Division of Geriatric Medicine

RSV Vaccine: Are We Ready for Prime Time?

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October 20, 2023

University of Pittsburgh

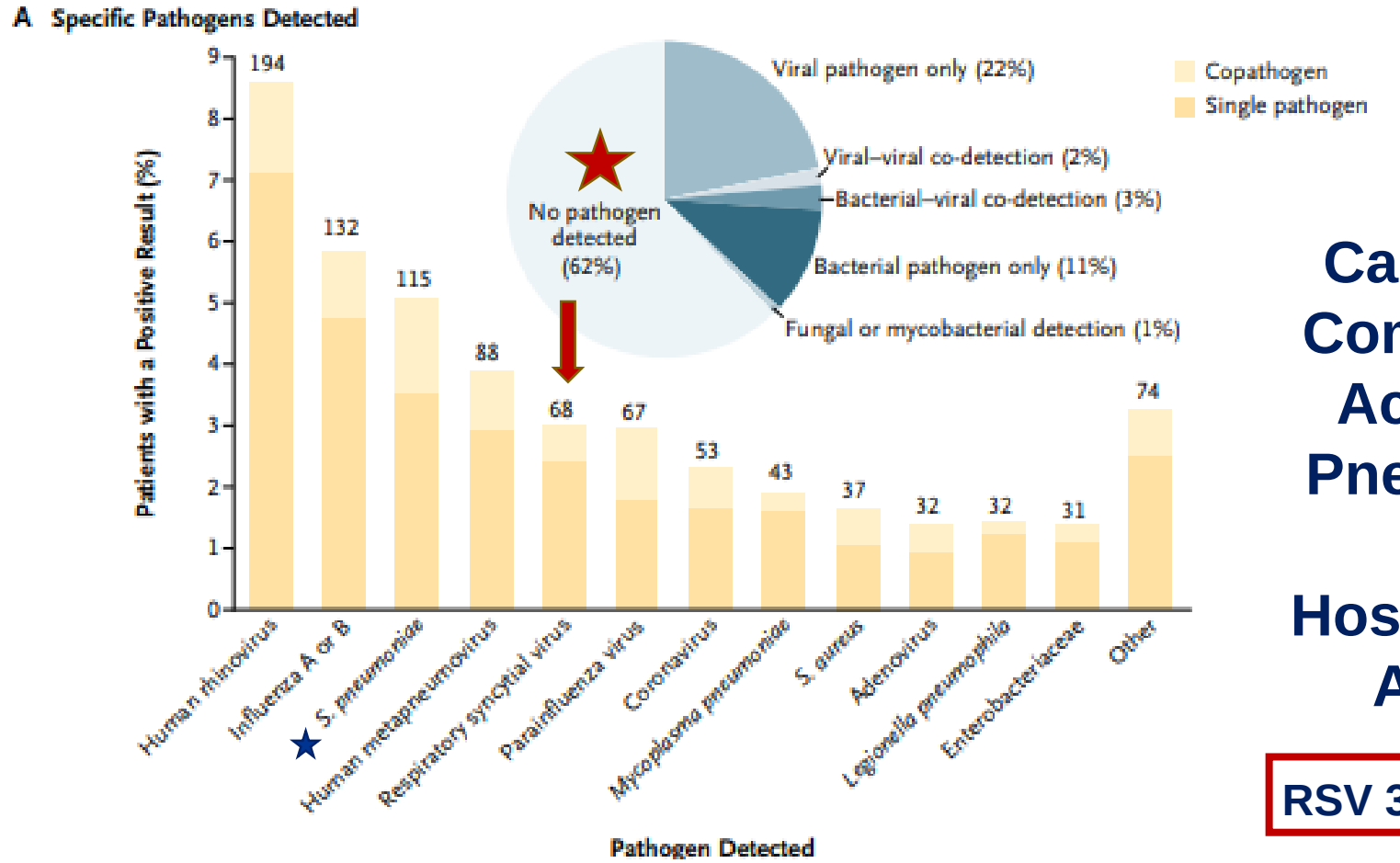
Disclosures

- Dr. Nace does not have any financial conflicts of interest related to this presentation.
- Dr. Nace serves on the ACIP Pneumococcal and Hepatitis Work Groups.
- Dr. Nace chaired the AMDA RSV Task Force and was a member of the AGS RSV Task Force which submitted comments to the ACIP regarding RSV.

Objectives

- Describe the impact of RSV among older adults
- Review data from clinical trials of two currently approved FDA approved RSV vaccines
- Discuss uncertainties surrounding use of the two RSV vaccines
- Outline future RSV vaccine research needs

