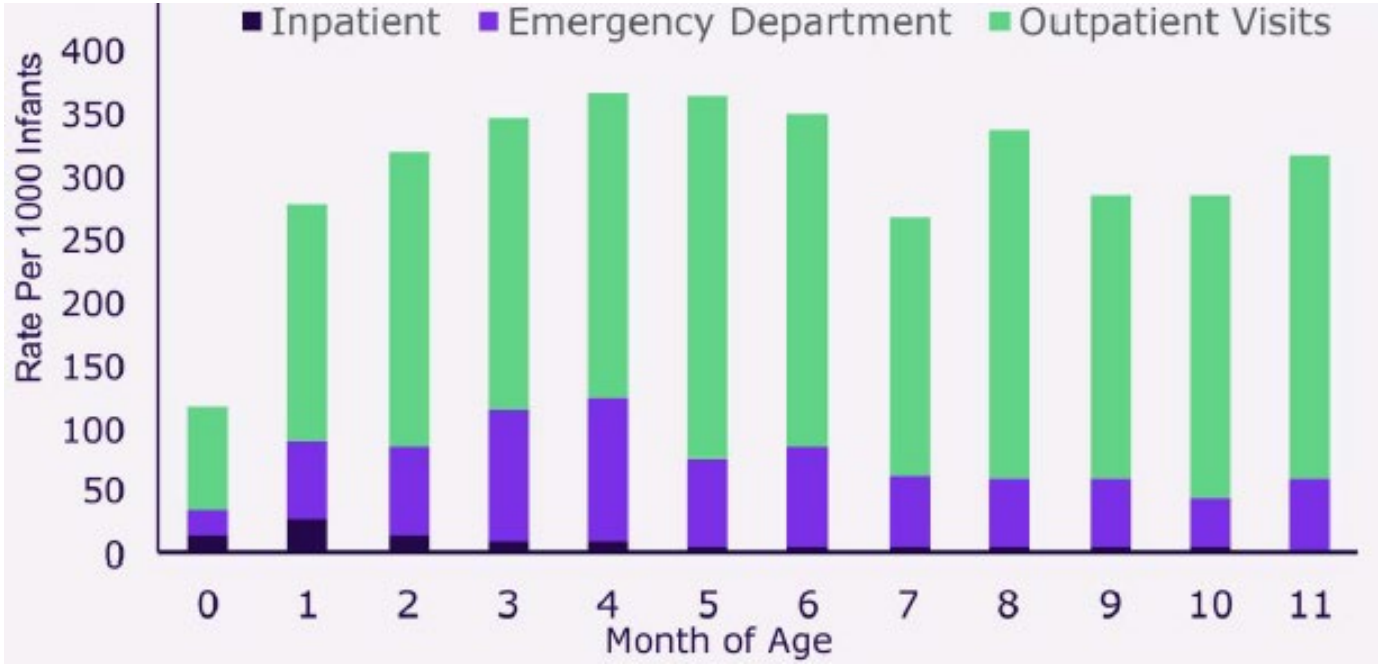


RSV Disease Across the Age Range



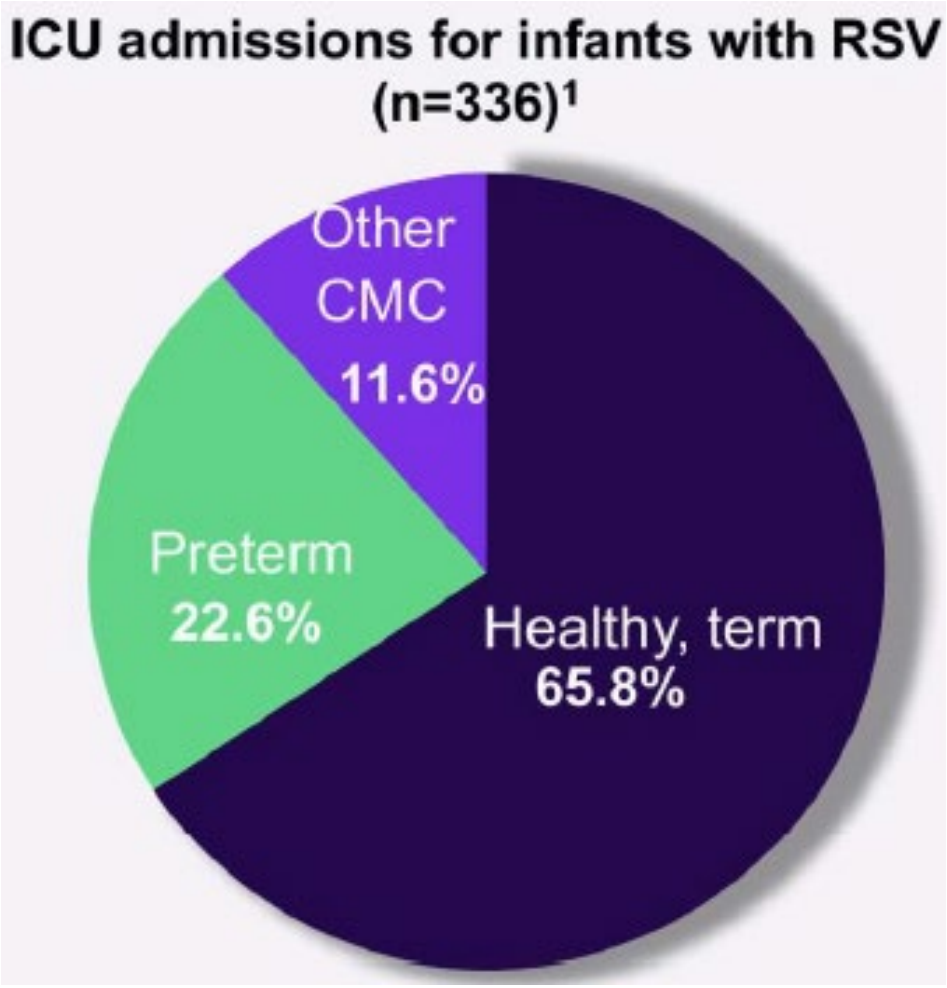
Burden of RSV Lower Respiratory Tract Infection in Children

- United States
  - The leading cause of hospitalizations in all infants
    - 6 per 1000 children < 2 years
    - 15 per 1000 children < 6 months
  - 58,000 - 80,000 hospitalizations and 200 deaths each year



U.S. RSV Hospitalizations

- Previously healthy infants - 72%
- Preterm infants -16%
- Infants with chronic medical conditions - 12%



Burden of RSV Lower Respiratory Tract Infection in Children

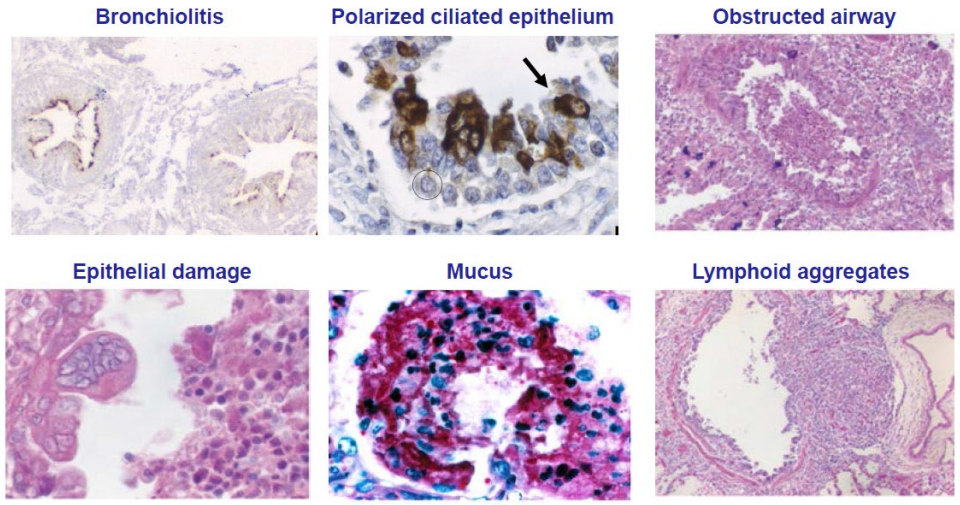
- Most children have acquired RSV by age 2 years
  - 70% upper respiratory
  - 30% lower respiratory
- Most common cause of LRTI in infants
  - Bronchiolitis
  - Pneumonia
- Hospitalized children generally improve with supportive care / brief hospitalization
- 1-3% of all infants develop severe RSV LRTI
  - Especially in first 6 months

What is Bronchiolitis?

- Clinical syndrome usually seen in children < 2 years
- Usually caused by viruses
  - RSV – 67%
- Initial upper respiratory symptoms and signs, followed by lower respiratory findings
- Associated with recurrent wheezing / asthma

Bronchiolitis – Pathophysiology

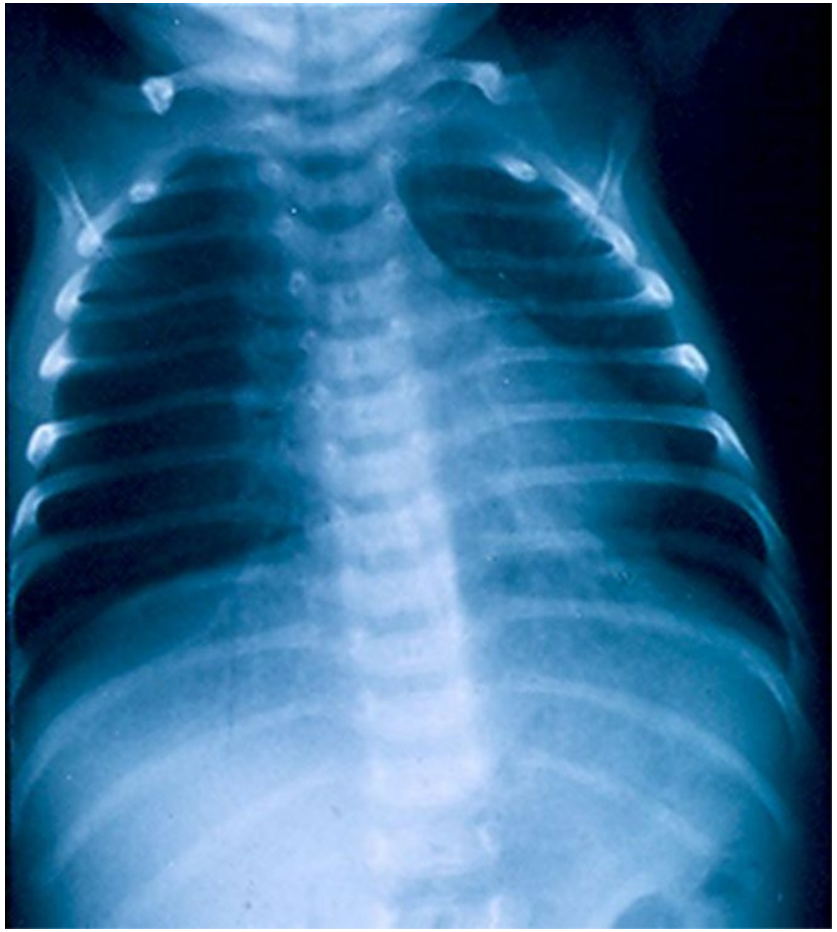
- Viruses infect respiratory epithelium in small bronchi and bronchioles
- Inflammation ensues
  - Ciliary dysfunction
  - Edema
  - Mucous
  - Sloughing of epithelium
  - Airway obstruction
- Atelectasis
- Impaired gas exchange



Johnson, *Modern Pathology*, 2007

Clinical Manifestations

- Fever, usually low grade
- Cough
- Signs of respiratory distress
  - Retractions
  - Grunting
  - Nasal flaring
- Physical findings
  - Wheezing
  - Rales
- Sometimes signs of dehydration
- Apnea



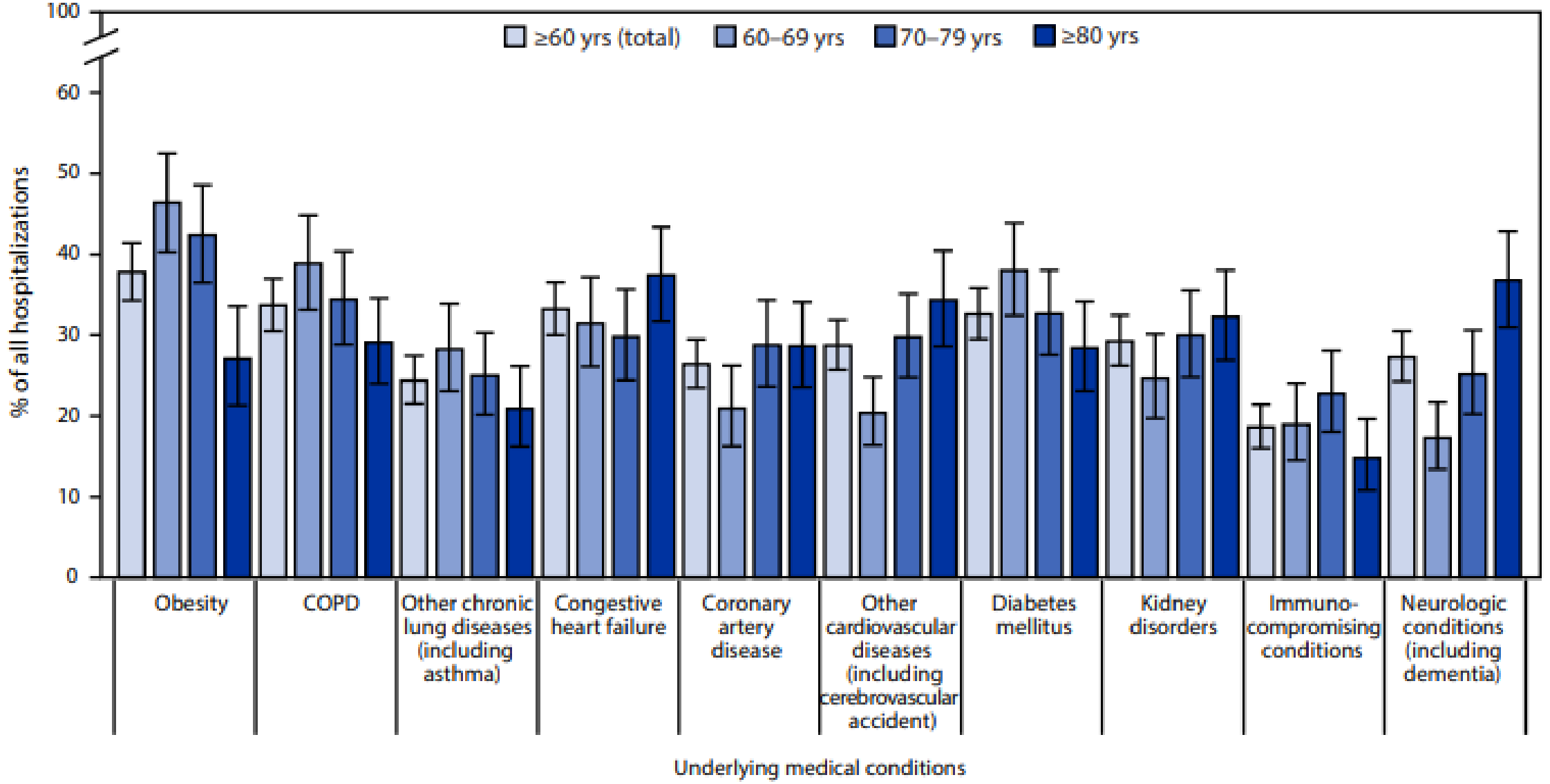
Risk Factors for Severe Disease

- Prematurity
- Age less than 12 weeks
- Chronic lung disease
  - BPD
  - Asthma
- Airway anomalies
- Congenital heart disease
- Immunodeficiency
- Neurologic disease
- Down syndrome

