Respiratory Syncytial Virus (RSV)

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ECHO
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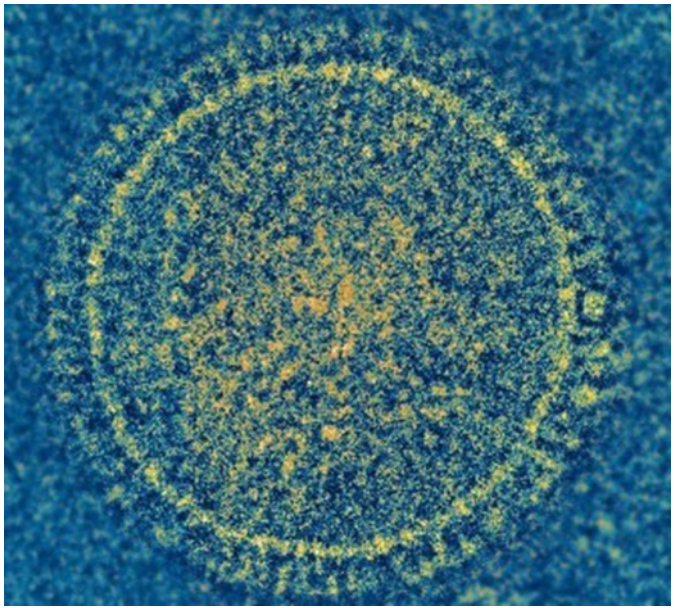


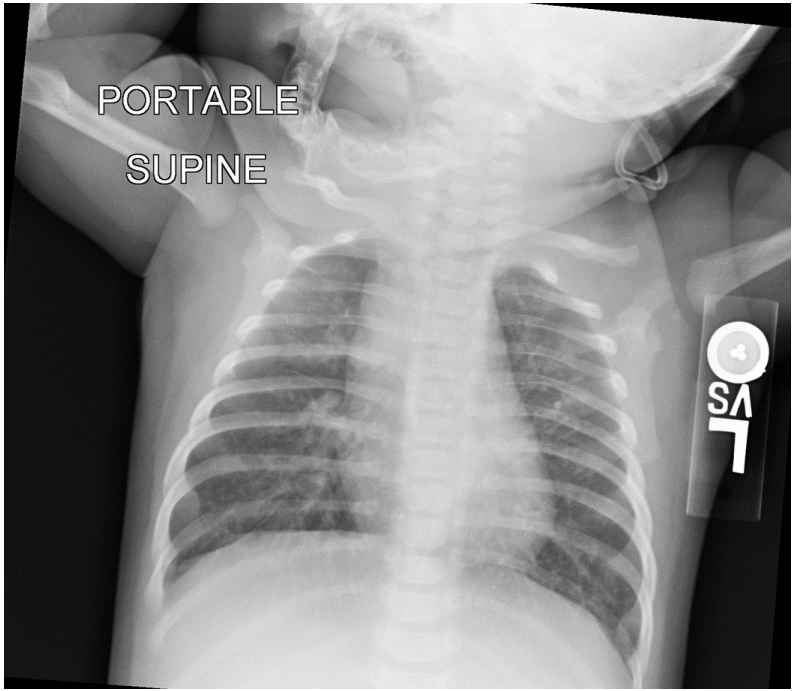
The Speaker has no disclosures and will be mentioning non-FDA approved vaccines in development.

The speaker is a federal employee but all views expressed are his own and do not represent views of the federal government.

Immunization schedules for 2024 are draft as presented at the October 2023 ACIP public meeting – subject to modification prior to February 2024 publication (MMWR)

Case

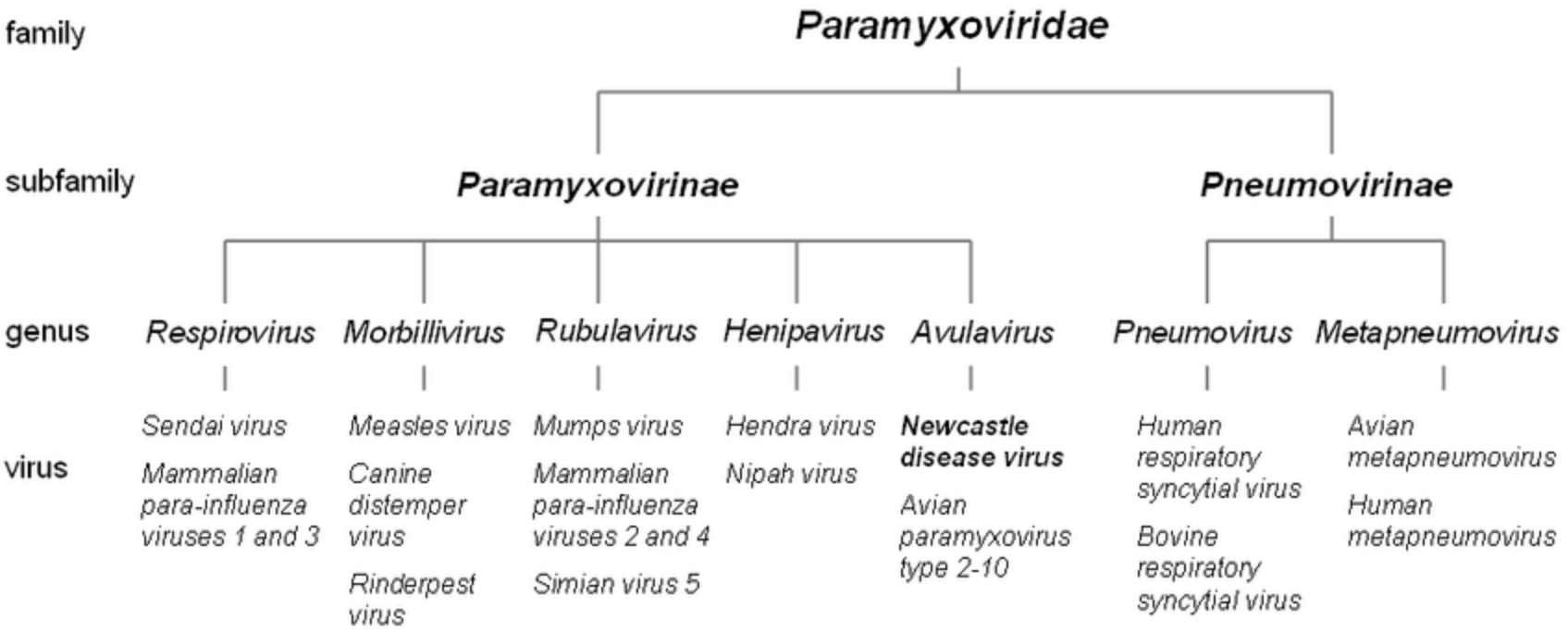
5.25 kg, T=36.6, RR = 67, P=216, O2 sat 67% RA
Alert, irritable, rapidly breathing with retractions. Exam with bilateral course breath sounds, no wheeze, otherwise non contributory.
SARS-CoV2/RSV/FluA/FluB – NP PCR sent
Helicopter called…..



Upon further review

Grandmother watches the child while mom works.

Grandmother is a 67 year old woman with anemia, hypertension, and type 2 diabetes who has never smoked. She notes that she has had a cough, runny nose and decreased energy and exercise tolerance for the past 5 days.


family
Paramyxoviridae
subfamily
Paramyxovirinae
Pneumovirinae
genus
Respirovirus
Morbillivirus
Rubulavirus
Henipavirus
Avulavirus
Pneumovirus
Metapneumovirus
virus
Sendai virus
Mammalian para-influenza viruses 1 and 3
Measles virus
Canine distemper virus
Rinderpest virus
Mumps virus
Mammalian para-influenza viruses 2 and 4
Simian virus 5
Hendra virus
Nipah virus
Newcastle disease virus
Avian paramyxovirus type 2-10
Human respiratory syncytial virus
Bovine respiratory syncytial virus
Avian metapneumovirus
Human metapneumovirus

Inactivated RSV Vaccine – 1960s

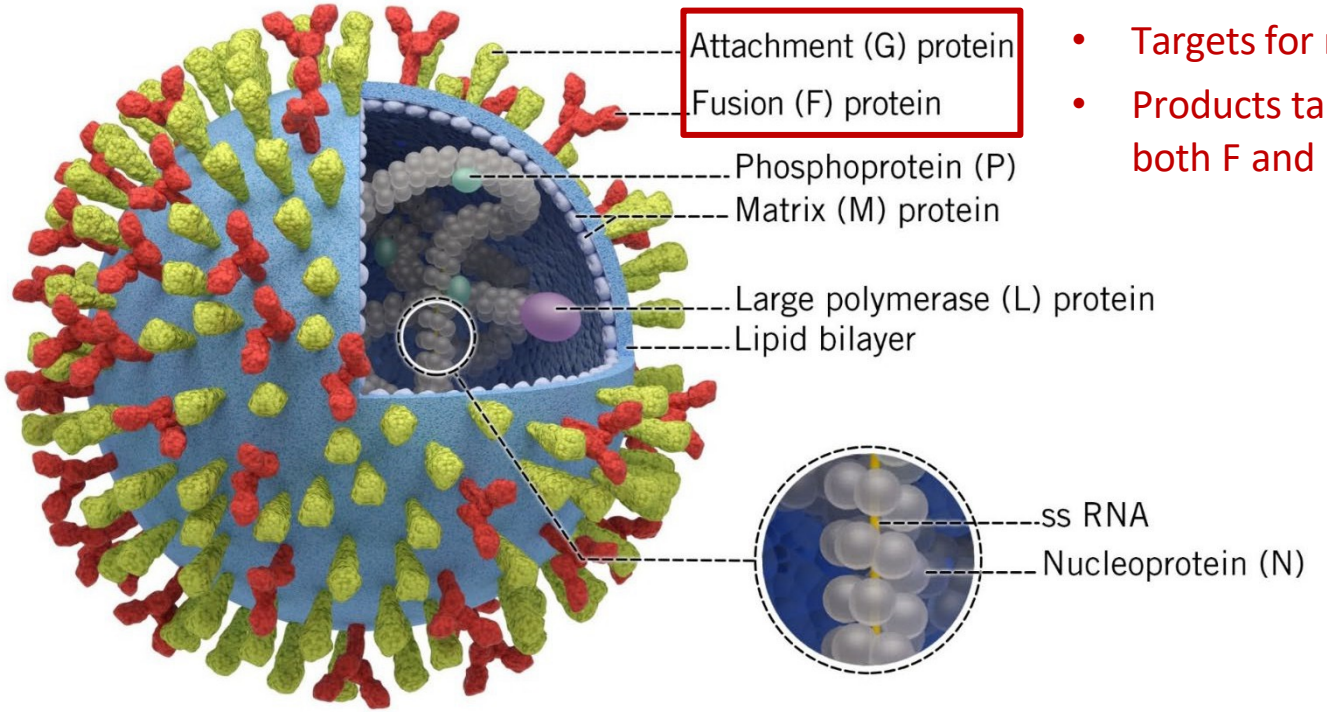
- Early trials with formalin-inactivated RSV vaccine led to enhanced disease in recipients.
- Two deaths in vaccinated children

