Medscape EDUCATION

Respiratory Syncytial Virus in Adults:
Why It Should Be on Your Radar

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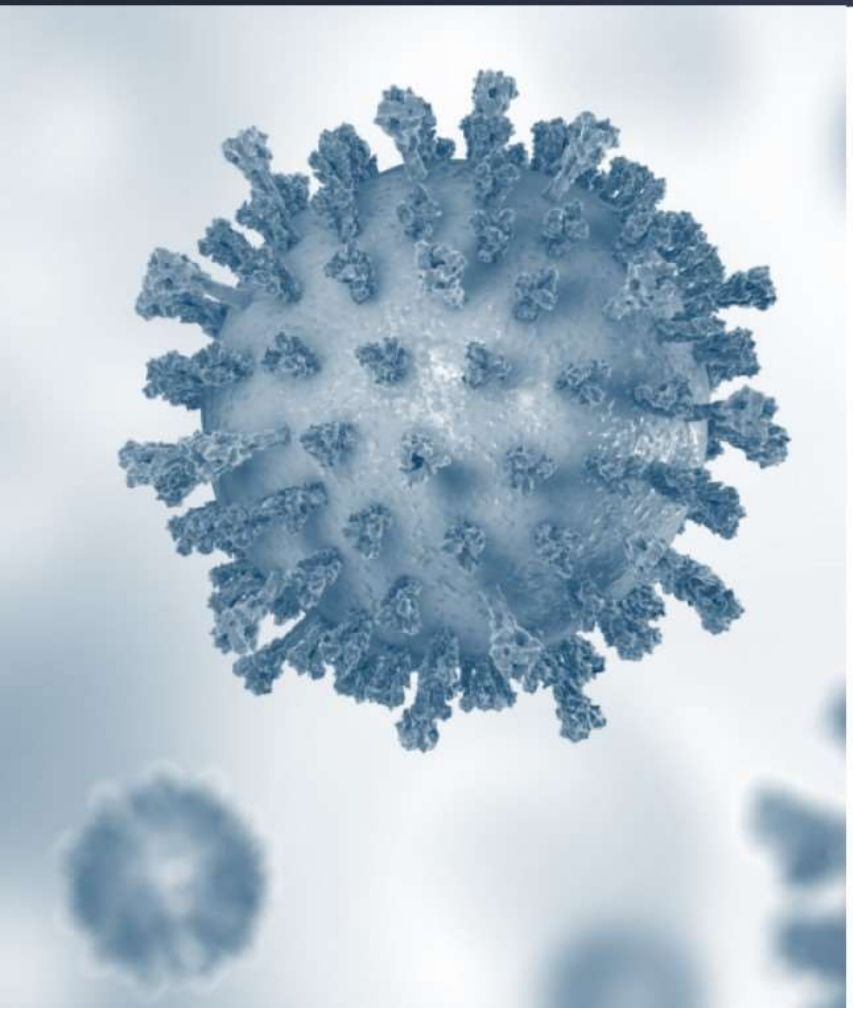
Introduction



RSV infection[a-c]

Remains one of the leading causes of lower RTIs

RSV impact on adults[b,c]

Although the burden is highest in children, RSV infections are also associated with high rates of hospitalization and morbidity in ≥ 65-y-olds and high-risk adults

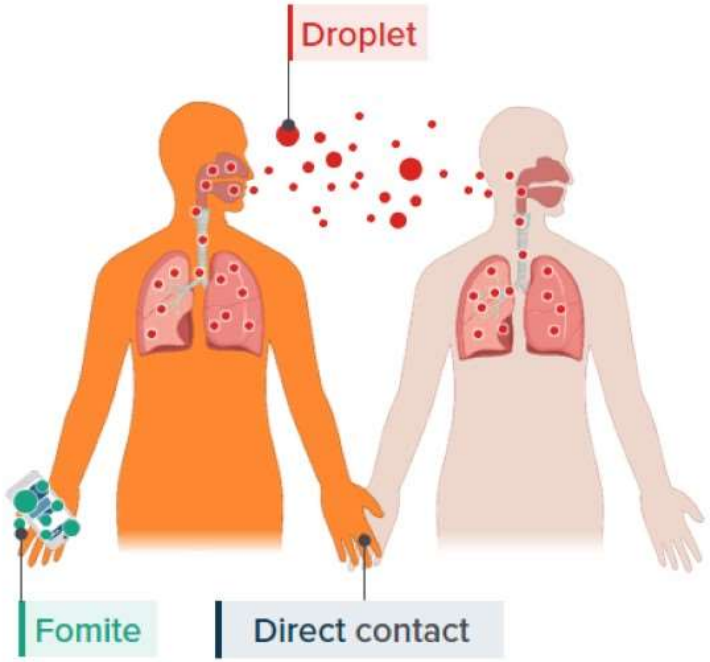
RSV, respiratory syncytial virus; RTI, respiratory tract infection.

a. Staadegaard L, et al. Open Forum Infect Dis. 2021;8:ofab159; b. Shi T, et al. J Infect Dis. 2020;222:S577-S583; c. Tin Tin Htar M, et al. Epidemiol Infect. 2020;148:e48.

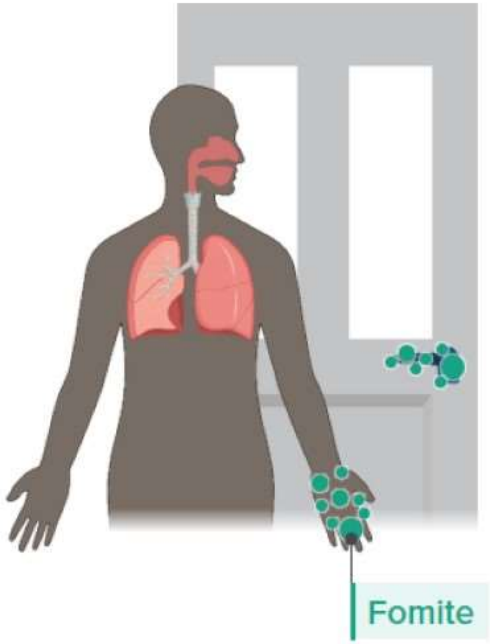
RSV Transmission

RSV spreads by air droplets or fomites[a,b]

Short-range transmission[a]



Long-range transmission[a]



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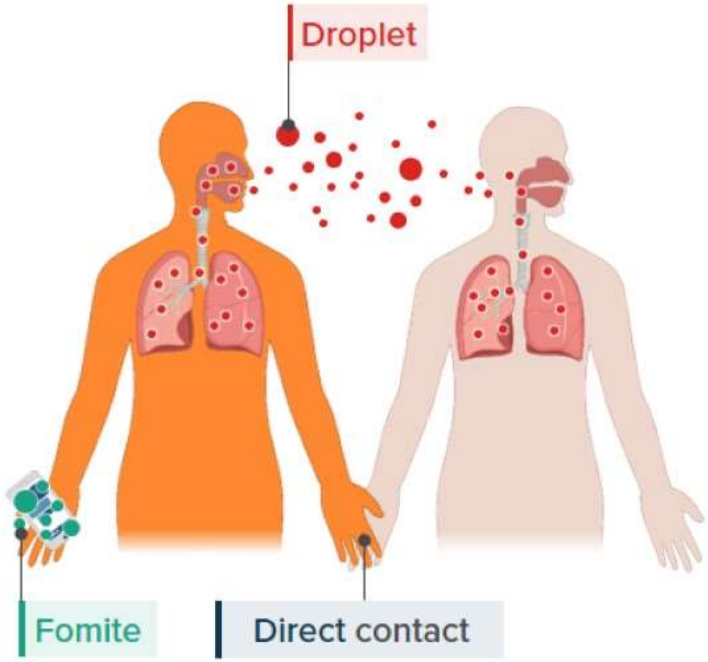

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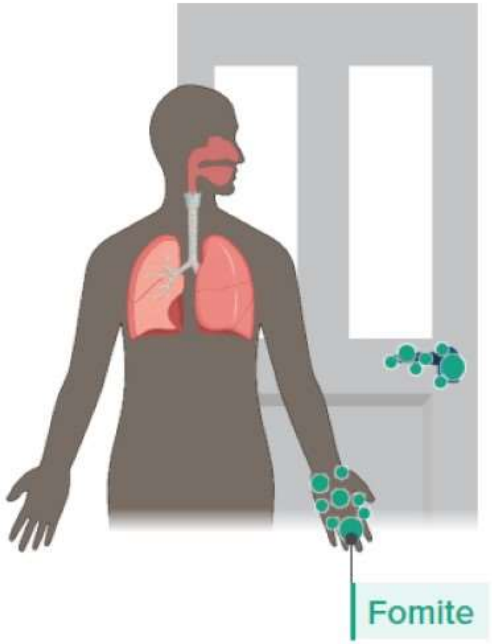


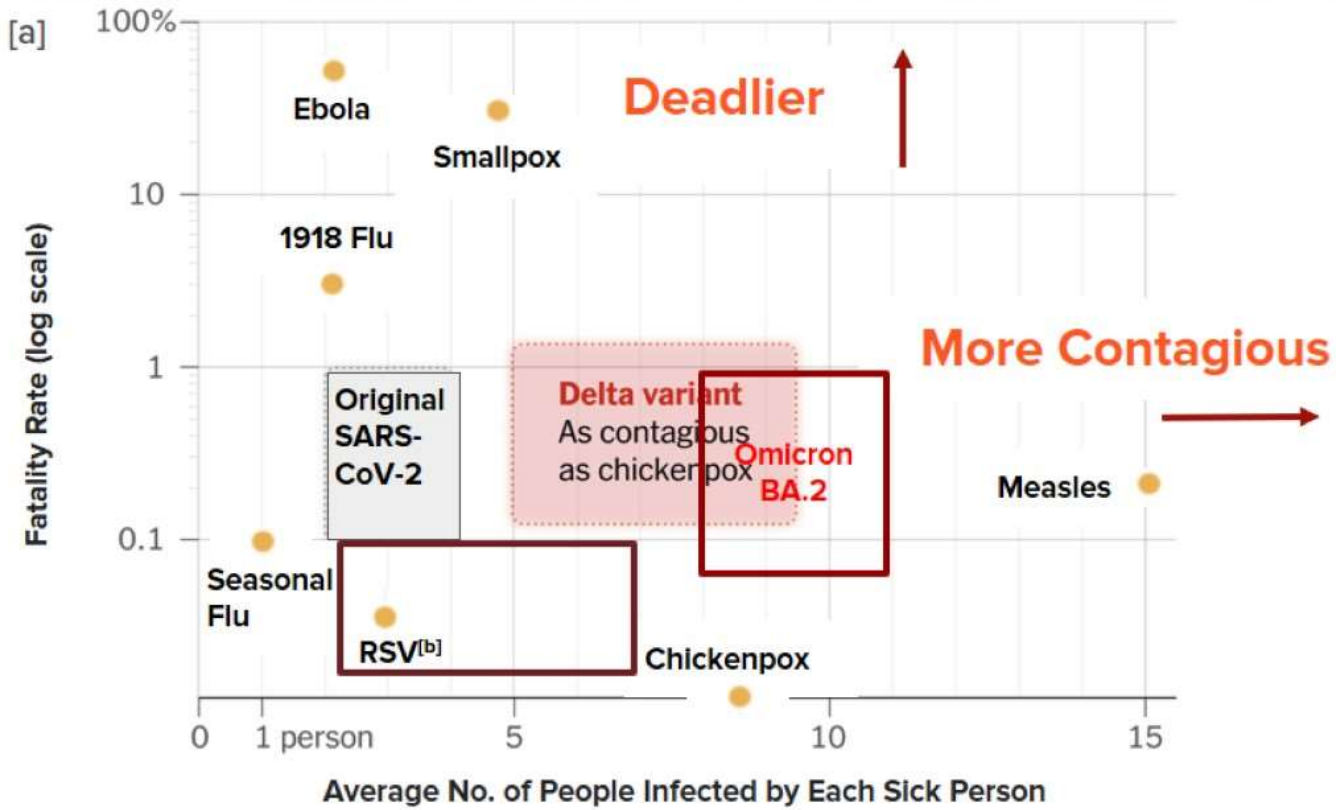
- R_0 has been estimated from 3 to 25 individuals, depending on model assumptions[c-f]
- R_0 of 3 predicts peak of outbreaks[d]

R_0, basic reproductive number.

a. Leung NHL. Nat Rev Microbiol. 2021;19:528-545; b. CDC. Updated December 18, 2020. Accessed June 29, 2022. https://www.cdc.gov/rsv/about/transmission.html; c. Weber A, et al. Math Biosci. 2001;172:95-113; d. Reis J, et al. PLoS Comput Biol. 2016;12:e1005133; e. van Boven M, et al. J Infect Dis. 2020;222:S688-S694; f. Stefan Gravenstein, MD, MPH communication.