Burden of RSV Lower Respiratory Tract Infection in Adults

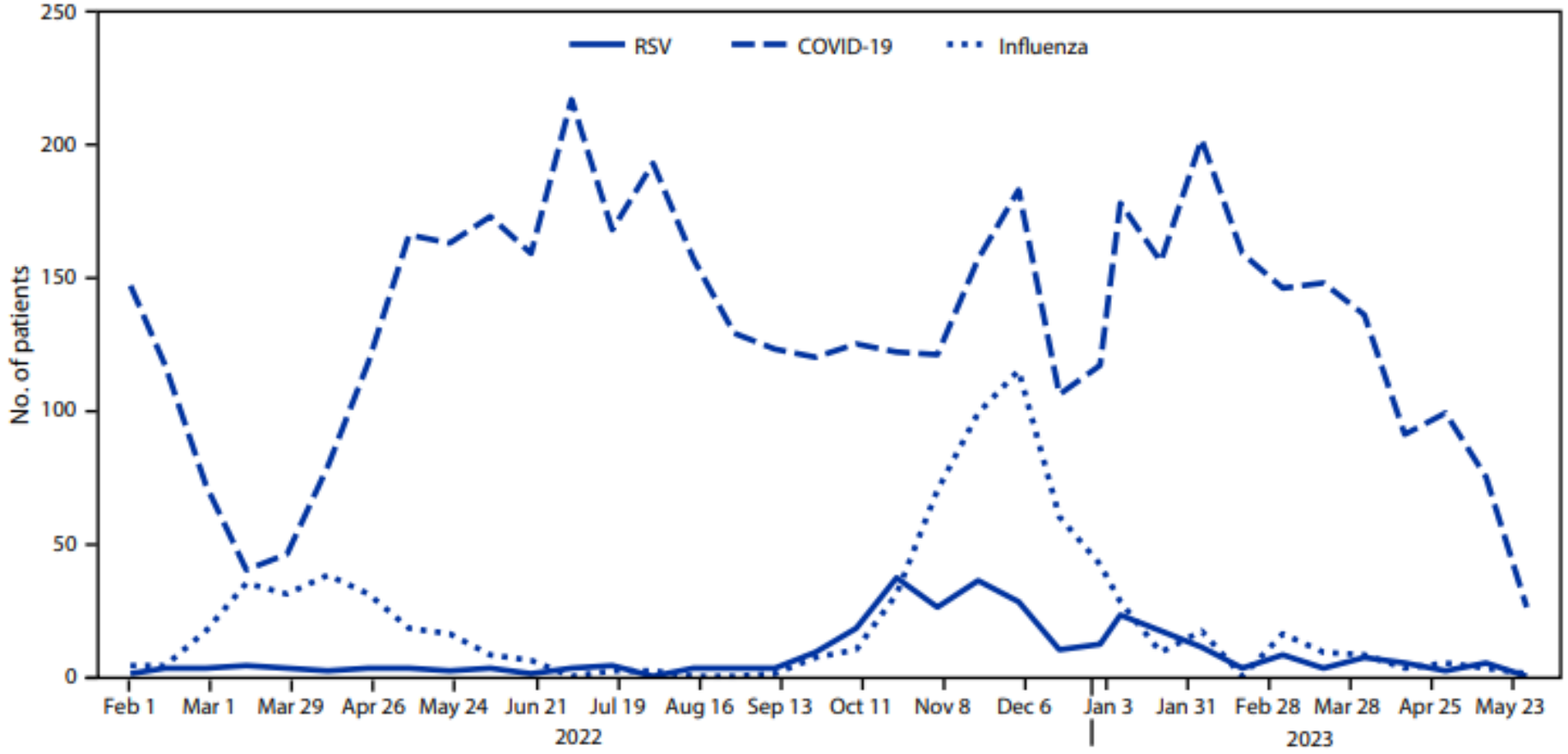
- RSV infections kill between 6,000 and 10,000 older U.S. adults every year and results in 60,000 to 120,000 hospitalizations
- Risk factors include lung and heart disease and immunocompromising conditions
- U.S. had an unusually severe RSV season in 2022 -2023 affecting older adults as well as children
  - Public largely stopped practicing public health measures implemented in response to the COVID-19 pandemic
  - High community level of RSV disease

FIGURE 1. Underlying medical conditions[*,†] among patients hospitalized with laboratory-confirmed respiratory syncytial virus infection[§] — Respiratory Syncytial Virus–Associated Hospitalization Surveillance Network, 12 states,[¶] October 2022–April 2023



MMWR Oct. 6 2023

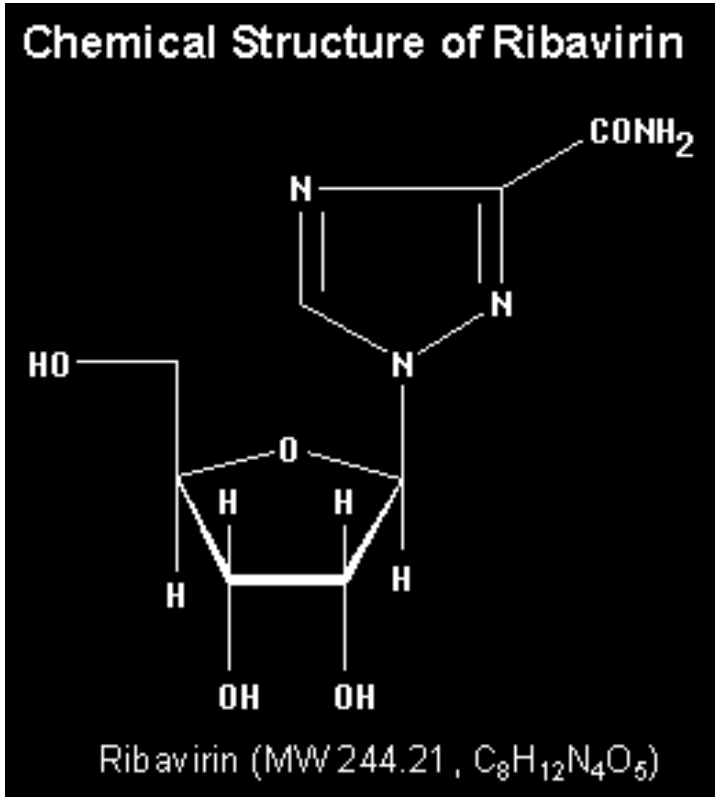
FIGURE. Date of admission for adults aged ≥60 years hospitalized with respiratory syncytial virus, COVID-19, or influenza — Investigating Respiratory Viruses in the Acutely Ill Network, 25 hospitals, 20 U.S. states,* February 1, 2022–May 31, 2023



"During February 2022–May 2023, hospitalizations for RSV were less frequent but were associated with more severe disease than were hospitalizations for COVID-19 or influenza, including receipt of standard flow oxygen therapy, high-flow nasal cannula or noninvasive ventilation, and intensive care unit admission." -- MMWR Oct. 6, 2023

Treatment of RSV Infection

- Ribavirin
  - Active *in vitro* against RSV
  - Numerous studies in infants
  - Improvement in oxygenation
  - No clear benefit in LOS and requirement for ventilation
  - Expensive
  - Concern for HCW exposure
  - Infrequently used
  - May be lifesaving in severely immunocompromised infants, children and adults



ELSEVIER

Virology

Volume 168, Issue 1, January 1989, Pages 147-158

Studies on the mechanism of the antiviral activity of ribavirin against reovirus

James T. Rankin Jr.[1], Stephen B. Eppes[2], James B. Antczak, Wolfgang K. Joklik

Novel Antivirals

- GS-5806 (presatovir)
- Novel, small molecule, oral antiviral agent
- Studied in adult volunteers
  - Lower viral load
  - Decreased mucous
  - Improved symptom scores
- Most research has focused on BMT patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral GS-5806 Activity in a Respiratory Syncytial Virus Challenge Study

John P. DeVincenzo, M.D., Richard J. Whitley, M.D., Richard L. Mackman, Ph.D., Cecilia Scaglioni-Weinlich, M.D., Lisa Harrison, M.L.T., Eric Farrell, B.S., Stephen McBride, B.S., Robert Lambkin-Williams, Ph.D., Robert Jordan, Ph.D., Yan Xin, Ph.D., Srini Ramanathan, Ph.D., Thomas O'Riordan, M.D., Sandra A. Lewis, M.S., Xiaoming Li, Ph.D., Seth L. Toback, M.D., Shao-Lee Lin, M.D., Ph.D., and Jason W. Chien, M.D.

ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) is a common cause of infant hospitalizations and is increasingly recognized as a cause of considerable morbidity and mortality. No accepted antiviral treatment exists.

METHODS

We conducted a double-blind, placebo-controlled study of GS-5806, an oral RSV-entry inhibitor, in healthy adults who received a clinical challenge strain of RSV intranasally. Participants were monitored for 12 days. At the time of a positive test for RSV infection or 5 days after inoculation, whichever occurred first, participants were randomly assigned to receive GS-5806 or placebo in one of seven sequential cohorts. Cohorts 1 to 4 received a first dose of 50 mg of GS-5806 and then 25 mg daily for the next 4 days, cohort 5 received a first dose of 50 mg and then 25 mg daily for the next 2 days, cohort 6 received one 100-mg dose, and cohort 7 received a first dose of 10 mg and then 5 mg daily for the next 4 days. Dose selection for cohorts 5, 6, and 7 occurred after an interim analysis of data for cohorts 1 to 4. The primary end point was the area under the curve (AUC) for the viral load, which was assessed after administration of the first dose through the 12th day after inoculation. Secondary end points were mucus weight and symptom scores.

RESULTS

Among the 54 participants in cohorts 1 to 4 who were infected with RSV, active treatment was associated with a lower viral load (adjusted mean, 250.7 vs. 757.7 $\log_{10}$ plaque-forming-unit equivalents [PFUe]×hours per milliliter; $P<0.001$), lower total mucus weight (mean, 6.9 g vs. 15.1 g; $P=0.03$), and a lower AUC for the change from baseline in symptom scores (adjusted mean, −20.2 vs. 204.9×hours; $P=0.005$). The results were similar in cohorts 5, 6, and 7. Adverse events, including low neutrophil counts and increased levels of alanine aminotransferase, were more common among participants receiving GS-5806.

CONCLUSIONS

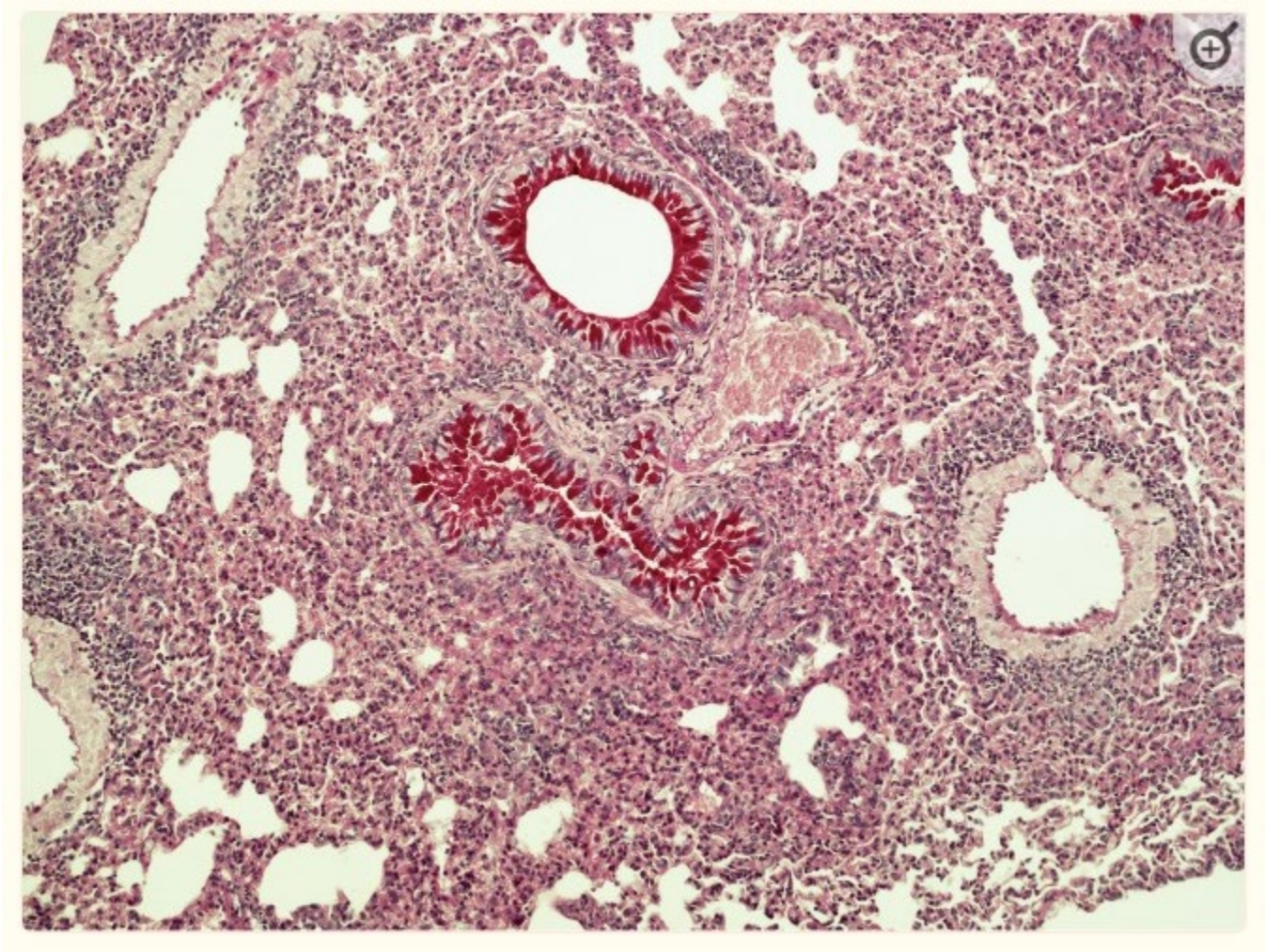
Treatment with GS-5806 reduced the viral load and the severity of clinical disease in a challenge study of healthy adults. (Funded by Gilead Sciences; ClinicalTrials.gov number, NCT01756482.)