Fulginiti VA, Eller JJ, Sieber OF, et al. Respiratory virus immunization I. A field trial of two inactivated respiratory virus vaccines an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. *Am. J. Epidemiol.* 1969;89:435–448.

Chin J, Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. *Am. J. Epidemiol.* 1969;89:449–463.

Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. *Am. J. Epidemiol.* 1969;89:405–421.

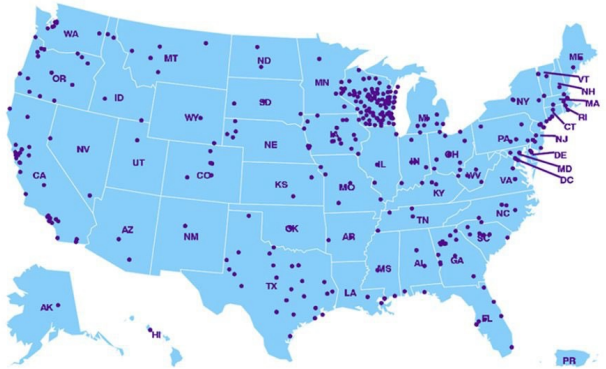
RSV – virion structure



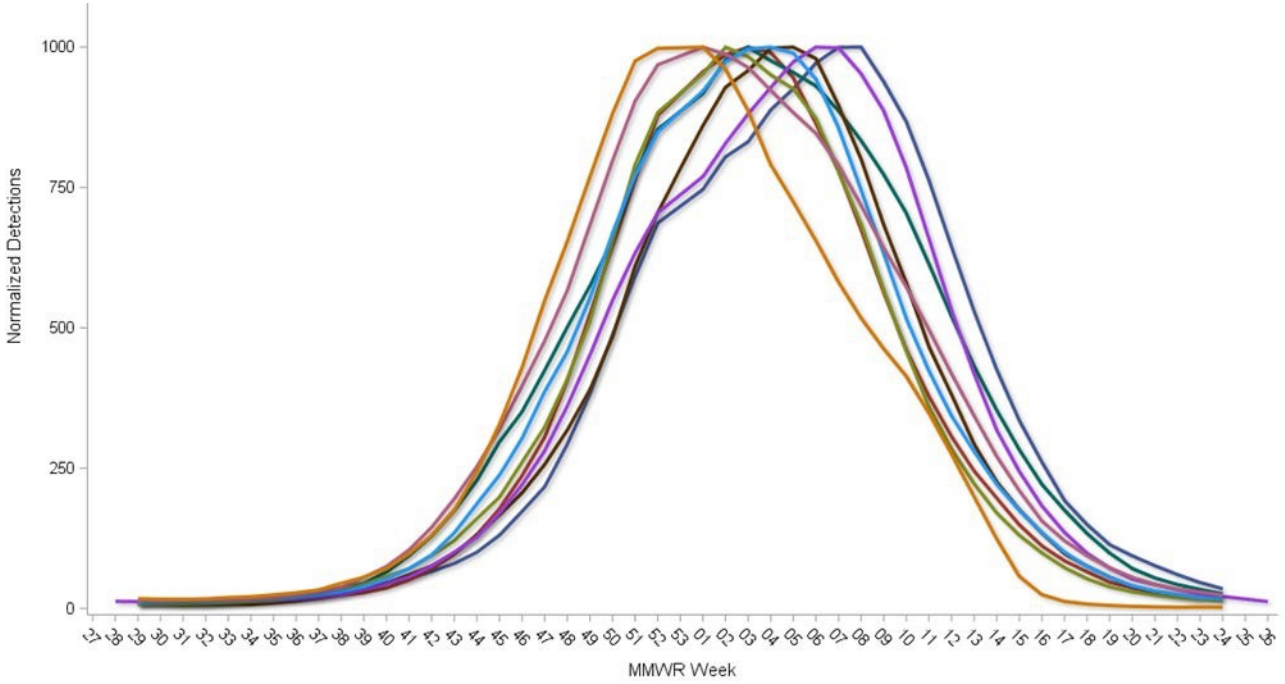
- Targets for neutralizing antibodies
- Products target F alone or have both F and G

National Respiratory and Enteric Virus Surveillance System (NREVSS) for monitoring RSV seasonality

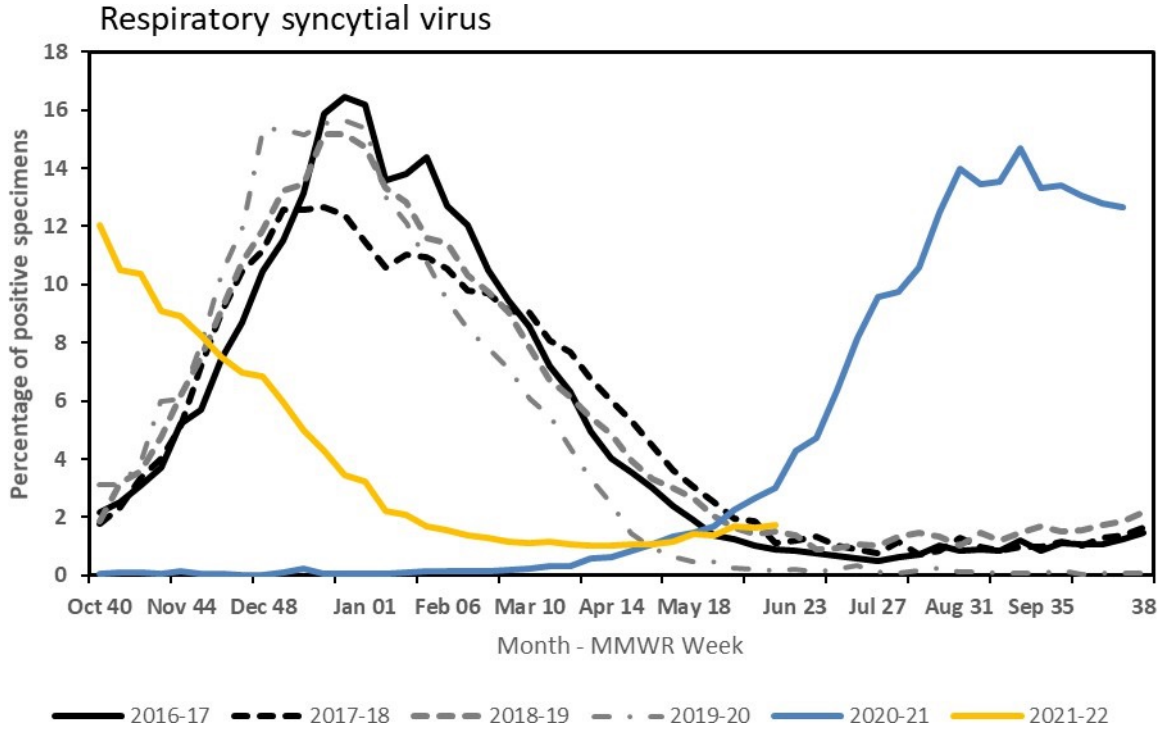
- Passive, laboratory-based surveillance
  - Commercial, hospital, and state/local public health laboratories
  - ~300 laboratories report RSV results
  - Weekly reporting of total tests performed and RSV positive tests
- All test types (majority PCR assays)
- Testing is clinician-directed
- All ages



During 2011-2020, RSV circulation was highly seasonal in the U.S. with predictable peak activity during December – February annually



Following over 1 year of limited RSV circulation, the U.S. experienced an intraseasonal RSV wave that peaked in early August 2021



The burden of RSV in U.S. children

RSV is the leading cause of hospitalization in U.S. infants

- Most (68%) infants are infected in the first year of life and nearly all (97%) by age 2[1]
- Premature infants born at <30 weeks gestation had hospitalization rates ~3x higher than term infants[2]
  - Preterm infants have higher rates of ICU admission, mechanical ventilation[3]
  - Average cost of hospitalization in infant <29 weeks ~4x higher than for term infant[3]
- 79% of children hospitalized with RSV aged <2 years had no underlying medical conditions[2]
- 2-3% of all infants will be hospitalized for RSV[2,4]

