RSV: Burden of Disease in Older Adults

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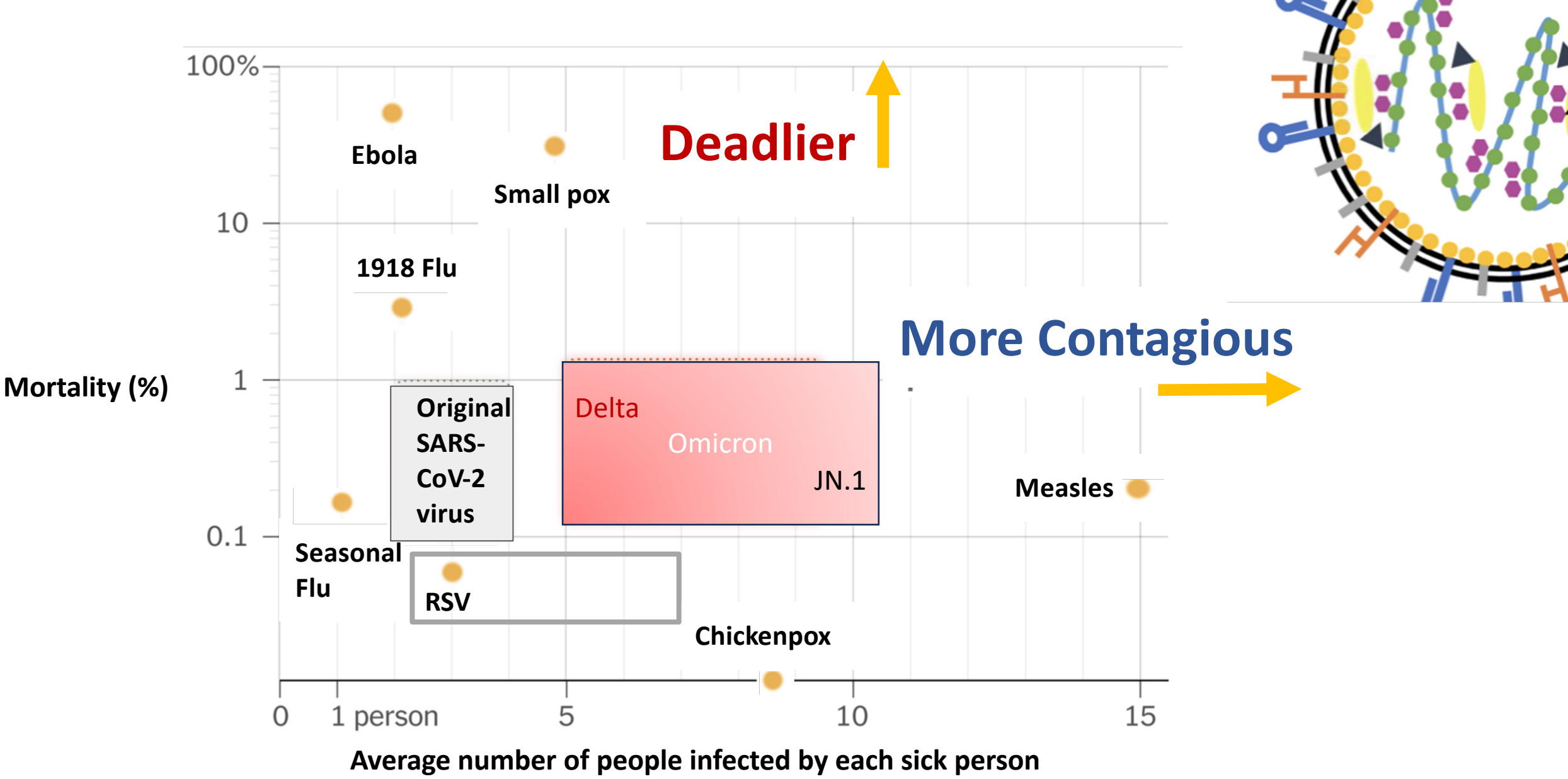
Disclosures

- I provide consulting services for most vaccine manufacturers, including those that market RSV vaccines (GSK, Pfizer)
- I will not discuss vaccines in this presentation

Objectives

- Provide context for the burden of RSV disease in older adults with Influenza and SARS-CoV-2 infection



References:

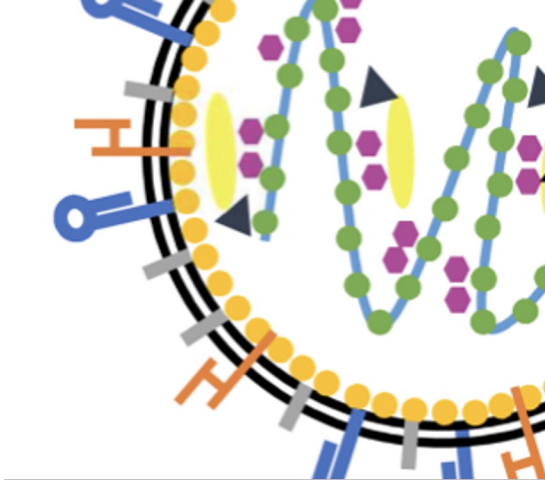
1. Adapted from the New York Times' graphic compiled from CDC and US and international health agencies with RSV information, and:
2. Reis J and Shaman J: Retrospective Parameter Estimation and Forecast of Respiratory Syncytial Virus in the United States. https://doi.org/10.7916/D8862GZP.
3. Weber A, Weber M, Milligan P. *Math Biosci*. 2001;172(2):95-113.

Fun Fact

- **Infants have nearly all of the airways and alveoli they will have as adults**
  - This means a huge surface area to volume and especially tiny airways
- This means that it takes less inflammation and bronchospasm to cause obstruction that results in wheezing and croup
- It's **one of three reasons** children present differently from older adults with RSV infection

Reference:
1. Hislop AA. *J Anat*. 2002;201(4):325-34.