Impact



Causes of Community Acquired Pneumonia in Hospitalized Adults

RSV 3% of adults

Jain S, et al. N Eng J Med 2015;373:415-27. DOI: 10.1056/NEJMoa1500245

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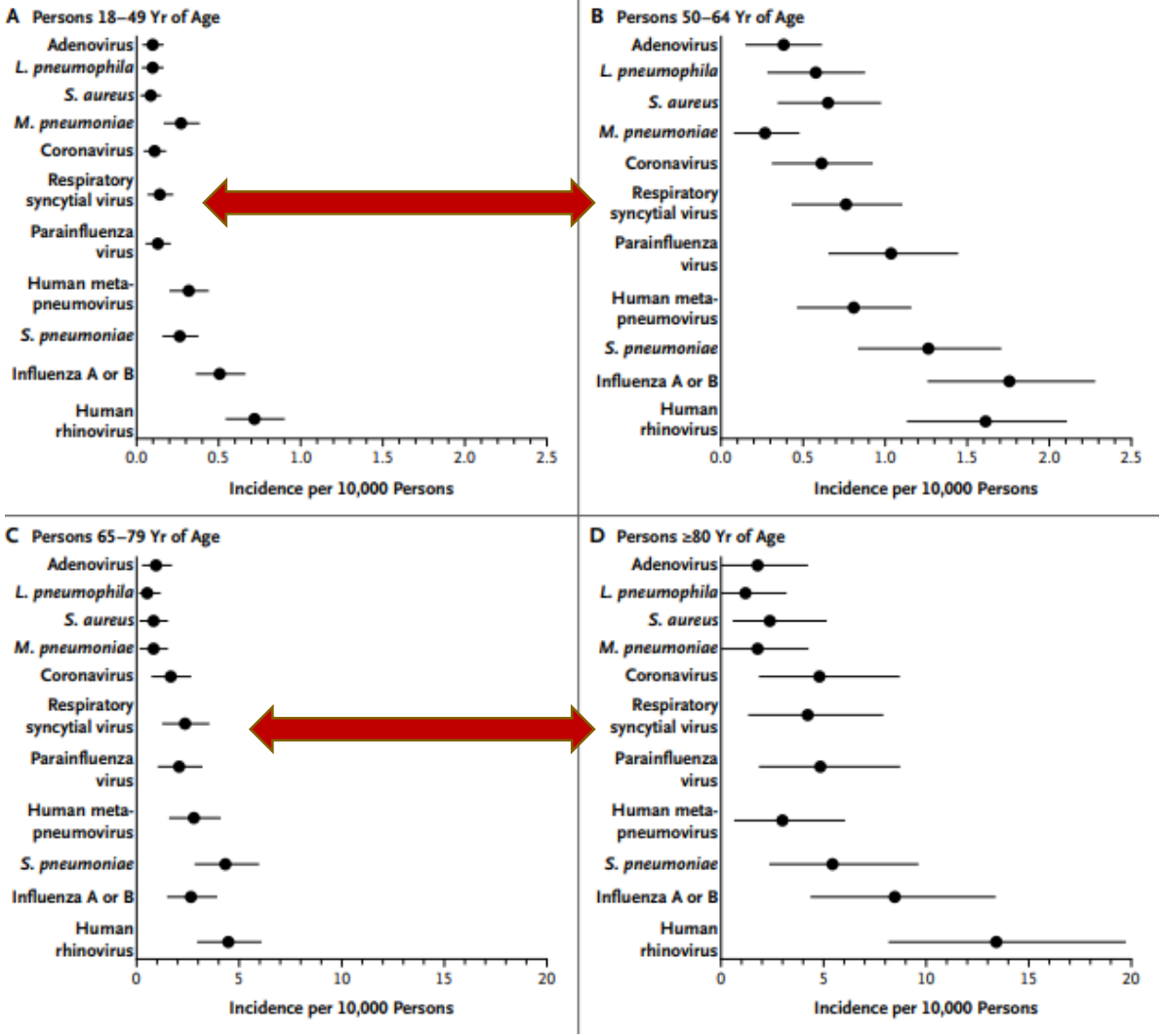


Annual Pathogen-Specific Incidence Rates of CAP Hospitalizations by Age Group

Jain S, et al. N Eng J Med 2015;373:415-27.