From the University of Tennessee School of Medicine (J.P.D., C.S.-W., L.H., E.F., S.M.) and Le Bonheur Children's Hospital, Children's Foundation Research Institute (J.P.D.) — both in Memphis; University of Alabama School of Medicine, Birmingham (R.J.W.); Gilead Sciences, Foster City, CA (R.L.M., R.J., Y.X., S.R., T.O., S.A.L., X.L., S.L.T., S.-L.L., J.W.C.); and Retroscreen Virology, London (R.L.-W.). Address reprint requests to Dr. DeVincenzo at the Children's Foundation Research Institute, Le Bonheur Children's Hospital, Rm. 400R, 50 North Dunlap St., Memphis, TN 38103, or at jdevincenzo@uthsc.edu.

N Engl J Med 2014;371:711-22.
DOI: 10.1056/NEJMoa1401184

First RSV Vaccine

- 1960s vaccine (FI-RSV Lot 100)
  - Formalin inactivated RSV particles
  - Studied in children 2 mo – 7 yr, 2 or 3 doses
- Disastrous results in the winter of 1966-67
  - More hospitalizations than placebo recipients and 2 deaths
  - “FI-RSV vaccine enhanced disease”



Photomicrograph of lung section from BALB/c mouse with enhanced RSV disease. Hematoxylin and periodic acid-Schiff stain shows peribronchiolar, perialveolar, and perivascular inflammation with abundant mucus production.

First RSV Vaccine

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  - Studied in children 2 mo – 7 yr, 2 or 3 doses
- Disastrous results in the winter of 1966-67
  - More hospitalizations than placebo recipients and 2 deaths
  - “FI-RSV vaccine enhanced disease”
- Serum from vaccinees showed aberrant response
  - Formalin selectively altered the protective epitopes in the F and G surface glycoproteins
  - Likely immune complex deposition / complement activation

Reduction of Respiratory Syncytial Virus Hospitalization Among Premature Infants and Infants With Bronchopulmonary Dysplasia Using Respiratory Syncytial Virus Immune Globulin Prophylaxis

The PREVENT Study Group*

ABSTRACT. *Objective.* To determine the safety and efficacy of monthly prophylaxis with respiratory syncytial virus immune globulin, intravenous (RSV-IGIV) for reduction of the incidence of RSV-associated hospitalization.

Methods. A randomized, double-blind, placebo-controlled clinical trial was conducted at 54 centers in the United States during the 1994 to 1995 RSV season. A total of 510 children with bronchopulmonary dysplasia and/or a history of prematurity were randomized to receive either 750 mg/kg RSV-IGIV (n = 250) or placebo (1% albumin; n = 260) intravenously every 30 days. Randomized groups were well balanced at entry for demographics, RSV risk factors, and birth characteristics. Children were monitored for adverse events and for RSV-associated hospitalization from randomization through 30 days after the last infusion visit; serious adverse events were monitored for an additional 30 days. For children hospitalized with RSV, data were collected regarding the total days of RSV stay, total days of increased oxygen requirement, total days with a moderate or severe lower respiratory tract illness, and frequency and duration of intensive care unit stay and mechanical ventilation. Ninety-five percent of participants completed the protocol and 85% received a complete course of infusions.

Results. The incidence of RSV hospitalization was reduced by 41% in children receiving RSV-IGIV prophylaxis; 35 (13.5%) of the children in the placebo group were hospitalized for RSV, compared with 20 (8.0%) RSV-IGIV recipients. RSV-IGIV recipients had a 53% reduction in the total number of RSV hospital days per 100 children, a 60% reduction in the number of RSV days with increased oxygen requirement, and a 54% reduction in the number of RSV hospital days with a moderate or severe lower respiratory tract illness. In addition, children receiving RSV-IGIV had a 38% reduction in hospitalization for respiratory illness of any cause and a 46% reduction in total hospital days for respiratory illness per 100 children. RSV-IGIV was safe and well tolerated, with a safety profile similar to other IGIV preparations. Between 1% to 3% of children had medically significant adverse events related to RSV-IGIV administration.

Conclusions. Monthly administration of 750 mg/kg of RSV-IGIV was safe and well tolerated and was effective in reducing the incidence and total days of both RSV hospitalization and overall respiratory hospitalization in infants with a history of prematurity or bronchopulmonary dysplasia or both. *Pediatrics* 1997;99:93–99; *respiratory syncytial virus, respiratory syncytial virus immune globulin, prophylaxis.*

ABBREVIATIONS. RSV, respiratory syncytial virus; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; RSV-IGIV, respiratory syncytial virus immune globulin, intravenous; LRI, lower respiratory infection/illness; ICU, intensive care unit.

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection in infancy and childhood.[1–4] Approximately 50% of infants and young children become infected with RSV each winter season, and it has been estimated that RSV causes more than 90 000 hospitalizations and 4500 deaths annually.[2,5,6] Children with underlying bronchopulmonary dysplasia (BPD), prematurity, immunodeficiency, or congenital heart disease (CHD) are known to be at high risk for severe RSV illness.[7–10]

Studies performed in cotton rats suggested that passive immunization with antibody enriched for RSV neutralizing activity may be a useful method for prevention of RSV.[11] The development of methods for production of an intravenous immune globulin for human use (respiratory syncytial virus immune globulin, intravenous [RSV-IGIV; RespiGam]) that is enriched for neutralizing antibody to RSV has paved the way for clinical evaluation of this approach.[12] RSV-IGIV is approximately sixfold enriched for neutralizing antibodies (compared with commercially available intravenous immune globulin) and is tenfold more potent in reducing pulmonary titers of RSV in cotton rats.[13] RSV-IGIV has been shown to neutralize a wide variety of subtype A and B strains of RSV in vitro.[13] A previous clinical trial of RSV-IGIV prophylaxis in high-risk infants (ie, prematurity, BPD, CHD) suggested that monthly administration of 750 mg/kg may be associated with a reduction in severity of RSV illness and reduction in the rate of RSV hospitalization.[14] The current study (PREVENT) was designed as a pivotal trial to determine the safety and efficacy of RSV-IGIV prophylaxis for reducing the rate of RSV hospitalization among children with BPD and/or a history of prematurity.

METHODS

PREVENT was a centrally randomized, double-blind, placebo-controlled clinical trial, conducted at 54 centers in the United States. Children were eligible if 1) they were 24 months old or younger and had BPD and a requirement for supplemental oxy-

From the PREVENT Study Group.
*The members of the PREVENT Study Group are listed on pages 98 and 99 in the Appendix.
Received for publication May 28, 1996; accepted Aug 21, 1996.
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PREVENT Study Group,
Pediatrics, 1997

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Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants

The IMpact-RSV Study Group*

ABSTRACT. *Objective.* To determine the safety and efficacy of prophylaxis with palivizumab in reducing the incidence of hospitalization because of respiratory syncytial virus (RSV) infection in high-risk infants.

Methods. A randomized, double-blind, placebo-controlled trial was conducted at 139 centers in the United States, the United Kingdom, and Canada. During the 1996 to 1997 RSV season, 1502 children with prematurity (≤35 weeks) or bronchopulmonary dysplasia (BPD) were randomized to receive 5 injections of either palivizumab (15 mg/kg) or an equivalent volume of placebo by intramuscular injection every 30 days. The primary endpoint was hospitalization with confirmed RSV infection. Children were followed for 150 days (30 days from the last injection). Those with hospitalization as a result of RSV infection were evaluated for total number of days in the hospital, total days with increased supplemental oxygen, total days with moderate or severe lower respiratory tract illness, and incidence and total days of intensive care and mechanical ventilation. The incidence of hospitalization for respiratory illness not caused by RSV and the incidence of otitis media were also evaluated. The placebo and palivizumab groups were balanced at entry for demographics and RSV risk factors. Ninety-nine percent of children in both groups completed the protocol and ~93% received all five scheduled injections.

Results. Palivizumab prophylaxis resulted in a 55% reduction in hospitalization as a result of RSV (10.6% placebo vs 4.8% palivizumab). Children with prematurity but without BPD had a 78% reduction in RSV hospitalization (8.1% vs 1.8%); children with BPD had a 39% reduction (12.8% vs 7.9%). When gender, entry age, entry weight, BPD, and gestational age were included in a logistic regression model, the effect of prophylaxis with palivizumab remained statistically significant. The palivizumab group had proportionally fewer total RSV hospital days, fewer RSV hospital days with increased oxygen, fewer RSV hospital days with a moderate/severe lower respiratory tract illness, and a lower incidence of intensive care unit admission. Palivizumab was safe and well tolerated. No significant differences were observed in reported adverse events between the two groups. Few children discontinued injections for related adverse events (0.3%). Reactions at the site of injection were uncommon (1.8% placebo vs 2.7% palivizumab); the most frequent reaction was mild and transient erythema. Mild or moderate elevations of aspartate aminotransferase occurred in 1.6% of placebo recipients and 3.6% of palivizumab recipients; for alanine aminotransferase these percentages were 2.0% and 2.3%, respectively. Hepatic and renal adverse events related to the study drug were similar in the two groups.

Conclusions. Monthly intramuscular administration of palivizumab is safe and effective for prevention of serious RSV illness in premature children and those with BPD. *Pediatrics* 1998;102:531–537; *respiratory syncytial virus, monoclonal antibody, prophylaxis, MEDI-493, palivizumab, Synagis, prematurity, bronchopulmonary dysplasia.*

ABBREVIATIONS. RSV, respiratory syncytial virus; IGIV, immune globulin, intravenous; BPD, bronchopulmonary dysplasia; IgG, immunoglobulin G; LRI, lower respiratory tract illness/infection; ICU, intensive care unit.

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory illness in children and is increasingly recognized as an important pathogen in the elderly and immune compromised patients of all ages.[1] In children, the risk of serious RSV illness is highest among those with prematurity, chronic lung disease, congenital heart disease, multiple congenital anomalies, and certain immunodeficiencies. In the United States, RSV infection accounts for more than 90 000 pediatric hospitalizations and 4500 deaths annually.[2]

Monthly infusions of respiratory syncytial virus

*Members of the IMpact-RSV Study Group are listed in the "Appendix."
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IMpact-RSV Study Group,
Pediatrics, 1998

Synagis for Prevention of RSV Disease

- Recommendations have changed multiple times
  - Data driven and cost driven
  - Payers pay close attention
- Infants < 29 weeks gestation at beginning of RSV season may be considered for palivizumab
- CLD in 2nd year requiring medical therapy should receive prophylaxis for next RSV season
- CHD: Discuss with cardiologist
- < 2% of infants eligible based on current criteria

Current AAP Red Book

RSV: The Future

- RSV vaccines
  - Adults
  - Children

- Alternative monoclonal antibodies for passive immunization of infants

2023

Structure-Based Design of a Fusion Glycoprotein Vaccine for Respiratory Syncytial Virus

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Respiratory syncytial virus (RSV) is the leading cause of hospitalization for children under 5 years of age. We sought to engineer a viral antigen that provides greater protection than currently available vaccines and focused on antigenic site Ø, a metastable site specific to the prefusion state of the RSV fusion (F) glycoprotein, as this site is targeted by extremely potent RSV-neutralizing antibodies. Structure-based design yielded stabilized versions of RSV F that maintained antigenic site Ø when exposed to extremes of pH, osmolality, and temperature. Six RSV F crystal structures provided atomic-level data on how introduced cysteine residues and filled hydrophobic cavities improved stability. Immunization with site Ø–stabilized variants of RSV F in mice and macaques elicited levels of RSV-specific neutralizing activity many times the protective threshold.

Respiratory syncytial virus (RSV) is one of the last remaining highly prevalent childhood pathogens without an approved vaccine. It is estimated to be responsible for 6.7% of deaths in children 1 month to 1 year of age and causes excess mortality in the elderly at levels comparable to influenza virus (*1*). Although RSV infection does not induce fully protective immunity, antibodies against the RSV fusion (F) glycoprotein can prevent severe disease in humans as demonstrated by passive prophylaxis with the F-directed antibody, palivizumab (Synagis) (*2*).

The proven success of palivizumab (*3*) has spurred vaccine efforts aimed at eliciting protective RSV F–directed antibodies. These efforts have been complicated by the conformational diversity of RSV F (*4*–*8*), a type I fusion glycoprotein that merges virus and host-cell membranes by using the difference in folding energy between two substantially different states: a metastable state adopted before virus-cell interaction (prefusion) and a stable state that occurs after merging of virus and cell membranes (postfusion). Both states exhibit epitopes targeted by neutralizing antibodies, and postfusion RSV F is being developed as a vaccine candidate (*6*, *9*). Recently, however, the major target of RSV-neutralizing antibodies elicited by natural infection was found to reside primarily on the prefusion conformation of RSV F (*10*). Antibodies such as 5C4 (*7*), AM22, and D25 (*11*, *12*) are substantially more potent than palivizumab and target antigenic site Ø (zero), a metastable site located at the membrane-distal apex of the prefusion RSV F trimer (*7*).

To enhance elicitation of similarly potent antibodies, we engineered soluble variants of RSV F with stably exposed antigenic site Ø. These variants were characterized antigenically and crystallographically and tested for immunogenicity in mice and nonhuman primates (rhesus macaques).