Risk Factors for Severe RSV Infection



- Age
- Overcrowding
- Smoke exposure (cooking, tobacco)
- Low socioeconomic status
- Asthmatic mother (for risk in children)
- **Co-morbidities** (and in older adults, **multimorbidity**)

Susceptibility in Older Adults

- RSV is among the top four causes of ILI (third before the advent of SARS-CoV-2), after enterovirus and influenza
  - But RSV was the second most common cause of hospitalization
    - Twice as likely as patients who had laboratory confirmation of influenza
- 95% of children have had RSV by age 2
  - Essentially all adults have survived prior RSV, and will have some underlying immunity
- P&I start increasing around age 50
  - Immune senescence
    - In elderly, greater susceptibility with lower RSV-specific Ig and nasal IgA
    - T-cell immunity declines with age

ILI, influenza-like illness

References:
1. Falsey AR, et al. *J Infect Dis*. 2014;209(12):1873-81.
2. Falsey AR, Walsh EE. *J Infect Dis.* 1998;177(2):463-6.
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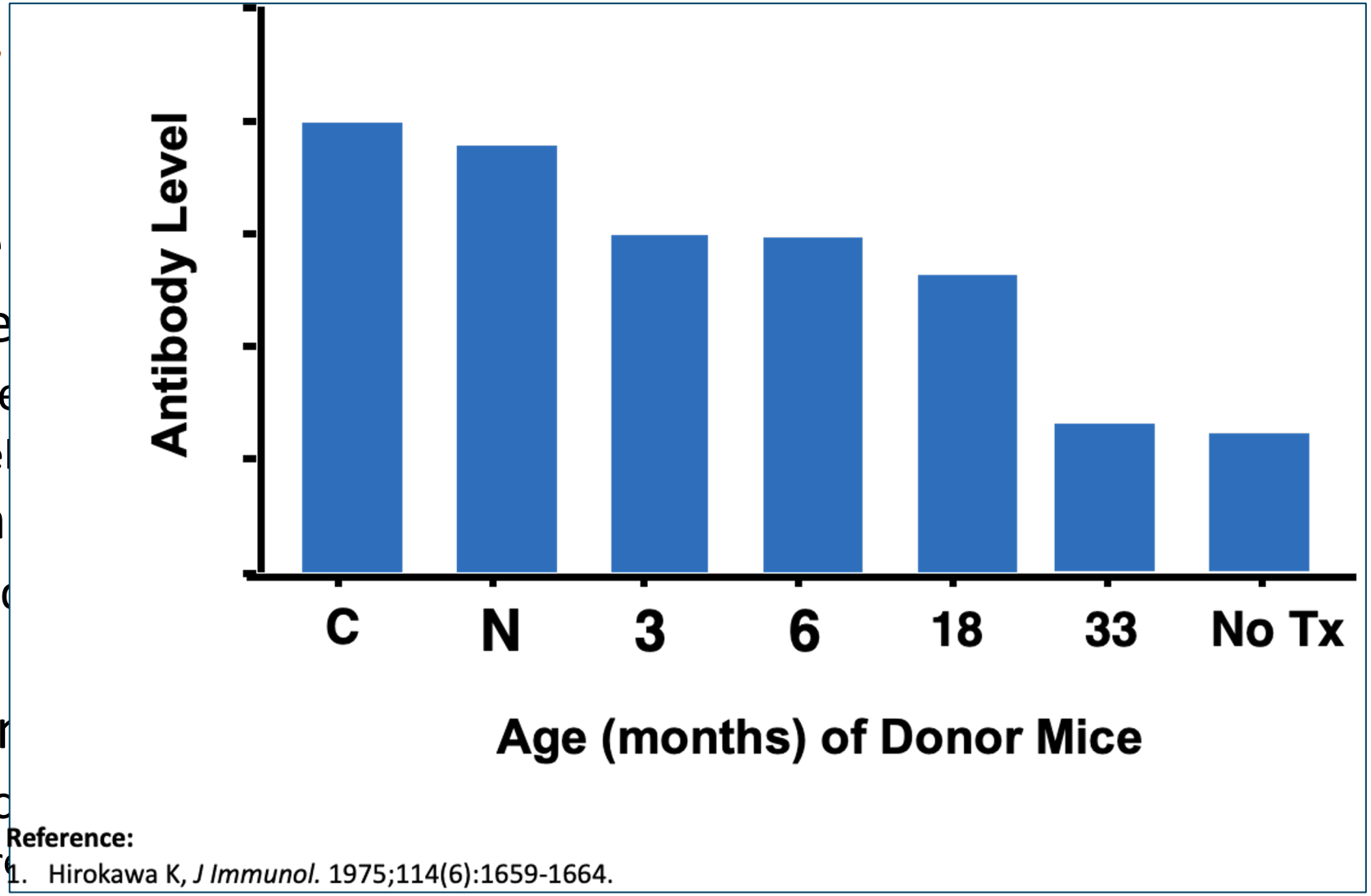

Reference:
1. Hirokawa K, *J Immunol.* 1975;114(6):1659-1664.

ILI, influenza-like illness

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Biologic Changes With Age Relate to Clinical Presentation

Biologic Change	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 pro-inflammatory state
Reduced T-cell help	Reduced response to infection, vaccination; less durable
Brain Aging	Risk for delirium, sleep/appetite disturbance with cytokine storm

Reference:
1. Gravenstein S, et al. *Med Health R I*. 2010;93(12):382-384.

Fun Fact

- Immune senescence is the second of three reasons why children present differently from older adults
  - Children produce more cytokine faster (therefore faster and higher fever), and other cytokine-mediated symptoms
  - Children may not have prior immunity, increasing peak viral shedding titers

Many Clinicians Don't Recognize that RSV is a Big Deal for Older Adults

- Each year, up to 10% of older adults are infected with RSV in the US
  - Closer to 10% in settings with close quarters (e.g., nursing homes, assisted living and senior housing)
- Older adults more likely than younger adults to be hospitalized or die

Associated Risk Condition	Odds Ratio (95% CI)	*P* Value
Stroke, heart failure, chronic lung disease	~2 (1.02-4)	<0.05
Solid organ transplant	2.52 (0.88-7.22)	0.085
Chronic kidney disease	4.37 (2.74-6.98)	<0.001
Hematologic malignancy	5.17 (2.02-13.20)	0.001

References:
1. Branche AR, et al. *Drugs Aging*. 2015;32(4):261-269.
2. Pastula ST, et al. *Open Forum Infect Dis*. 2017;4(1):ofw270.
3. Wyffels V, et al. *Adv Ther*. 2020;37:1203-1217.