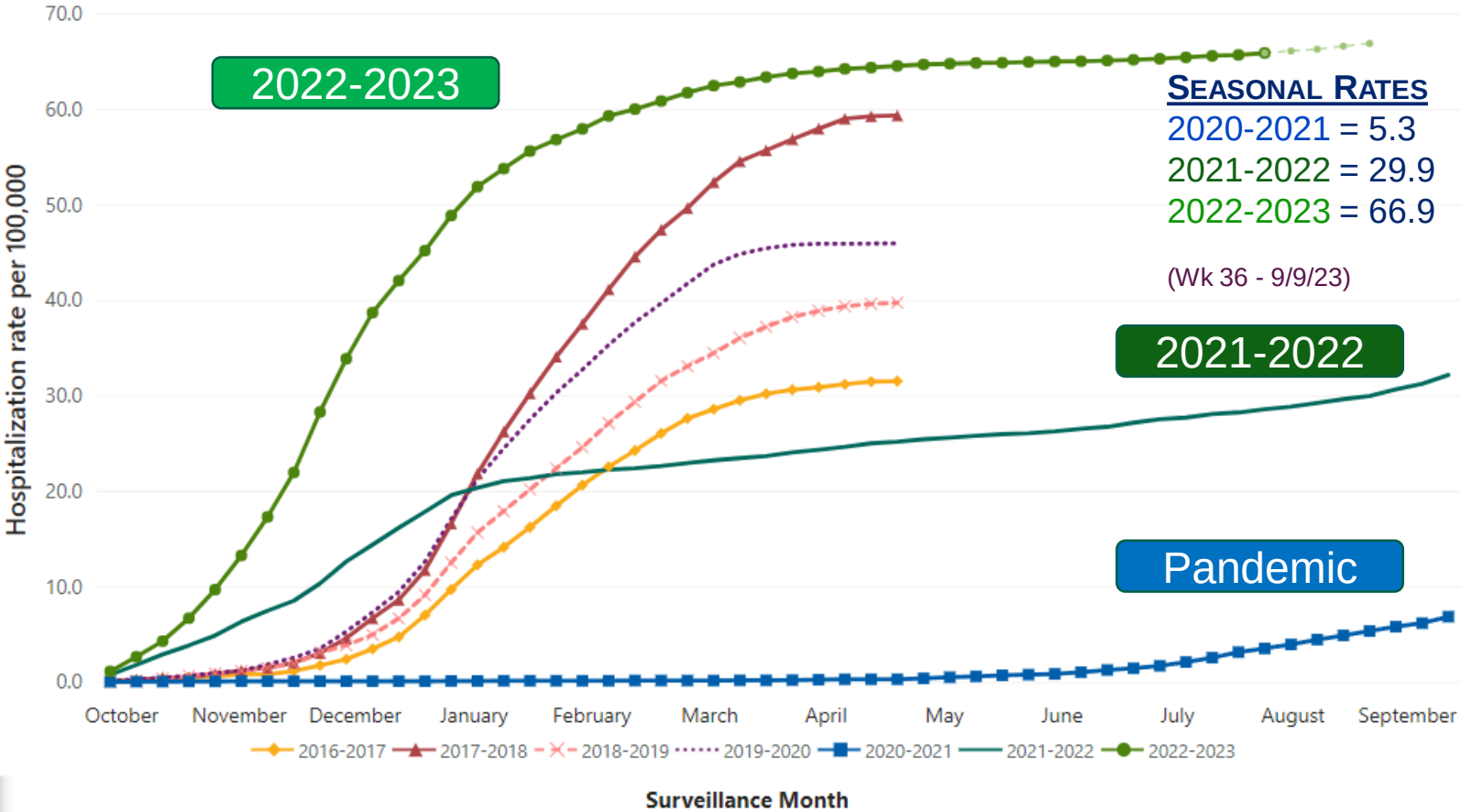
Cumulative Rates of RSV-Associated Hospitalization by Season

View

- Monthly Rates
- Weekly Rates
- Weekly Rates (All Seasons)
- Cumulative Rates

Filters

- Season: All
- Site: RSV-NET
- Age Group: 65+ years
- Race/Ethnicity: All
- Sex: All



Data last updated: 09/13/2023 | **Accessibility:** Hover over graph area to display options such as show data as table and copy visual.
Note: AI/AN, American Indian or Alaska Native; A/PI, Asian and Pacific Islander.

CDC

Download Data

Weekly Rates of RSV-Associated Hospitalization by Season

View

- Monthly Rates
- Weekly Rates
- Weekly Rates (All Seasons)
- Cumulative Rates

Filters

Site: RSV-NET

Age Group: 65+ years

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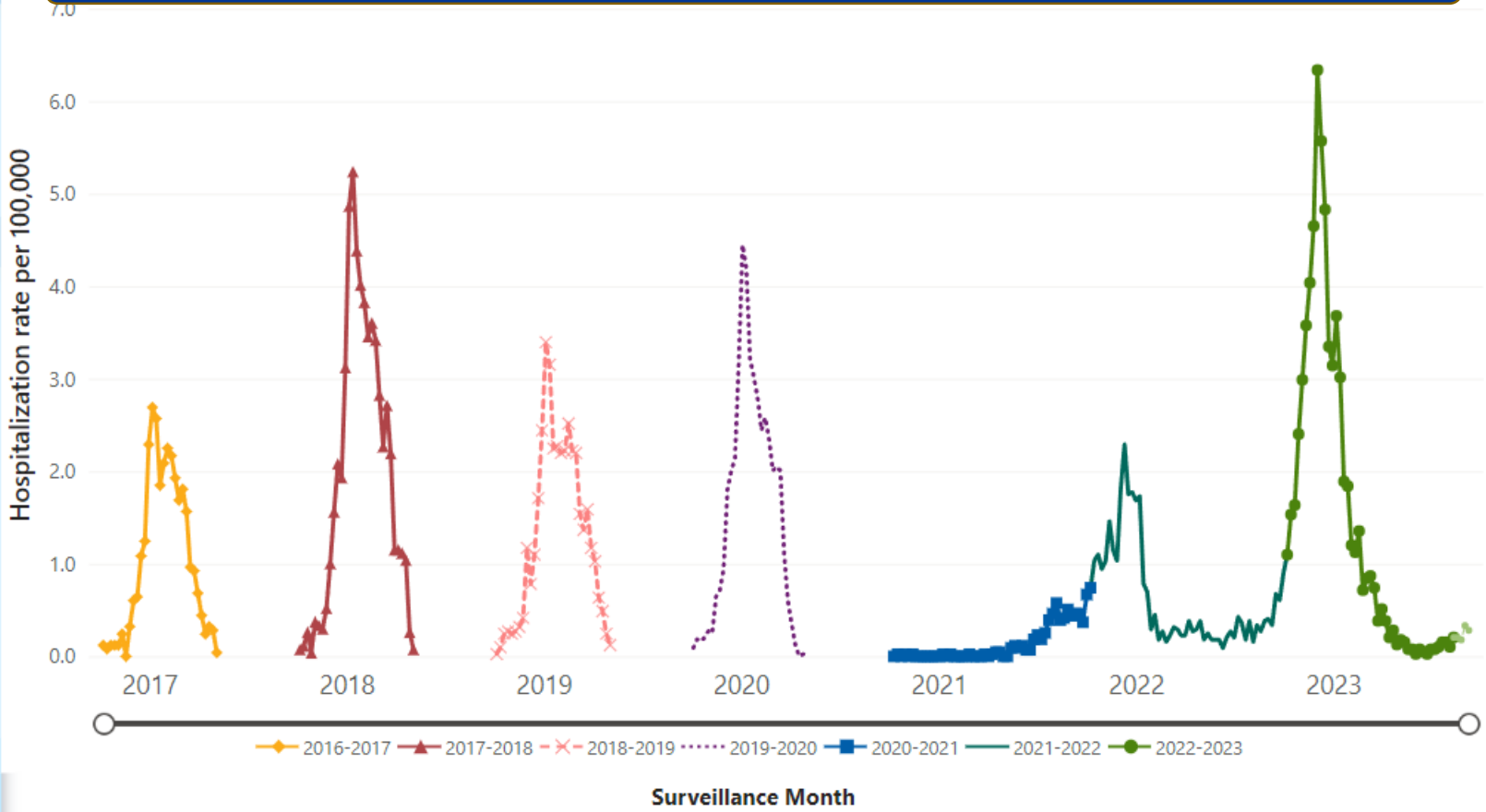