Structure-Based Vaccine Strategy

We and others have engineered antigenicity (*13*–*17*) through structure-based design of the epitopes recognized by template neutralizing antibodies. For example, the crystal structure of motavizumab (a variant of palivizumab) bound to its F glycoprotein epitope (*18*) allowed us to create epitope scaffolds, which stably presented the motavizumab epitope on heterologous proteins (*19*). Although motavizumab-epitope scaffolds could elicit immune responses that recognized F, substantial neutralizing activity was not induced (*19*). We hypothesized that instead of a single epitope recognized by a single template antibody, it would be advantageous to present a "supersite" (*20*), comprising a collection of overlapping epitopes recognized by multiple antibodies. Even more preferable would be for such a site to be ultrasensitive to neutralization. These considerations led to a "neutralization-sensitive site" strategy: (i) to identify a viral site targeted by multiple antibodies with extremely potent neutralizing activity, (ii) to determine the structure of the site in complex with a representative antibody, (iii) to engineer the stable presentation of the site in the absence of recognizing antibody, and (iv) to elicit high-titer protective responses through immunization with engineered antigens that stably present the neutralization-sensitive site (fig. S1).

Engineering of RSV F Antigens

Antigenic site Ø was chosen as the target site because of its recognition by RSV-neutralizing antibodies that are 10- to 100-fold more potent than palivizumab (*7*, *11*, *12*). We previously determined the structure of antigenic site Ø in complex with the D25 antibody (*7*). Structure determination involved appending the T4-phage fibritin trimerization domain ("foldon") (*21*, *22*) to the C terminus of the RSV F ectodomain (*5*) and binding of the prefusion-specific D25 antibody. Although these approaches stabilized antigenic site Ø, D25 binding sterically occluded the target site. To stably present antigenic site Ø in the absence of D25, we retained the C-terminal trimerization domain and combined it with other means of stabilization, including the introduction of cysteine pairs or cavity-filling hydrophobic substitutions.

The β-carbons of serine residues 155 and 290 are 4.4 Å apart in the D25-bound RSV F structure (*7*) and 12.4.2 Å apart in the postfusion structure (*5*) (Fig. 1 and fig. S2). A S155C-S290C double mutant (DS) [in which cysteine replaced serine at positions 155 and 290 (*23*)] formed stable RSV F trimers, expressed at 1.4 mg/liter, retained antigenic site Ø, and was homogeneous as judged by negative-stain electron microscopy (Table 1 and fig. S3) (*24*, *25*). Other intrachain cysteine modifications, such as those between regions of RSV F that do not rearrange between pre- and postfusion states (e.g., S403C and T420C), did not stabilize antigenic site Ø (Table 1). We also tested potential interchain double-cysteine modifications, but none expressed at levels sufficient for enzyme-linked immunosorbent assay (ELISA) detection (table S1) (*26*).

We analyzed the D25-bound RSV F structure for hydrophobic cavities unique to the D25-bound conformation of RSV F that abutted regions that differed in the prefusion and postfusion states (*27*). Several such cavities were identified in the membrane-distal "head" of the prefusion structure, close to the binding site of D25, and we engineered hydrophobic substitutions to fill these cavities. S190F and V207L substitutions were predicted to adopt prevalent side-chain conformations with minimal clashes, whereas K87F, V90I., V220I., and V296F showed less steric compatibility. We assessed the impact of filling these cavities with pairs of changed residues. A S190F-V207L pair (Cav1) (Fig. 1), formed stable RSV F trimers, expressed at 2.2 mg/liter, and retained antigenic site Ø (Table 1). Moreover, K87F-V90I., S190F-

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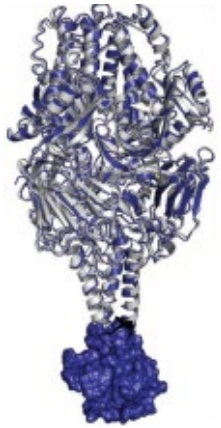
 Corrected 18 September, 2014; see full text.

RSV F Glycoprotein Vaccine

- Prefusion conformation
- Appears safe
  - Mice and macaques
- High levels of RSV neutralizing antibody (subtypes A and B)
- This study set the stage for multiple clinical trials



ORIGINAL ARTICLE

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

A. Papi, M.G. Ison, J.M. Langley, D.-G. Lee, I. Leroux-Roels, F. Martinon-Torres, T.F. Schwarz, R.N. van Zyl-Smit, L. Campora, N. Dezutter, N. de Schrevel, L. Fissette, M.-P. David, M. Van der Wielen, L. Kostanyan, and V. Hulstrøm, for the AReSVi-006 Study Group*

ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) is an important cause of acute respiratory infection, lower respiratory tract disease, clinical complications, and death in older adults. There is currently no licensed vaccine against RSV infection.

METHODS

In an ongoing, international, placebo-controlled, phase 3 trial, we randomly assigned, in a 1:1 ratio, adults 60 years of age or older to receive a single dose of an $AS01_E$-adjuvanted RSV prefusion F protein–based candidate vaccine (RSVPreF3 OA) or placebo before the RSV season. The primary objective was to show vaccine efficacy of one dose of the RSVPreF3 OA vaccine against RSV-related lower respiratory tract disease, confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR), during one RSV season. The criterion for meeting the primary objective was a lower limit of the confidence interval around the efficacy estimate of more than 20%. Efficacy against severe RSV-related lower respiratory tract disease and RSV-related acute respiratory infection was assessed, and analyses according to RSV subtype (A and B) were performed. Safety was evaluated.

RESULTS

A total of 24,966 participants received one dose of the RSVPreF3 OA vaccine (12,467 participants) or placebo (12,499). Over a median follow-up of 6.7 months, vaccine efficacy against RT-PCR–confirmed RSV-related lower respiratory tract disease was 82.6% (96.95% confidence interval [CI], 57.9 to 94.1), with 7 cases (1.0 per 1000 participant-years) in the vaccine group and 40 cases (5.8 per 1000 participant-years) in the placebo group. Vaccine efficacy was 94.1% (95% CI, 62.4 to 99.9) against severe RSV-related lower respiratory tract disease (assessed on the basis of clinical signs or by the investigator) and 71.7% (95% CI, 56.2 to 82.3) against RSV-related acute respiratory infection. Vaccine efficacy was similar against the RSV A and B subtypes (for RSV-related lower respiratory tract disease: 84.6% and 80.9%, respectively; for RSV-related acute respiratory infection: 71.9% and 70.6%, respectively). High vaccine efficacy was observed in various age groups and in participants with coexisting conditions. The RSVPreF3 OA vaccine was more reactogenic than placebo, but most adverse events for which reports were solicited were transient, with mild-to-moderate severity. The incidences of serious adverse events and potential immune-mediated diseases were similar in the two groups.

CONCLUSIONS

A single dose of the RSVPreF3 OA vaccine had an acceptable safety profile and prevented RSV-related acute respiratory infection and lower respiratory tract disease and severe RSV-related lower respiratory tract disease in adults 60 years of age or older, regardless of RSV subtype and the presence of underlying coexisting conditions. (Funded by GlaxoSmithKline Biologicals; AReSVi-006 ClinicalTrials.gov number, NCT04886596.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Hulstrøm can be contacted at veronica.x.hulstrom@gsk.com or at GSK, Ave. Fleming 20, 1300 Wavre, Belgium.

*A list of the members of the Adult Respiratory Syncytial Virus (AReSVi-006) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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CME at NEJM.org

ORIGINAL ARTICLE

Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) infection causes considerable illness in older adults. The efficacy and safety of an investigational bivalent RSV prefusion F protein–based (RSVpreF) vaccine in this population are unknown.

METHODS

In this ongoing, phase 3 trial, we randomly assigned, in a 1:1 ratio, adults (≥60 years of age) to receive a single intramuscular injection of RSVpreF vaccine at a dose of 120 μg (RSV subgroups A and B, 60 μg each) or placebo. The two primary end points were vaccine efficacy against seasonal RSV-associated lower respiratory tract illness with at least two or at least three signs or symptoms. The secondary end point was vaccine efficacy against RSV-associated acute respiratory illness.

RESULTS

At the interim analysis (data-cutoff date, July 14, 2022), 34,284 participants had received RSVpreF vaccine (17,215 participants) or placebo (17,069 participants). RSV-associated lower respiratory tract illness with at least two signs or symptoms occurred in 11 participants in the vaccine group (1.19 cases per 1000 person-years of observation) and 33 participants in the placebo group (3.58 cases per 1000 person-years of observation) (vaccine efficacy, 66.7%; 96.66% confidence interval [CI], 28.8 to 85.8); 2 cases (0.22 cases per 1000 person-years of observation) and 14 cases (1.52 cases per 1000 person-years of observation), respectively, occurred with at least three signs or symptoms (vaccine efficacy, 85.7%; 96.66% CI, 32.0 to 98.7). RSV-associated acute respiratory illness occurred in 22 participants in the vaccine group (2.38 cases per 1000 person-years of observation) and 58 participants in the placebo group (6.30 cases per 1000 person-years of observation) (vaccine efficacy, 62.1%; 95% CI, 37.1 to 77.9). The incidence of local reactions was higher with vaccine (12%) than with placebo (7%); the incidences of systemic events were similar (27% and 26%, respectively). Similar rates of adverse events through 1 month after injection were reported (vaccine, 9.0%; placebo, 8.5%), with 1.4% and 1.0%, respectively, considered by the investigators to be injection-related. Severe or life-threatening adverse events were reported in 0.5% of vaccine recipients and 0.4% of placebo recipients. Serious adverse events were reported in 2.3% of participants in each group through the data-cutoff date.

CONCLUSIONS

RSVpreF vaccine prevented RSV-associated lower respiratory tract illness and RSV-associated acute respiratory illness in adults (≥60 years of age), without evident safety concerns. (Funded by Pfizer; RENOIR ClinicalTrials.gov number, NCT05035212; EudraCT number, 2021-003693-31.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Gurtman can be contacted at alejandra.gurtman@pfizer.com or at Vaccine Research and Development, Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965.

*The members of the RENOIR Clinical Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Walsh and Pérez Marc contributed equally to this article.

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Efficacy of Adult RSV Vaccines for LRT Disease

Arexvy (GSK)

- Overall
  - 82.6% in first RSV season
  - 56.1% for second RSV season
- For severe disease
  - 94.1% in first RSV season
  - 78.8% over two seasons

Abrysvo

- For LRTD with at least three symptoms (cough, wheezing, sputum, SOB, tachypnea)
  - 88.9% in first season
  - 78.6% midway through second season

RSV Infections Prevented Over Two Seasons

	Number prevented per 1 million vaccinations among: **Adults aged ≥65 years**	Number prevented per 1 million vaccinations among: **Adults aged 60–64 years**
Outpatient visits[a]	25,000	19,000
Hospitalizations[b]	2,500	960
Deaths[c]	130	37

Cost-Effectiveness – ACIP

- Multiple assumptions
  - Two seasons of effectiveness
  - Vaccine cost $200
  - RSV epidemiology and severity
- $94,673 / QALY for ≥ 65 years
- $218,350 / QALY for 60-64 years

TABLE 2. Safety* of 1 dose of GSK respiratory syncytial virus RSVPreF3 vaccine in adults aged ≥60 years — multiple countries, 2021–2023

Safety event	Risk for event		
	RSVPreF3 recipients no./No. (%)†	Placebo recipients no./No. (%)§	Relative risk (95% CI)¶
Serious AE**	549/12,570 (4.4)	540/12,604 (4.3)	1.02 (0.91–1.15)
Severe reactogenicity events††	37/979 (3.8)	9/976 (0.9)	4.10 (1.99–8.45)
Inflammatory neurologic events§§	3 events in trials without placebo recipients¶¶	—¶¶	—¶¶

3 / 17,922 subjects
One case of GBS
Two cases of ADEM

TABLE 4. Safety* of 1 dose of Pfizer respiratory syncytial virus RSVpreF vaccine in adults aged ≥60 years — multiple countries, 2021–2023

Safety event	Risk for event		
	RSVpreF recipients no./No. (%)†	Placebo recipients no./No. (%)§	Relative risk (95% CI)¶
Serious AE**	792/18619 (4.3%)	749/18334 (4.1%)	1.04 (0.94–1.15)
Severe reactogenicity events††	36/3673 (1.0%)	24/3491 (0.7%)	1.43 (0.85–2.39)
Inflammatory neurologic events§§	3/18622 (—)¶¶	0/18335 (—)	—¶¶

3 / 20,255 subjects
Two cases of GBS
One case of polyneuropathy

Both RSV Vaccines Recommended by CDC

- Shared clinical decision-making for adults ≥ 60 years
  - Patient's risk for acquiring RSV
  - Patient's risk for severe RSV disease

BOX. Underlying medical conditions and other factors associated with increased risk for severe RSV disease

Chronic underlying medical conditions associated with increased risk

- Lung disease (such as chronic obstructive pulmonary disease and asthma)
- Cardiovascular diseases (such as congestive heart failure and coronary artery disease)
- Moderate or severe immune compromise*
- Diabetes mellitus
- Neurologic or neuromuscular conditions
- Kidney disorders
- Liver disorders
- Hematologic disorders
- Other underlying conditions that a health care provider determines might increase the risk for severe respiratory disease

Other factors associated with increased risk

- Frailty†
- Advanced age§
- Residence in a nursing home or other long-term care facility
- Other underlying factors that a health care provider determines might increase the risk for severe respiratory disease

Both RSV Vaccines Recommended by CDC

- Shared clinical decision-making for adults ≥ 60 years
  - Patient's risk for acquiring RSV
  - Patient's risk for severe RSV disease
  - Patient's characteristics, values and preferences
- Single dose
  - Insufficient data for re-vaccination
- Offer before and during RSV season
- Coadministration with other adult vaccines acceptable
- Only contraindication is previous severe allergic reaction to any vaccine component
- So far, 15% of eligible adults have received one of the RSV vaccines

Why Not a Universal Recommendation?