Chronic Conditions as Risk Factors for RSV-Associated Hospitalization

- CDC/ACIP Evaluated 9 conditions as risk factors for RSV hospitalization
  - Asthma
  - Chronic kidney disease (CKD)
  - Chronic obstructive pulmonary disease (COPD)
  - Coronary artery disease (CAD
  - Current smoking
  - Diabetes mellitus
  - Obesity (body mass index 30-39 kg/m2)
  - Severe obesity (body mass index ≥40 kg/m2)
  - Stroke

Reference:
1. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/03-RSV-Adults-Woodruff-508.pdf presented by Rebecca Woodruff, PhD for CDC at ACIP 29FEB2024

Chronic Conditions as Risk Factors for RSV-Associated Hospitalization

- Compared RSV-associated hospitalization in older adults between people with and without those conditions
  - Numerator
    - RSV-NET for RSV hospitalizations
      - >300 hospitals, about 8.6% of US population
      - RSV + test in two weeks prior to hospitalization
  - Denominator
    - Behavioral Risk Factor Surveillance System (BRFSS)
    - Census population counts
    - Annual telephone surveillance with self reported conditions representative of state populations

Reference:
1. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/03-RSV-Adults-Woodruff-508.pdf presented by Rebecca Woodruff, PhD for CDC at ACIP 29FEB2024

RSV-linked hospitalization in community elderly 2017-2018 vs without condition: adjusted rate ratio

*Preliminary Data

Age	All	CKD	BMI (kg/m²) >40 vs <30	BMI (kg/m²) 30-39 vs <30	COPD	Asthma	Active smoker	CAD	DM	Stroke
50-64 aRR		7.9	4.2	1.5	5.8	3.3	2.4	3.7	2.8	1.4
Per 100k	~75	~340	~290	~80	~210	~140	~250	~250	~200	~180

- Shaded values confidence intervals cross 1

Reference (adapted from):

1. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/03-RSV-Adults-Woodruff-508.pdf presented by Rebecca Woodruff, PhD for CDC at ACIP 29FEB2024

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65-74 aRR		6.1	4.5	1.5	4.2	3.3	2.3	2.5	2.2	1.6
Per 100k	~150	~550	~450	~150	~350	~350	~250	~250	~200	~180

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Per 100k	~150	~550	~450	~150	~350	~350	~250	~250	~200	~180
>75 aRR		6.1	2.9	1.1	4.2	2.9	0.9	1.9	1.6	1.9
Per 100k	~400	~1300	~900	~300	~900	~800	~300	~500	~400	~400

- Rate/100k for hospitalization increases between ages 50-64 to 65-74, and for 65-74 to >75 for conditions of CKD, severe obesity, COPD, asthma
- Shaded values confidence intervals cross 1

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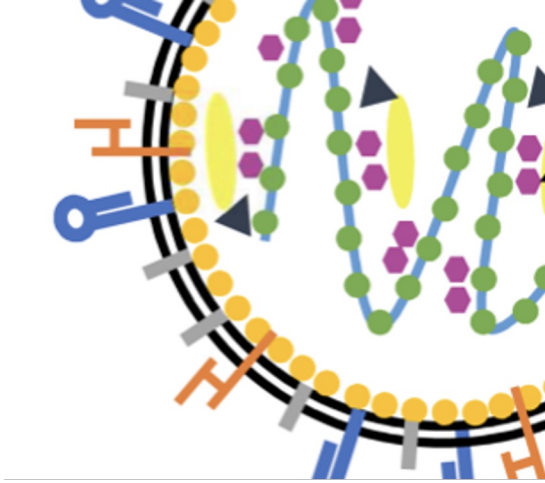
1. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/03-RSV-Adults-Woodruff-508.pdf presented by Rebecca Woodruff, PhD for CDC at ACIP 29FEB2024

Susceptibility in Older Adults



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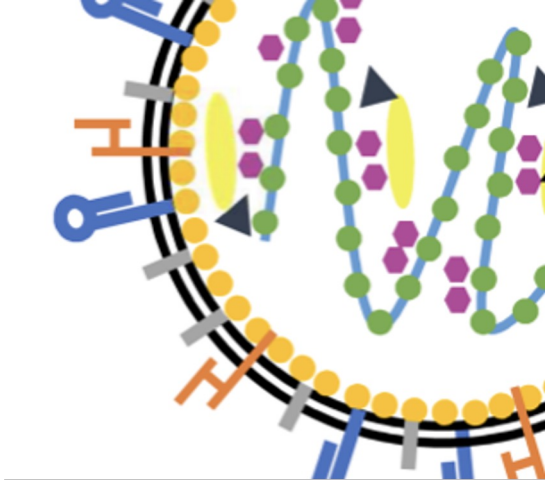
- 95% of children have had RSV by age 2
- P&I begin increasing around age 50
  - Immune senescence
    - In elderly, greater susceptibility with lower RSV-specific Ig and nasal IgA
    - T-cell immunity declines with age: reduced CD8 cytotoxic T-cell function; shift Th1 to Th2
  - Decline in DC function
- Older adults with severe RSV do show CD4 and CD8 T-cell responses *but unclear if severe disease is due to **immunosenescence** or "just" impaired T-cell responses and/or dysfunctional antibody*

References:

1. Falsey AR, et al. *J Infect Dis*. 2014;209(12):1873-81.
2. Falsey AR, Walsh EE. *J Infect Dis.* 1998;177(2):463-6.
3. Walsh EE, Falsey AR. *J Infect Dis.* 2004;190(2):373-8.

