RESPIRATORY SYNCYTIAL VIRUS

Recognizing and Mitigating Risk in Vulnerable Adults

VME Vemco MedEd

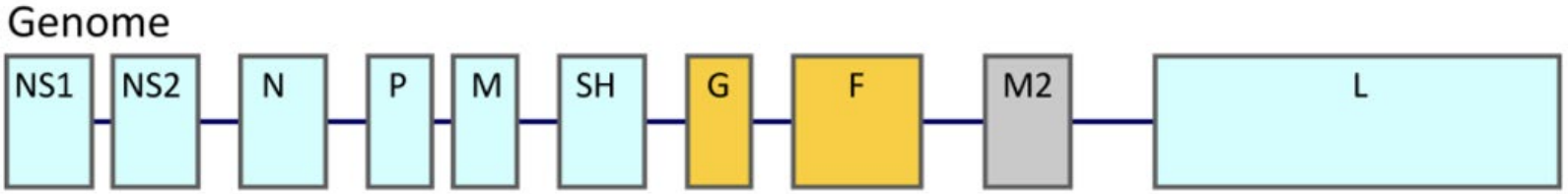
CENTER FOR Independent Healthcare Education

Jointly provided by Center for Independent Healthcare Education and Vemco MedEd

Supported by an educational grant from Janssen Therapeutics, Division of Janssen Products, LP.

Respiratory Syncytial Virus Basics: The Virus

- Synonyms: Human RSV or hRSV; human orthopneumovirus
- Negative sense, single stranded RNA virus



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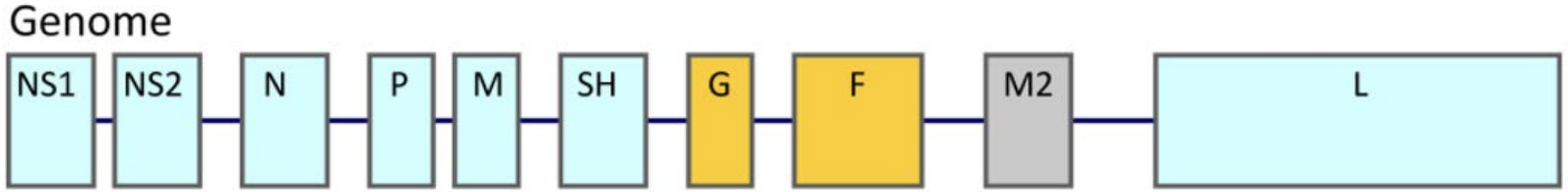

us

- Synonyms: Human RSV or hRSV; human orthopneumovirus
- **Negative sense, single stranded RNA virus**
  - 150nm diameter (some filamentous species can be several micrometers long)
  - Codes for
    - Key internal structural proteins: Matrix protein [M], Nucleoprotein [N]
    - Proteins for the polymerase complex (P and L)
    - Nonstructural proteins [NS-1 and NS-2]: help evade innate immune response
    - Externally exposed transmembrane glycoproteins: small hydrophobic protein [SH], glycoprotein [G], **Fusion protein [F]**
    - Regulatory protein M2 proteins (M2-1 antitermination protein and M2-2, transcription/replication regulators)
- **RNA copying is error prone**, allowing for rapid generation of single nucleotide polymorphisms...