RSV Transmission

RSV is underestimated because it is not as contagious and deadly as are other viruses



Slide courtesy of Stefan Gravenstein, MD, MPH. Figure adapted from Mandavilli A. *New York Times*. July 30, 2021. Accessed June 29, 2022. https://www.nytimes.com/2021/07/30/health/covid-cdc-delta-masks.html; b. Reis J, et al. PLoS Comput Biol. 2016;12:e1005133.

Risk Factors for Severe RSV Infection

a. Griffiths C, et al. Clin Microbiol Rev. 2017;30:277-319; b. Young M, et al. Infect Dis Ther. 2021;10:35-45.

RSV Infection

Before the '90s, RSV was considered to be a **disease of early childhood**[a]

Since the 2000s, RSV has been recognised as a **significant problem in elderly adults**, both in the community and in long-term care facilities[b]

a. Hall CB. Yale J Biol Med. 1982;55:219-223; b. Falsey AR. N Engl J Med. 2005;352:1749-1759.

Incidence of RSV and Influenza in Adults

3% to 7% of older adults and 4% to 10% of high-risk adults experience RSV disease annually[a]

PCR, polymerase chain reaction; RESCEU, REspiratory Syncytial Virus Consortium in Europe.
a. Falsey AR, et al. N Engl J Med. 2005;352:1749-1759; b. Korsten K, et al. Eur Respir J. 2021;57:2002688.

Incidence of RSV and Influenza in Adults

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Incidence of PCR-Confirmed RSV and Influenza A and B Virus Infection

No./Total No. With Illness (%)	Healthy Older Adults (Falsey)[a]	High-Risk Adults (Falsey)[a]	Older Adults 2017-2018 (RESCEU)[b]	Older Adults 2018-2019 (RESCEU)[b]
RSV	46/519 (8.8)	56/524 (10.6)	22/527 (4.2)	37/513 (7.2)
Influenza A and B virus	31/519 (5.9)	32/524 (6.1)	42/527 (8.0)	17/513 (3.3)

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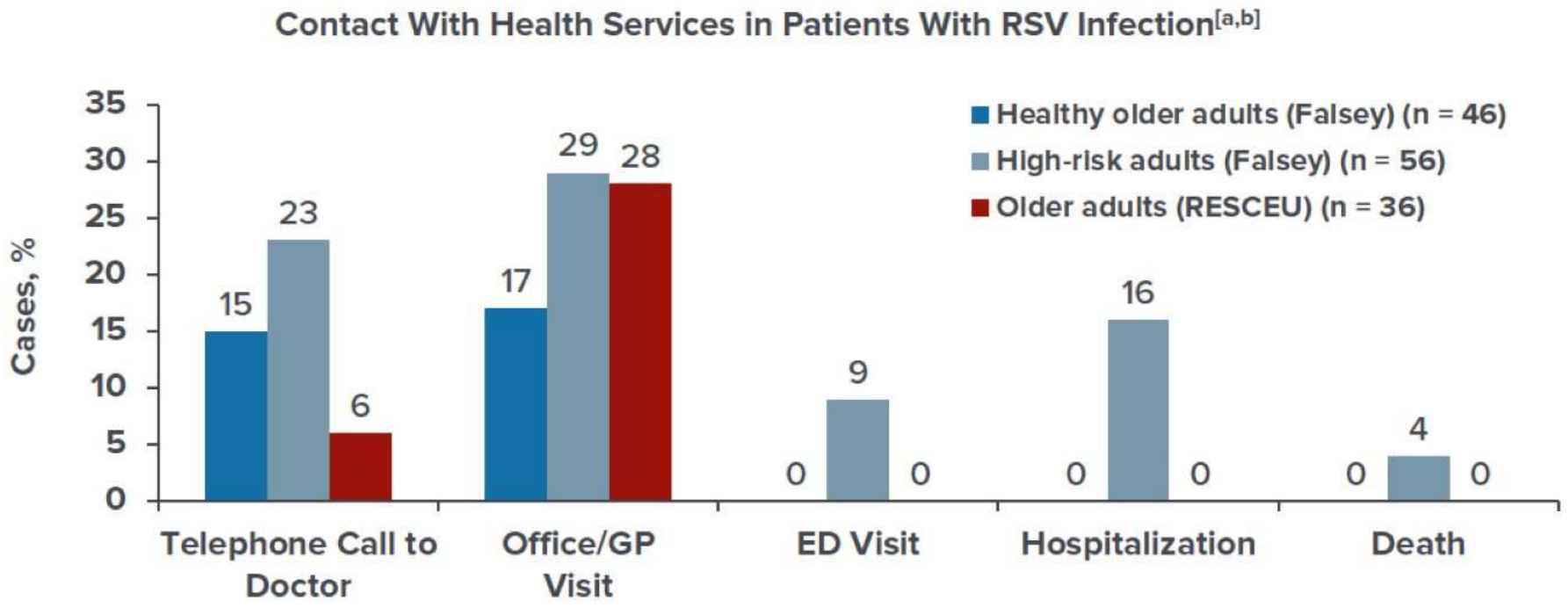
RSV-Related MRU in Healthy and High-Risk Adults

RSV Infection Causes Considerable MRU in Older and High-Risk Adults



ED, emergency department; GP, general practice; MRU, medical resource use.

a. Falsey AR, et al. N Engl J Med. 2005;352:1749-1759; b. Korsten K, et al. Eur Respir J. 2021;57:2002688.

Burden of RSV Disease in Older Adults in the United States

Annual attack rates[a]

- **2% to 10%** in older adults within the community
- **5% to 10%** in older adults within congregate settings

a. Branche AR. Drugs Aging. 2015;32:261.

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Mortality[b,c]

- **80%** of deaths are in adults ≥ 65 y of age

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Disease burden is underestimated[a,d]

- Expected to increase considering the aging population

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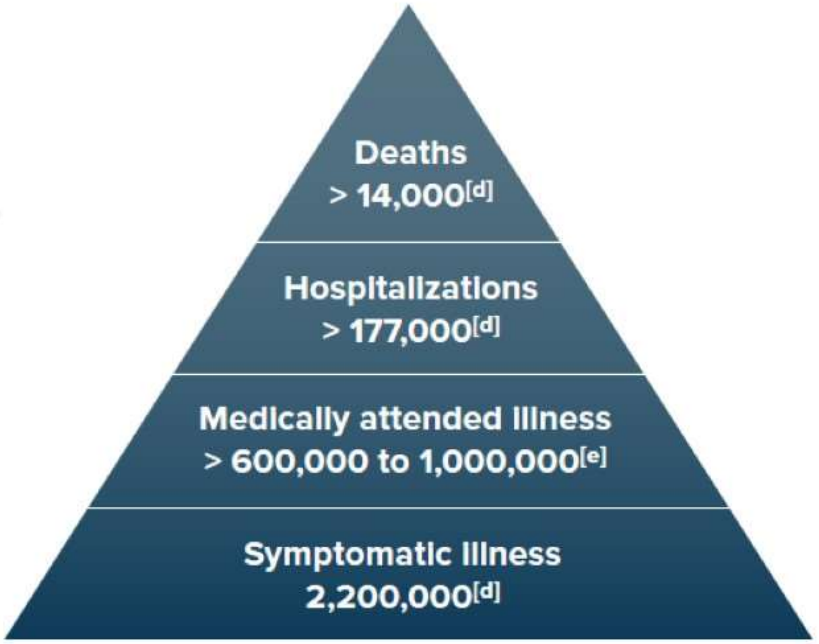
Mortality[b,c]

- Up to **90%** of deaths are in adults ≥ 65 y of age

Disease burden is underestimated[a,d]

- Expected to increase considering the aging population

Estimated Annual RSV Cases in Adults Aged ≥ 65 y



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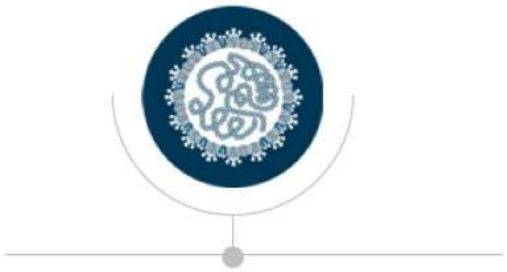
Deaths From Respiratory Infections in Adults in the United States



SARS-CoV-2[a]

Since March 2020, > 1 million
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Pneumococcus[c]

~25,000 pneumococcus-related deaths were reported annually in individuals aged > 50 y

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Pneumococcus[c]

~25,000 pneumococcus-related deaths were reported annually in individuals aged > 50 y

RSV[d]

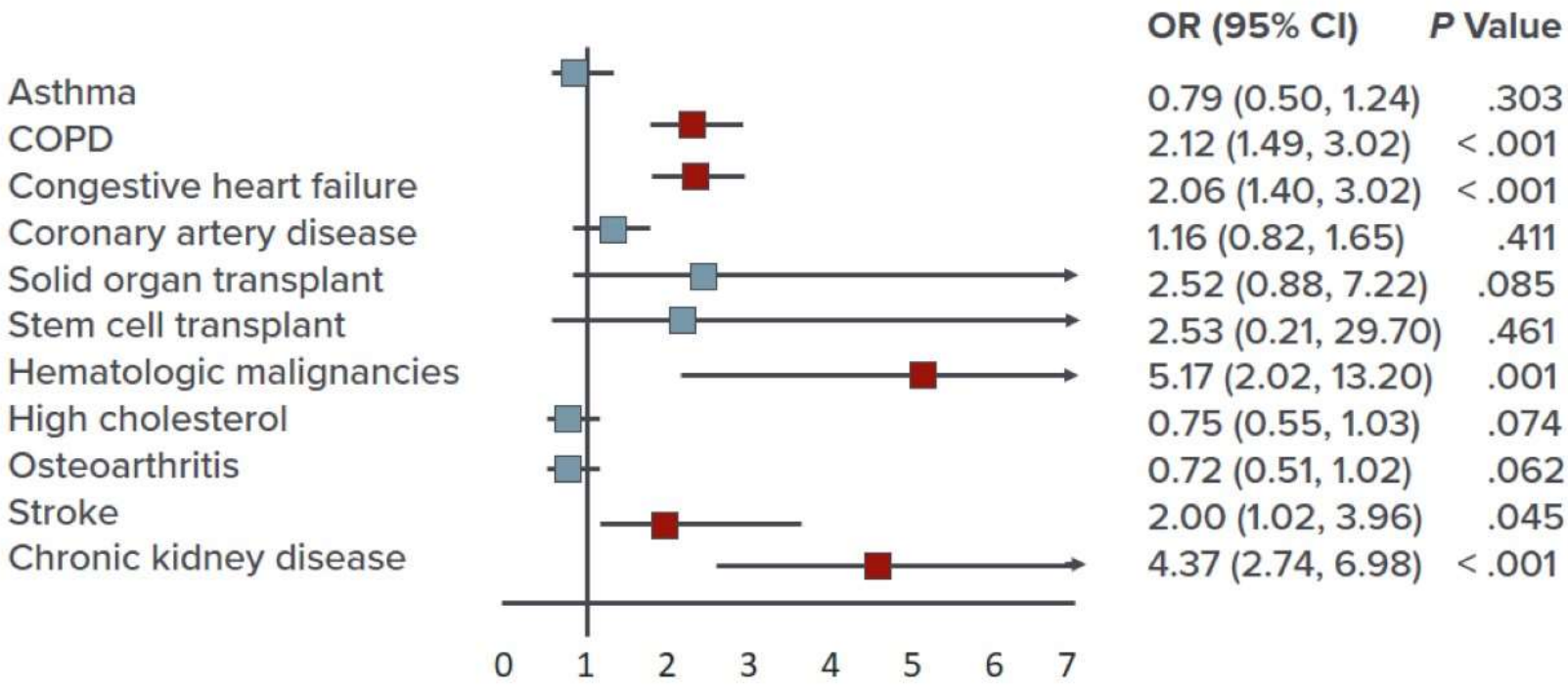
~14,000 in-hospital RSV-ARI-related deaths were estimated to be reported annually in older adults