Clinical Considerations

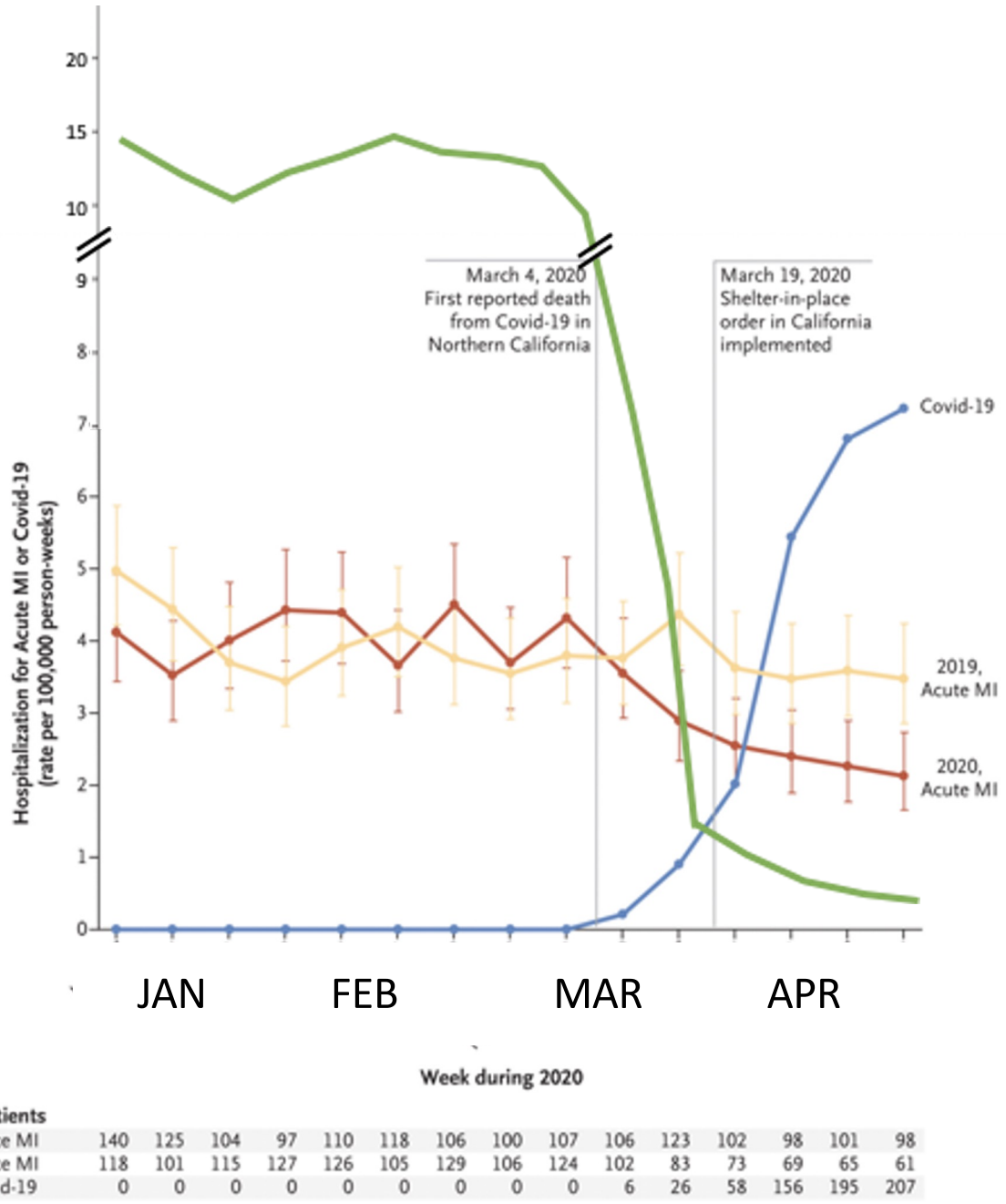


- Include RSV in differential diagnosis if it's "in season"
  - RSV season starts with influenza and beta-coronavirus season, but may last 1-2 months longer (Nov-May)
    - Adenovirus and human metapneumovirus circulates all year
    - Rhinovirus and parainfluenza circulate mostly late spring to fall
  - More likely to be RSV if known RSV-infected contact
  - **For adults, prior RSV infection does not reduce likelihood of future RSV infection**
- In healthy adults, usually mild URI with symptoms clearing in about 5 days
  - Wheezing, cough less common
- In adults with underlying heart or lung disease, weakened immune system, may present with lower respiratory tract infection
  - Asthma, COPD, HF
  - Wheezing, cough common
- Viral shedding longer in older adults and infants

COVID, Flu & AMI

- COVID associated with strokes and heart attacks due to coagulopathy, viral invasion
- Kaiser Permanente Northern California with 4.4 million lives.[1]
  - January through April 2020 (red), weekly AMI (STEMI and NSTEMI) hospitalization compared to 2019 (yellow)
  - AND COVID-19 incidence rates (blue)
  - 48% decrease in AMI hospitalization during COVID-19, both STEMI and NSTEMI
- Laboratory-confirmed influenza hospitalization (green) declined by over 90% in March
  - Opposite the increase in COVID-19 hospitalization

Figure adapted from CDC's FluView and Solomon et al.[4,5]