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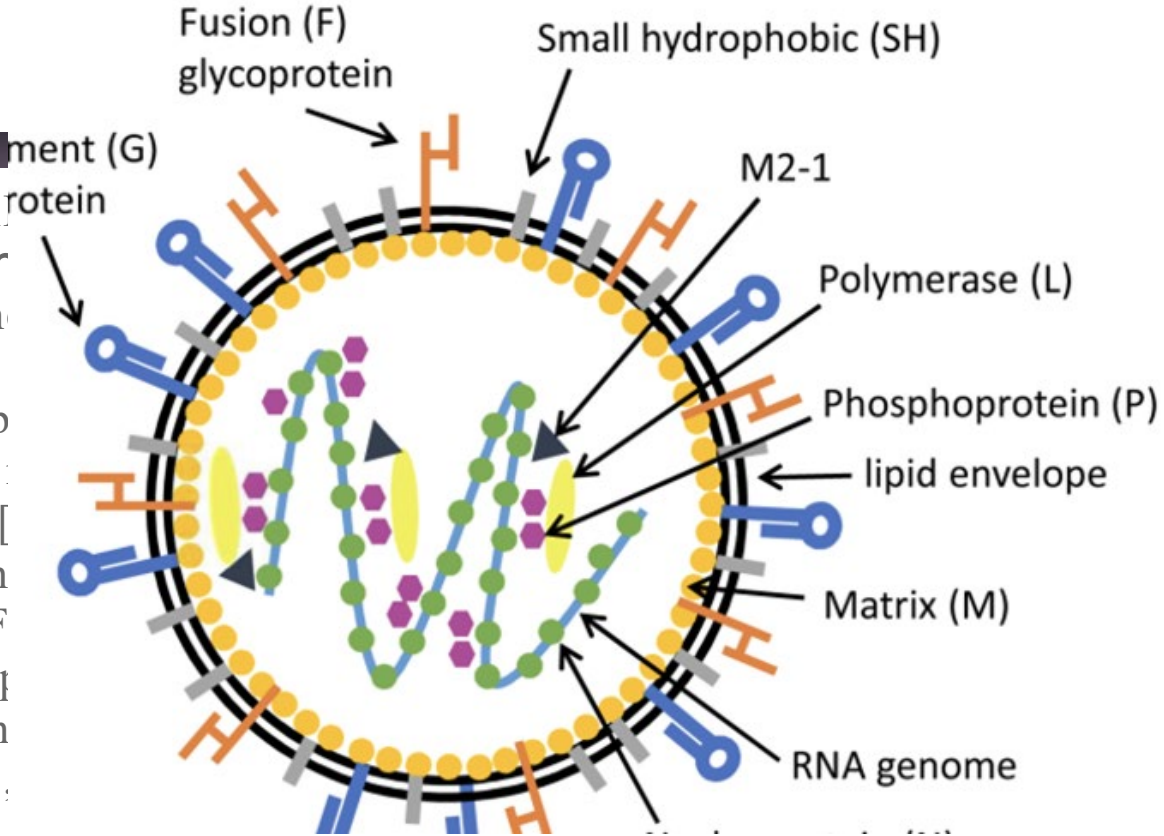

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- Infected cells fuse to form large cells, or syncytia
- **Spreads by air droplets or fomites**
  - Lands in eyes, nose or mouth