Data last updated: 09/13/2023 | **Accessibility:** Hover over graph area to display options such as show data as table and copy visual.
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Download Data

Older Adult Burden of RSV

Hospitalizations

- 60,000 to 160,000 per year

ED Visits

- 120,000 visits per year

Outpatient Visits

- 1.36 million per year

Deaths

- 6,000-13,000 per year

Clear Under-Reporting of Cases

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Respiratory Mortality – 65+ Age Group

RSV Respiratory Deaths

- 88% of all RSV respiratory deaths are in older adults

RSV Mortality Rate

- Highest mortality rate across age groups (14.7 per 100,000)

Influenza Respiratory Deaths

- 88% of all Influenza deaths are in older adults

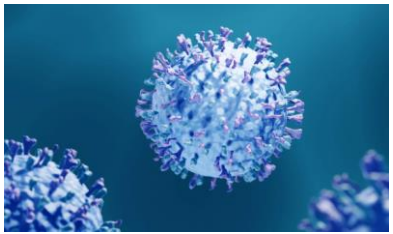
Influenza Mortality Rate

- Highest mortality rate across all age groups (20.5 per 100,000)

Hansen CL, et al. JAMA Netw Open. 2022;5(2):e220527. doi:10.1001/jamanetworkopen.2022.0527

Respiratory Syncytial Virus (RSV)