ARI, acute respiratory infection.

a. Our World in Data. Accessed June 29, 2022. https://ourworldindata.org/covid-deaths; b. CDC. 2020. Accessed July 2, 2022. https://www.cdc.gov/flu/about/burden/past-seasons.html; c. Weinberger B. Immun Ageing. 2021;18:38; d. CDC. June 23, 2022. Accessed June 29, 2022. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-22-23/04-rsv-havers-508.pdf

Predictors of Hospitalization in Adult Patients With ASV

- Predictors of initial hospitalization in 756 adults aged > 18 y diagnosed with RSV were estimated using the 5% US Medicare database (2011-2015)



	OR (95% CI)	*P* Value
Asthma	0.79 (0.50, 1.24)	.303
COPD	2.12 (1.49, 3.02)	< .001
Congestive heart failure	2.06 (1.40, 3.02)	< .001
Coronary artery disease	1.16 (0.82, 1.65)	.411
Solid organ transplant	2.52 (0.88, 7.22)	.085
Stem cell transplant	2.53 (0.21, 29.70)	.461
Hematologic malignancies	5.17 (2.02, 13.20)	.001
High cholesterol	0.75 (0.55, 1.03)	.074
Osteoarthritis	0.72 (0.51, 1.02)	.062
Stroke	2.00 (1.02, 3.96)	.045
Chronic kidney disease	4.37 (2.74, 6.98)	< .001

COPD, chronic obstructive pulmonary disease; OR, odds ratio.
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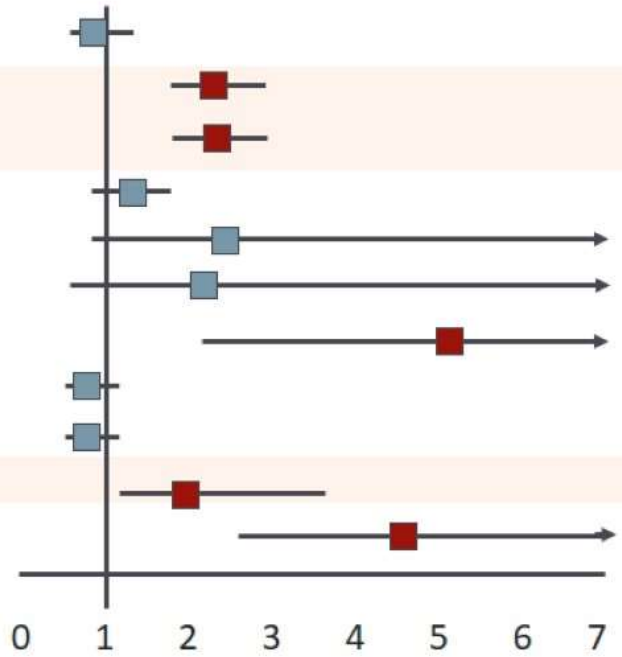

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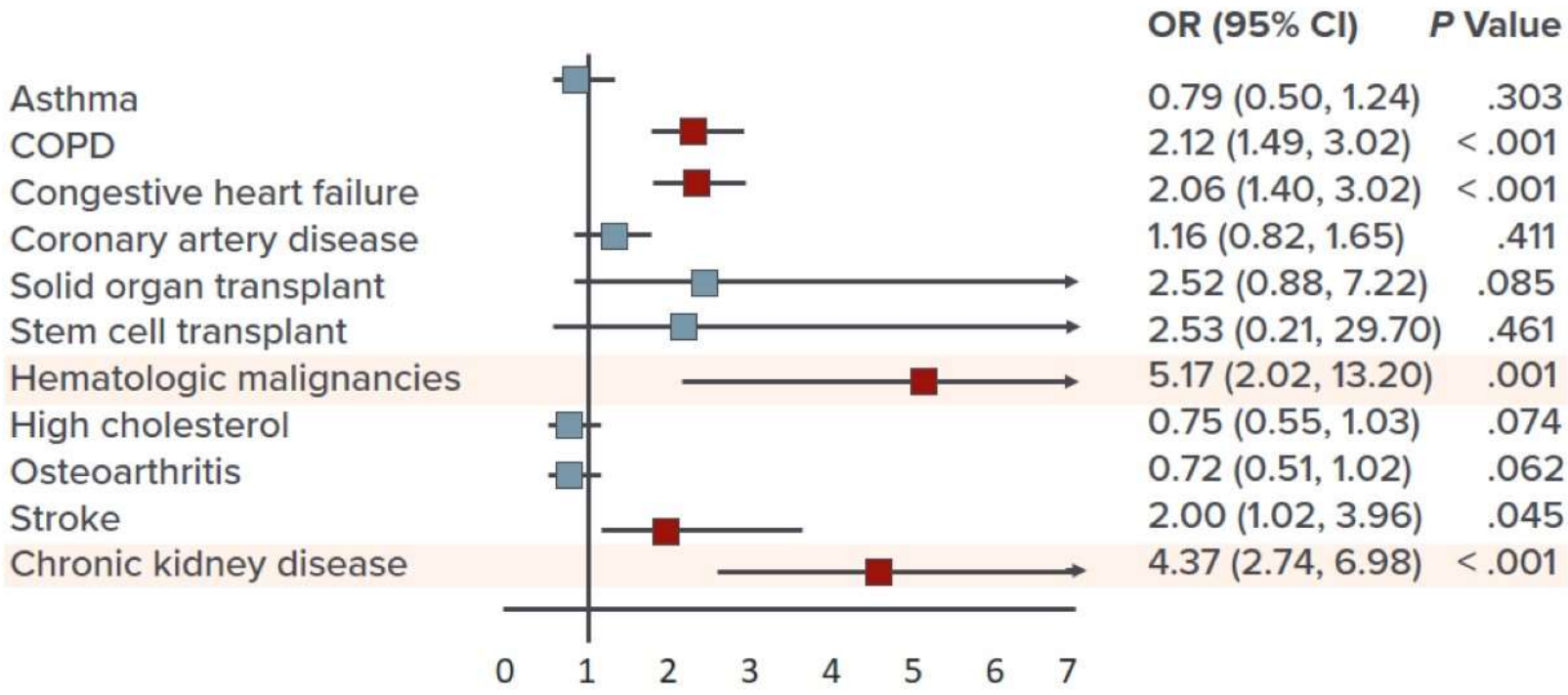

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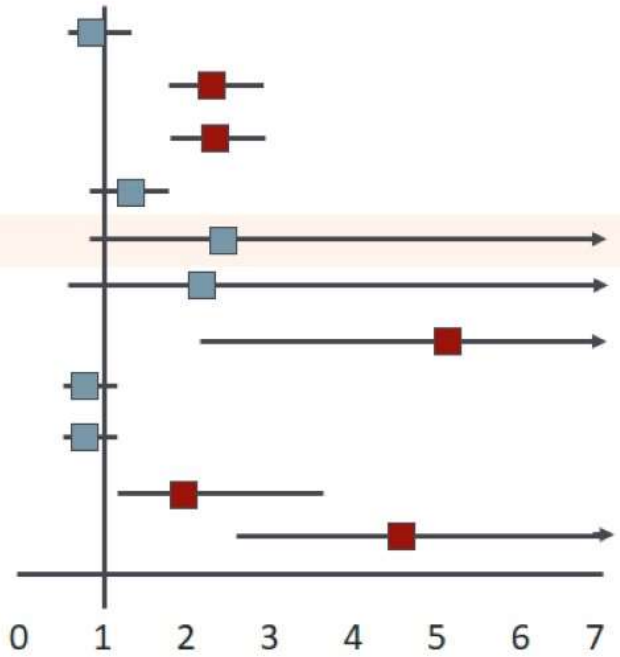

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Immunosenescence and RSV Infection

Older adults have greater susceptibility to infection because of lower RSV-specific Ig and nasal IgA[a,b]

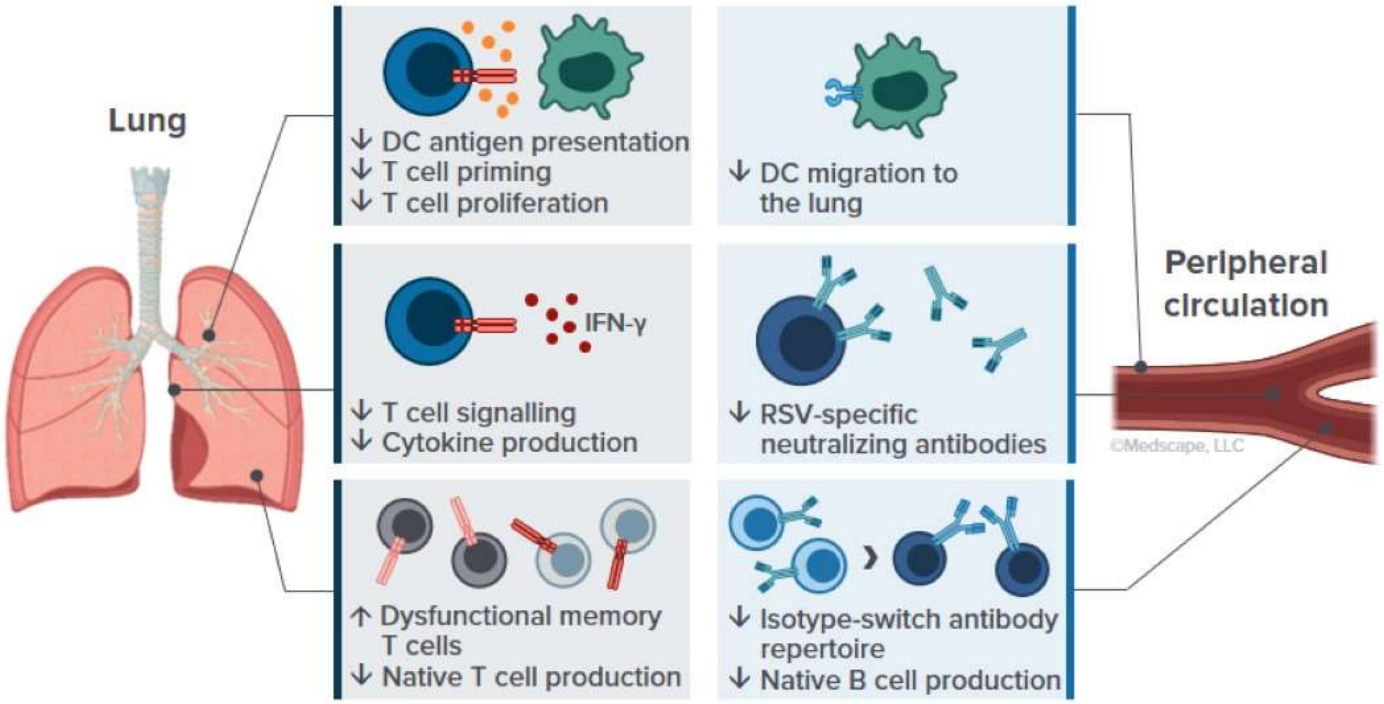
IgA, immunoglobulin A.

a. Walsh EE, et al. J Infect Dis. 2004;190:373-378; b. Griffiths C, et al. Clin Microbiol Rev. 2017;30:277-319.