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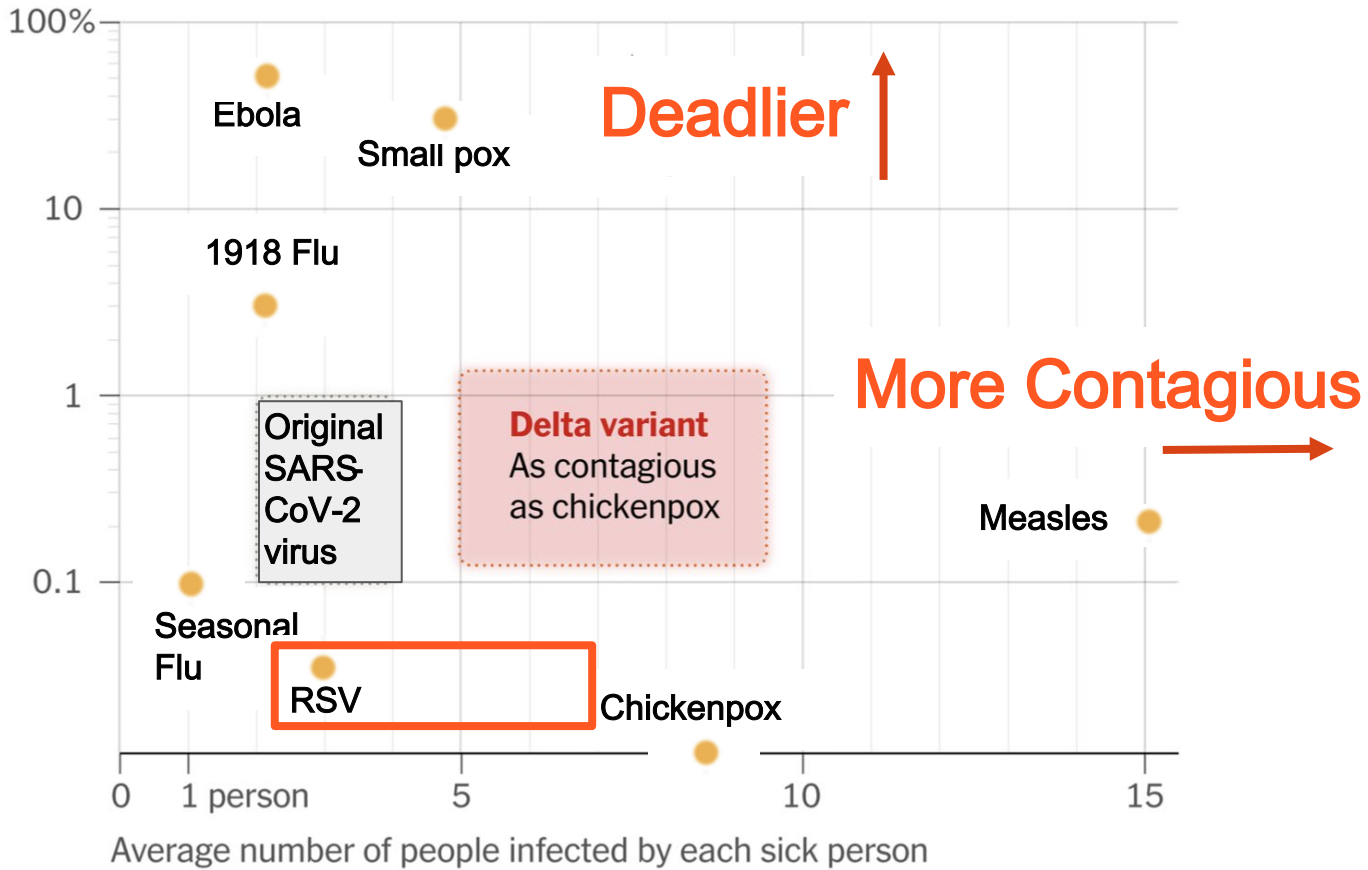

Adapted from the New York Times' graphic compiled from CDC and US and international health agencies with RSV information, and:
Reis J and Shaman J: Retrospective Parameter Estimation and Forecast of Respiratory Syncytial Virus in the United States. https://doi.org/10.7916/D8862GZP.
Weber A, Weber M,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

RSV Basics: The Virus

- Synonyms: Human RSV or hRSV; human orthopneumovirus
- Negative sense, single stranded RNA virus
- Infected cells fuse to form large cells, or syncytia
- **Spreads by droplets or fomites: it's pretty contagious!**
  - Lands on eyes, nose or mouth, transmits through the air and by fomite
  - Binds to and infects airway epithelial cells
  - R_0 has been estimated anywhere from 3 to 25 depending on model assumptions, but the value closer to 3 works well with predicting peak of outbreaks
    - 70% of forecasts predict peak magnitude of RSV activity 4 weeks ahead of time
  - **CDC recommends "contact precautions" and contagious from 3 days to 4 weeks**

Reis J, Shaman J (2016). *PLoS Comput Biol*. 2016;12(10): e1005133.
Griffiths C, Drews SJ, Marchant DJ. *Clin Microbiol Rev*. 2017;30(1):277-319.
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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

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

Risk Factors for Severe RSV Infection

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

SES, socio-economic status

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
- Respiratory infections and related hospitalizations begin increasing around age 50 (P&I)
  - Immune senescence
    - In elderly, greater susceptibility with lower RSV-specific Ig and nasal IgA
    - T-cell immunity declines with age