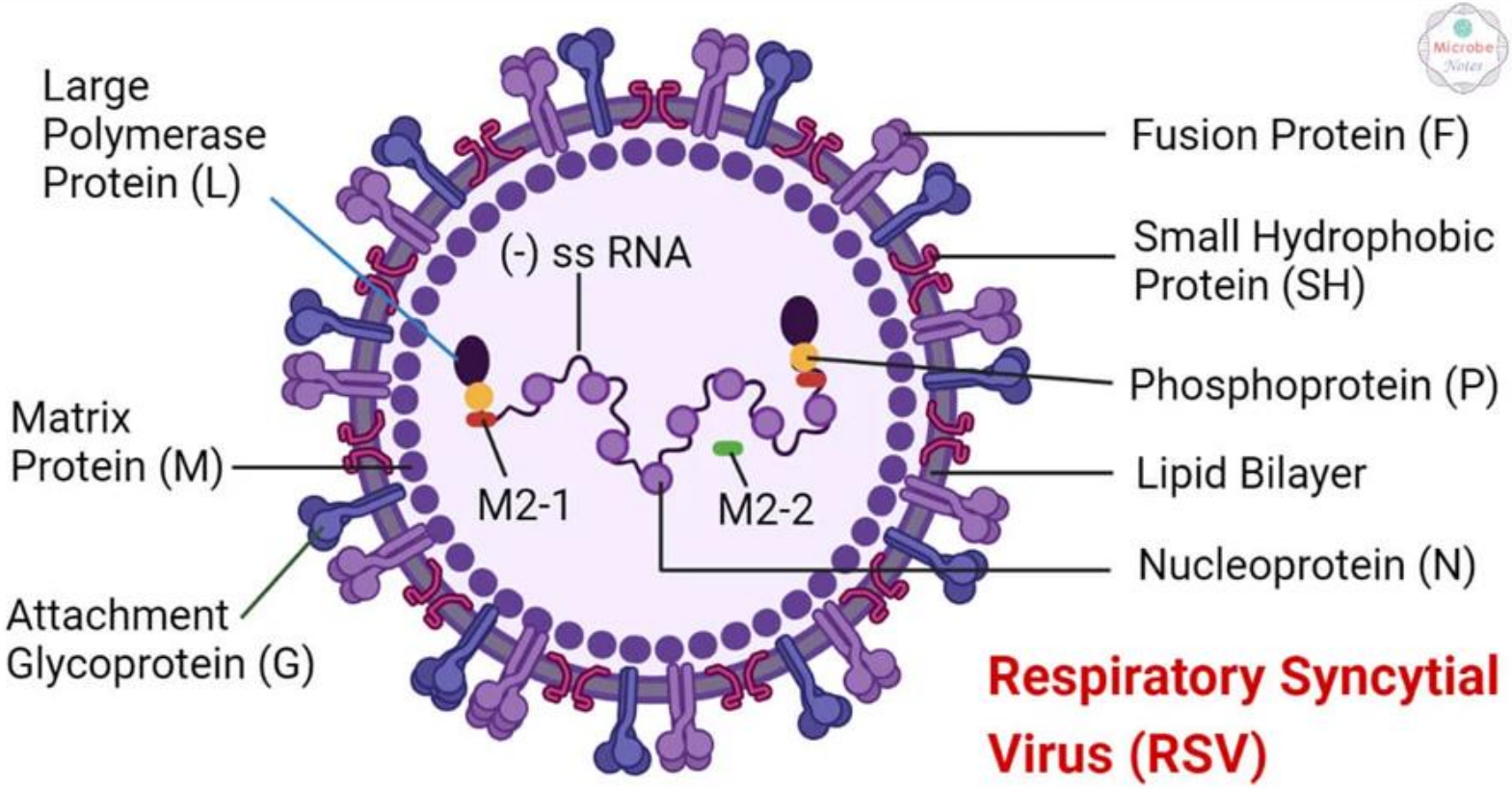
- Negative sense, single stranded, enveloped RNA virus
  - Orthopneumovirus
  - Two types – A & B



- Causes full spectrum of respiratory infection
  (depending on age, risk factors and immune function)
- Non-segmented → no genetic re-assortment → no shifts → no large pandemics
- Reinfection occurs throughout life

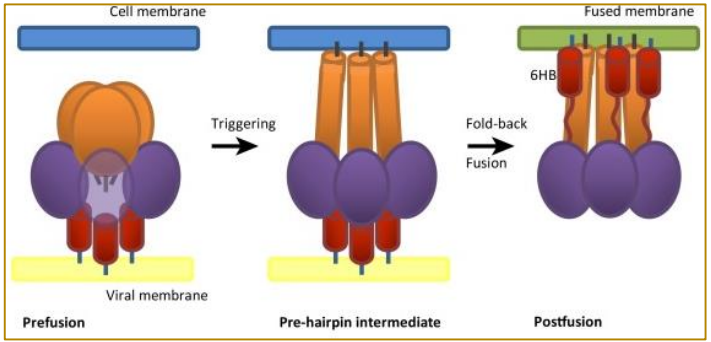
Nguyen-Van-Tam JS, et al Euro Resp Review doi.org/10.1183/16000617.0105-2022

Respiratory Syncytial Virus (RSV)



F Protein

- F protein - responsible for fusion of the viral and host cell membrane



- F protein exists in several forms
  - PreF, Fusion, PostF
- PreF contains the antigenic site Ø which is the primary target of neutralizing antibodies in the body

https://www.cell.com/trends/microbiology/fulltext/S0966-842X%2817%2930214-7

Phase III RSV Vaccine Studies

Case 1

- Alison is a 75 year old, recently widowed female with hypothyroidism and lumbar radiculopathy who presents for a 6-month follow up exam.

- She recently saw a magazine ad for a new RSV vaccine. For reasons unknown, she respects your opinion. She asks you if she should get the vaccine.

Case 1

You respond:

A. Heaven’s no, are you crazy?
B. Yes, the vaccine is FDA approved, so works.
C. Yes, the vaccine is FDA approved, so is safe.
D. Yes, it is both FDA approved and ACIP recommended.
E. I have no clue, call Dr. Nace.
F. Well it depends…

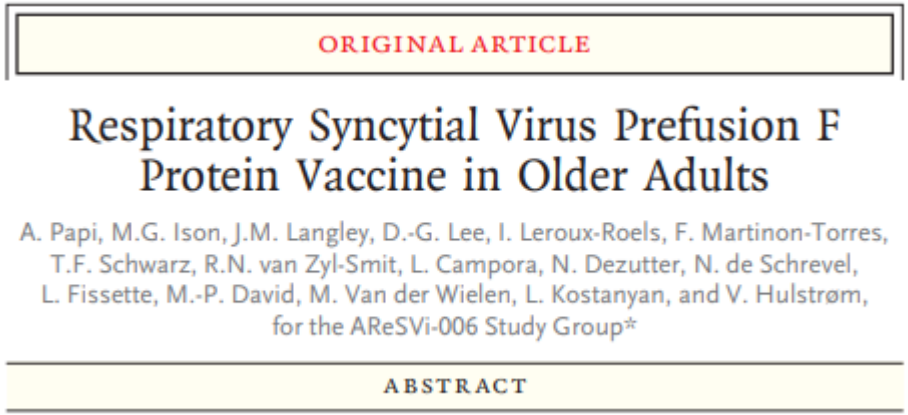
GSK Adjuvanted Vaccine
(RSVPreF3 OA, GSK)