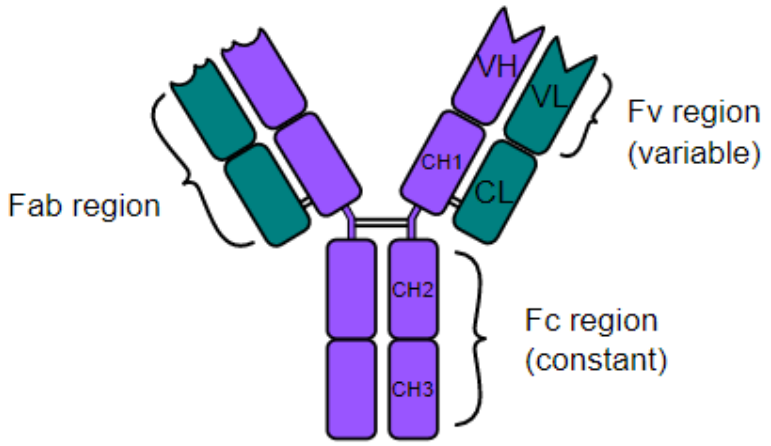
- Highest risk adults not included in trials
- Cost-effectiveness concerns
- Uncertainty about relationship of vaccine to neuro-inflammatory events
  - “Whether these events occurred due to chance, or whether RSV vaccination increases the risk for inflammatory neurologic events is currently unknown. Until additional evidence becomes available from postmarketing surveillance clarifying the existence of any potential risk, RSV vaccination in older adults should be targeted to those who are at highest risk for severe RSV disease and therefore most likely to benefit from vaccination.” MMWR, July21, 2023

RSV Immunization of Infants: Potential Approaches

	Maternal Immunization	Infant Vaccines	Long-acting monoclonal Ab
PROS	Trans-placental transfer of IgG	Replicating vaccines (live attenuated or vectored)	Prolonged half life
PROS	Independent of infant immune function	Potential for multi-season protection	Single dose at birth or at start of RSV season
PROS	Works for influenza and pertussis	T-cell as well as antibody response	Independent of infant immune function
CONS	May not work for preterm infants	May require multiple doses	Potential cost
CONS	Protection may not last for entire season ($T_{1/2}$ = 23 days)	Youngest infants may not be eligible	Potential for anti-drug antibodies
CONS	Suboptimal uptake	Preterm infants may not respond well	Potential for viral escape by loss of epitope

Nirsevimab (Sanofi and AstraZeneca)

- Recombinant neutralizing human IgG1κ long-acting monoclonal antibody
- Binds to prefusion conformation of the RSV F protein
- Modified with a triple amino acid substitution in Fc region to extend serum half-life
  - $T_{1/2}$ = 69 ± 11 days
  - Compare to palivizumab – 23 days



Phase 3 Pivotal Study in Healthy Infants

- 1490 infants randomized 2:1 to receive either mAb or placebo
- Single IM injection prior to RSV season
- Safety
  - SAEs similar between groups
  - 6.1% antidrug antibodies
- Efficacy
  - 74.5% for MALRTI due to RSV
    - P < 0.001
  - 62.1% for RSV hospitalization
    - P = 0.07

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Laura L. Hammitt, M.D., Ron Dagan, M.D., Yuan Yuan, Ph.D., Manuel Baca Cots, M.D., Miroslava Bosheva, M.D., Shabir A. Madhi, Ph.D., William J. Muller, Ph.D., Heather J. Zar, Ph.D., Dennis Brooks, M.D., Amy Grenham, M.Sc., Ulrika Wählby Hamrén, Ph.D., Vaishali S. Mankad, M.D., Pin Ren, Ph.D., Therese Takas, B.Sc., Michael E. Abram, Ph.D., Amanda Leach, M.R.C.P.C.H., M. Pamela Griffin, M.D., and Tonya Villafana, Ph.D., for the MELODY Study Group*

ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection and hospitalization in infants. Nirsevimab is a monoclonal antibody to the RSV fusion protein that has an extended half-life. The efficacy and safety of nirsevimab in healthy late-preterm and term infants are uncertain.

METHODS

We randomly assigned, in a 2:1 ratio, infants who had been born at a gestational age of at least 35 weeks to receive a single intramuscular injection of nirsevimab or placebo before the start of an RSV season. The primary efficacy end point was medically attended RSV-associated lower respiratory tract infection through 150 days after the injection. The secondary efficacy end point was hospitalization for RSV-associated lower respiratory tract infection through 150 days after the injection.

RESULTS

A total of 1490 infants underwent randomization: 994 were assigned to the nirsevimab group and 496 to the placebo group. Medically attended RSV-associated lower respiratory tract infection occurred in 12 infants (1.2%) in the nirsevimab group and in 25 infants (5.0%) in the placebo group; these findings correspond to an efficacy of 74.5% (95% confidence interval [CI], 49.6 to 87.1; P<0.001) for nirsevimab. Hospitalization for RSV-associated lower respiratory tract infection occurred in 6 infants (0.6%) in the nirsevimab group and in 8 infants (1.6%) in the placebo group (efficacy, 62.1%; 95% CI, −8.6 to 86.8; P=0.07). Among infants with data available to day 361, antidrug antibodies after baseline were detected in 58 of 951 (6.1%) in the nirsevimab group and in 5 of 473 (1.1%) in the placebo group. Serious adverse events were reported in 67 of 987 infants (6.8%) who received nirsevimab and in 36 of 491 infants (7.3%) who received placebo.

CONCLUSIONS

A single injection of nirsevimab administered before the RSV season protected healthy late-preterm and term infants from medically attended RSV-associated lower respiratory tract infection. (Funded by MedImmune/AstraZeneca and Sanofi; MELODY ClinicalTrials.gov number, NCT03979313.)

From the Department of International Health, Johns Hopkins University, Baltimore (L.L.H.), and AstraZeneca, Gaithersburg (Y.Y., D.B., A.G., P.R., T.T., M.E.A., A.L., M.P.G., T.V.) — both in Maryland; the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel (R.D.); Quirónsalud Málaga Hospital, Malaga, Spain (M.B.C.); University Multiprofile Hospital for Active Treatment, St. George Medical University, Plovdiv, Bulgaria (M.B.); the South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit and African Leadership in Vaccinology Expertise, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg (S.A.M.), and the Department of Paediatrics and Child Health, Red Cross Children's Hospital, and the Medical Research Council Unit on Child and Adolescent Health, University of Cape Town, Cape Town (H.J.Z.) — all in South Africa; Ann and Robert H. Lurie Children's Hospital of Chicago and Northwestern University Feinberg School of Medicine, Chicago (W.J.M.); AstraZeneca, Gothenburg, Sweden (U.W.H.); and AstraZeneca, Durham, NC (V.S.M.). Dr. Villafana can be contacted at tonya.villafana@astrazeneca.com or at AstraZeneca, One MedImmune Way, Gaithersburg, MD 20878.

*A list of the MELODY Study Group members is provided in the Supplementary Appendix, available at NEJM.org.

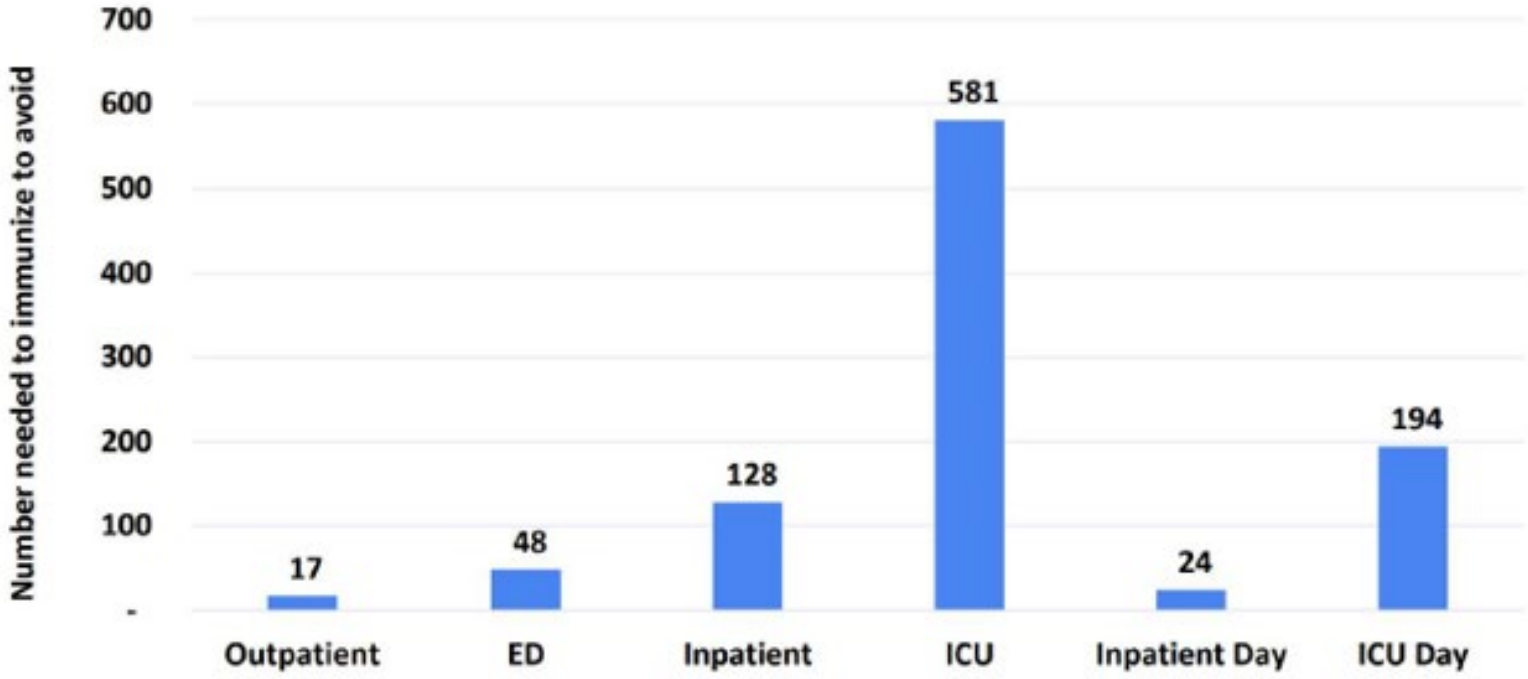
N Engl J Med 2022;386:837-46.
DOI: 10.1056/NEJMoa2110275

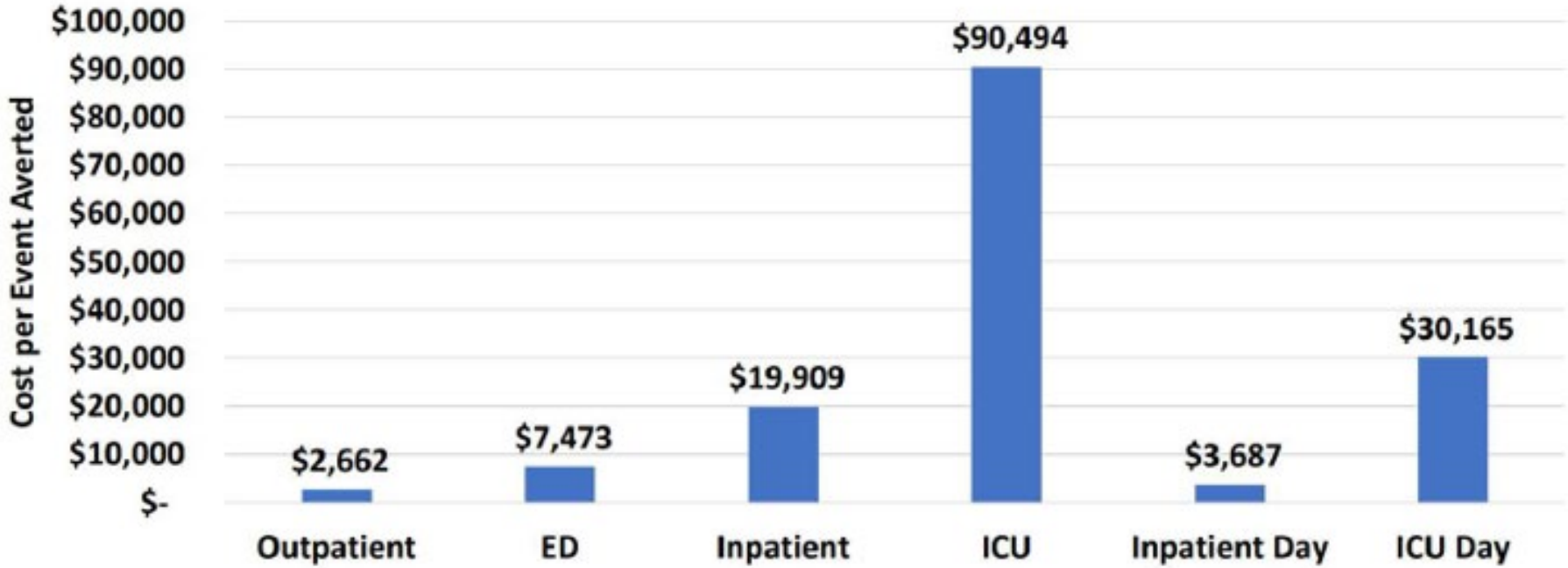
Nirsevimab: Efficacy and Safety from Pooled Results of Phase 2b and Phase 3 Trials of Infants

- At 150 days, compared with placebo, nirsevimab:
  - Reduced medically attended RSV lower respiratory tract infection by 79.0%
  - Reduced RSV-associated hospitalizations by 80.6%
  - Reduced RSV-associated ICU admission by 90.0%
- Serious adverse events were similar in nirsevimab and placebo recipients
- Minor side effects uncommon
  - Rash
  - Injection site reactions

Nirsevimab: Results for High-Risk Infants Entering Their 2nd RSV Season

- Study enrolled 615 former preterm infants (< 35 weeks) and 310 toddlers with either chronic lung disease or hemodynamically significant congenital heart disease
- Subjects received 200 mg dose of nirsevimab or palivizumab
- Efficacy against LRTI were extrapolated from pharmacologic data
- Nirsevimab levels comparable to those of younger babies entering first RSV season
- Rates of severe adverse events not different between the groups


Number needed to immunize to avoid
700
600
500
400
300
200
100
-
17
48
128
581
24
194
Outpatient
ED
Inpatient
ICU
Inpatient Day
ICU Day


Cost per Event Averted
$100,000
$90,000
$80,000
$70,000
$60,000
$50,000
$40,000
$30,000
$20,000
$10,000
$-
$2,662
$7,473
$19,909
$90,494
$3,687
$30,165
Outpatient
ED
Inpatient
ICU
Inpatient Day
ICU Day

Nirsevimab: Cost Effectiveness

- Cost per dose:
  - 50 and 100 mg $495
  - 200 mg $890
- First RSV season
  - $102,811 per quality adjusted life year
- High risk toddlers entering second RSV season
  - Much less expensive than 5 doses of palivizumab