ILI, influenza-like illness

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

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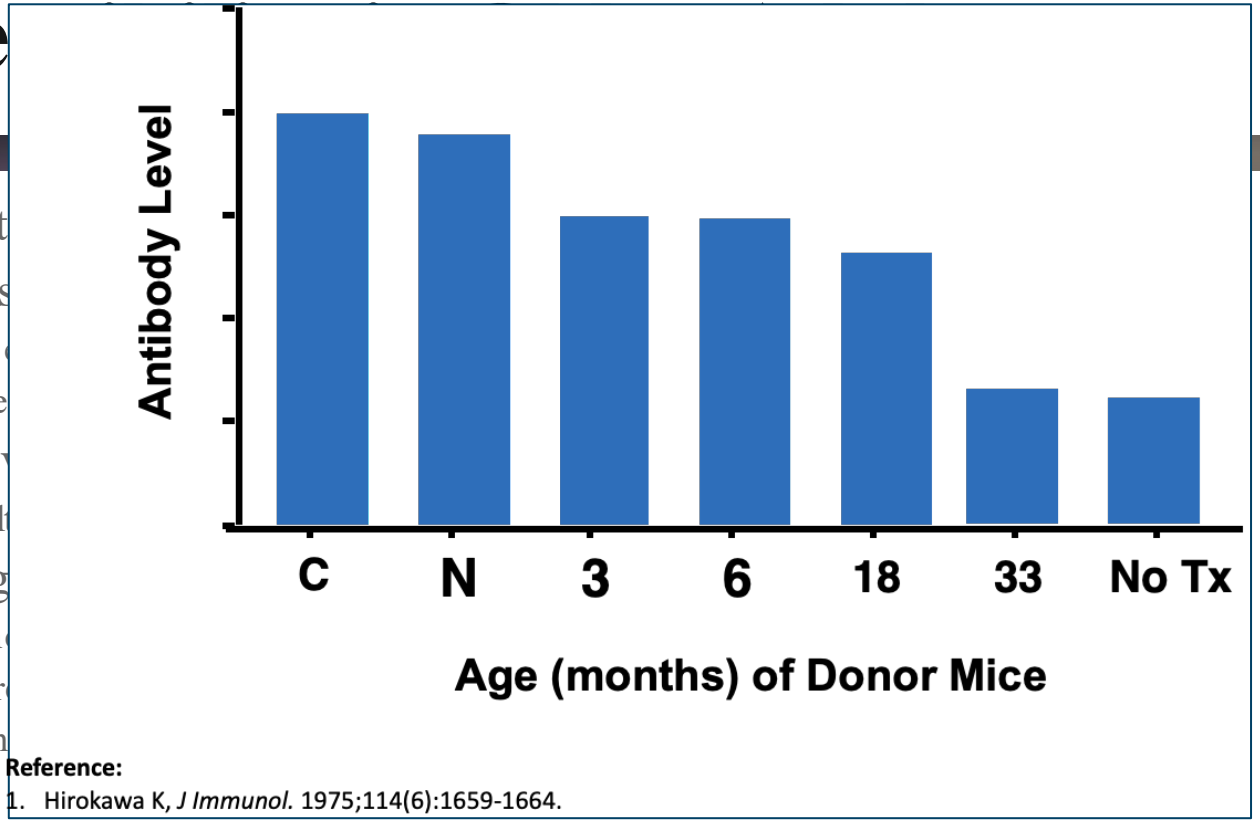

Reference:
1. Hirokawa K, *J Immunol.* 1975;114(6):1659-1664.