Interim Analysis

- Phase III multinational study
- 3 consecutive RSV seasons Northern Hemisphere
- **May 25, 2021 – April 11, 2022**

- ≥ 60 years
- Stable chronic medical conditions
- Randomized, placebo controlled

- Contact Q 2 weeks starting day 30



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

Papi A, et al. N Engl J Med 2023;388:595-608 DOI: 10.1056/NEJMoa2209604

Objectives

PCR Confirmed RSV

- Primary
  - Prevention of RSV lower respiratory tract disease (LRTD) **during one season**
- Secondary
  - RSV acute respiratory disease
  - Severe RSV lower respiratory disease
  - RSV lower respiratory tract disease by subtype (RSV A & RSV B)
  - RSV lower respiratory tract disease by
    - Age, frailty, comorbid conditions
  - Safety, reactogenicity, immunogenicity

Papi A, et al. N Engl J Med 2023;388:595-608 DOI: 10.1056/NEJMoa2209604

Definitions

- Acute respiratory infection
  - ≥ 2 respiratory signs/symptoms, or
  - ≥ 1 respiratory sign/symptom & 1 systemic symptom

- LRTD ***(primary outcome)***
  - ≥ 1 lower respiratory symptom and 1 sign, or
  - ≥ 3 lower respiratory symptoms

- Severe LRTD
  - LRTD signs & assessed as *"severe"* by investigator, or
  - LRTD & oxygen, or CPAP, or mechanical ventilation

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Papi A, et al. N Engl J Med 2023;388:595-608 DOI: 10.1056/NEJMoa2209604
FDA Briefing Document VRBPAC Meeting March 1, 2023

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Results

- 24,960 participants
  - Mean age = 69.5 yr
  - Coexisting conditions = 39%
  - Mean f/u = 6.7 mos

IR-Incidence Rate
(events/1000 pt-yrs)

	Events-Vaccine *(population)*	IR Vaccine	Events-Placebo *(population)*	IR Placebo	Vaccine Efficacy *(CI)*
LRTD	**7** *(12,466)*	1.0	**40** *(12,494)*	5.8	**82.6** *(57.9-94.1)*
Severe LRTD*	**1** *(12,466)*	0.1	**17** *(12,494)*	2.5	**94.1** *(62.4-99.9)*
60-69 yrs	**4** *(6963)*	1.0	**21** *(6979)*	5.5	**81.0** *(43.6-95.3)*
70-79 yrs	**1** *(4487)*	0.4	**16** *(4487)*	6.5	**93.8** *(60.2-99.9)*
≥ 70 yrs	**3** *(5503)*	1.0	**19** *(5515)*	6.3	**84.4** *(46.9-97.0)*
≥ 80 yrs	**2** *(1016)*	3.6	**3** *(1028)*	5.4	**33.8** *(-477.7-94.5)*

* Only 2 cases of severe LRTD occurred using the more stringent definition (both placebo)

“Frailty” Analysis

	Gait Speed (m/sec)
Frail	**< 0.4 m/sec**
Prefrail	**0.4 - 0.99 m/sec**
Fit	**≥ 1.0 m/sec**

IR-Incidence Rate
(events/1000 pt-yrs)

	Events-Vaccine *(population)*	IR Vaccine	Events-Placebo *(population)*	IR Placebo	Vaccine Efficacy *(CI)*
Frail	**1** *(189)*	10.4	**1** *(177)*	10.8	**NS**
Prefrail	**1** *(4792)*	0.4	**14** *(4778)*	5.5	**92.9** *(53.4-99.8)*
Fit	**5** *(7464)*	1.2	**25** *(7519)*	5.9	**80.0** *(46.7-94.0)*

Papi A, et al. N Engl J Med 2023;388:595-608 DOI: 10.1056/NEJMoa2209604

Authors' Conclusions

- RSVPreF3 vaccine efficacy in adults 60+ yrs
  - 82% against LRTD
  - 94% against severe RSV LRTD
  - 71.7% against acute respiratory disease
- Acceptable safety profile

Papi A, et al. N Engl J Med 2023;388:595-608 DOI: 10.1056/NEJMoa2209604

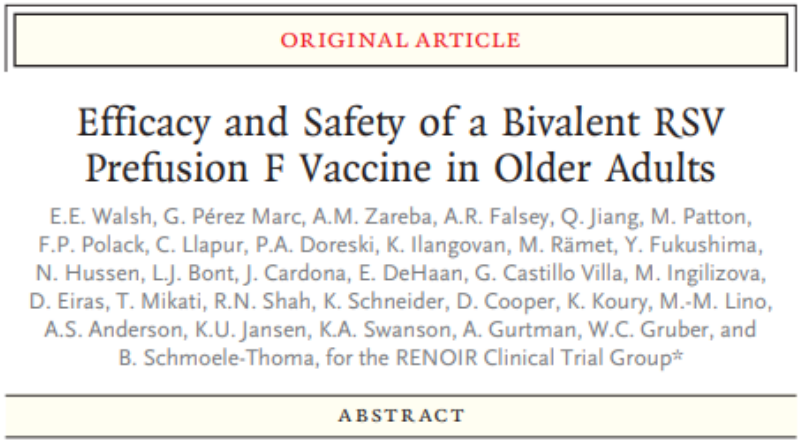
Pfizer Vaccine
(RSVpreF)