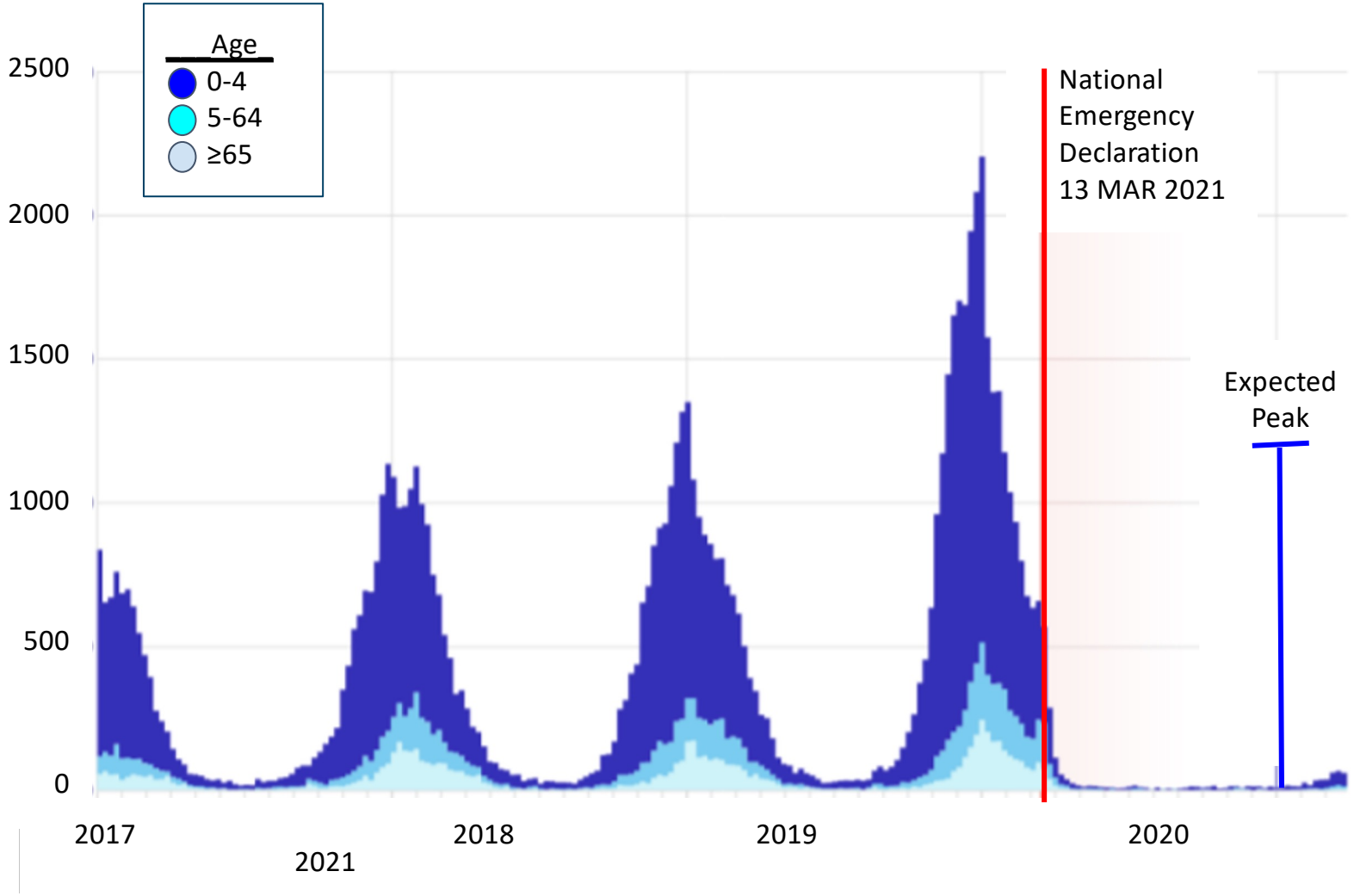
No. of Patients															
2019, Acute MI	140	125	104	97	110	118	106	100	107	106	123	102	98	101	98
2020, Acute MI	118	101	115	127	126	105	129	106	124	102	83	73	69	65	61
2020, Covid-19	0	0	0	0	0	0	0	0	0	6	26	58	156	195	207

Referenes:

1. Sawlani V, et al. *Clin Radiol.* 2020:S0009-9260(20)30392-5.
2. Jørstad, H.T., Piek, J.J. *Neth Heart J*. 2020;28:563-4. Editorial.
3. Basso C, et al. *Eur Heart J.* 2020;41(39):3827-3835.
4. Solomon MD, et al., *N Engl J Med* 2020;383:691-693.
5. CDC. https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html accessed 9 OCT 2020.

Total Weekly RSV Positive Lab Results by Age

Like with influenza, RSV and other respiratory virus activity and associated hospitalizations declines with the "lockdown" response to the SARS-CoV-2 pandemic