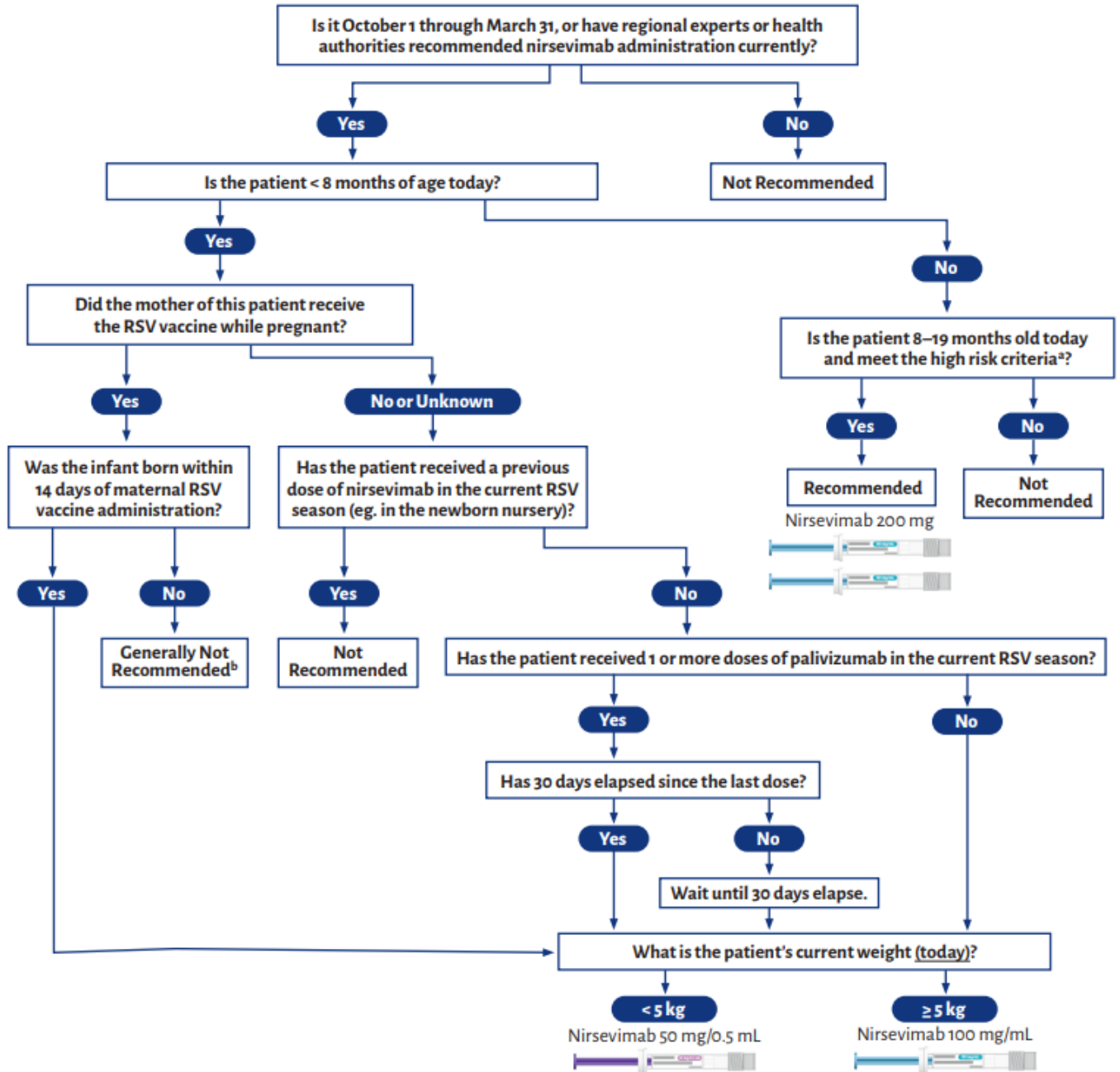
RSV Season	Patient Characteristic	Additional Dose & Frequency
Nirsevimab		
1st RSV Season	Weight < 5 kg regardless of time elapsed since initial dose	50 mg IM once
	Weight ≥ 5 kg and ≤ 90 days since initial dose	100 mg IM once
	Weight ≥ 5 kg and > 90 days since initial dose	50 mg IM once
2nd RSV Season	≤ 90 days since initial dose	200 mg IM once
	> 90 days since initial dose	100 mg IM once

Nirsevimab: Recommendations for Use

- All infants < 8 months shortly before start of RSV season
- Infants born shortly before or during RSV season within 1 week of birth
  - Prior to discharge from birth hospitalization
  - Outpatient setting
- High risk toddlers shortly before start of second RSV season
  - Chronic lung disease of prematurity requiring medical intervention
  - Severely immunocompromised
  - Cystic fibrosis with significant lung disease
  - American Indians and Alaskan Natives

Nirsevimab Administration Visual Guide

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®



Nirsevimab Administration Visual Guide

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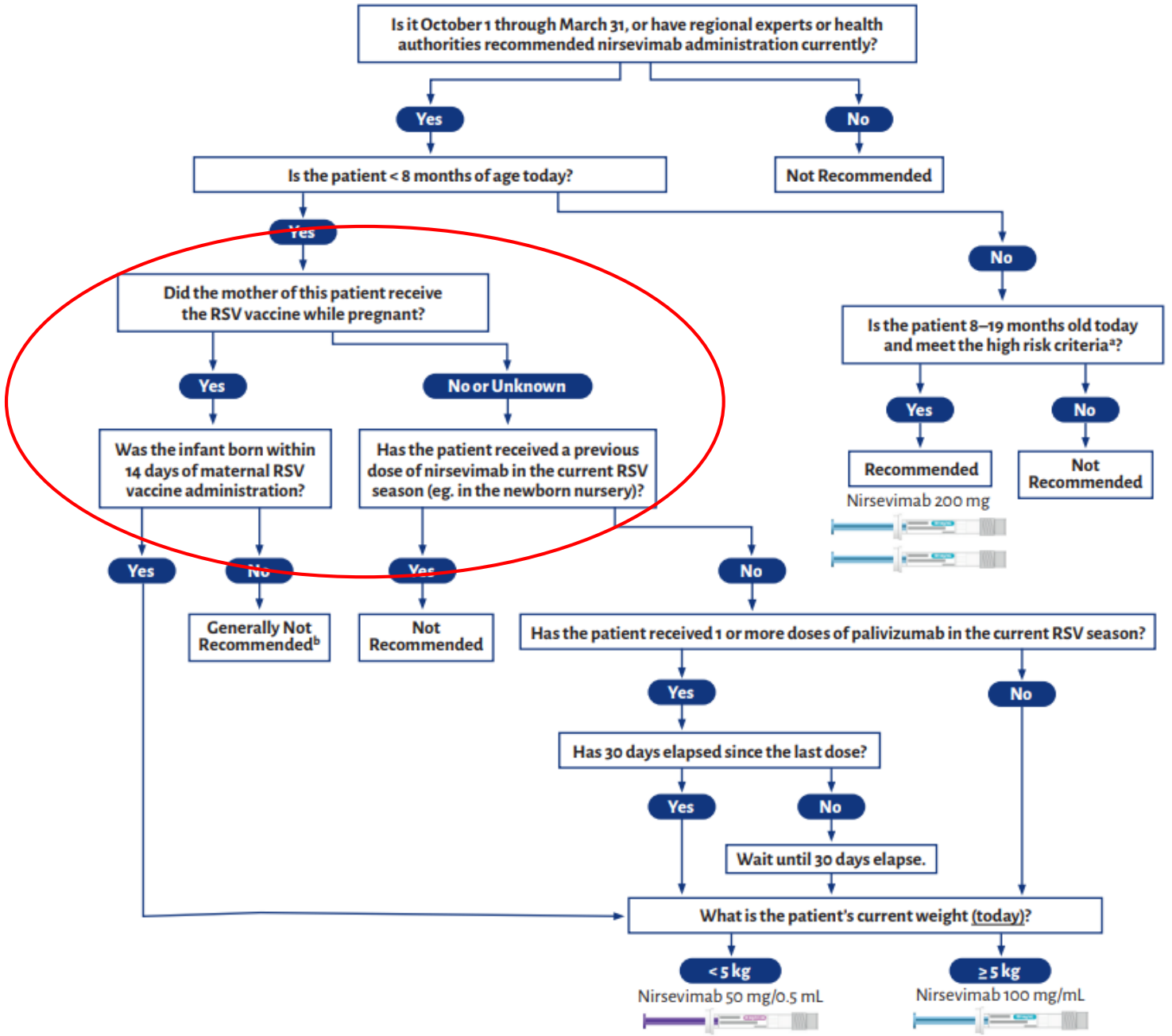


IMMUNIZATION INFORMATION STATEMENT

Respiratory Syncytial Virus (RSV) Preventive Antibody:

What You Need to Know

Why get immunized with a RSV preventive antibody?

A respiratory syncytial virus (RSV) preventive antibody can prevent severe lung disease caused by RSV.

RSV is a common respiratory virus that usually causes mild, cold-like symptoms but can also affect the lungs. Symptoms of RSV infection may include runny nose, decrease in appetite, coughing, sneezing, fever, or wheezing.

Anyone can become infected by RSV, and almost all children get an RSV infection by the time they are 2 years old. While most children recover from an RSV infection in a week or two, RSV infection can be dangerous for infants and some young children, causing difficulty breathing, low oxygen levels, and dehydration. In the United States, RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lungs) and pneumonia (infection of the lungs) in children younger than 1 year of age. Children who get sick from RSV may need to be hospitalized, and some might even die.

RSV Preventive Antibodies

The RSV preventive antibody (generic name nirsevimab, trade name Beyfortus) is a shot that prevents severe RSV disease in infants and young children. Antibodies are proteins that the body's immune system uses to fight off harmful germs. Like traditional vaccines, preventive antibodies are immunizations that provide protection against a specific pathogen. While both are immunizations, the way they provide immunity is different. Nirsevimab is an immunization that provides antibodies directly to the recipient. Traditional vaccines are immunizations that stimulate the recipient's immune system to produce antibodies.

Infants born during the RSV season (typically fall through spring) should receive a single dose of the RSV Immunization within 1 week after birth. Most infants whose mothers got the RSV vaccine don't need to get nirsevimab, too. Both protect infants from severe RSV by providing antibodies, either from the mother to the infant or directly to the infant. Most infants will likely only need protection from either the maternal RSV vaccine or nirsevimab (not both). However, there may be some situations in which nirsevimab would be recommended for an infant after the mother received an RSV vaccine.

Infants born outside of the RSV season who are younger than 8 months should receive a single dose of the RSV Immunization shortly before their first RSV season (typically the fall), but infants who are younger than 8 months who have not yet received a dose may receive a dose at any time during the season.

Some infants and young children who are at increased risk for severe RSV disease may need a single dose of the RSV antibody before or during their second RSV season.

RSV preventive antibodies can be given at the same time as vaccines routinely recommended for infants and young children.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Talk with your health care provider

Tell your health care provider if the person getting the preventive antibody has a:

- History of serious allergic reactions to an RSV preventive antibody (nirsevimab) or any of its components,
- Bleeding disorder, or
- Moderate or severe acute illness.

In some cases, your child's health care provider may decide to postpone giving RSV preventive antibodies until a future visit.

People who have a minor illness, such as a cold, can safely receive an RSV preventive antibody. People who are moderately or severely ill should usually wait until they recover.

Your health care provider can give you more information.

Risks of a reaction to RSV preventive antibodies

After getting an RSV preventive antibody, your child might have temporary pain, redness, swelling where the injection was given, or a rash.

As with any medicine, there is a very remote chance that RSV Immunization could cause a severe allergic reaction, other serious injury, or death.

An allergic reaction could occur after your child leaves the hospital or clinic. If you see signs of a severe allergic reaction (for example, hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, or weakness), call 9-1-1 and get your child to the nearest hospital.

Call your health care provider if you see any other symptoms that concern you.

What if there is a serious problem?

If your child got an RSV preventive antibody without getting a vaccine at the same time, and you suspect an adverse reaction, you or your health care provider can submit a report through https://www.fda.gov/medwatch or by phone at 1-800-FDA-1088.

If your child got an RSV preventive antibody and a vaccine at the same time and you suspect an adverse reaction, you or your health care provider should report it to the Vaccine Adverse Event Reporting System (VAERS) https://vaers.hhs.gov/ or call 1-800-822-7967. In your report, note that your child got an RSV Immunization along with a vaccine.

Note: MedWatch and VAERS are only for reporting reactions. MedWatch and VAERS staff members do not give medical advice.

How can I learn more?

- Ask your health care provider.
- Call your local or state health department.
- Visit U.S. Food and Drug Administration website at Drugs@FDA: FDA-Approved Drugs.
- Contact the Centers for Disease Control and Prevention (CDC):
  - Call 1-800-232-4636 (1-800-CDC-INFO) or
  - Visit the CDC website https://www.cdc.gov/rsv/about/prevention.html

This is an official

CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
October 23, 2023, 3:30 PM ET
CDCHAN-00499

Limited Availability of Nirsevimab in the United States—Interim CDC Recommendations to Protect Infants from Respiratory Syncytial Virus (RSV) during the 2023–2024 Respiratory Virus Season

Summary
The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Advisory to provide options for clinicians to protect infants from respiratory syncytial virus (RSV) in the context of a limited supply of nirsevimab, a long-acting monoclonal antibody immunization product recommended for preventing RSV-associated lower respiratory tract disease in infants.

In the context of limited supply during the 2023–2024 RSV season, CDC recommends prioritizing available nirsevimab 100mg doses for infants at the highest risk for severe RSV disease: young infants (age <6 months) and infants with underlying conditions that place them at highest risk for severe RSV disease. Recommendations for using 50mg doses remain unchanged at this time. Avoid using two 50mg doses for infants weighing ≥5 kilograms (≥11 pounds) to preserve supply of 50mg doses for infants weighing <5 kilograms (<11 pounds). Providers should be aware that some insurers may not cover the cost of two 50mg doses for an individual infant.

CDC further recommends that providers suspend using nirsevimab in palivizumab-eligible children aged 8–19 months for the 2023–2024 RSV season. These children should receive palivizumab per American Academy of Pediatrics (AAP) recommendations. Nirsevimab should continue to be offered to American Indian and Alaska Native children aged 8–19 months who are not palivizumab-eligible and who live in remote regions, where transporting children with severe RSV for escalation of medical care is more challenging or in communities with known high rates of RSV among older infants and toddlers. Prenatal care providers should discuss potential nirsevimab supply concerns when counseling pregnant people about RSVpreF vaccine (Abrysvo, Pfizer) as maternal vaccination is effective and will reduce the number of infants requiring nirsevimab during the RSV season.

Background
RSV is a common cause of respiratory infection in U.S. infants, most of whom are infected with RSV during their first year of life (*1, 2*). RSV is the leading cause of hospitalization among U.S. infants *(3)*. The highest incidence of RSV-associated hospitalization occurs in infants aged <3 months and then decreases with increasing age (*4*). Because of the high incidence of severe RSV disease in the first months of life, RSV prevention products focus on passive immunization of young infants through maternal immunization or immunoprophylaxis with monoclonal antibodies.