ILI, influenza-like illness

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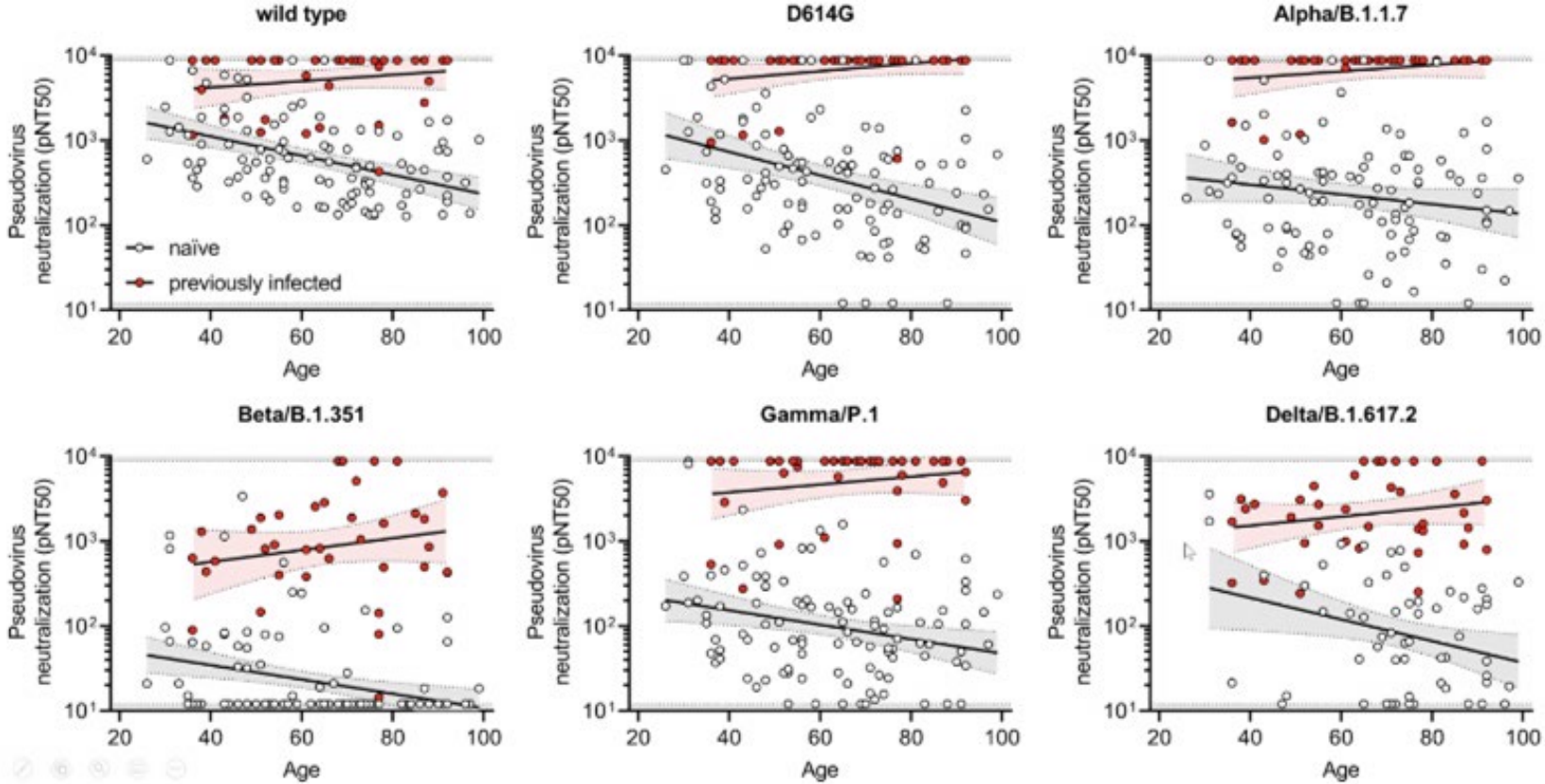
Immune Senescence

- T-cells change with age
  - Reduced numbers of new T-cells and naive T-cells: reduced B-cell stimulation
    - B-cells make less antibody, reduced neutralizing antibody, isotype switched Ab repertoire
  - Increased pool of memory T-cells
    - Memory T-cells have increasing dysfunction
      - Reduced IFN-gamma, cytokine production
- Dendritic cells (DC) present antigens to T-cells
  - DC function is to present antigens to T-cells
  - DC number and phenotype stable with age, but have declining function
    - Less able to process and present antigens, and to migrate to infected site (lung)
    - Increased level of pro-inflammatory cytokines on stimulation, and failure to recognize self (IL-6, TNF, INF-a)
    - Reduced TLR expression

Stephens LM, Varga SM. *Vaccines (Basel)*. 2021;9(6):624.
Agrawal A, Gupta S. *Ageing Res Rev.* 2011;10(3):336-45.

Reduced Neutralizing Ab with Age after SARS-CoV-2 Vaccination



Garcia-Beltran WF, et al. *Cell.* 2022;185:457-466.e4.
Canaday DH, et al. *Clin Infect Dis*. 2021;73:2112-2115.