Immunosenescence and RSV Infection

Older Adults Have Greater Susceptibility to Infection Due to Lower RSV-specific Ig and nasal IgA[a,b]

Older adults exhibit decline in T cell immunity, DC function and humoral immunity following exposure to RSV[d]



DC, dendritic cell; IgA, immunoglobulin A.

a. Walsh EE, et al. J Infect Dis. 2004;190:373-378; b. Griffiths C, et al. Clin Microbiol Rev. 2017;30:277-319; c. Stephens LM, et al. Vaccines (Basel). 2021;9:624.

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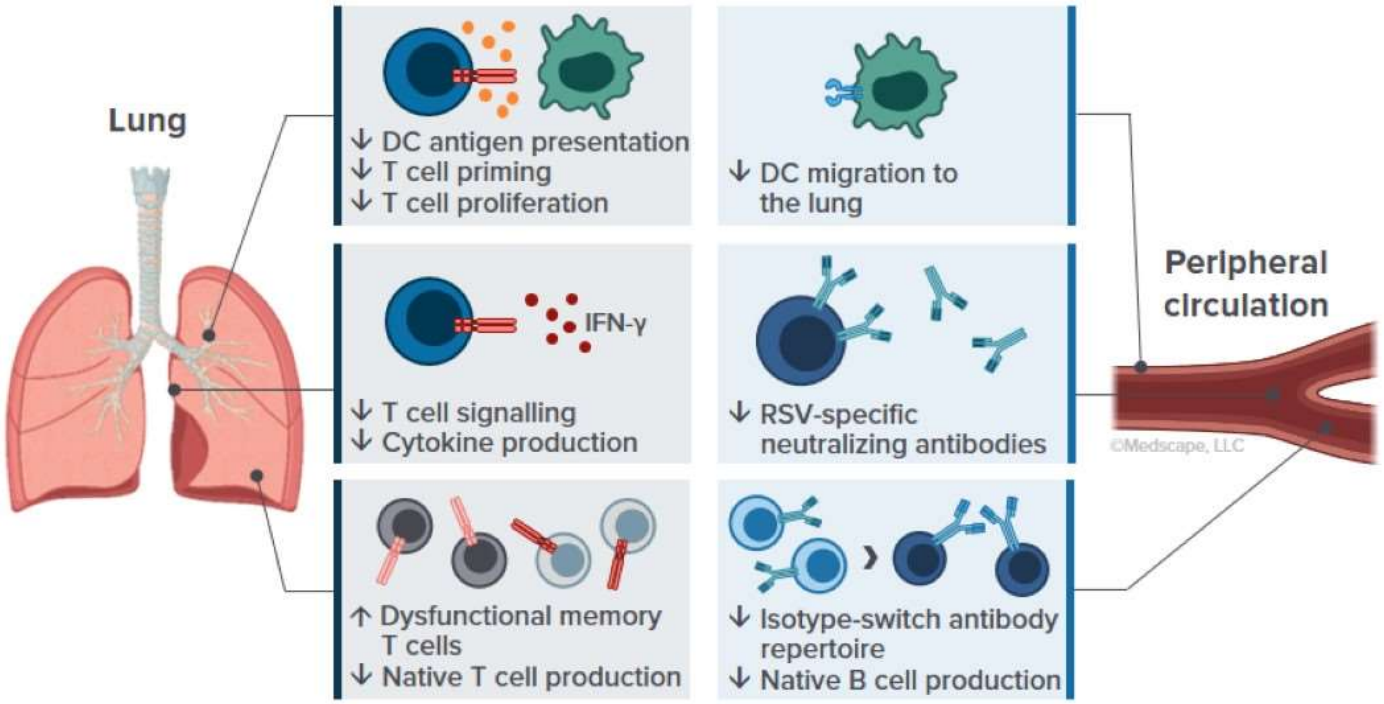


- Even if older adults with severe RSV have more robust CD4 and CD8 T cells during infection, it is unclear if severe disease is due to immunosenescence or "just" impaired T-cell responses and/or dysfunctional antibody[c,d]

Ab, antibody; DC, dendritic cell; IgA, immunoglobulin A.

a. Walsh EE, et al. J Infect Dis. 2004;190:373-378; b. Griffiths C, et al. Clin Microbiol Rev. 2017;30:277-319; c. Stephens LM, et al. Vaccines (Basel). 2021;9:624; d. Roumanes D, et al. J Infect Dis. 2018;218:418-428.

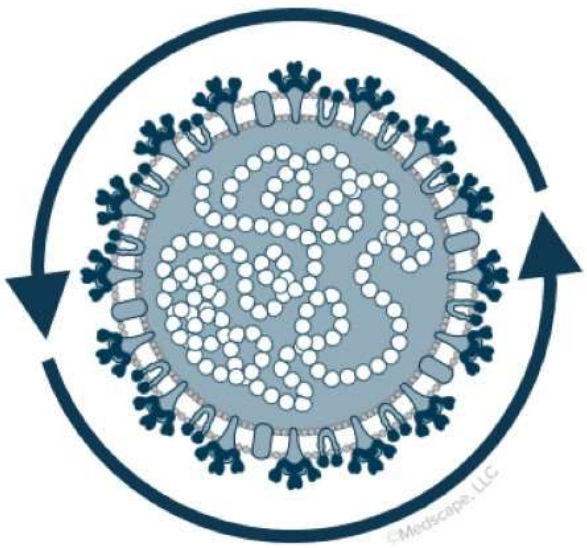
Biological Changes With Age and Clinical Presentation

Biological changes	Clinical effect
Reduced IL-6	Reduced fever, less-efficient viral clearance
Impaired respiratory tract mucociliary function	Reduced cough, less-efficient viral and mucous clearance
Delayed cytokine increase	Fewer symptoms at onset
Delayed cytokine normalization	Slower improvement and prolonged proinflammatory state
Reduced T-cell help	Reduced response to infection, vaccination; less durable

IL-6, interleukin 6.

Gravenstein S, et al. Med Health R I. 2010;93:382-384.

RSV Reinfection



Reinfections can occur throughout lifespan[a,b]

- First infection occurs in early childhood

Reinfections can occur within sequential years[a]

- Those occurring at close intervals were associated with decreasing symptoms and shedding

Lack of durable immunity[a,c]

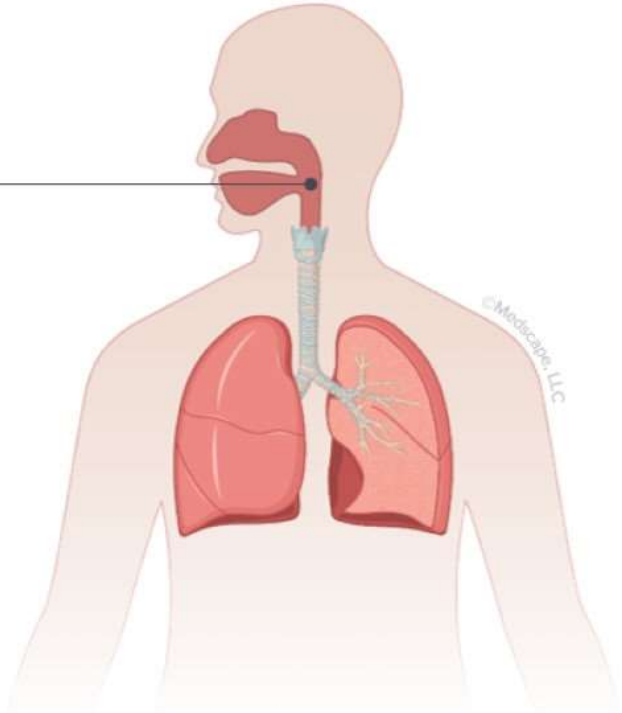
- A challenge study showed that adults became reinfected at 2, 3, 6 after the natural infection[c]

a. Walsh EE, et al. In: Bennett JE, et al, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier; 2015:1948-1960.e3; b. Hall CB, et al. J Infect Dis. 1991;163:693-698.

RSV Symptoms in Adults

Upper respiratory tract infection

- Sputum production[a]
- Headache[b]
- Voluminous rhinorrhea[a,b]
- Cough[a,b]
- Nasal congestion[a,b]



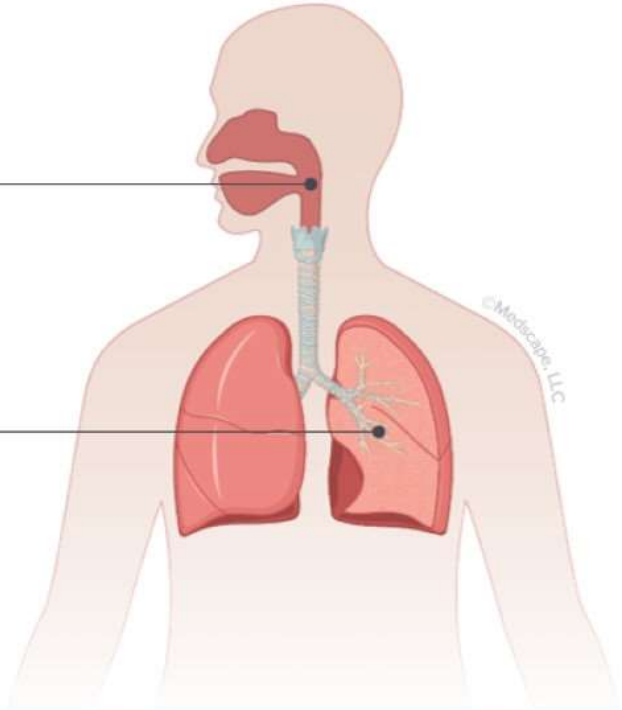
a. NFID. 2019. Accessed June 29, 2022. https://www.nfid.org/wp-content/uploads/2019/08/rsv-report.pdf; b. Walsh EE, et al. In: Bennett JE, et al, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier; 2015:1948-1960.e3.

Progression of RSV Infection in Adults

Upper respiratory tract infection

- Sputum production[a]
- Headache[b]
- Voluminous rhinorrhea[a,b]
- Cough[a,b]
- Nasal congestion[a,b]

- High fever[b,c]
- Respiratory failure[c]
- Wheezing or rales[b,c]
- Dyspnea[c]



Progression to LRT in adults at high risk and with comorbidities

- Patients with RSV present to the ED on day 5 to 7 of illness[a]
- Spread of RSV infection to the LRT can result in:
  - Pneumonia[a]
  - Acute bronchitis[a]
  - Exacerbations of COPD/asthma[a]
  - CHF[a,c]

CHF, congestive heart failure; LRT, lower respiratory tract.

a. NFID. 2019. Accessed June 29, 2022. https://www.nfid.org/wp-content/uploads/2019/08/rsv-report.pdf; b. Walsh EE, et al. In: Bennett JE, et al, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier; 2015:1948-1960.e3; c. Lee N, et al. Clin Infect Dis. 2013;57:1069-1077.