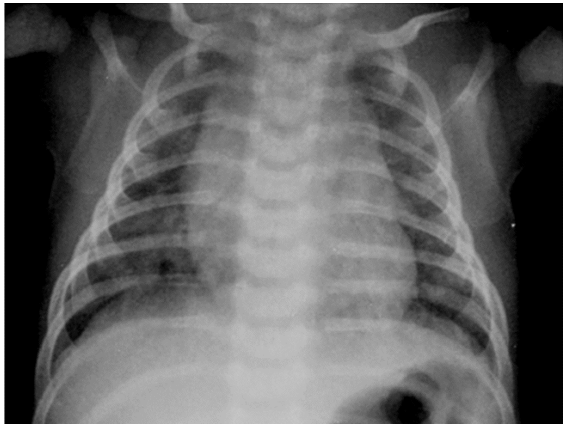
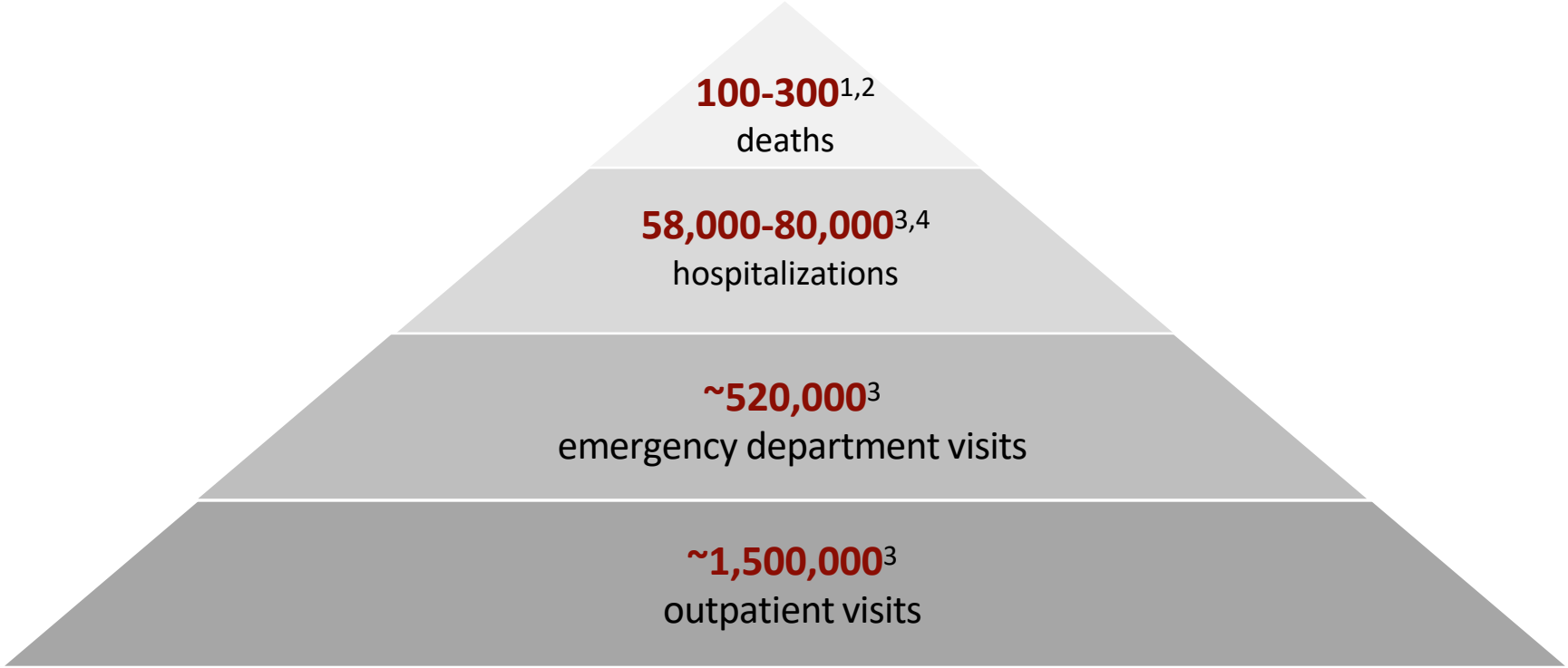


Image: Goncalves et al. Critical Care Research and Practice 2012

[1]Glezen et al, Arch Dis Child, 1986; [2]Hall et al, Pediatrics, 2013; [3]McLaurin et al, J Perinatol, 2016; [4]Langley & Anderson, PIDJ, 2011

Each year in U.S. children aged less than 5 years, RSV is associated with…



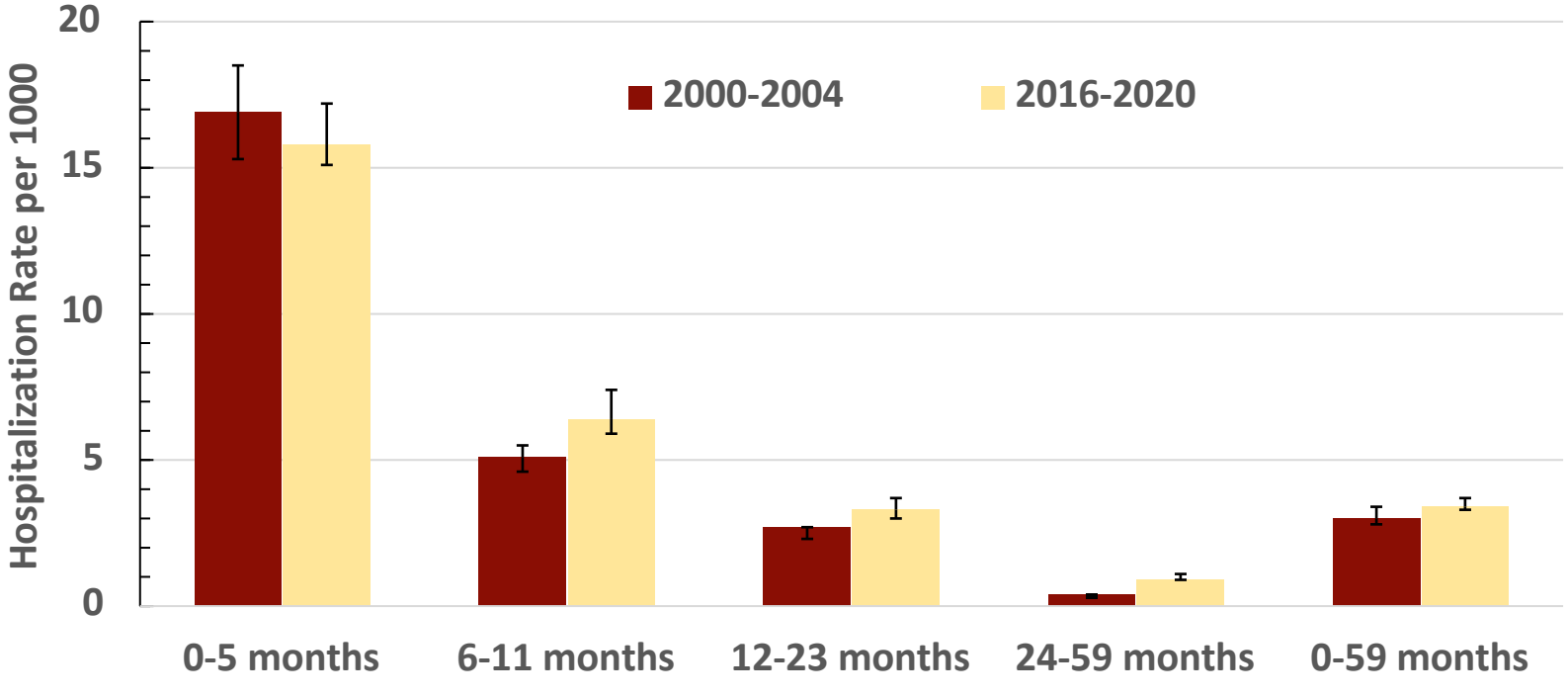
[1]Thompson et al, JAMA, 2003; [2]Hansen et al, JAMA Network Open, 2022; [3]Hall et al, NEJM, 2009; [4]McLaughlin et al, J Infect Dis, 2022
(*estimate 80,000 hospitalizations in infants <1y)

The burden of RSV in U.S. adults

RSV-associated disease burden estimates from the New Vaccine Surveillance Network (NVSN)