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
Reduced nutrition	Reduced physiologic reserve, more difficult rehabilitation
Brain Aging	Risk for delirium, sleep/appetite disturbance with cytokine storm

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

Most Clinicians Don't Know 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

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

Susceptibility in Older Adults

- **RSV is among the top four viral causes of ILI** (third before the advent of SARS-CoV-2), after enterovirus and influenza
- 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*

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

Clinical Considerations

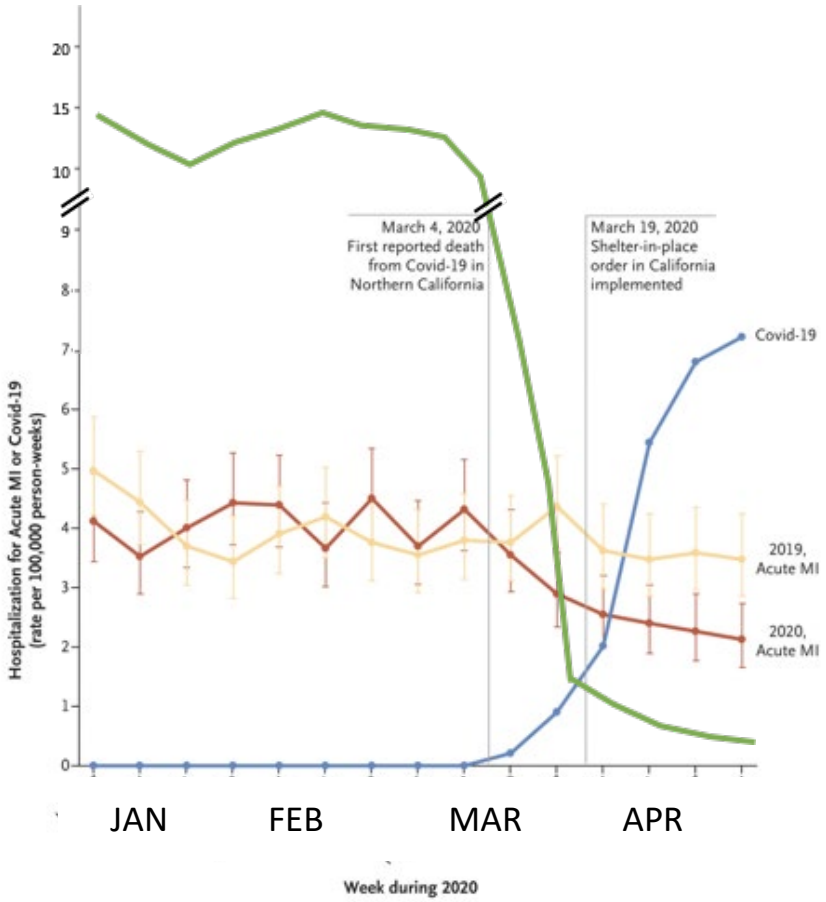
- Include RSV in differential diagnosis if it's "in season"
  - RSV season starts with influenza and beta-coronavirus season, but may last 1-2 months longer (Nov-May)
    - Adenovirus and metapneumovirus circulates all year
    - Rhinovirus and parainfluenza circulate mostly late spring to fall
  - More 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

Haber N. *Med Mal Infect*. 2018;48:377-82.

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]