Symptoms of Respiratory Infections in Adults and Older Adults

Symptoms of RSV, Influenza, and COVID-19 Overlap

RSV[a]

- Fever
- Runny nose
- Sore throat
- Cough
- Fatigue
- Headache

Influenza (Flu)[b]

- Fever/chills
- Cough
- Shortness of breath
- Fatigue
- Sore throat
- Runny nose/congestion
- Muscle pain/body aches
- Headache
- Vomiting/diarrhea
- Change/loss of taste or smell

COVID-19[b]

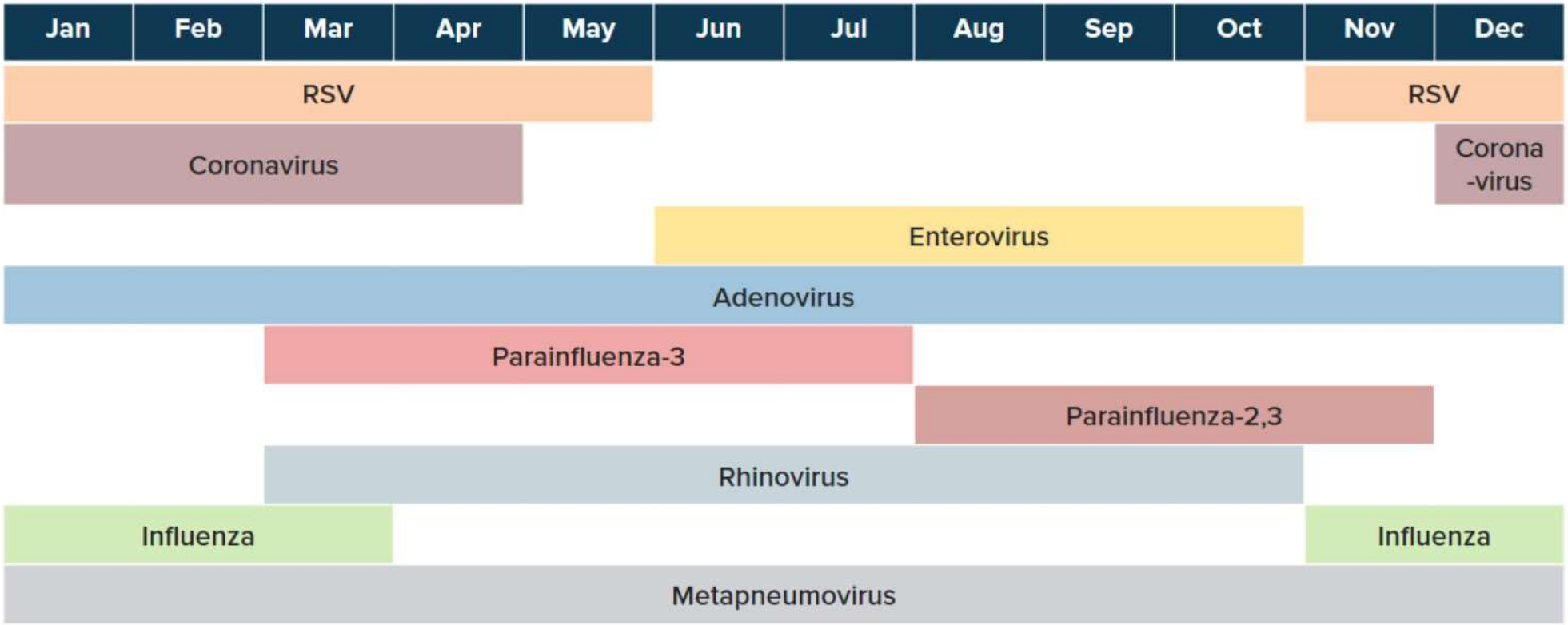
- Fever/chills
- Cough
- Shortness of breath
- Fatigue
- Sore throat
- Runny nose/congestion
- Muscle pain/body aches
- Headache
- Vomiting/diarrhea
- Change/loss of taste or smell*

*More common with COVID-19.

a. CDC. 2020. Accessed June 30, 2022. https://www.cdc.gov/rsv/clinical/index.html; b. CDC. 2022. Accessed June 30, 2022. https://www.cdc.gov/flu/symptoms/flu-vs-covid19.htm

Overlapping Seasonality of RSV and Other Respiratory Viruses

RSV should be included in the differential diagnosis if it is "in season"



Slide courtesy of Angela Branche, MD.

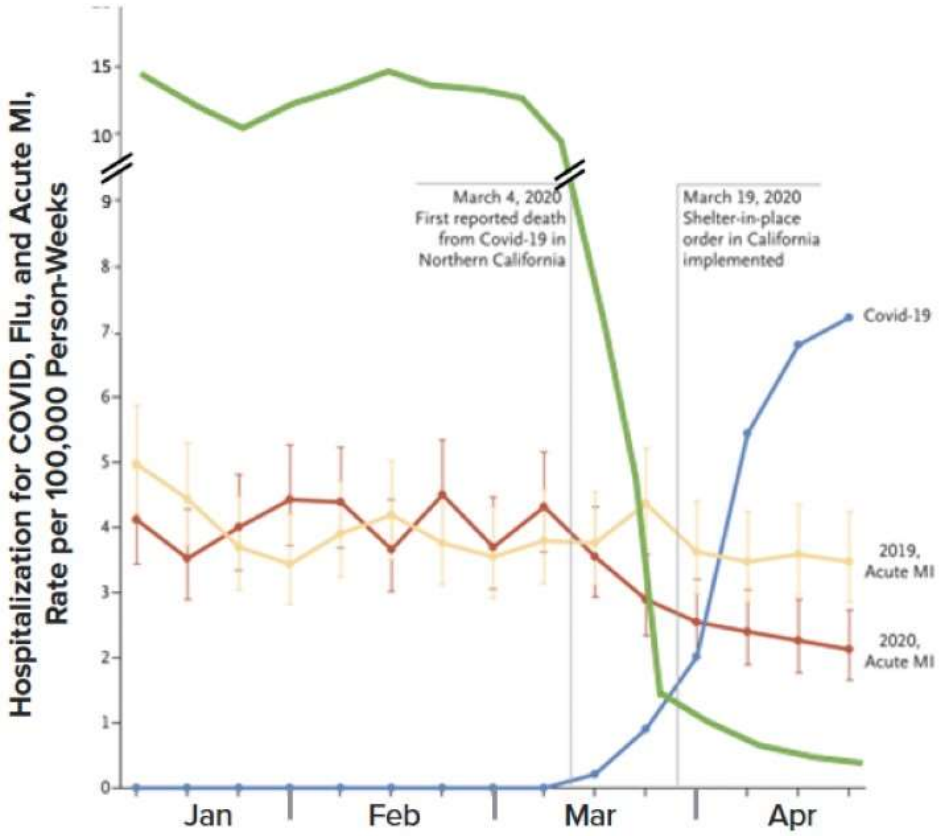
COVID, Flu, and Acute MI

Kaiser Permanente Northern California health system

(data from **43,017,810 person-weeks**)

- From January 1-April 14, 2020 (red), weekly **acute MI hospitalizations dropped** vs 2019 (yellow) AND **COVID-19 incidence rates increased** (blue)
- **Laboratory-confirmed influenza hospitalization** (green) **declined** by > 90% in March

Incidence of Hospitalization for COVID, Flu, and Acute MI



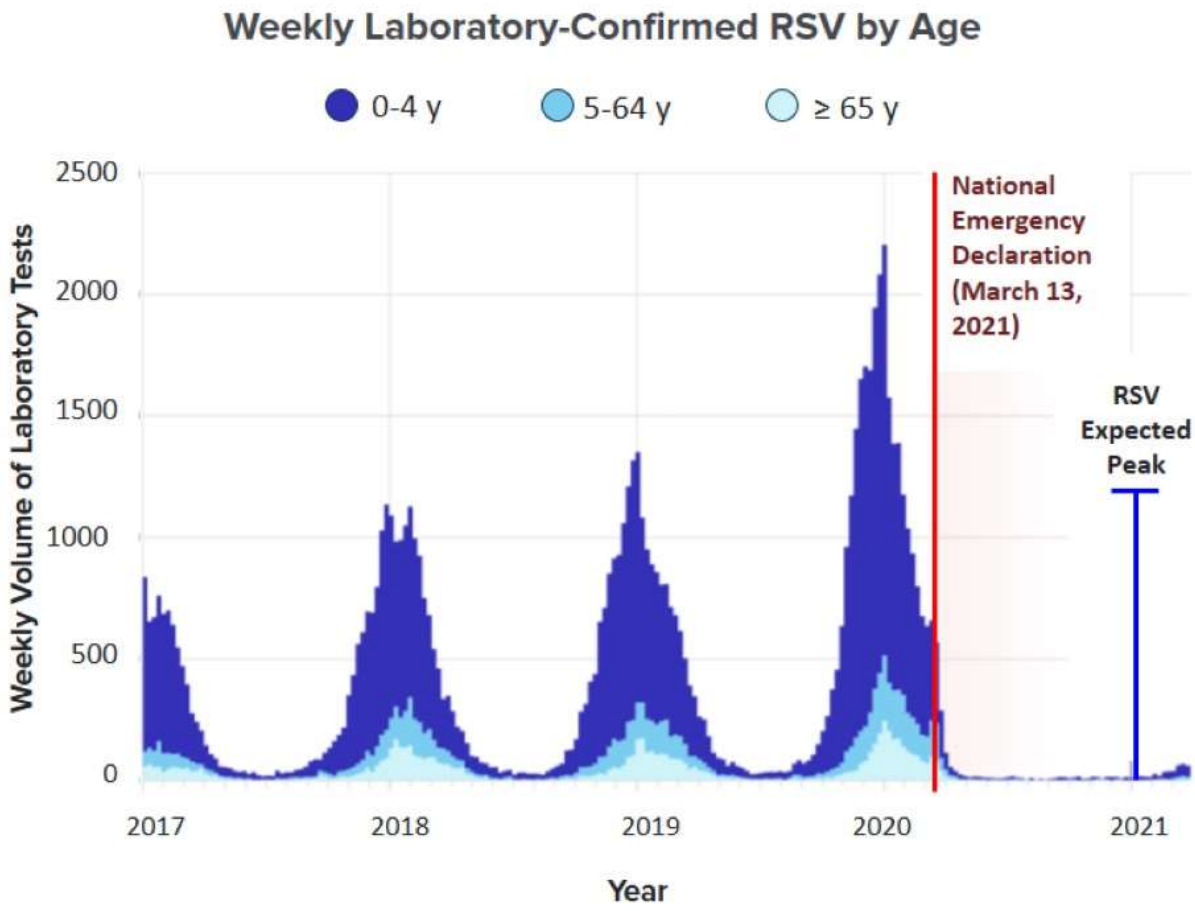
MI, myocardial infarction.
Graph adapted by Stefan Gravenstein, MD, MPH; Solomon MD, et al. N Engl J Med. 2020;383:691-693.

Laboratory-Confirmed RSV

Cosmos data set

50 million patients from 46 states in the US during January 2017 to March 2021

- **RSV cases dropped by 97% during COVID-19 pandemic**

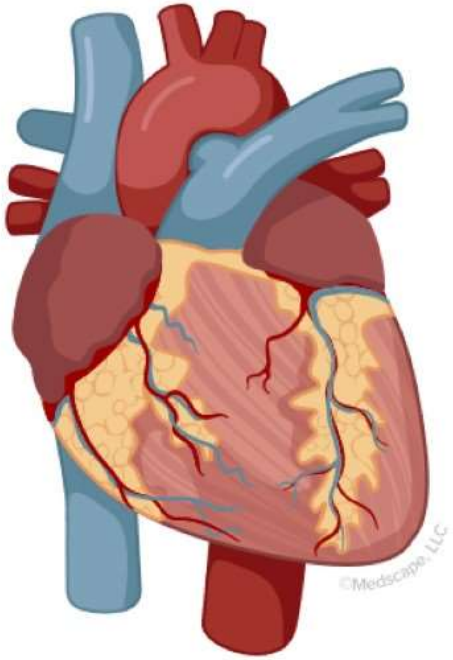


EHRN. 2021. Accessed July 14, 2022. https://epicresearch.org/articles/rsv-cases-dr

Acute MI After Viral Infections in Older Adults

Viral infections[a-c]

Atherosclerosis[b]