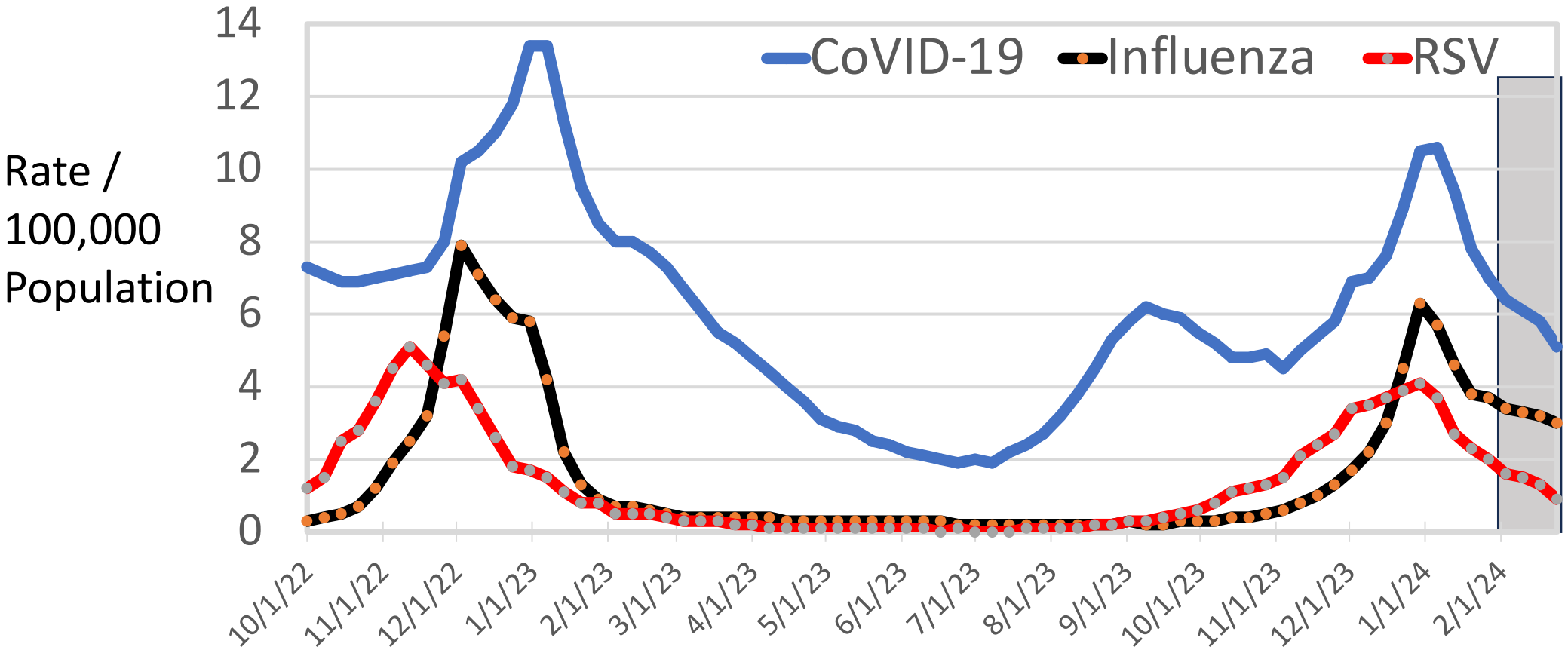


Weekly volumes of +RSV lab tests by age January 2017 to March 31 2021

Reference:

1. Fox B, et al. *Epic Health Research Network*. June 7, 2021. https://epicresearch.org/articles/rsv-cases-dropped-by-97-during-the-pandemic.

COVID-19, Flu, RSV Hospitalization Rates: 2022-2024



Weekly hospitalization rates reported per 100,000 population in the US. Based on findings from participating sites in 58 counties in 12 states. Preliminary data are shaded in gray.

Reference:

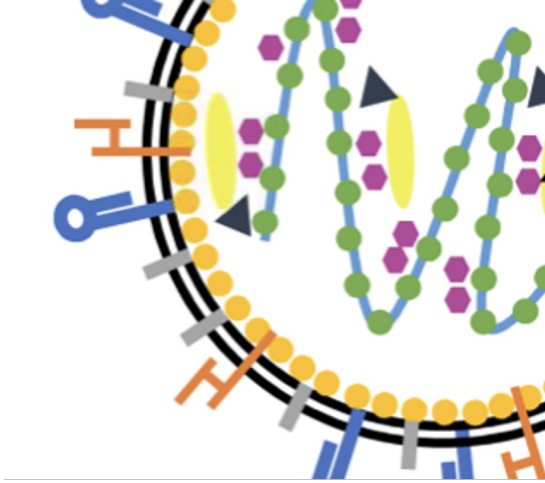
1. https://www.cdc.gov/respiratory-viruses/data-research/dashboard/illness-severity.html, accessed 04MAR2024

Estimated Impact of RSV in adults ≥ age 60 in Japan

Parameter	3 years
Total population	43,681,000
RSV-ARI	5,311,823
RSV-URTD	2,783,250
RSV-LRTD	2,528,573
RSV-URTD-related OP visits	1,327,194
RSV-URTD-related hospitalizations	3,120
RSV-LRTD-related OP visits	2,130,180
RSV-LRTD-related hospitalizations	531,045
RSV-LRTD deaths	25,455

Reference:
1. Kurai D, et al. Expert Rev Vaccines. 2024 Jan-Dec;23(1):303-311. doi: 10.1080/14760584.2024.2323128. Epub 2024 Mar 1. PMID: 38426479.

RSV in Older Adults



- **RSV and influenza similar** for ICU use and mortality[1]
  - **LOS longer (14 vs 8 days)**
  - ICU use (15 vs 12%) and mortality (8 vs 7% similar)
- RSV accounted for 11% of COPD exacerbations and pneumonia admissions[1]
  - 7% of asthma and 5% of HF admissions
- Also roughly similar proportionately to influenza in proportion of hospitalized patients who have pneumonia diagnosis and getting ventilator support[1]
- **Study 842 respiratory hospitalizations (771 patients), 41% had viral infection[2]**
  - 212 hospitalizations (**61%** of the 348 with viral infection) had ***only* a viral infection**
  - **Procalcitonin** evidenced **mixed** viral/bacterial RI in **21%; these were older and often with PNA**
  - **90% received antibiotics** (both groups)
    - 4 of 10 deaths were complications of *C. difficile* colitis

References:
1. Falsey A, et al. *N Engl J Med.* 2005;352(17):1749-1759.
2. Falsey AR, et al. *J Infect Dis*. 2013;208(3):432-441.

RSV and Acute MI

Table 2. Incidence Ratios for Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection.*

Variable	Incidence Ratio (95% CI)
Primary analysis: risk interval, days 1–7	6.05 (3.86–9.50)
Days 1–3	6.30 (3.25–12.22)
7 days before exposure	6.02 (3.83–9.45)
Alternative exposure	
RSV	3.51 (1.11–11.12)
Respiratory virus other than influenza or RSV	2.77 (1.23–6.24)
Illness with no respiratory virus identified‡	3.30 (1.90–5.73)
Hospitalization for diabetes and associated complications§	1.35 (0.50–3.62)