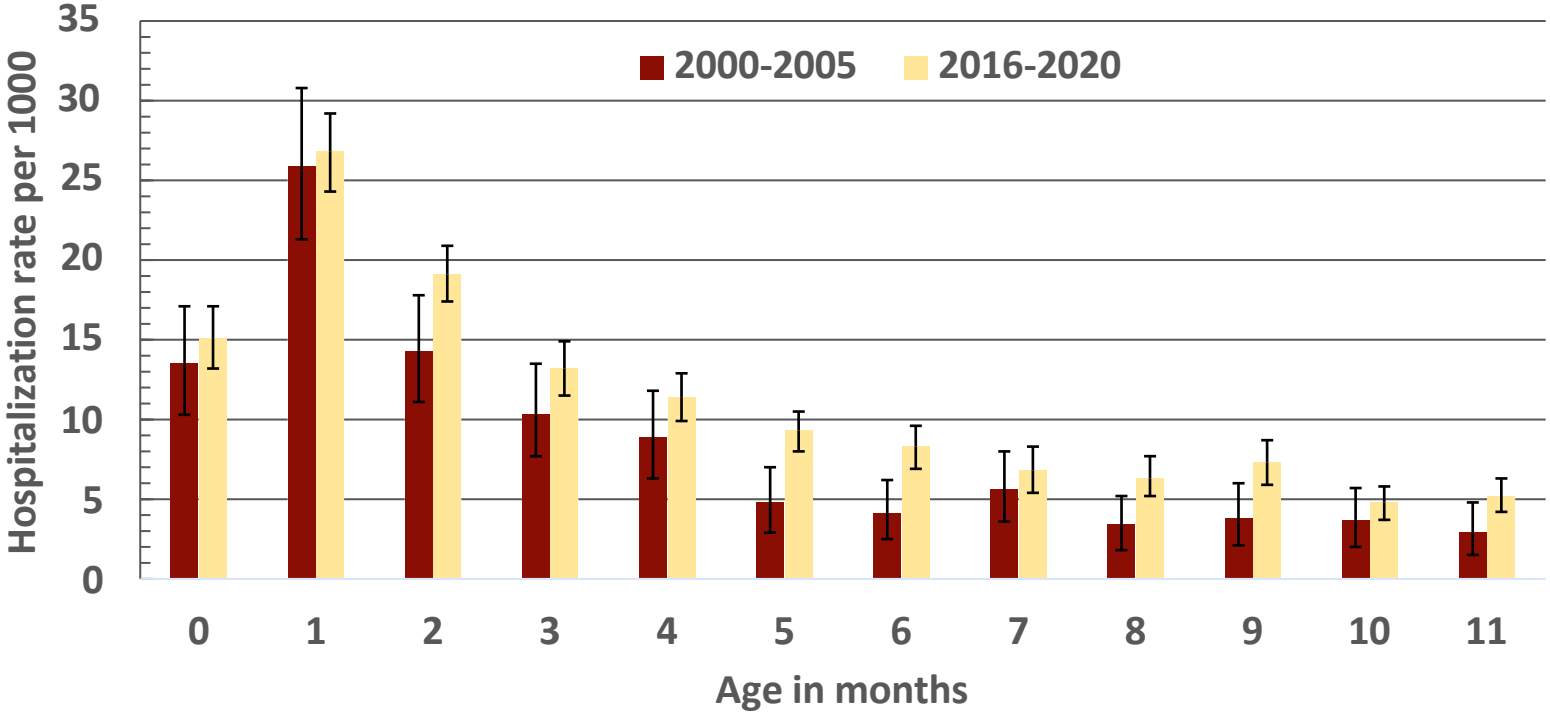
- Year-round acute respiratory illness (ARI) surveillance at 3 sites during 2000-2009
- Expanded to 7 sites during 2016-2021
- Prospective surveillance in inpatient, ED, outpatient clinics
- PCR testing for multiple respiratory viruses, including RSV
- Population denominators and market share used to estimate disease burden

RSV-associated hospitalization rates are highest in children aged 0-5 months and decrease with increasing age, NVSN



2000-2004: Adapted from Hall et al, NEJM 2009; 2016-2020: CDC unpublished data

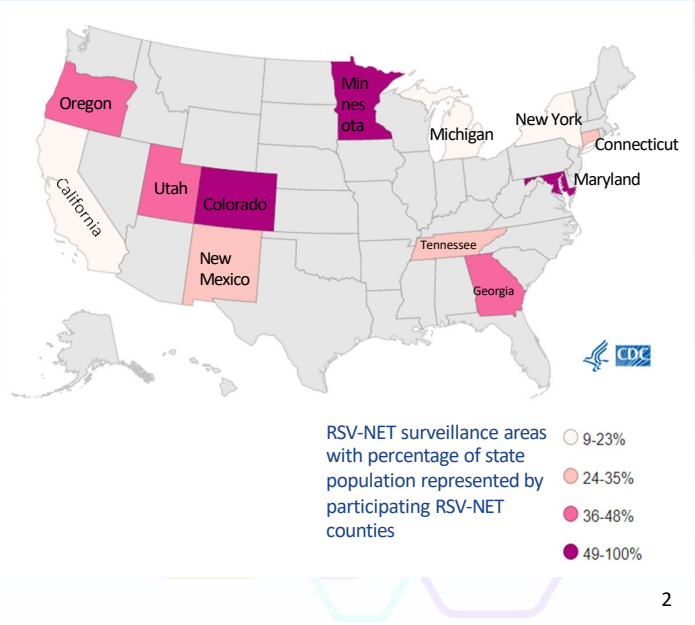
RSV-associated hospitalization rates in children aged 0-11 months, NVSN



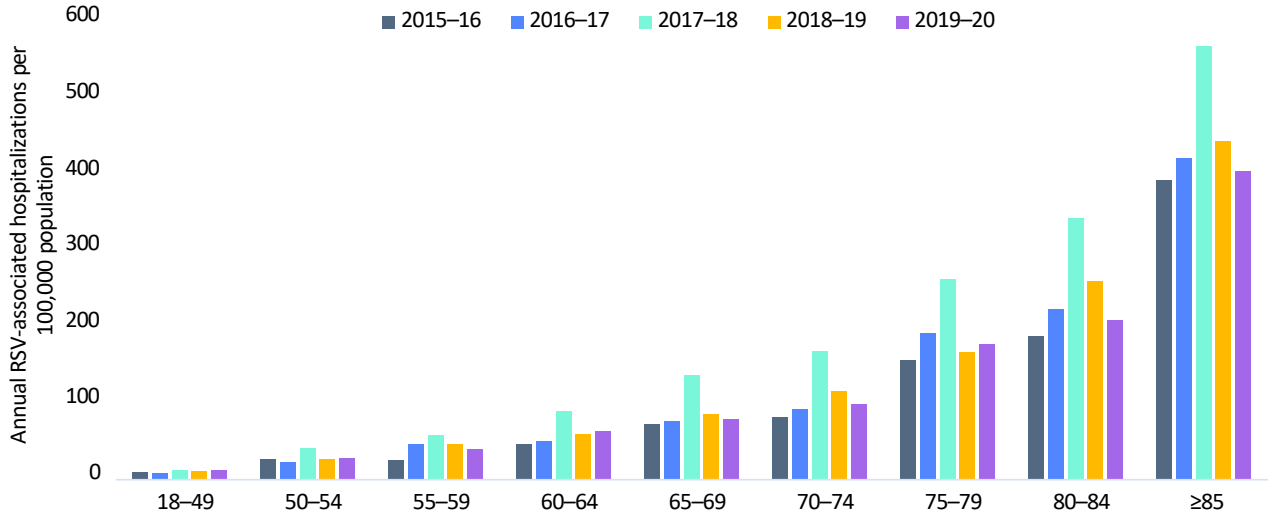
2000-2005: Adapted from Hall et al, Pediatrics 2013; 2016-2020: CDC unpublished data

RSV-NET: A RESP-NET population-based hospitalization surveillance platform

- RESP-NET: RSV-NET, COVID-NET, FluSurv-NET
- Active, population-based surveillance of laboratory-confirmed RSV-associated hospitalizations
  - >300 acute-care hospitals, 58 counties in 12 states
  - ~8.6% of U.S. population
- Tests positive for RSV within 14 days prior to or during hospitalization
  - Clinician-driven testing
- Clinical data: random sample of RSV-NET patients stratified by age and site



Adjusted RSV-associated hospitalization rates* per 100,000 adults ≥18 years by 5-year age group and year, RSV-NET, 2015–2016 to 2019–2020



*Unpublished data. Rates are adjusted for the frequency of RSV testing during each season and the sensitivity of RSV diagnostic tests.

Underlying medical conditions* among non-pregnant adults ≥18 years with RSV-associated hospitalizations — RSV-NET, 2014–2015 to 2017–2018 and 2022–2023

Major underlying condition categories	Unweighted N=7,479	Weighted %
Cardovascular disease (overall)	5,141	57.4
Obesity	2,798	39.0
Diabetes	2,484	34.1
COPD	2,248	31.4
Heart failure	1,984	28.0
Chronic kidney disease	2,003	27.0
Asthma	1,789	24.0
Coronary artery disease (includes CABG, MI)	1,718	24.0
Neurologic condition	1,628	22.6
Immune compromised	1,567	20.8
Chronic metabolic disease, not including diabetes	1,417	19.3
Other chronic lung disease	995	17.1
Chronic liver disease	538	7.2
Autoimmune/inflammatory disease	310	4.5
Blood disorders	287	4.1

94.3% of adults ≥18 years with RSV- associated hospitalization had at least one underlying medical condition:

- 31.4%: 1–2 conditions
- 62.9%: ≥3 conditions

*Clinical data, including underlying medical conditions, were collected for all patients with laboratory-confirmed RSV hospitalizations during the 2014–2015 to 2017–2018 seasons, and for an age- and site-stratified random sample of patients with laboratory-confirmed RSV hospitalizations during the 2022–2023 season. Data are presented as unweighted case counts and weighted percentages that were weighted for the probability of selection.

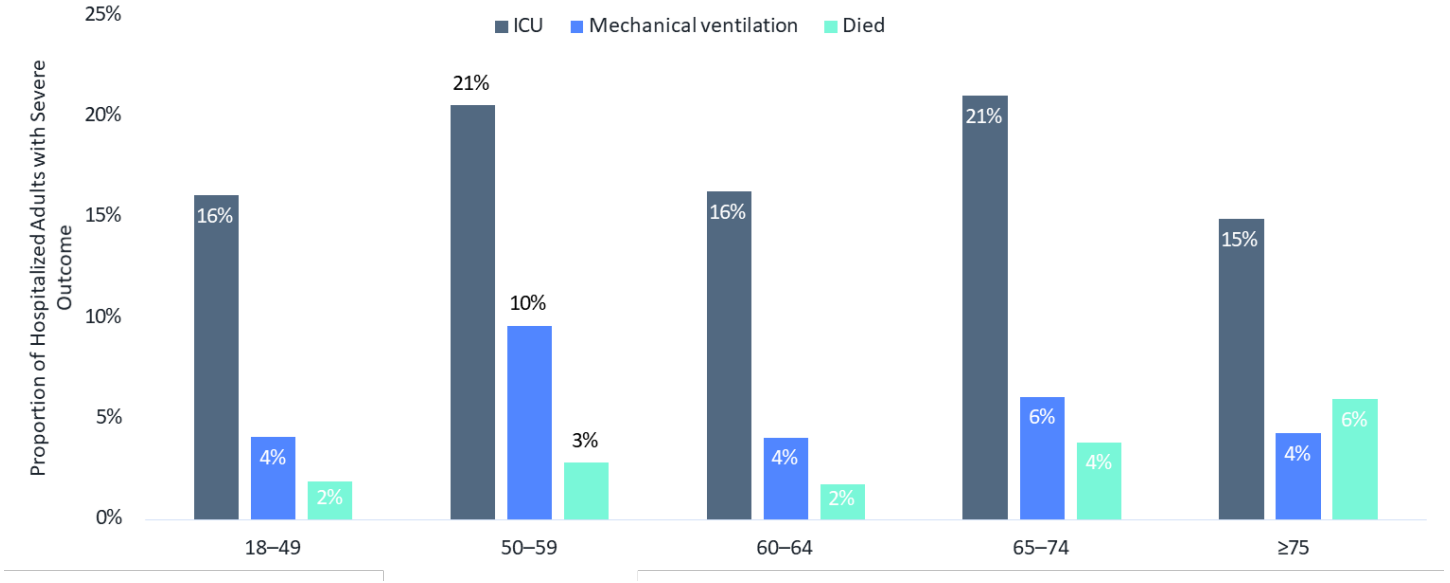
Prevalence of certain medical conditions* among non-pregnant adults with RSV-associated hospitalizations (RSV-NET, 2014–2015 to 2017–2018 and 2022–2023) and among the general population (National Center for Health Statistics†, 2022) by age group