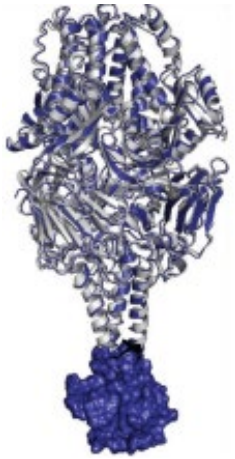
In July 2023, the Food and Drug Administration (FDA) approved nirsevimab (Beyfortus™, Sanofi and AstraZeneca), a long-acting monoclonal antibody, for passive immunization to prevent RSV-associated lower respiratory tract disease among infants and young children. On August 3, 2023, CDC's Advisory Committee on Immunization Practices (ACIP) recommended nirsevimab for all infants aged <8 months who are born during or entering their first RSV season and for infants and children aged 8–19 months who are at increased risk for severe RSV disease and are entering their second RSV season (*5*). The recommended dosing of nirsevimab for infants weighing <5 kilograms (kg) (<11 pounds (lb)) is 50mg. For infants aged <8 months weighing ≥5 kg (≥11 lb), the recommended dose is 100mg. For infants aged 8–19 months at increased risk of severe RSV disease entering their second season, the recommended dose is

CDC: During nirsevimab shortage, prioritize infants at risk, encourage maternal vaccination

ORIGINAL ARTICLE

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

B. Kampmann, S.A. Madhi, I. Munjal, E.A.F. Simões, B.A. Pahud, C. Llapur, J. Baker, G. Pérez Marc, D. Radley, E. Shittu, J. Glanternik, H. Snaggs, J. Baber, P. Zachariah, S.L. Barnabas, M. Fausett, T. Adam, N. Perreras, M.A. Van Houten, A. Kantele, L.-M. Huang, L.J. Bont, T. Otsuki, S.L. Vargas, J. Gullam, B. Tapiero, R.T. Stein, F.P. Polack, H.J. Zar, N.B. Staerke, M. Duron Padilla, P.C. Richmond, K. Koury, K. Schneider, E.V. Kalinina, D. Cooper, K.U. Jansen, A.S. Anderson, K.A. Swanson, W.C. Gruber, and A. Gurtman, for the MATISSE Study Group*



ABSTRACT

BACKGROUND

Whether vaccination during pregnancy could reduce the burden of respiratory syncytial virus (RSV)–associated lower respiratory tract illness in newborns and infants is uncertain.

METHODS

In this phase 3, double-blind trial conducted in 18 countries, we randomly assigned, in a 1:1 ratio, pregnant women at 24 through 36 weeks' gestation to receive a single intramuscular injection of 120 μg of a bivalent RSV prefusion F protein–based (RSVpreF) vaccine or placebo. The two primary efficacy end points were medically attended severe RSV-associated lower respiratory tract illness and medically attended RSV-associated lower respiratory tract illness in infants within 90, 120, 150, and 180 days after birth. A lower boundary of the confidence interval for vaccine efficacy (99.5% confidence interval [CI] at 90 days; 97.58% CI at later intervals) greater than 20% was considered to meet the success criterion for vaccine efficacy with respect to the primary end points.

RESULTS

At this prespecified interim analysis, the success criterion for vaccine efficacy was met with respect to one primary end point. Overall, 3682 maternal participants received vaccine and 3676 received placebo; 3570 and 3558 infants, respectively, were evaluated. Medically attended severe lower respiratory tract illness occurred within 90 days after birth in 6 infants of women in the vaccine group and 33 infants of women in the placebo group (vaccine efficacy, 81.8%; 99.5% CI, 40.6 to 96.3); 19 cases and 62 cases, respectively, occurred within 180 days after birth (vaccine efficacy, 69.4%; 97.58% CI, 44.3 to 84.1). Medically attended RSV-associated lower respiratory tract illness occurred within 90 days after birth in 24 infants of women in the vaccine group and 56 infants of women in the placebo group (vaccine efficacy, 57.1%; 99.5% CI, 14.7 to 79.8); these results did not meet the statistical success criterion. No safety signals were detected in maternal participants or in infants and toddlers up to 24 months of age. The incidences of adverse events reported within 1 month after injection or within 1 month after birth were similar in the vaccine group (13.8% of women and 37.1% of infants) and the placebo group (13.1% and 34.5%, respectively).

CONCLUSIONS

RSVpreF vaccine administered during pregnancy was effective against medically attended severe RSV-associated lower respiratory tract illness in infants, and no safety concerns were identified. (Funded by Pfizer; MATISSE ClinicalTrials.gov number, NCT04424316.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Munjal can be contacted at iona.munjal@pfizer.com or at Vaccine Research and Development, Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965.

*The members of the MATISSE Study Group are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Kampmann, Madhi, and Munjal contributed equally to this article.

This article was published on April 5, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2216480

Burden of RSV in Pregnancy

J Infect Dis, 2023

- Among 8126 pregnant women, the proportion with respiratory infections that tested (+) for RSV was 3.4%
- Incidence → 26 per 1000 person years
- Hospitalization → 2.7 per 1000 person years
- No deaths
- Comparing RSV (+) to RSV (-) women, no differences in miscarriage, stillbirth, LBW or SGA

Maternal RSV Vaccination

- Prefusion F vaccines developed by both Pfizer and GSK
- Trials enrolled women from 24 to 36 weeks gestation
- Both GSK and Pfizer vaccine trials showed non-significant increases in preterm deliveries in vaccinees vs placebo recipients
  - Low to middle income countries
  - Uncertain mechanism
  - GSK abandoned research program
- Only Pfizer’s vaccine FDA approved and recommended by CDC

Abrysvo for Pregnant Women

- Placebo-controlled trial involving 7392 pregnant women
- Efficacy against infant RSV hospitalization:
  - 68% at 90 days
  - 57% at 180 days
- Minimal maternal side effects
- No infant adverse effects
  - Other than ***possible*** preterm birth

Use of the Pfizer Respiratory Syncytial Virus Vaccine During Pregnancy for the Prevention of Respiratory Syncytial Virus–Associated Lower Respiratory Tract Disease in Infants: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023

Katherine E. Fleming-Dutra, MD[1,*]; Jefferson M. Jones, MD[1,*]; Lauren E. Roper, MPH[1]; Mila M. Prill, MSPH[1]; Ismael R. Ortega-Sanchez, PhD[1]; Danielle L. Moulia, MPH[1]; Megan Wallace, DRPH[1]; Monica Godfrey, MPH[1]; Karen R. Broder, MD[2]; Naomi K. Tepper, MD[3]; Oliver Brooks, MD[4]; Pablo J. Sánchez, MD[5]; Camille N. Kotton, MD[6]; Barbara E. Mahon, MD[1]; Sarah S. Long, MD[7]; Meredith L. McMorrow, MD[1]

On October 6, 2023, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.cdc.gov/mmwr).*

Abstract

Respiratory syncytial virus (RSV) is the leading cause of hospitalization among U.S. infants. Nirsevimab (Beyfortus, Sanofi and AstraZeneca) is recommended to prevent RSV-associated lower respiratory tract infection (LRTI) in infants. In August 2023, the Food and Drug Administration (FDA) approved RSVpreF vaccine (Abrysvo, Pfizer Inc.) for pregnant persons as a single dose during 32–36 completed gestational weeks (i.e., 32 weeks and zero days through 36 weeks and 6 days gestation) to prevent RSV-associated lower respiratory tract disease in infants aged <6 months. Since October 2021, CDC's Advisory Committee on Immunization Practices (ACIP) RSV Vaccines Pediatric/Maternal Work Group has reviewed RSV epidemiology and evidence regarding safety, efficacy, and potential economic impact of pediatric and maternal RSV prevention products, including RSVpreF vaccine. On September 22, 2023, ACIP and CDC recommended RSVpreF vaccine using seasonal administration (i.e., during September through end of January in most of the continental United States) for pregnant persons as a one-time dose at 32–36 weeks' gestation for prevention of RSV-associated LRTI in infants aged <6 months. Either maternal RSVpreF vaccination during pregnancy or nirsevimab administration to the infant is recommended to prevent RSV-associated LRTI among infants, but both are not needed for most infants. All infants should be protected against RSV-associated LRTI through use of one of these products.

Introduction

In August 2023, the Food and Drug Administration (FDA) approved RSVpreF vaccine (Abrysvo, Pfizer Inc.) for pregnant persons to prevent RSV-associated lower respiratory tract disease and severe lower respiratory tract disease in infants aged <6 months (*1*,*2*). The Pfizer bivalent RSVpreF vaccine, which is the same formulation and dose approved for use in adults aged ≥60 years, contains stabilized prefusion F glycoproteins from RSV A and RSV B and is approved as a single 0.5 mL intramuscular dose administered during 32 through 36 weeks' gestation.

In clinical trials among pregnant persons at 24–36 weeks' gestation, more preterm births (<37 weeks' gestation) were observed among RSVpreF vaccine recipients than placebo recipients, although the differences were not statistically significant (*1*,*2*). Available data were insufficient to establish or exclude a causal relationship between preterm birth and RSVpreF vaccine. FDA labeled the potential risk for preterm birth as a warning and approved RSVpreF vaccine for use in pregnant persons at 32–36 weeks' gestation to avoid the potential risk for preterm birth at <32 weeks' gestation, which is associated with increased risk for morbidity and mortality (*2*). More hypertensive disorders of pregnancy were observed among RSVpreF vaccine recipients compared with placebo recipients, although the differences were not statistically significant. FDA determined that, when RSVpreF is administered during 32–36 weeks' gestation, the benefit of vaccination in preventing RSV-associated LRTI in infants outweighed risks, including the potential risk for preterm birth and hypertensive disorders of pregnancy (*1*,*2*).

On August 3, 2023, CDC's Advisory Committee on Immunization Practices (ACIP) and CDC recommended nirsevimab (Beyfortus, Sanofi and AstraZeneca), a long-acting monoclonal antibody for prevention of severe RSV disease, for infants aged <8 months who are born during or entering their first RSV season and for children aged 8–19 months at increased risk for severe RSV disease entering their second RSV season (*3*). On September 22, 2023, ACIP and CDC recommended RSVpreF vaccine for pregnant persons as a one-time dose during 32–36 completed weeks' gestation using seasonal administration (September–January in most of the continental United States) to prevent RSV-associated lower respiratory tract infection (LRTI) in infants. Either maternal RSVpreF vaccination during pregnancy or nirsevimab administration to the infant is recommended to prevent RSV-associated LRTI in infants, but both are not needed for most infants. This report describes new recommendations for the use of maternal RSVpreF during pregnancy

*These authors contributed equally to this report.

Vaccinations Needed During Pregnancy

The table below shows which vaccinations you may or may not need during your pregnancy.

Vaccine	Do you need it during your pregnancy?
COVID-19	***Yes!*** All adults, including those who are pregnant and people who have had COVID-19 illness, are recommended to be up to date with COVID-19 vaccinations. It's safe to get the vaccine at any time during your pregnancy.
Influenza (Flu)	***Yes!*** You need a flu shot every fall or winter for your protection and for the protection of your baby. It's safe to get the vaccine at any time during your pregnancy.
Tetanus, diphtheria, and whooping cough (Tdap; Td)	***Yes!*** Everyone who is pregnant is recommended to get a dose of Tdap vaccine (the adult whooping cough vaccine) during ***each*** pregnancy, preferably in the early part of the third trimester. Tdap vaccine during pregnancy will help protect your baby from whooping cough in the first few months after birth. Consult your healthcare professional if you haven't had at least 3 tetanus- and diphtheria-toxoid containing shots sometime in your life or if you have a deep or dirty wound.
Hepatitis B (HepB)	***Yes!*** All adults younger than 60 years, including those who are pregnant, should get HepB vaccine if they are not already immune. If vaccination is needed during pregnancy, Engerix-B, Recombivax HB, or Twinrix (combination with hepatitis A vaccine) may be used. Any HepB vaccine may be used while breastfeeding. A screening blood test for hepatitis B infection is recommended during every pregnancy, regardless of vaccination status.
Respiratory Syncytial Virus (RSV)	***Yes!*** To prevent serious RSV illness in infants, either the Pfizer RSV vaccine (Abrysvo) should be given between 32 weeks, 0 days and 36 weeks and 6 days of pregnancy ***OR*** a dose of nirsevimab (RSV preventive antibody) should be given to the infant after birth. RSV vaccination during pregnancy is generally offered only between September and the end of January.
Pneumococcal PPSV23; PCV15; PCV20	***Maybe.*** If you are at increased risk of severe illness from pneumococcal disease, your healthcare professional might recommend pneumococcal vaccination during pregnancy or recommend waiting until after pregnancy. If you inadvertently get a pneumococcal vaccine during your pregnancy, this is not a cause for concern.
Hepatitis A (HepA)	***Maybe.*** You need this vaccine if you have a specific risk factor for hepatitis A.* The vaccine is usually given in 2 doses, 6–18 months apart. If you need to get or continue the HepA vaccine series, it's safe to do so during pregnancy.
Haemophilus influenzae type b (Hib)	***Maybe.*** Some adults with certain high-risk conditions,* for example, lack of a functioning spleen, need vaccination with Hib. If you need to get Hib vaccine, it's safe to receive it at any time during your pregnancy.
Meningococcal ACWY (MenACWY)	***Maybe.*** You need MenACWY if you are a first-year college student living in a residence hall and (1) you have not had a dose since turning 16, or (2) it has been more than 5 years since your last dose. Anyone age 19 through 21 can have a catch-up dose if they have not had one since turning 16. You may also need MenACWY vaccine if you have one of several health conditions,* for example, if you don't have a spleen. During pregnancy, if you need MenACWY, it is safe to get it.
Meningococcal B (MenB)	***Maybe.*** You need MenB if you have one of several health conditions,* for example, if you do not have a functioning spleen. You may also get MenB vaccine if you are age 23 or younger (even if you don't have a high-risk medical condition) after a discussion with your healthcare professional. Because no studies have been conducted on MenB vaccine in pregnancy, talk with your healthcare professional to determine if the benefits of vaccination outweigh the potential risks.
Human papillomavirus (HPV)	***No.*** This vaccine is not recommended to be given during pregnancy, but if you inadvertently receive it, this is not a cause for concern. HPV vaccine is recommended for all people age 26 or younger, so if you are in this age group, make sure you are vaccinated before or after your pregnancy. People age 27 through 45 may also be vaccinated against HPV after a discussion with their healthcare professional. The vaccine is given in 2 or 3 doses (depending on the age at which the first dose is given) over a 6-month period.
Measles, mumps, rubella (MMR)	***No.*** MMR vaccine is not recommended during pregnancy, but if you inadvertently get it, this is not a cause for concern. At least 1 dose of MMR is recommended for you if you were born in 1957 or later. (And you may need a 2nd dose.*) During your prenatal care, your healthcare professional will test your blood to assess your need for MMR following your delivery. It's best for you (and any future baby) to get the protection vaccination provides before trying to become pregnant.
Chickenpox (Varicella; Var)	***No.*** Varicella vaccine is not recommended to be given during pregnancy, but if you inadvertently get it, this is not a cause for concern. If you've never had chickenpox, never were vaccinated, or were vaccinated but got only 1 dose, it's best for you (and any future baby) to be protected with the vaccine before trying to become pregnant, or after you've completed your pregnancy. The vaccine is given in 2 doses 4–8 weeks apart.
Zoster (Shingles)	***No.*** If you are age 50 or older or, if you are age 19–49 years and immunocompromised, you are recommended to get the 2-dose series of the Shingrix brand of shingles vaccine. But, since the safety of Shingrix vaccine during pregnancy is unknown, talk with your healthcare professional to determine if the benefits of Shingrix vaccination during pregnancy outweigh the potential risks.