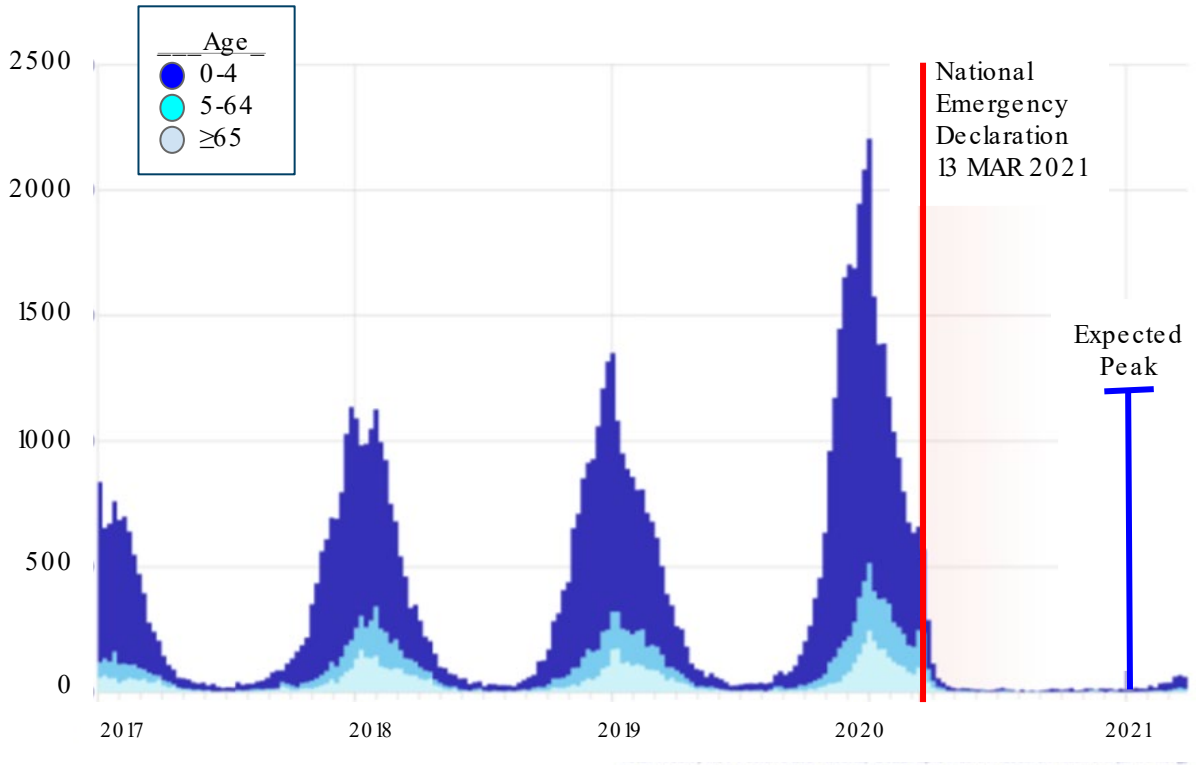


No. of Patients															
2019, Acute MI	140	125	104	97	110	118	106	100	107	106	123	102	98	101	98
2020, Acute MI	118	101	115	127	126	105	129	106	124	102	83	73	69	65	61
2020, Covid-19	0	0	0	0	0	0	0	0	0	6	26	58	156	195	207

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 312021

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

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

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

- Of 277k respiratory virus tests, 19k influenza
- 499 of these hospitalized for AMI
- Of these, 332 unique patients and had flu in week before AMI
  - Risk AMI (incidence ratio) 6-fold higher in week after flu
- **Risk also increased for AMI following RSV** and other viruses by about 3-fold

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

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)
Days 4–7	5.78 (3.17–10.53)
Days 8–14	0.60 (0.15–2.41)
Days 15–28	0.75 (0.31–1.81)
Sensitivity analyses	
Controlled for calendar month	6.19 (3.88–9.88)
Control interval limited to postexposure observation time	8.08 (5.04–12.95)
Control interval limited to preexposure observation time	4.84 (3.06–7.65)
Control interval limited to 2 months before and after influenza detection	5.01 (3.04–8.27)
Includes AMI cases with specimen obtained during admission	4.45 (2.85–6.97)
Induction interval†	
2 days before exposure	5.72 (3.65–8.98)
4 days before exposure	5.92 (3.77–9.29)
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)

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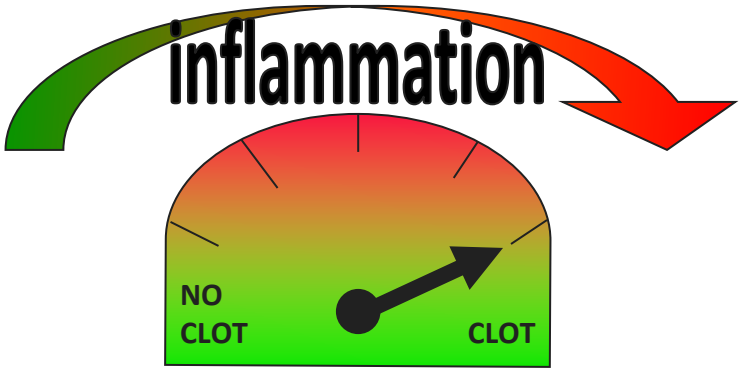
“Thrombometer” – The Propensity to Clot