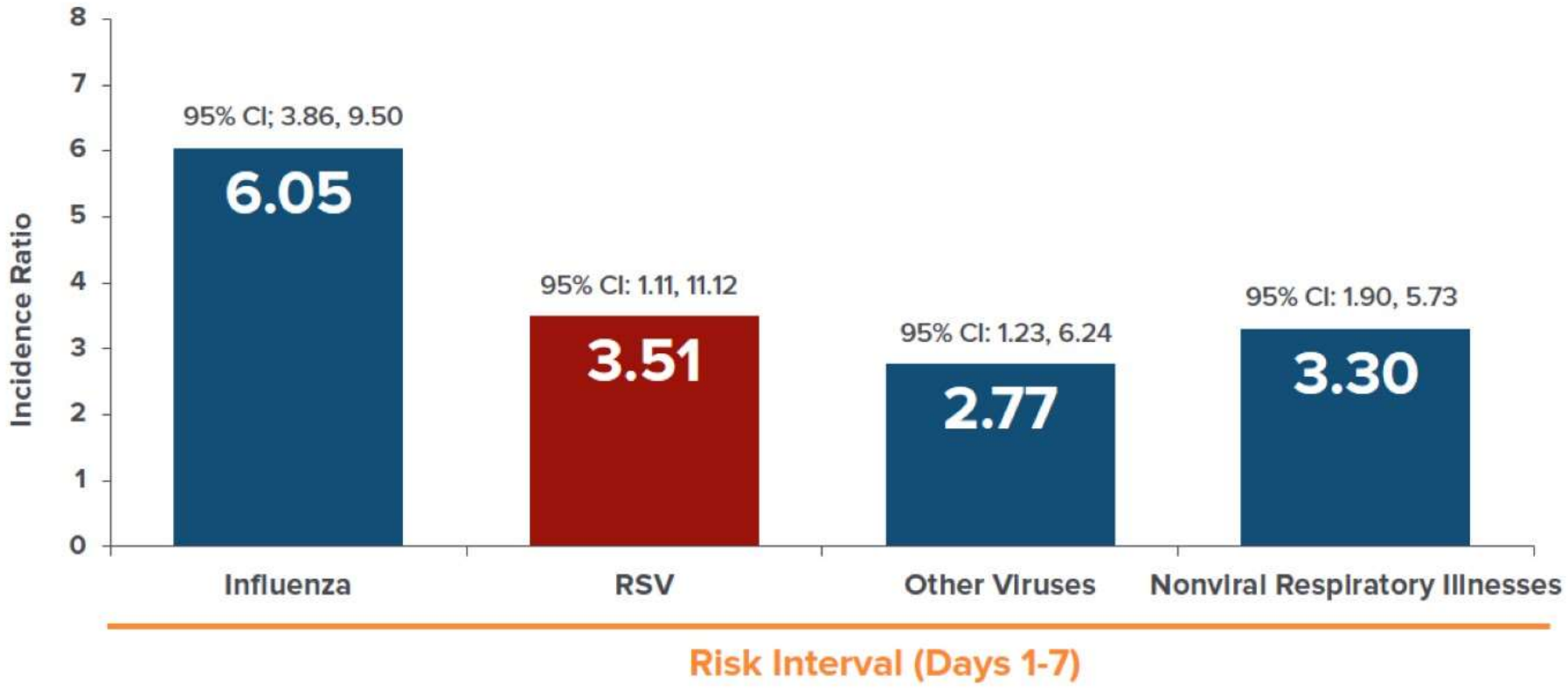


Mechanisms involved in acute MI[b,c]

- IL-6
- Cytokines
- Hypoxia
- Vasoconstriction
- Platelet aggregations and coronary plaque disruption
- Thrombogenesis
- Emboli

a. Kwong JC, et al. N Engl J Med. 2018;378:345-353; b. MacIntyre CR, et al. Heart. 2016;102:1953-1956; c. Raghavan S, et al. Front Cardiovasc Med. 2021;8:670659.

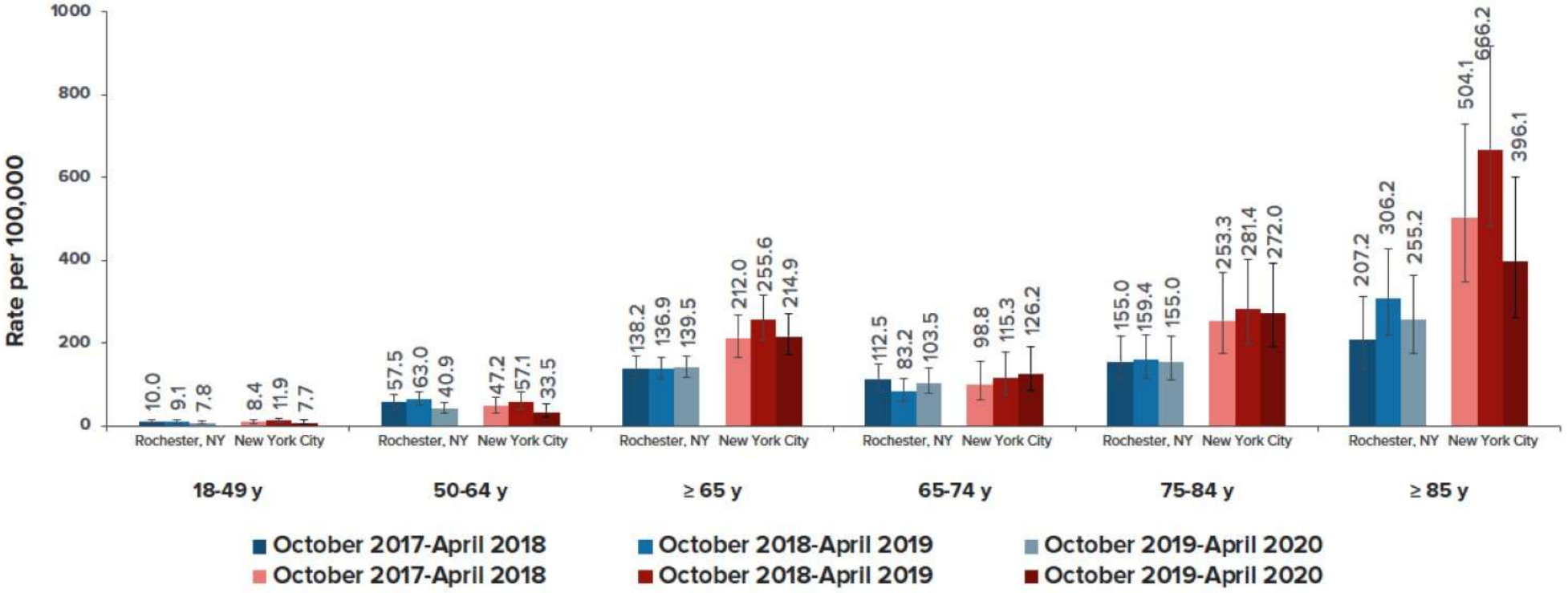
Incidence of Hospitalizations for Acute MI



Kwong JC, et al. N Engl J Med. 2018;378:345-353.

Annual Incidence of RSV Across 3 Seasons

Incidence of RSV infection is substantial among hospitalized adults and increases with age



Branche AR, et al. Clin Infect Dis. 2022;74:1004-1011.

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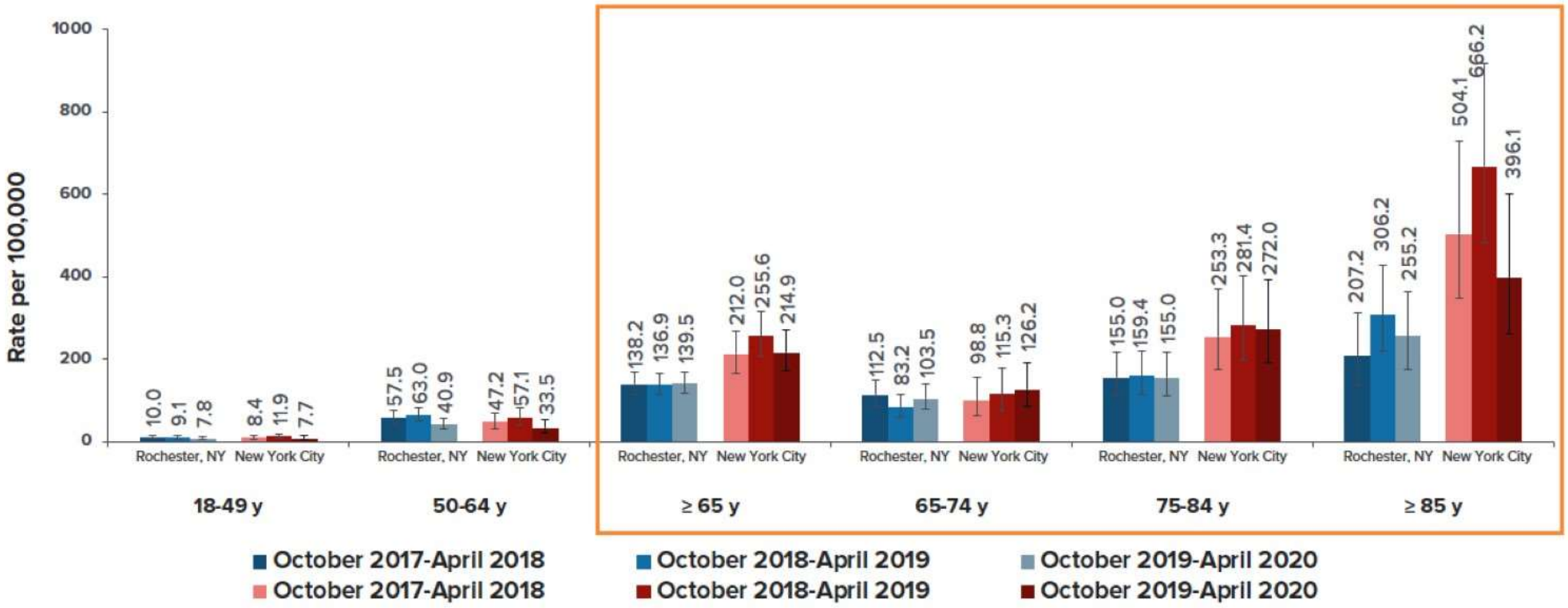
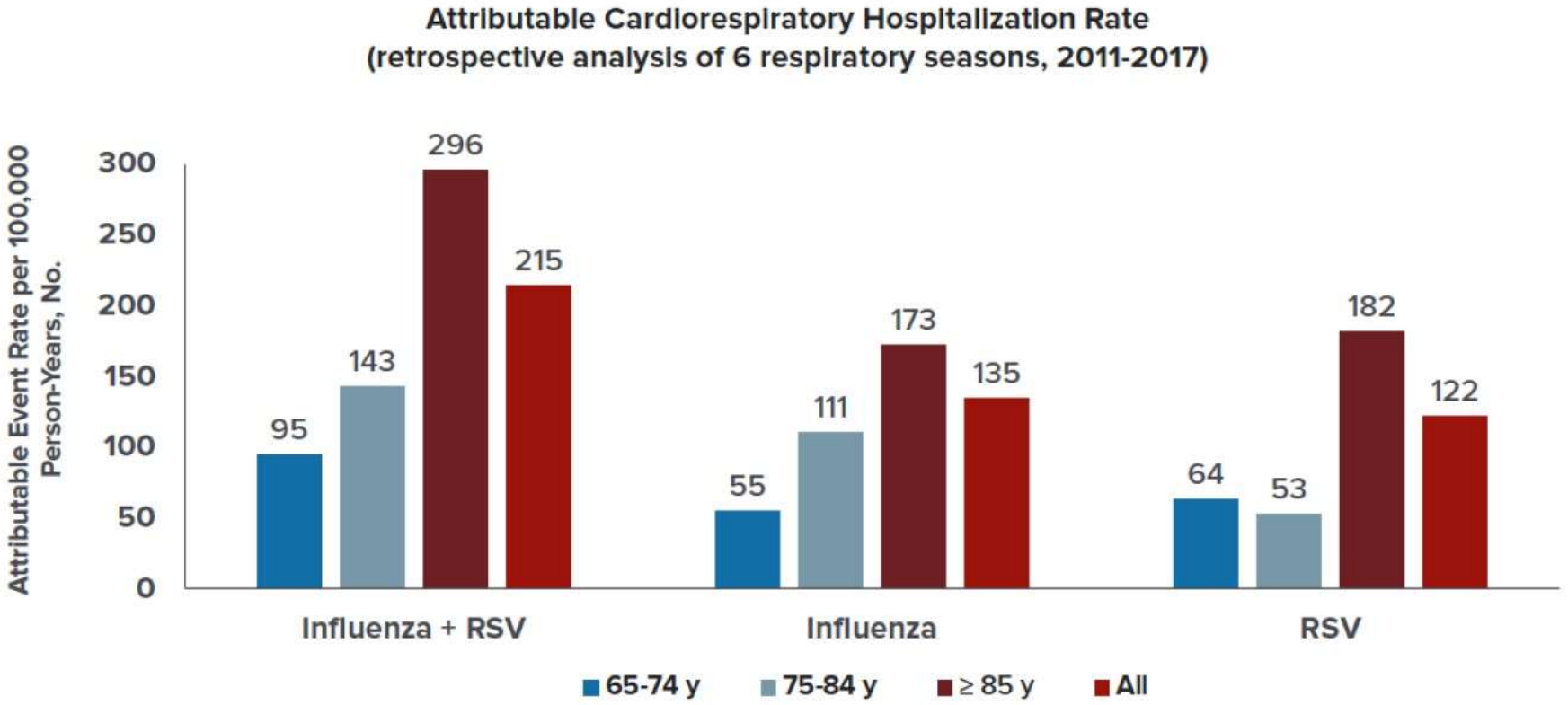


Branche AR, et al. Clin Infect Dis. 2022;74:1004-1011.