Condition	50–64 years			≥65 years		
	General population % (95% CI)	RSV-NET % (95% CI)	RSV-NET/ Pop	General population % (95% CI)	RSV-NET % (95% CI)	RSV-NET/ Pop
Coronary artery disease	5.0 (4.4, 5.6)	18.9 (16.9, 21.0)	3.8	15.3 (14.4, 16.2)	31.3 (29.1, 33.6)	2.0
COPD	6.2 (5.5, 6.9)	35.4 (32.9, 37.9)	5.7	9.8 (9.1, 10.5)	33.2 (30.1, 35.5)	3.4
Diabetes mellitus	13.8 (12.9, 14.7)	37.7 (35.1, 40.4)	2.7	20.1 (19.1, 21.1)	31.8 (29.6, 34.1)	1.6
Asthma	9.1 (8.4, 9.9)	28.6 (26.3, 31.0)	3.1	8.0 (7.3, 8.6)	17.6 (15.8, 19.4)	2.2
Obesity	37.6 (36.2, 38.9)	46.4 (43.7, 49.0)	1.2	30.4 (29.2, 31.6)	28.4 (26.1, 30.8)	0.9

*Clinical data were collected for all patients with laboratory-confirmed RSV hospitalizations during the 2014–2015 to 2017–2018 seasons, and for an age- and site-stratified random sample of patients with laboratory-confirmed RSV hospitalizations during the 2022–2023 season. Displayed percentages were weighted for the probability of selection.

†National Center for Health Statistics. United States, 2022. National Health Interview Survey. Generated interactively: Oct 17, 2023 from https://wwwn.cdc.gov/NHISDataQueryTool/SHS_adult/index.html

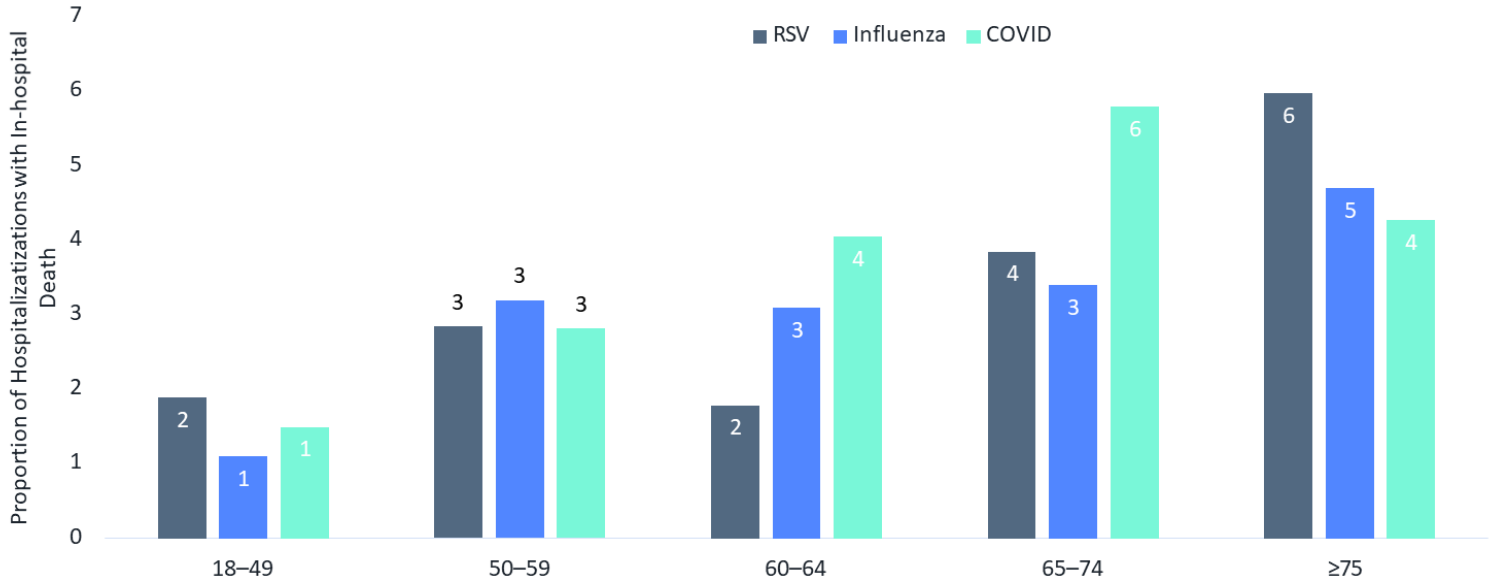
Percentages of non-pregnant adults ≥18 years with RSV-associated hospitalization who experienced severe outcomes by age group, RSV-NET, 2022–2023



ICU = intensive care unit

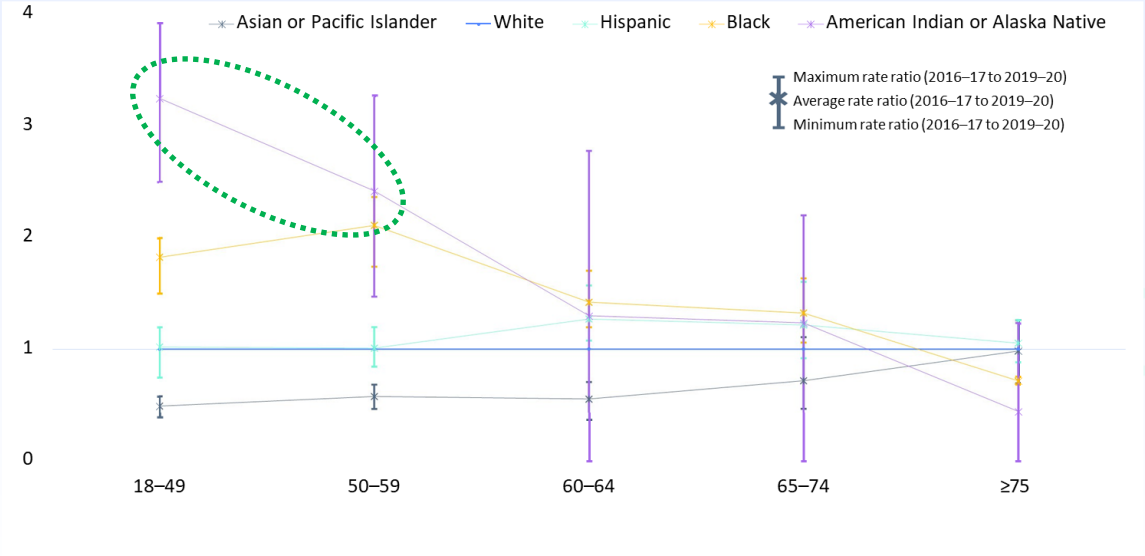
*Clinical data, including severe outcomes, were collected for an age- and site-stratified random sample of patients with laboratory-confirmed RSV hospitalizations during the 2022–2023 season. Displayed percentages were weighted for the probability of selection.

Percentages of non-pregnant adults ≥18 years with laboratory-confirmed hospitalization with in-hospital death*, RSV-NET, FluSurv-NET, COVID-NET,



†Patients with severe disease may be more likely to be tested for RSV, Influenza, or COVID-19 which may overestimate proportions of patients admitted to the ICU.
‡Data shown here does not take patient vaccination or treatment status into account.
§FluSurv-NET surveillance occurred during October 2022–April 2023; RSV-NET and COVID-NET surveillance occurred year-round.

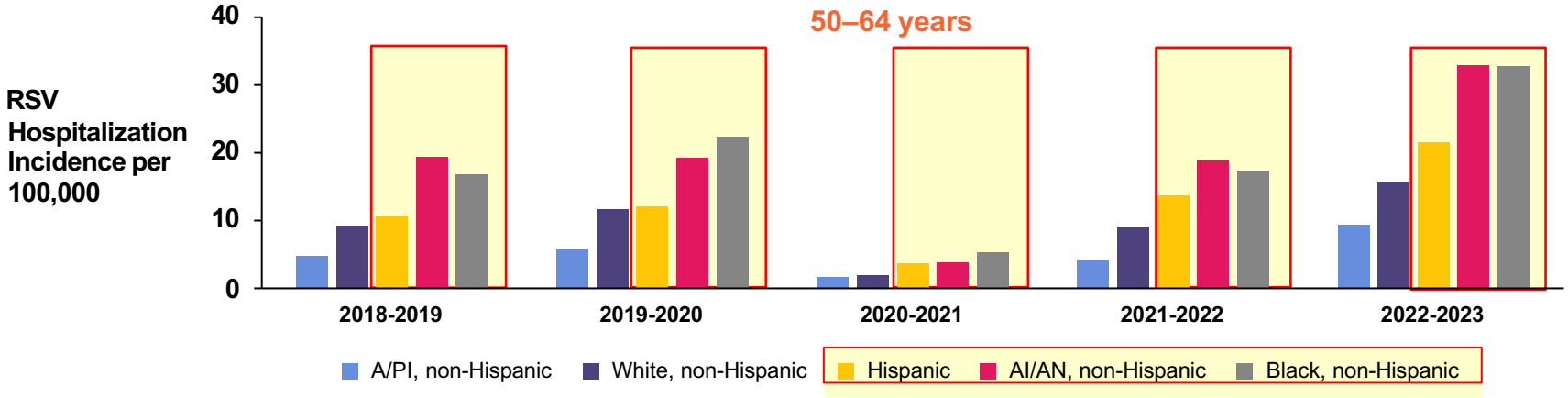
Burden-adjusted hospitalization rate ratios among adults ≥18 years by race and ethnicity* — RSV-NET, 2016–2017 to 2019–2020



*Black, White, American Indian/Alaska Native and Asian/Pacific Islander people were categorized as non-Hispanic; Hispanic people could be of any race.