Alternative exposure

RSV	3.51 (1.11–11.12)
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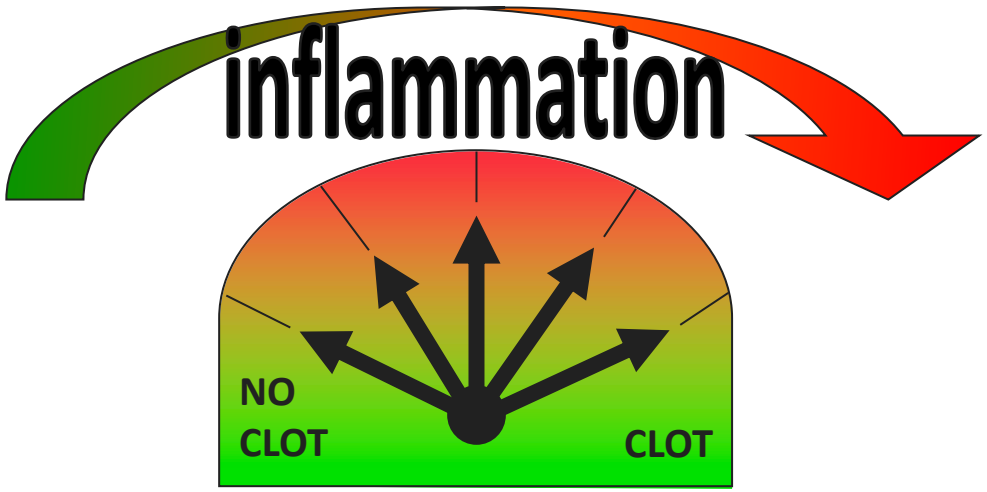
Illness with no respiratory virus identified‡	3.30 (1.90–5.73)
Hospitalization for diabetes and associated complications§	1.35 (0.50–3.62)

by about 3-fold

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

“Thrombometer” – The Propensity to Clot



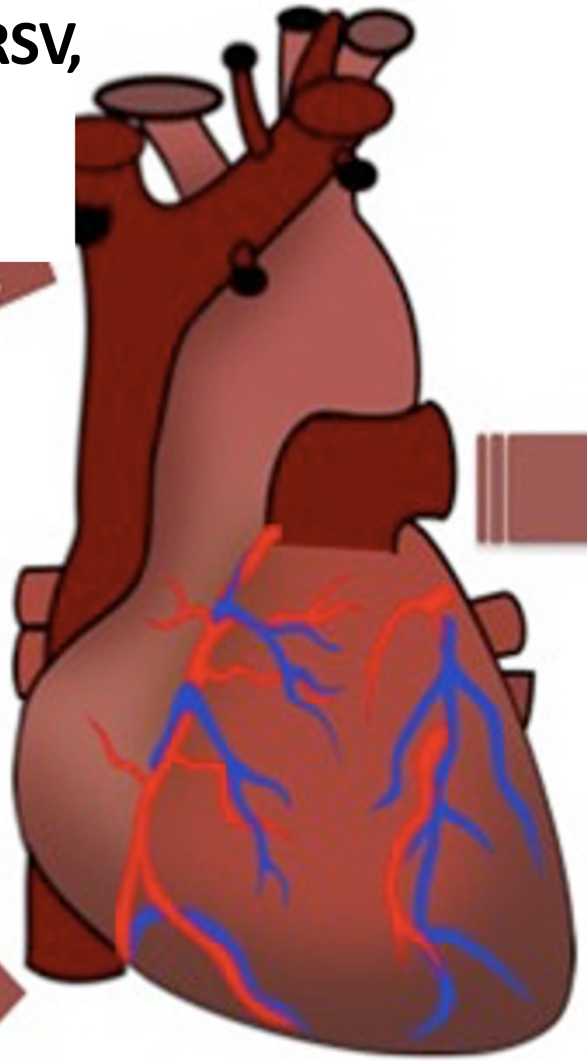
LOW	HIGH
CRP IL-1, 6 TNF-alpha	DVT Stroke MI Delirium Dementia

Increases with age
- Inflammatory markers of age
- IL-6, IL-8, C-reactive protein

Increases with disease
- Obesity
- Diabetes
- Arthritis, vascular disease
- Dementia
- COPD

Increases following infection
- Influenza, RSV
- SARS-CoV-2
- Community acquired pneumonia
- Shingles
- Bladder infection
- Pressure sores

Influenza virus, **RSV,**
SARS-CoV-2, etc
INFECTION



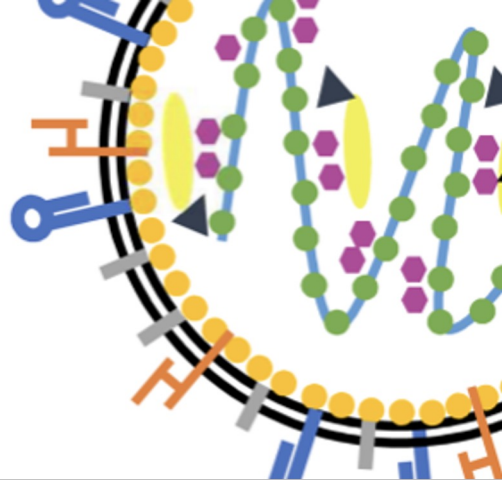
Atherosclerosis

- Protein C and S
- Serum Amyloid A
- Cytokines
- Catecholamines,
- Hypoxia
- Vasoconstriction
- Platelet aggregations and coronary plaque disruption
- Thrombogenesis
- Emboli

Acute myocardial infarction

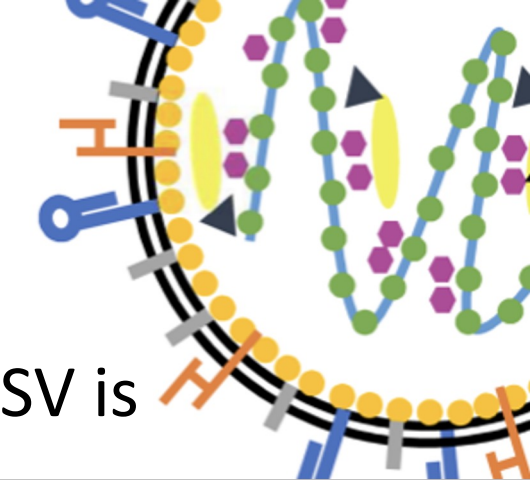
Reference (adapted from):
1. MacIntyre CR, et al. *Hear*t. 2016;102(24):1953-1956.