RSV Cardiovascular Hospitalizations in Older Adults

RSV is an important cause of cardiorespiratory hospitalizations in long-stay* residents of LTCFs



*≥ 100 d.

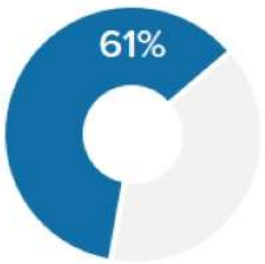
LTCF, long-term care facility.

Bosco E, et al. JAMA Netw Open. 2021;4:e2111806.

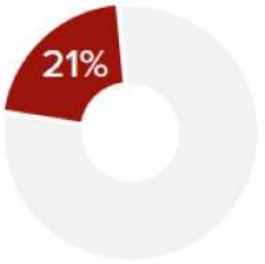
Bacterial Coinfections and Antibiotic Use in Adults

Bacterial coinfection is associated with ~40% of viral RTIs requiring hospitalization

348/842
had viral infection



212/348
had ***only*** a viral infection



72/348
had a ***mixed*** viral/bacterial respiratory infection*

Across 842 hospitalizations and 771 patients included in the study:

- Patients hospitalized with mixed viral-bacterial infections were older and had more commonly received a diagnosis of pneumonia
- **> 90% of patients received antibiotics**

*Measured by the serum level of procalcitonin.
Falsey AR, et al. J Infect Dis. 2013;208:432-441.

Rationale for RSV Testing

Patients with RTIs signs and symptoms

Antimicrobial stewardship

- Avoiding overuse of broad-spectrum antibiotics[a,b]

a. NFID. 2019. Accessed June 29, 2022. https://www.nfid.org/wp-content/uploads/2019/08/rsv-report.pdf; b. O'Callaghan K, et al. Infect Dis Health. 2019;24:147-151.

Rationale for RSV Testing

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- Avoiding overuse of broad-spectrum antibiotics[a,b]

Diagnostic stewardship

- PCR is highly sensitive when virus is present[c]
- Dual infection (RSV + SARS-Cov-2) is uncommon[c]
- Limits unnecessary testing for other pathogens[d]

a. NFID. 2019. Accessed June 29, 2022. https://www.nfid.org/wp-content/uploads/2019/08/rsv-report.pdf; b. O'Callaghan K, et al. Infect Dis Health. 2019;24:147-151; c. Sapra M, et al. Virusdisease. 2022;33:57-64; d. Lee N, et al. J Infect Dis. 2019;220:969-979.

Rationale for RSV Testing

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Diagnostic stewardship

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- Dual infection (RSV + SARS-Cov-2) is uncommon[c]
- Limits unnecessary testing for other pathogens[d]

Multiplex testing

- Not available in all institutions due to the high cost and the need for specialized equipment to process the test[d]

a. NFID. 2019. Accessed June 29, 2022. https://www.nfid.org/wp-content/uploads/2019/08/rsv-report.pdf; b. O'Callaghan K, et al. Infect Dis Health. 2019;24:147-151; c. Sapra M, et al. Virusdisease. 2022;33:57-64; d. Lee N, et al. J Infect Dis. 2019;220:969-979.

Respiratory Multiplex Rapid Detection Tests in Adults

Pathogens	FilmArray RP[a]	FilmArray RP2[a]	ePlex RP/RP2[b]	Verigene RP Flex[c]	NxTAG RP[d]
Bacteria					
Bordetella pertussis	✓	✓		✓	
Bordetella parapertussis		✓			
Bordetella parapertussis/ B bronchiseptica				✓	
Bordetella holmesii				✓	
Chlamydophila pneumoniae	✓	✓	✓		✓
Mycoplasma pneumoniae	✓	✓	✓		✓
Viruses					
Adenovirus	✓	✓	✓	✓	✓
Coronavirus			✓		
Coronavirus HKU1, NL63, 229E, and OC43	✓	✓	✓		✓
Human bocavirus					✓
Human metapneumovirus	✓	✓	✓	✓	✓
Human rhinovirus				✓	
Human rhinovirus/enterovirus	✓	✓	✓		✓
Influenza A, A/H1, A/H3			✓	✓	✓
Influenza A, A/H1, A/H3, A/H1-2009	✓	✓	✓		
Influenza B	✓	✓	✓	✓	✓
Parainfluenza virus			✓		
Parainfluenza virus 1, 2, 3					
Parainfluenza virus 1, 2, 3, and 4	✓	✓	✓	✓	✓
RSV A and B			✓	✓	✓
RSV	✓	✓			

a. bioMérieux. Accessed June 30, 2022. www.biofiredx.com/products/the-filmarray-panels/filmarrayrp; b. GenMarkDx. Accessed June 30, 2022. https://genmarkdx.com/panels/eplex-panels/respiratory-pathogen-panel; c. Luminex. Accessed June 30, 2022. www.luminexcorp.com/respiratory-pathogens-flex-test/#overview; d. NxTAG. Accessed June 30, 2022. www.luminexcorp.com/nxtag-respiratory-pathogen-panel/; e. CDC. Updated December 10, 2020. Accessed June 30, 2022. www.cdc.gov/flu/professionals/diagnosis/table-flu-covid19-detection.html

RSV Diagnostic Tests in Adults

Most common RSV clinical laboratory tests performed on upper and lower respiratory specimens:

rRT-PCR

More sensitive than culture and antigen testing

Antigen testing

Highly sensitive in children, but not sensitive in adults

rRT-PCR, real time reverse transcription polymerase chain reaction.

CDC. Updated December 18, 2020. Accessed June 30, 2022. https://www.cdc.gov/rsv/clinical/index.html

Management of RSV in Adults

Patients with RSV disease

Supportive Therapy[a]

- Bronchodilators & corticosteroids (not FDA approved for this indication), supplemental oxygen, fluid replacement, etc.

FDA, Food and Drug Administration.

a. Walsh E, et al. Health Sci Rep. 2022;5:e556.

Management of RSV in Adults

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Contact precautions[b]

- Frequent hand hygiene, mask wearing, clean and disinfected high-touch surfaces, isolation of infected patients

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Contact precautions[b]

- Frequent hand hygiene, mask wearing, clean and disinfected high-touch surfaces, isolation of infected patients

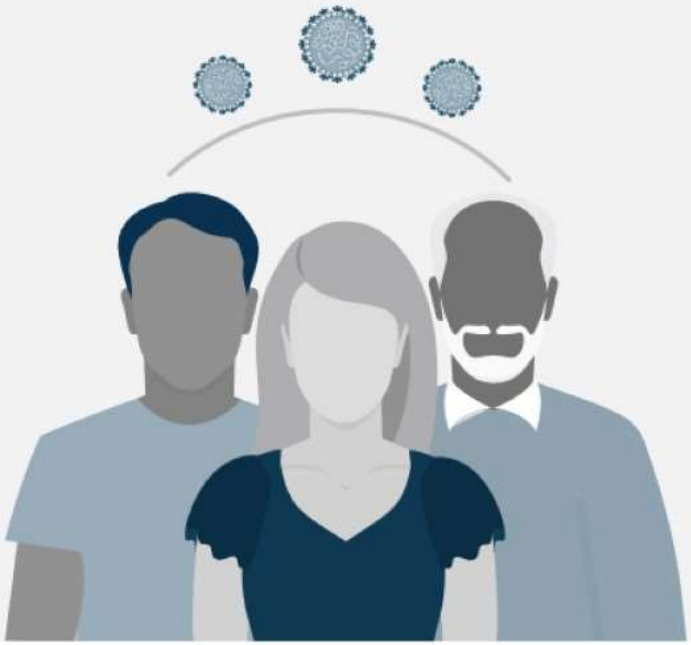
Ribavirin* treatment[a]

- Available, ***but are generally not used*** and not FDA approved for this indication **in older adults**

*Off-label.
FDA, Food and Drug Administration.
a. Walsh E, et al. Health Sci Rep. 2022;5:e556; b. CDC. 2020. Accessed June 30, 2022. https://www.cdc.gov/rsv/about/prevention.html

The Path Forward

Prevention from RSV Infection is the Key



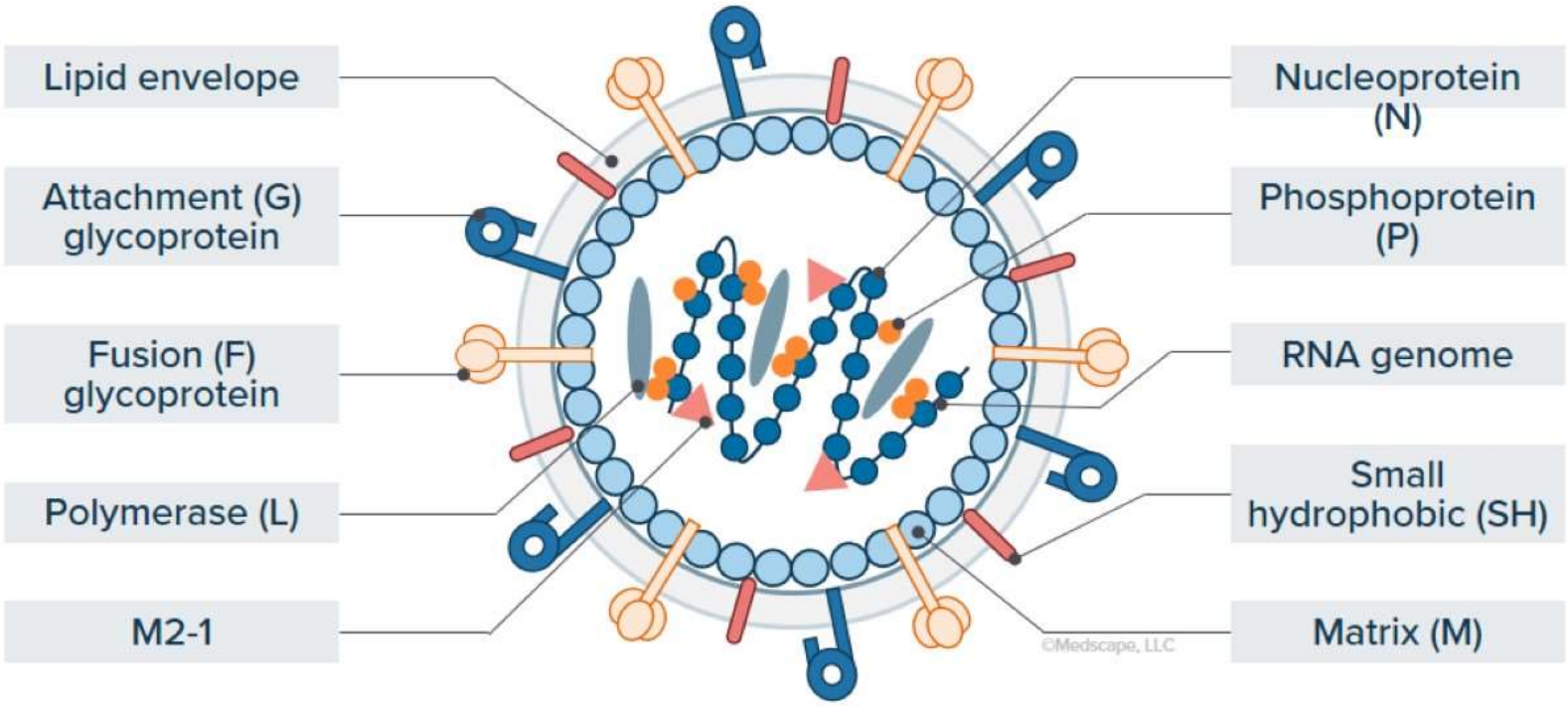
Vaccines in the Spotlight

Phase 3 Clinical Trials Ongoing

Branche AR, et al. Clin Infect Dis. 2022;74:1004-1011.