Disparities by Race and Ethnicity in RSV Hospitalization Rates Particularly Pronounced in Adults 50–64 Years

Unadjusted RSV-related hospitalization incidence per 100,000 by race / ethnicity and season from RSV-NET data[1]



Among adults aged **50–64 YOA**, **unadjusted RSV-related hospitalization rates** (vs White, non-Hispanic) during 2018–2023 were:

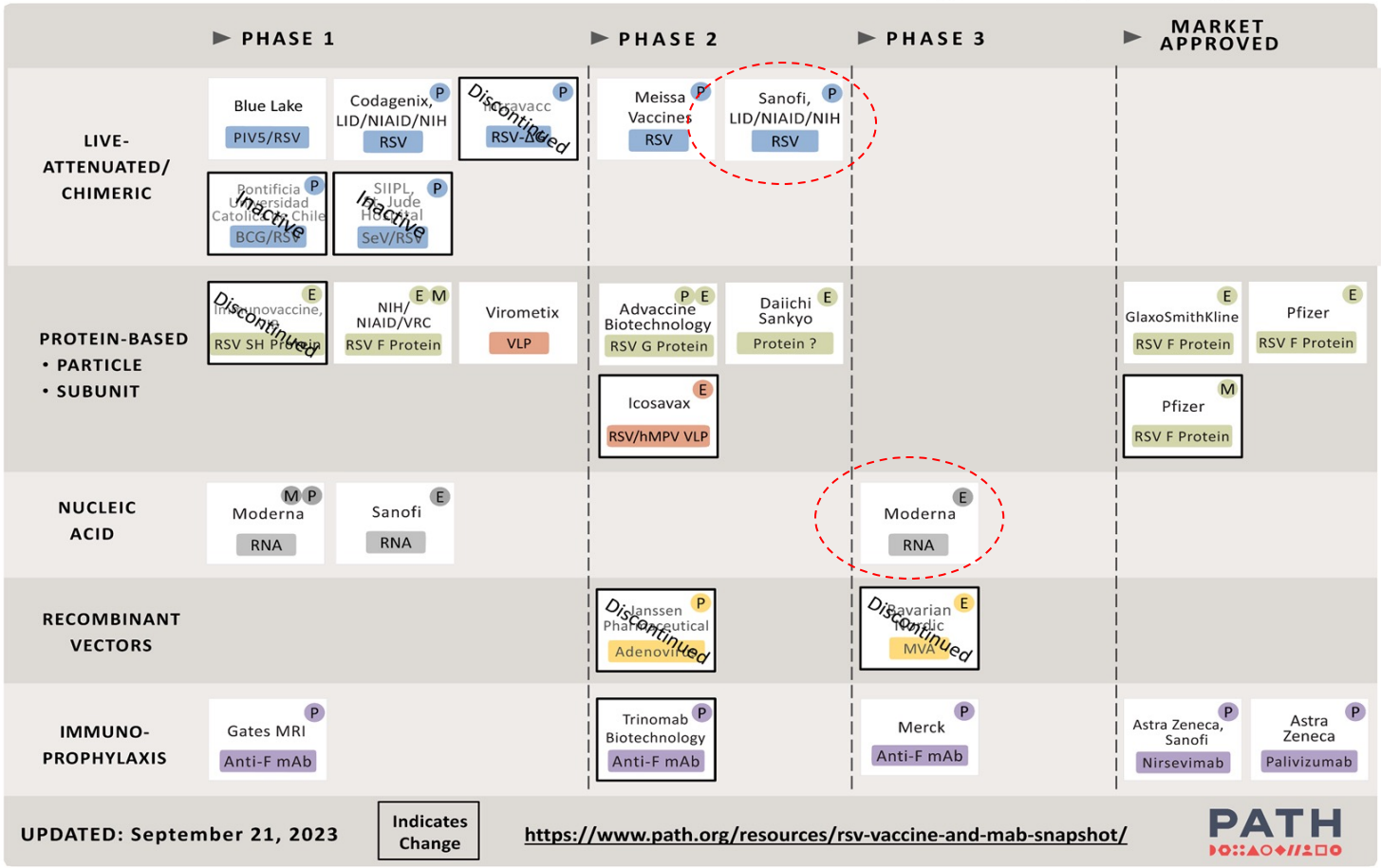
- **Hispanic: 1.0-1.9 times higher**
- **AI/AN, non-Hispanic: 1.6-2.1 times higher**
- **Black, non-Hispanic: 1.8-2.7 times higher**

A/PI, Asian and Pacific Islander, AI/AN, America Indian or Alaska Native;

1. CDC, https://www.cdc.gov/rsv/research/rsv-net/dashboard.html. (accessed October 2023)

RSV prevention

RSV Vaccine and mAb Snapshot



GSK pulled it's maternal vaccine due to elevated pre-term delivery

Pfizer maternal and elderly – same product

mAb - immunoprophylaxis (passive antibody)

Sanofi (live attenuated) and Moderna (mRNA) moving forward

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

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

Hammitt LL et al. DOI: 10.1056/NEJMoa2110275

CLINICAL PROBLEM

Nirsevimab — a monoclonal antibody against the respiratory syncytial virus (RSV) fusion protein that has an extended half-life — has been shown to protect healthy preterm infants from RSV-associated lower respiratory tract infection, but its efficacy and safety in late-preterm and term infants are unknown.

CLINICAL TRIAL

Design: A multinational, phase 3, randomized, placebo-controlled trial assessed the efficacy and safety of nirsevimab for preventing RSV-associated lower respiratory tract infection in healthy infants born at a gestational age of at least 35 weeks.

Intervention: 1490 infants were randomly assigned, in a 2:1 ratio, to receive a single intramuscular injection of nirsevimab or placebo before entering their first RSV season. The primary efficacy end point was medically attended RSV-associated lower respiratory tract infection through day 150 after the injection.

RESULTS

Efficacy: The incidence of medically attended RSV-associated lower respiratory tract infection was significantly lower in the nirsevimab group than in the placebo group.

Safety: Similar types of adverse events occurred in the two groups, at similar frequencies. Most adverse events were grade 1 or 2 in severity.

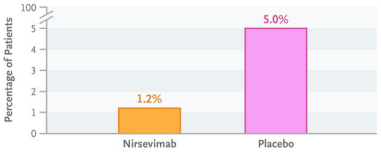
LIMITATIONS AND REMAINING QUESTIONS

- The efficacy of nirsevimab was relatively lower among younger infants (≤3 months vs. >3 months of age) and among those who weighed less (<5 kg vs. ≥5 kg), although small numbers preclude firm conclusions.
- The trial enrolled infants in the northern hemisphere and in South Africa (southern hemisphere). Although the overall incidence of RSV during the trial was as expected in the northern hemisphere, measures to control the Covid-19 pandemic in South Africa limited RSV circulation, resulting in low enrollment there.

Links: Full Article | NEJM Quick Take

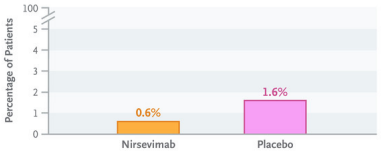
Medically Attended Lower Respiratory Tract Infection through Day 150

Efficacy, 74.5%; 95% CI, 49.6 to 87.1; P<0.001

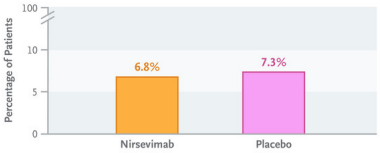


Hospitalization for Lower Respiratory Tract Infection through Day 150

Efficacy, 62.1%; 95% CI, −8.6 to 86.8; P=0.07



Serious Adverse Events through Day 361



CONCLUSIONS

A single dose of nirsevimab given before the RSV season lowered the risk of medically attended RSV-associated lower respiratory tract infection in healthy late-preterm and term infants, with no safety concerns.

- **Single dose** of mAb before RSV season significantly lowered the risk of medically attended RSV-associated lower respiratory tract infection in late pre-term and term infants. Duration at least 150 days.
- Efficacy was 79-86% for reduction in medically attended RSV disease and severe disease, respectively.
- Ongoing studies comparing to palivizumab in defined high risk babies.
- ESPID Conference – open label N=8058 – efficacy against RSV hospitalization 83%
- Wilkin et. Al. *Nature Communications 2023* – High levels of RSV Ab throughout first season and infants developed natural Ab.
- ACIP recommends for *all* infants under 8 months of age entering their first RSV season *if* mom did not appropriately receive RSV vaccination during pregnancy.
- ACIP recommends all AI/AN age 8-19 months entering their second season also receive a dose.