Interim Analysis

- Phase III multinational study
- 2 consecutive RSV seasons
- **Aug 31, 2021 – July 14, 2022**

- ≥ 60 years
- Stable chronic medical conditions
- Randomized, placebo controlled

- Weekly electronic diary entries



ORIGINAL ARTICLE

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

E.E. Walsh, G. Pérez Marc, A.M. Zareba, A.R. Falsey, Q. Jiang, M. Patton, F.P. Polack, C. Llapur, P.A. Doreski, K. Ilangovan, M. Rämet, Y. Fukushima, N. Hussen, L.J. Bont, J. Cardona, E. DeHaan, G. Castillo Villa, M. Ingilizova, D. Eiras, T. Mikati, R.N. Shah, K. Schneider, D. Cooper, K. Koury, M.-M. Lino, A.S. Anderson, K.U. Jansen, K.A. Swanson, A. Gurtman, W.C. Gruber, and B. Schmoele-Thoma, for the RENOIR Clinical Trial Group*

ABSTRACT

Walsh EE, et al. N Engl J Med 2023; 388:1465-1477 DOI: 10.1056/NEJMoa2213836

Objectives

PCR Confirmed RSV

- Primary
  - Prevention of RSV lower respiratory tract disease (LRTD) with 2 symptoms
  - Prevention of RSV lower respiratory tract disease (LRTD) with 3 symptoms
- Secondary
  - RSV acute respiratory disease
  - Severe RSV lower respiratory tract disease
  - Safety, reactogenicity, immunogenicity

Walsh EE, et al. N Engl J Med 2023; 388:1465-1477 DOI: 10.1056/NEJMoa2213836

Definitions

- Acute respiratory infection
  - ≥ 1 respiratory signs/symptoms
- LRTD *(primary outcome)*
  - ≥ 2 lower respiratory signs/symptoms, or
  - ≥ 3 lower respiratory signs/symptoms
- Severe LRTD
  - LRTD met, plus
  - Hospitalization due to RSV, or
  - New / increased oxygen need, or
  - New / increased mechanical ventilation or CPAP

Walsh EE, et al. N Engl J Med 2023; 388:1465-1477 DOI: 10.1056/NEJMoa2213836
FDA Briefing Document VRBPAC Meeting February 28 2023 - March 1, 2023

Results

- 34,284 participants
  - Mean age = 67 yr
  - Coexisting conditions = 52%
  - Mean f/u = 7 mos

IR-Incidence Rate
(events/1000 pt-yrs)

	Events-Vaccine *(population)*	IR Vaccine	Events-Placebo *(population)*	IR Placebo	Vaccine Efficacy *(CI)*
LRTD ≥ 2 s/s	**11** *(16,306)*	1.19	**33** *(16,308)*	3.58	**66.7** *(28.8-85.8)*
LRTD ≥ 3 s/s	**2** *(16,306)*	0.22	**14** *(16,308)*	1.52	**85.7** *(32.0-98.7)*

LRTD ≥ 2 s/s	Percent of Participants*	Events-Vaccine	Events-Placebo	Vaccine Efficacy *(CI)*
60-69 yrs	**62.4%** *(21,393)*	**8**	**19**	**57.9** *(-7.4-95.3)*
70-79 yrs	**31.9%** *(10,937)*	**2**	**9**	**77.8** *(-18.7-98.1)*
≥ 80 yrs	**5.7%** *(1,954)*	**1**	**5**	**80.0** *(-104.3-99.7)*

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* Population data derived from population percentages in VRBPAC briefing documents

Walsh EE, et al. N Engl J Med 2023; 388:1465-1477

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Authors' Conclusions

- RSVpreF vaccine efficacy in adults 60+ yrs
  - 66.7% against LRTD ≥ 2 s/s
  - 85.7% against LRTD ≥ 3 s/s
- Not enough cases of severe LRTD to evaluate vaccine efficacy (2 in placebo)
- Acceptable safety profile

Papi A, et al. N Engl J Med 2023;388:595-608 DOI: 10.1056/NEJMoa2209604

What Do We Make Of This Data?