Fun Fact

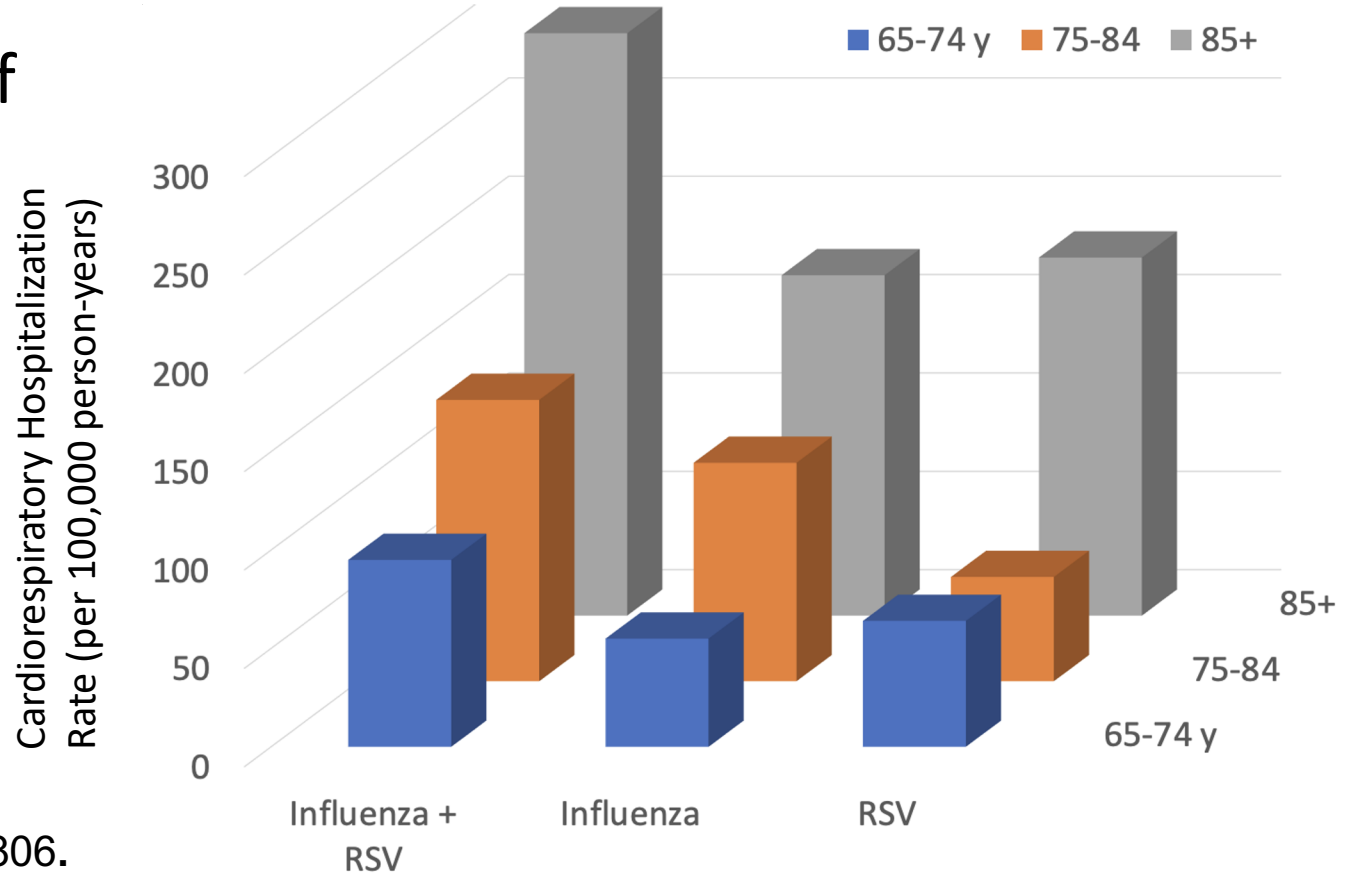


- **Children have a better mucociliary escalator than older adult**
  - With age, fewer cells and less efficient viral clearance on top of greater likelihood of polypharmacy--including drugs that dry secretions) change ability to clear virus
  - So early, wheezing, whooping more prominent with greater consequences from inflammation and earlier coughing
  - In older adults, productive coughing likely delayed a bit in course of illness and less wheezing
- Children also don’t typically have the other underlying conditions
  - So diagnostic confusion for other etiology (HF or COPD exacerbation) not as easily confounded by a diagnostic heuristic

RSV in Old-Older Adults



- In the long-term care setting (a “canary in the coal mine”), RSV is particularly burdensome
- For the 6 seasons 2011-2017 of permanent nursing home residents, attributable cardiorespiratory hospitalization burden from RSV and influenza was similar



Reference:
1. Bosco E, et al. *JAMA Netw Open*. 2021;4(6):e2111806.

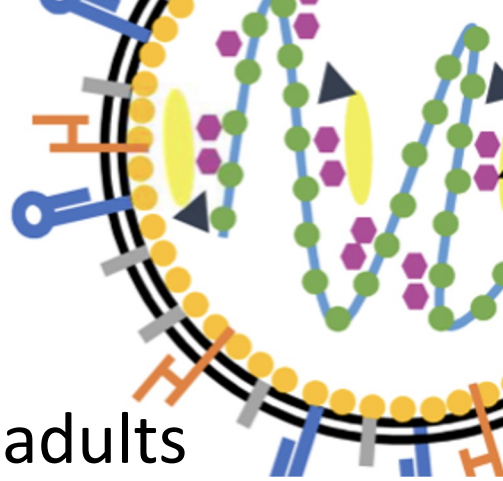
RSV and Influenza Associated Hospitalizations Annually[1]

	Disease Associated Hospitalizations per 1 million per year in the US
RSV	1700-2800 among adults 65 years old and older
Influenza	3200-9200 among adults 65 years old and older

References:

1. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/08-RSV-Adults-Britton-508.pdf accessed 04MAR2024, presented by Amadea Britton, MD
2. CDC RSV-NET data 2016-2020, 2022-2023 (unpublished)
3. CDC Influenza burden 2016-2020, 2022-2023: https://www.cdc.gov/flu/about/burden/past-seasons.html accessed 03MAR2024

Summary



- RSV relatively unrecognized as a significant burden for older adults
  - If not tested for, it won't be recognized
- RSV a greater burden for those with underlying conditions
- Consequences of RSV infection (like for influenza) risk being under appreciated
  - For example, hospitalization following infection, heart attacks, etc.