Clinical trials showed significant efficacy against lower respiratory tract disease/illness caused by RSV

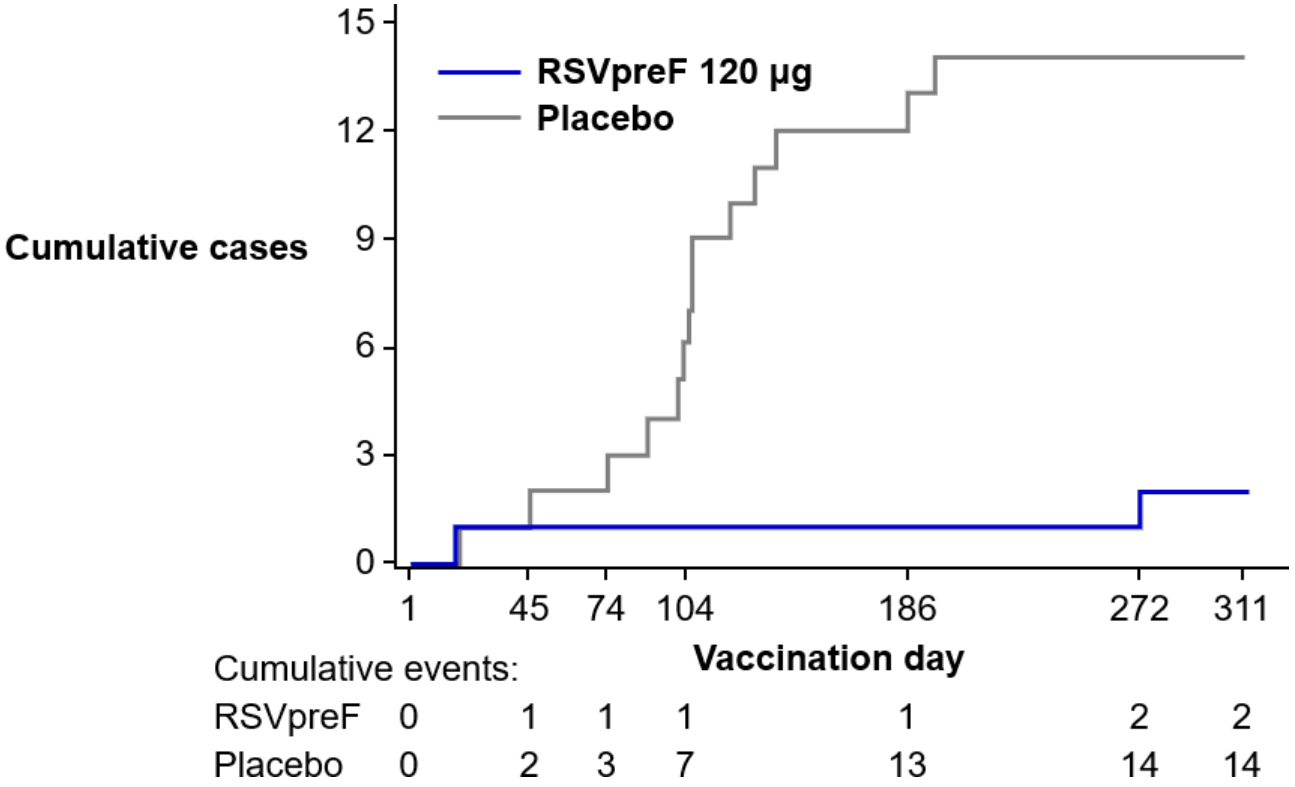
- Efficacy point estimates against the primary outcomes in both trials exceeded 60%

GSK		Pfizer	
Outcome	**Efficacy (%), 96.95% CI**	**Outcome**	**Efficacy (%), 95% CI**
RSV LRTD[a]	**82.6** (57.9–94.1)	RSV LRTI ≥2 symptoms[b]	**66.7** (32.5–84.8)
		RSV LRTI ≥3 symptoms[b]	**85.7** (37.9–98.4)

[a] Lower respiratory tract disease: ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours

[b] Lower respiratory tract illness: ≥2 or ≥3 lower respiratory signs/symptoms lasting more than 1 day

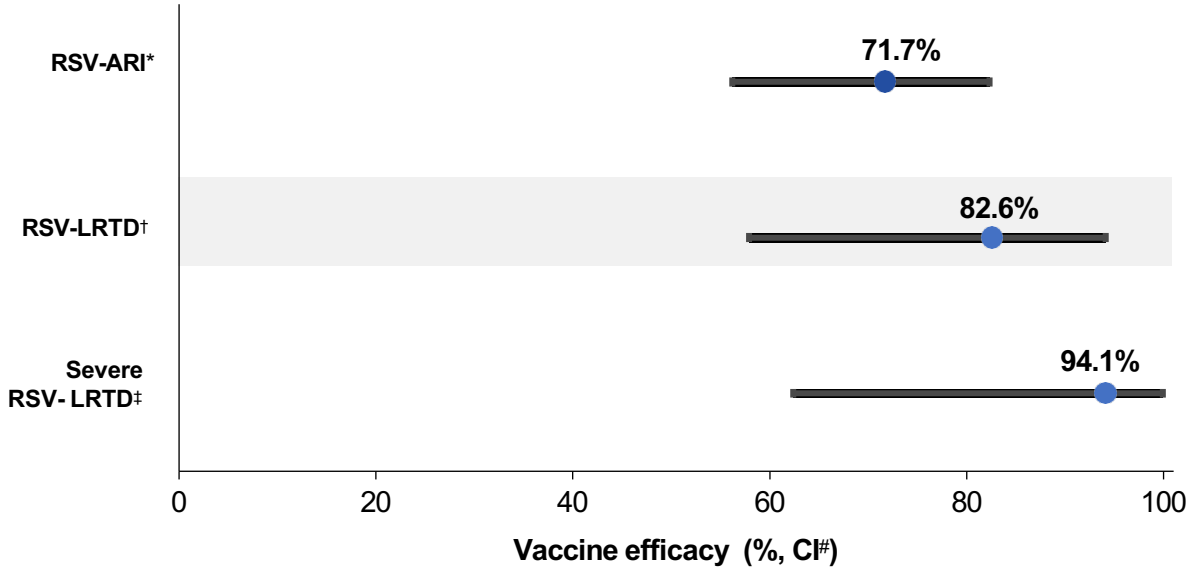
RSVpreF (Pfizer) efficacy against RSV-LRTI with ≥ 3 symptoms



Mean active surveillance: 7 months

Abbreviations: RSV-LRTI, lower respiratory tract illness due to respiratory syncytial virus

GSK Vaccine Efficacy – presented at ACIP October 2022



	Number of events	
	RSVPreF3 OA N=12,466	Placebo N=12,494
RSV-ARI*	27	95
RSV-LRTD†	7	40
Severe RSV- LRTD‡	1	17

*ARI defined as ≥2 respiratory symptoms/signs for ≥24 hours or ≥1 respiratory symptom/sign + 1 systemic symptom/sign for ≥24 hours; †LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign or ≥3 lower respiratory symptoms for ≥24 hours; ‡severe LRTD defined as LRTD with ≥2 LRTD signs or assessed as severe by the Investigator. All RSV cases confirmed by RT-PCR; #96.95% Confidence Interval (CI) for primary endpoint, 95% CI for all secondary endpoints; ARI, acute respiratory infection; LRTD, lower respiratory tract disease; RT-PCR, reverse transcriptase polymerase chain reaction. ClinicalTrials.gov, 2022. NCT04886596. https://clinicaltrials.gov/ct2/show/NCT04886596 (accessed October 2022).

Presentation by GSK to the ACIP Oct 20, 2022

Trials were underpowered to estimate efficacy against more severe RSV outcomes (e.g., hospitalization, death)

- There were <5 RSV hospitalizations in each trial, and no RSV-associated deaths
- However, the burden of RSV-associated hospitalizations is high among older adults in the United States
- Industry-sponsored 2022 meta-analysis* estimated ≥**106,165** annual RSV hospitalizations among adults aged ≥65 years

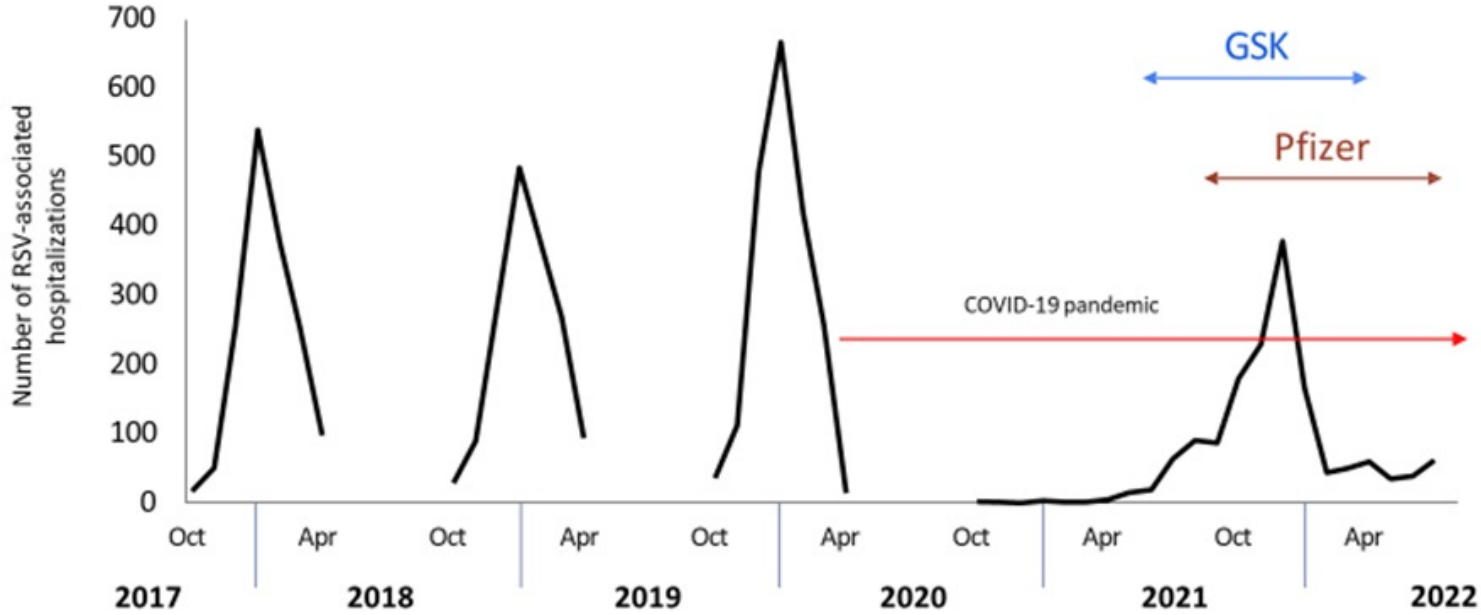
*McLaughlin JM, et al. Rates of Medically Attended RSV Among US Adults: A Systematic Review and Meta-analysis. Open Forum Infect Dis. 2022 Jun 17;9(7):ofac300.