Under-Representation of Key Populations

- 80+ age group under-represented (both studies)
- PALTC population minimal (309 LTC - GSK only)
- Can’t determine vaccine response across frailty states
- Frailty characterization & scoring not adequate (GSK only)

Vaccine Response Questions

- Atypical season (2021-2022) with low RSV rate
- Minimal cases of severe disease
- Uncertain impact of COVID mitigation efforts
- No information on duration of protection or immunogenicity

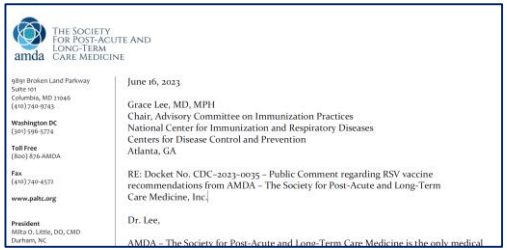
Safety Questions

	GSK	Pfizer
SAE	4.2% Vax vs 4.0% Pcb	3.3% Vax vs 3.2% Pcb
Fatal SAE	0.3% Vax vs 0.4% Pcb	0.3% Vax vs 0.3 Pcb
Guillian-Barre Syndrome (GBS)	Vaccine = 1 • Occurred in earlier phase non-placebo controlled w/i 42 days	Vaccine = 3 • 2 w/i 42 days • 1 @ 8 months Placebo = 1 @ 14 months
Acute Disseminated Encephalomyelitis	Vaccine = 2 • ***Both co-administered with flu vaccine*** • 1 fatal	None
Deaths in Phase III trial	3 (blinded per VRBPAC data) • Vaccine = 2 • Placebo = 1	None

Recommendations

AMDA Recommendations to ACIP

1. AMDA should recommend use of the licensed GSK and Pfizer RSV vaccines through a shared-decision making process. The Task Force notes that many PALTC residents are at particularly high risk for RSV. Demonstration of the risk alone is insufficient to warrant a definite recommendation for vaccination. Despite a promising overall vaccine efficacy in the reported phase III trials, the limitations noted above are significant. Continued evaluation of the vaccines, particularly regarding vaccine effectiveness, duration of immunity, and vaccine safety among PALTC residents must occur. the Task Force believes thoughtful, shared-decision making between PALTC residents and providers is essential.



THE SOCIETY FOR POST-ACUTE AND LONG-TERM CARE MEDICINE

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President
Milta O. Little, DO, CMD
Durham, NC

June 16, 2023

Grace Lee, MD, MPH
Chair, Advisory Committee on Immunization Practices
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

RE: Docket No. CDC-2023-0035 – Public Comment regarding RSV vaccine recommendations from AMDA – The Society for Post-Acute and Long-Term Care Medicine, Inc.

Dr. Lee,

AMDA – The Society for Post-Acute and Long-Term Care Medicine is the only medical

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AMDA Recommendations to ACIP

2. AMDA should recommend continuation of clinical trials of the RSV vaccines across several vaccines seasons, focusing on both vaccine effectiveness and safety.

3. AMDA should recommend studies of PALTC residents, frail individuals, and further study among a larger number of individuals at advanced age (80 years and older).

4. AMDA should recommend evaluation of duration of vaccine immunity across community, frail, and PALTC populations.

5. AMDA should recommend analysis of the kinetics of RSV spread among PALTC populations.

AMDA Recommendations to ACIP

6. AMDA should recommend that neither vaccine be given simultaneously with influenza vaccine or other vaccines until further studies are conducted.

7. AMDA should not at this time support quality metrics targeting uptake of RSV vaccine. Given the concerns raised above, it is premature to consider clear support for vaccination across the 60+ age group.

8. AMDA should not make a preferential recommendation of one RSV vaccine over another given the limited clinical trial data available.

Current Status

- Both GSK and Pfizer **approved** by FDA in May 2023

- ACIP recommended both vaccines on June 21, 2023
  - Adults 60+ years
  - **Shared-decision making**
  - Not a blanket decision - meaning the provider and patient must jointly decide

- CMS coverage rule pending

RSV Vaccine Pipeline Status

Approved / In-Development

Company	Vaccine Type	FDA Status (Older Adults)	ACIP Status
GSK	Adjuvanted	Approved (60+ yrs)	Recommended
Pfizer	Adjuvanted	Approved (60+ yrs)	Recommended
Moderna	mRNA	Submitted to FDA	N/A

Discontinued / Halted

Janssen	Adenovirus	70-80% efficacy in CYPRESS Phase 2b, but Phase 3 EVERGREEN study stopped (“company re-alignment”)
Bavarian Nordic	Poxvirus	Phase 3 trial > 59% efficacy 2 symptom LRTD, but only 42.9% against 3 symptom severe LRTD

Case 1

- Alison is a 75 year old, recently widowed female with hypothyroidism and lumbar radiculopathy who presents for a 6 month follow up exam.

- She recently saw a magazine ad for a new RSV vaccine. For reasons unknown, she respects your opinion. She asks you if she should get the vaccine.

Case 1

You respond:

A. Heaven's no, are you crazy?
B. Yes, the vaccine is FDA approved, so works.
C. Yes, the vaccine is FDA approved, so is safe.
D. Yes, it is both FDA approved and ACIP recommended.
E. I have no clue, call Dr. Nace.
F. **Well it depends…**

Additional References

- AMA Discussion with Dr. Sandra Fryhofer
  - https://www.ama-assn.org/print/pdf/node/105016
- FDA Vaccines and Related Biological Products Advisory Committee. (Meeting Calendar & Documents)
  - https://www.fda.gov/advisory-committees/advisory-committee-calendar
- ACIP Information
  - https://www.cdc.gov/vaccines/acip/meetings/index.html

Thank You!

Questions?

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