*Consult your healthcare professional to determine your level of risk for infection and your need for this vaccine.

Immunize.org

ACOG
The American College of Obstetricians and Gynecologists

FOR PROFESSIONALS www.immunize.org / **FOR THE PUBLIC** www.vaccineinformation.org

www.immunize.org/catg.d/p4040.pdf
Item #P4040 (11/3/2023)

RSV – Yes!

To prevent serious RSV illness in infants, either the Pfizer RSV vaccine (Abrysvo) should be given between 32 weeks, 0 days and 36 weeks and 6 days of pregnancy OR a dose of nirsevimab (RSV preventive antibody) should be given to the infant after birth. RSV vaccination during pregnancy is generally offered only between September and the end of January.

NB: GSK vaccine should not be used

RSV – Yes!

To prevent serious RSV illness in infants, either the Pfizer RSV vaccine (Abrysvo) should be given between 32 weeks, 0 days and 36 weeks and 6 days of pregnancy OR a dose of nirsevimab (RSV preventive antibody) should be given to the infant after birth. RSV vaccination during pregnancy is generally offered only between September and the end of January.

Given in this time window, cost will be $167,280 per QALY saved.

RSV Vaccination for Pregnant People

CDC recommends two ways to protect babies from getting very sick with Respiratory Syncytial Virus (RSV):

- An RSV vaccination given during pregnancy
  Pfizer's bivalent RSVpreF vaccine (Abrysvo) is recommended for use during pregnancy (maternal RSV vaccine). It is given during RSV season to people who are 32 through 36 weeks pregnant. **Or,**

- An RSV immunization given directly to infants and some older babies

Babies born to mothers who get RSV vaccine at least 2 weeks before delivery will have protection and, in most cases, should not need an RSV immunization later.

When is RSV season?

In most regions of the United States RSV season starts in the fall and peaks in the winter, but the timing and severity of RSV season can vary from place to place and year to year. RSV season is likely to be different for people living in Alaska, parts of Florida, Hawaii, Puerto Rico, US Virgin Islands, Guam, and the U.S.-affiliated Pacific Islands.

The goal of maternal RSV vaccination is to protect babies from getting very sick with RSV during their first RSV season. In most of the continental United States, this means maternal RSV vaccine will be given in September through January.

If you live in Alaska, Florida, or outside the continental U.S., talk to your healthcare provider about when RSV season is expected where you live, so that your infant can be protected against RSV disease.

Who should get the maternal RSV vaccine?

People who are 32 through 36 weeks pregnant during September through January should get one dose of maternal RSV vaccine to protect their babies. RSV season can vary around the country. If you live in Alaska, Florida, or outside the continental U.S., talk to your healthcare provider about when RSV season is expected where you live.

How is the maternal RSV vaccine administered?

Maternal RSV vaccine is given as a shot into the mother's upper arm. Only a single dose (one shot) of maternal RSV vaccine is recommended. It is not yet known whether another dose might be needed in later pregnancies.

How well does the maternal RSV vaccine work?

When someone gets RSV vaccine, their body responds by making a protein that protects against the virus that causes RSV. The process takes about 2 weeks. When a pregnant person gets RSV vaccine, their protective proteins (called antibodies) also pass to their baby. So, babies who are born at least 2 weeks after their mother gets RSV vaccine are protected at birth, when infants are at the highest risk of severe RSV disease. The vaccine can reduce a baby's risk of being hospitalized from RSV by 57% in the first six months after birth.

What are the possible side effects of the maternal RSV vaccine?

In the clinical trials, the side effects most often reported by pregnant people who received the maternal RSV vaccine were pain at the injection site, headache, muscle pain, and nausea.

Although not common, a dangerous high blood pressure condition called pre-eclampsia occurred in 1.8% of pregnant people who received the maternal RSV vaccine compared to 1.4% of pregnant people who received a placebo.

The clinical trials identified a small increase in the number of preterm births in vaccinated pregnant people. It is not clear if this is a true safety problem related to RSV vaccine or if this occurred for reasons unrelated to vaccination.

To reduce the potential risk of preterm birth and complications from RSV disease, FDA approved the maternal RSV vaccine for use during weeks 32 through 36 of pregnancy while additional studies are conducted.

FDA is requiring the manufacturer to do additional studies that will look more closely at the potential risk of preterm births and pregnancy-related high blood pressure issues in mothers, including pre-eclampsia.

Severe allergic reactions to vaccines are rare but can happen after any vaccine and can be life-threatening. If you see signs of a severe allergic reaction after vaccination (hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, or weakness), seek immediate medical care by calling 911. As with any medicine or vaccine there is a very remote chance of the vaccine causing other serious injury or death after vaccination.

Adverse events following vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS), even if it's not clear that the vaccine caused the adverse event. You or your doctor can report an adverse event to CDC and FDA through VAERS. If you need further assistance reporting to VAERS, please email info@VAERS.org or call 1-800-822-7967.

If you have any questions about side effects from the maternal RSV vaccine, talk with your healthcare provider.

Do I need a prescription for a maternal RSV vaccine?

Depending on where you live and where you go to get the vaccine, you might need a prescription. See CDC's Where to Find Vaccines for information on prescriptions for vaccines.

Important Details Regarding Maternal RSV Vaccine

- Recommended to prevent RSV disease in infant, not necessarily mother
- Approved by ChristianaCare P&T and available for distribution to practices
- IM injection for mom vs IM injection for baby
- Cost of Abrysvo $250 vs $495 for nirsevimab
- Counseling about both options (maternal vaccine and mAb) should be provided during pregnancy
- Important to document maternal vaccination for the purposes of management of infant (shot of nirsevimab or not)

Active RSV Vaccines for Infants

- Many challenges to overcome
  - Hauntings from the 1960s FI-RSV vaccine – must not result in enhanced RSV disease
  - Possible suppression of immune response by maternal antibody
  - Must protect against antigenically distinct strains
- Live attenuated RSV vaccines currently being developed and tested
  - Some insufficiently attenuated for use in young infants

Pursuing Infant RSV Vaccine

- Phase 1/2 study
- 82 toddlers
- GSK chimpanzee-derived adenovirus vector expressing 3 RSV proteins
- Well tolerated
- Immunogenic

- Infant study underway

The Journal of Infectious Diseases
MAJOR ARTICLE

Safety and Immunogenicity of a ChAd155-Vectored Respiratory Syncytial Virus (RSV) Vaccine in Healthy RSV-Seropositive Children 12–23 Months of Age

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Background. Safe and effective respiratory syncytial virus (RSV) vaccines remain elusive. This was a phase I/II trial (NCT02927873) of ChAd155-RSV, an investigational chimpanzee adenovirus-RSV vaccine expressing 3 proteins (fusion, nucleoprotein, and M2-1), administered to 12–23-month-old RSV-seropositive children followed up for 2 years after vaccination.

Methods. Children were randomized to receive 2 doses of ChAd155-RSV or placebo (at a 1:1 ratio) (days 1 and 31). Doses escalated from 0.5×10^{10} (low dose [LD]) to 1.5×10^{10} (medium dose [MD]) to 5×10^{10} (high dose [HD]) viral particles after safety assessment. Study end points included anti–RSV-A neutralizing antibody (Nab) titers through year 1 and safety through year 2.

Results. Eighty-two participants were vaccinated, including 11, 14, and 18 in the RSV-LD, RSV-MD, and RSV-HD groups, respectively, and 39 in the placebo groups. Solicited adverse events were similar across groups, except for fever (more frequent with RSV-HD). Most fevers were mild (≤38.5°C). No vaccine-related serious adverse events or RSV-related hospitalizations were reported. There was a dose-dependent increase in RSV-A Nab titers in all groups after dose 1, without further increase after dose 2. RSV-A Nab titers remained higher than prevaccination levels at year 1.

Conclusions. Three ChAd155-RSV dosages were found to be well tolerated. A dose-dependent immune response was observed after dose 1, with no observed booster effect after dose 2. Further investigation of ChAd155-RSV in RSV-seronegative children is warranted.

Clinical Trials Registration. NCT02927873.

Keywords. immunogenicity; neutralizing antibodies; respiratory syncytial virus; safety; vaccine.

Lay summary. Respiratory syncytial virus (RSV) is among the main causes of bronchiolitis and pneumonia regularly leading to hospitalization in children. A safe and effective vaccine to prevent RSV infection in this age group has not yet been found, despite great efforts over several decades. This study tested a new candidate RSV vaccine, expressing 3 important pieces of the virus, in toddlers who already had a previous RSV infection. The vaccine was generally well tolerated. Vaccination triggered antibodies against RSV that were able to block the virus in laboratory tests and that persisted for 1 year.

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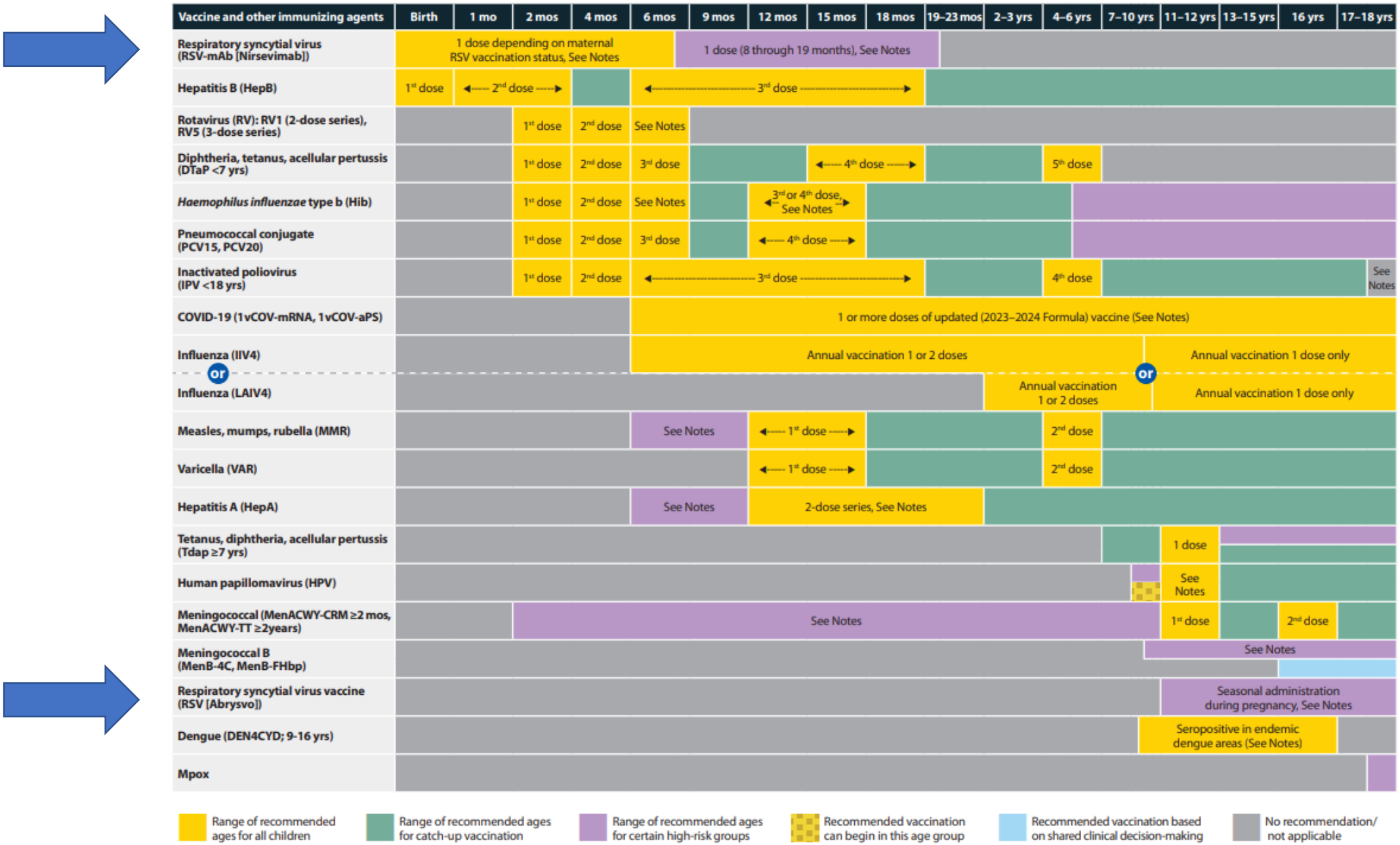
Table 1 Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2024

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars.
To determine minimum intervals between doses, see the catch-up schedule (Table 2).



GET THE FACTS

COVID-19, Flu and RSV in Children

In the US, more than **15 million children** have tested positive for COVID-19 since the start of the pandemic. But COVID-19 isn't the only infection we need to look out for.

COVID-19

Caused **22,000 hospitalizations** and **800 deaths** in children since 2020

FLU

Caused **20,000 hospitalizations** and **100 deaths in children** last year

RSV

Causes **58,000-80,000 hospitalizations** and **100-300 deaths** in children each year

FACT: **Vaccines can protect children and their families against all of these severe infections.**

Protect your home against unwanted 'intruders' this season by getting vaccinated.

Go to vaccines.gov to check your eligibility for vaccines and to find vaccine appointments near you.

For more information on vaccines, visit:
COVID19LearningNetwork.org

COVID-19 Real-Time Learning Network
Brought to you by CDC and IDSA

AAFP · American College of Emergency Physicians · ATS · PIDS · Society of Critical Care Medicine · shm Society of Hospital Medicine · SIDP

10/30/2023