RSV season (October–April)	Estimated U.S. Hospitalizations in adults aged ≥60 years	95% confidence interval
2016-17	64,428	44,382 to 117,495
2017-18	80,652	58,778 to 128,458
2018-19	66,548	50,851 to 96,264
2019-20	84,941	64,105 to 125,848

CDC unpublished data from RSVNET (https://www.cdc.gov/rsv/research/rsv- net.html). Note that rates are adjusted for test sensitivity (using 95% for rRT- PCR testing) and undertesting for RSV among patients with acute respiratory illnesses. Data are preliminary and subject to change.

Estimates for 2018-19 and 2019-20:
Havers et al. Hospitalization rates and outcomes for RSV-associated hospitalizations in adults ≥18 years in the United States during two respiratory seasons, October 2018 - April 2020.

Monthly RSV-associated hospitalizations among adults aged ≥65 years reported to RSV-NET, 2017–2022



RSV-NET: unpublished data. Data are preliminary and subject to change.

RSV-NET: unpublished data. Data are preliminary and subject to change.

Cases of Guillain Barré syndrome (GBS) were reported after vaccination with both investigational vaccines

GSK	Pfizer
No cases of GBS observed in main phase 3 trial (N=24,966 participants, 12,467 received investigational vaccine) 1 case of GBS was reported in a randomized open-label study evaluating safety & long- term immunogenicity of different revaccination schedules (N=1,650 participants) • Onset 9 days after receipt of investigational vaccine	2 cases of GBS (1 case Miller-Fisher syndrome) observed in main phase 3 trial (N=34,283 participants, 17,214 received investigational vaccine) • Onset 8 and 11 days after receipt of investigational vaccine No cases of GBS observed in any other trials of this investigational vaccine
Total: 1 case of GBS / ~15,000 persons who received the investigational vaccine	**Total: 2 cases of GBS / ~26,000 persons who received the investigational vaccine**

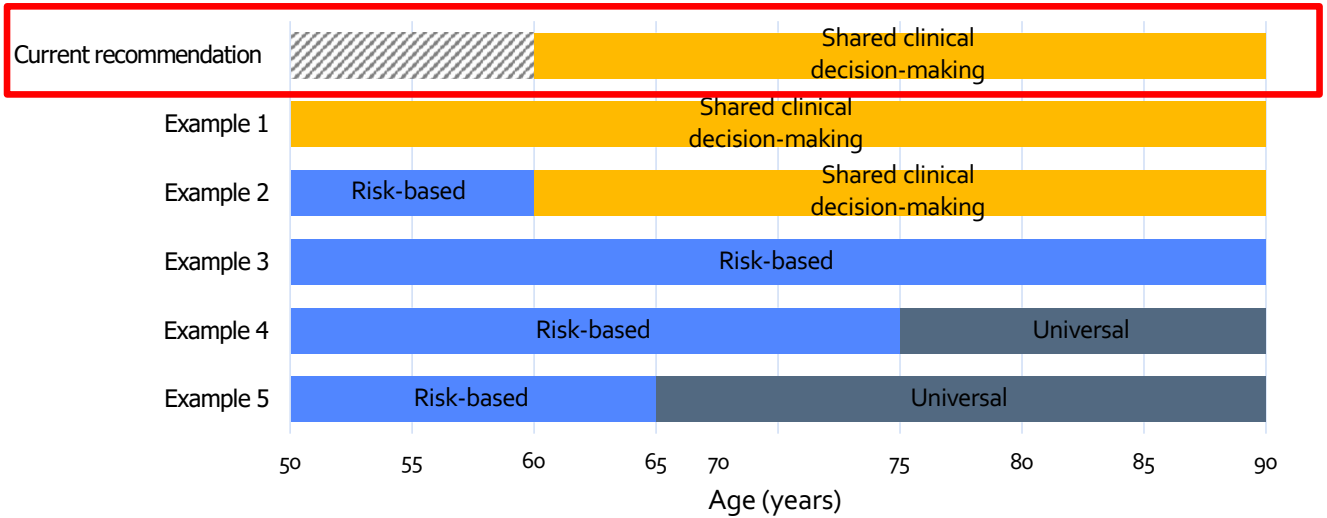
GBS occurs unrelated to vaccine and peaks in age 60-64 at ~6-7/100,000
Over 2 million doses of GSK vaccine administered to date with no additional safety signals

Number needed to vaccinate (NNV): GSK RSVpreF3

Number of vaccinations required to prevent…	Adults aged ≥65 years	Adults aged ≥60 years
1 RSV outpatient visit[a]	84 vaccinations	90 vaccinations
1 RSV hospitalization[b]	1,097 vaccinations	1,348 vaccinations
1 RSV death[c]	21,442 vaccinations	27,284 vaccinations

[a] Incidence rates of RSV illness requiring outpatient visit taken from McLaughlin et al, OFID (2022) (unadjusted for RSV under-detection by NP swab RT-PCR). Vaccine efficacy (VE) against this outcome assumed to be equal to that against medically attended acute respiratory illness (ARI) caused by RSV (GSK AReSVi-006 trial, unpublished).
[b] Incidence rates of RSV hospitalization taken from RSV-NET 2015–2019 (unpublished). VE against RSV-associated hospitalization assumed to be equal to that against medically attended lower respiratory tract disease (LRTD) caused by RSV (GSK AReSVi-006 trial, unpublished).
[c] Probability of in-hospital death among adults hospitalized for RSV taken from RSV-NET 2015–2019 (unpublished). VE against RSV-associated death assumed to be equal to that against medically attended lower respiratory tract disease (LRTD) caused by RSV (GSK AReSVi-006 trial, unpublished).

Example ***potential*** policy options – pending FDA approval for age 50-59



The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

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

Kampmann B et al. DOI: 10.1056/NEJMoa2216480

CLINICAL PROBLEM

In infants, respiratory syncytial virus (RSV) is a common cause of acute lower respiratory tract illness and a leading cause of death, particularly in low- and middle-income countries. A phase 2b trial showed that maternal vaccination with a bivalent RSV prefusion F protein–based (RSVpreF) vaccine has promise in protecting infants against RSV-associated illness.

CLINICAL TRIAL

Design: An international, phase 3, randomized, placebo-controlled trial examined the efficacy and safety of vaccinating women with an uncomplicated singleton pregnancy at 24 through 36 weeks' gestation to prevent RSV-associated illness in infants.

Intervention: 7392 women were randomly assigned to receive one 120-μg dose of 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.

RESULTS

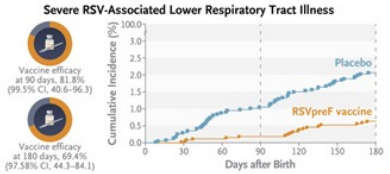
Efficacy: At this prespecified interim analysis, the RSVpreF vaccine was effective against medically attended severe RSV-associated lower respiratory tract illness within 90 days after birth, and protection was maintained through 180 days. The statistical success criterion for vaccine efficacy was not met for medically attended RSV-associated lower respiratory tract illness (the second primary end point).

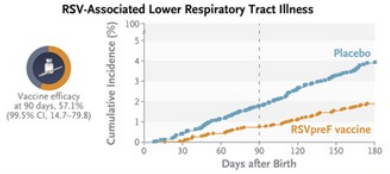
Safety: No safety signals were detected in maternal participants or in infants and toddlers up to 24 months of age. The incidences of adverse events reported within 1 month after injection or within 1 month after birth were similar in the two groups.

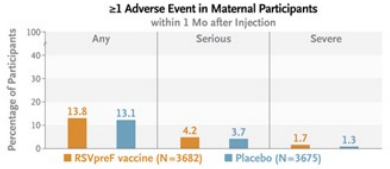
LIMITATIONS AND REMAINING QUESTIONS

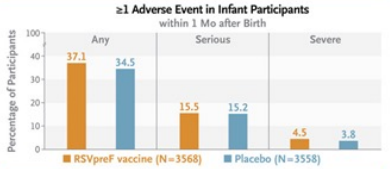
- Women with high-risk pregnancies were excluded from the trial, which limits generalizability of the results, since the offspring in such cases could be at higher risk for severe illness.
- Given the small sample size, safety data were limited.
- Limited data were available from low-income countries, where the vaccine could have the greatest effect.

Links: Full Article | NEJM Quick Take | Editorial









CONCLUSIONS

When administered to women late in pregnancy, RSVpreF vaccine was effective against medically attended severe RSV-associated lower respiratory tract illness in infants.

- Vaccination of pregnant women protected newborns against RSV disease through 6 months of age,
- Based upon a non-statistically significant increased rate of pre-term delivery, ACIP recommended use between 32 and 36 weeks of gestation (trial was 26-36 weeks)
- GSK halted its trial in pregnancy due to increase rate of pre-term delivery