RSV Basics: The Virus

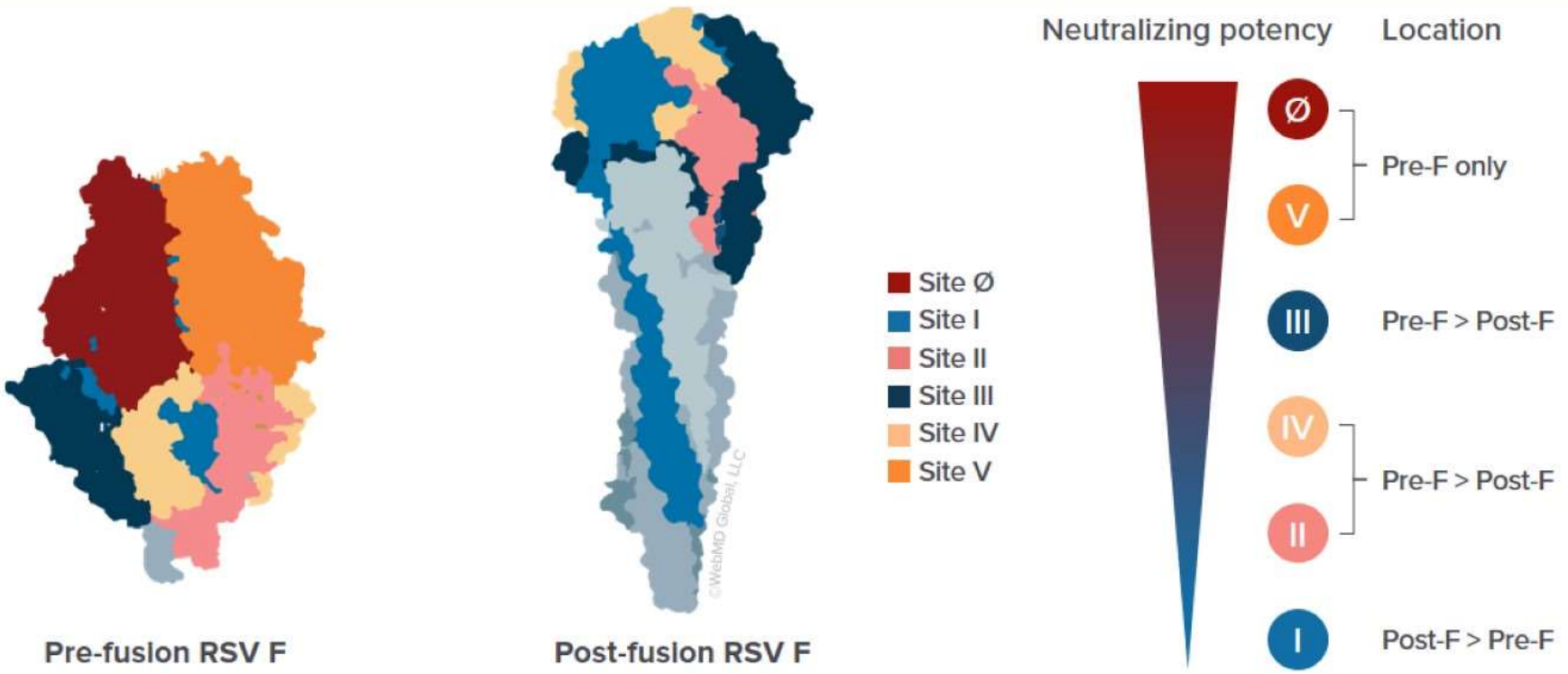
RSV G and F carry the antigenic determinants that elicit the production of neutralizing antibodies



Mejias A, et al. Ann Allergy Asthma Immunol. 2020;125:36-46.

RSV Basics: Antigenic Sites of the RSV F-Protein and mAbs

The neutralization sensitivity of each antigenic site is directly related to exclusive or preferential binding to the pre-F conformation[a]



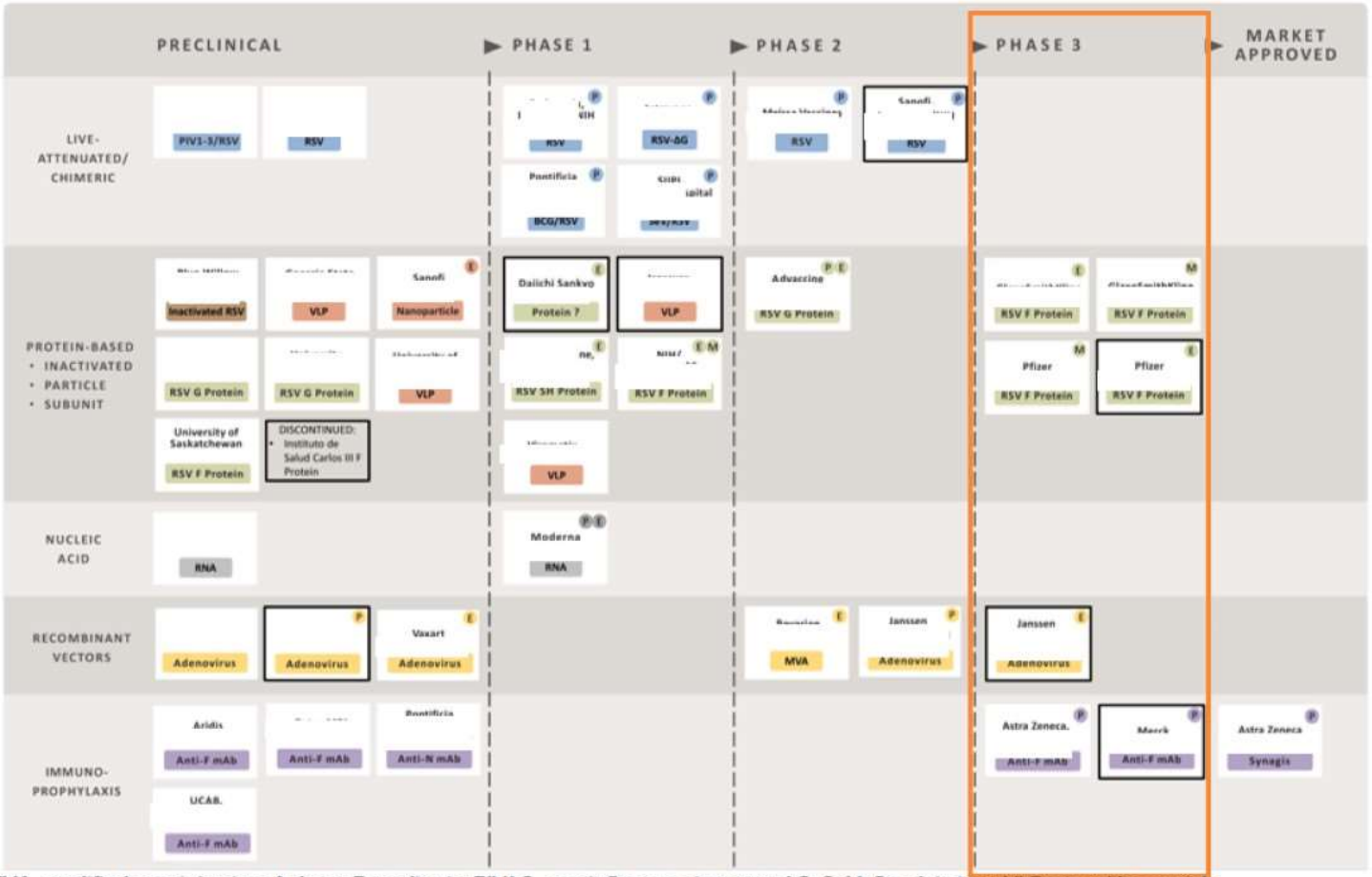
Pre-fusion RSV F

Post-fusion RSV F

mAb, monoclonal antibody.

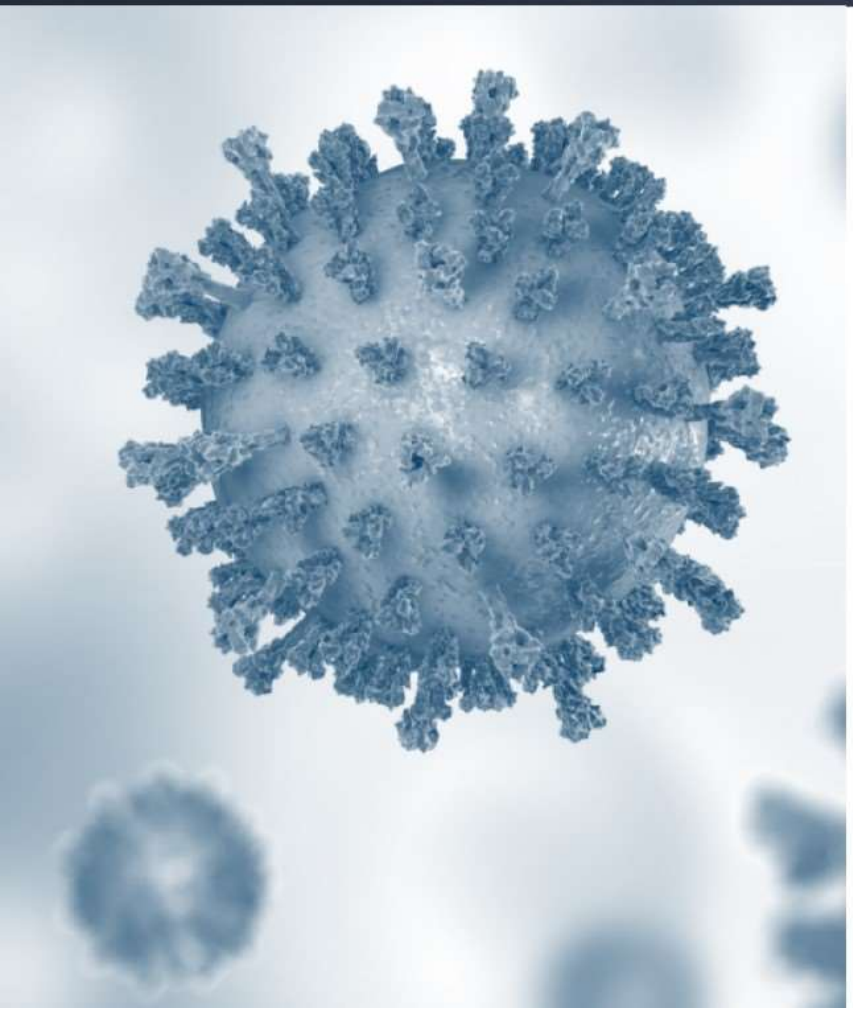
Graham BS. Curr Opin Virol. 2017;23:107-112.

RSV Vaccine and mAb Snapshot



E, elderly; M, maternal; MVA, modified vaccinia virus Ankara; P, pediatric; PIV1-3, parainfluenza virus type 1-3; SeV, Sendai virus; VLP, virus-like particle.
PATH. Accessed June 30, 2022. https://media.path.org/documents/RSV-snapshot_28SEP2021_HighResolution.pdf?_gl=1*131jzvo*_ga*NDQ0NzAzMTUyLjE2NTc4NTY5Nzl.*_ga_YBSE7ZKDQM*MTY1Nzg1Njk3Mi4xLjAuMTY1Nzg1Njk3Mi4w

Conclusions



- RSV is underrecognized in older adults
- RSV disease is clinically indistinguishable from that of other RTIs
- Awareness of RSV infection and multiplex testing use for RSV diagnosis may improve:
  - Antimicrobial stewardship
  - Diagnostic stewardship
  - Workforce and resource stability in LTCFs
- Vaccination could be the key for primary prevention

Medscape EDUCATION

Thank you for participating in this activity.

Check out the right side of the program page for helpful tools and resources for both you and/or your patients.