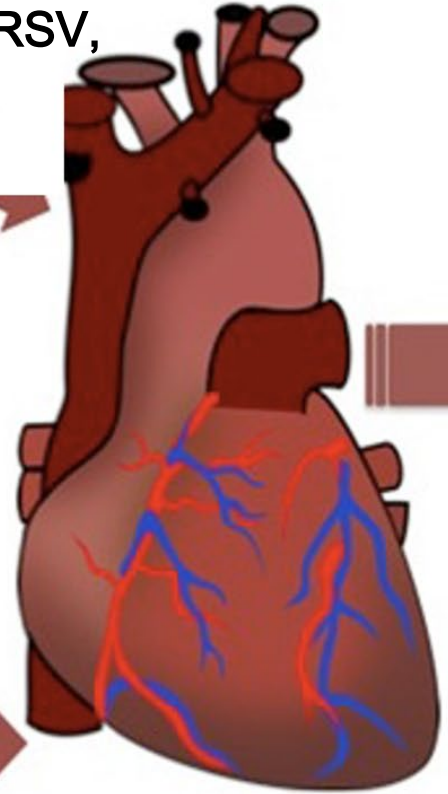


Increases with age
- Inflammatory markers of age
- IL-6, IL-8, C-reactive protein

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

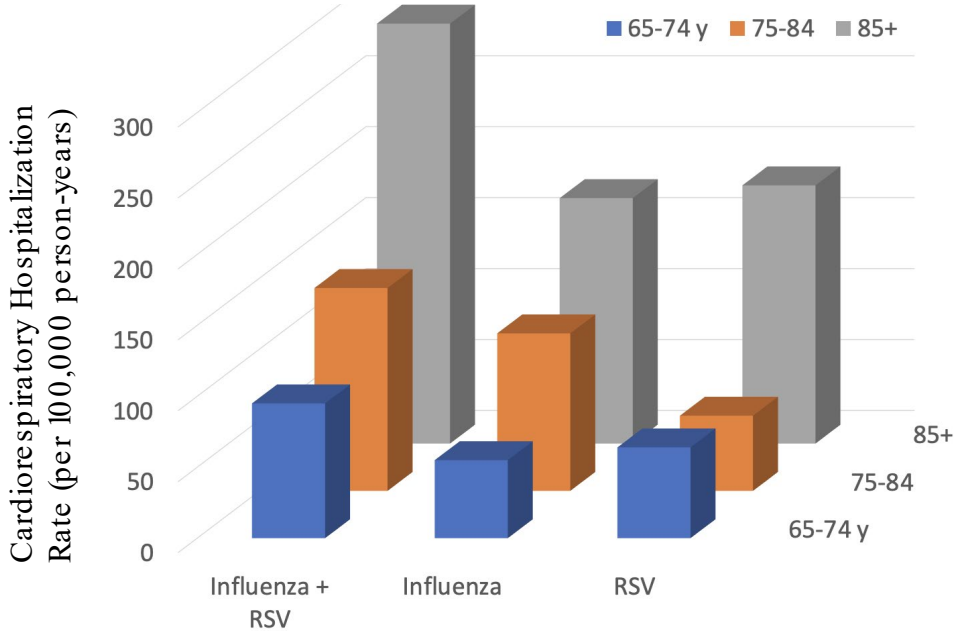
- Protein C and S
- Serum Amyloid A
- Cytokines
- Catecholamines,
- Hypoxia
- Vasoconstriction
- Platelet aggregations and coronary plaque disruption
- Thrombogenesis
- Emboli

Acute myocardial infarction

MacIntyre CR, et al. *Heart*. 2016;102(24):1953-1956.

RSV in Old-Older Adults

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



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

Fun Fact

- Children have a better mucociliary escalator than older adults
  - 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

Rationale for RSV Testing in Older Adults

- **Antibiotic stewardship**
  - As in Falsey study, antibiotic use high, and often potentially inappropriate
- In the era of CoVID, **diagnostic stewardship**
  - Clinically, at onset RSV, SARS-CoV-2/CoVID, influenza, parainfluenza, etc. indistinguishable
    - Index of suspicion with one virus over another has context with diagnosed close contacts
  - Context: a negative SARS-CoV-2 test does not preclude SARS-CoV-2 infection
    - PCR is highly sensitive when virus is present
      - It can take days, sometimes weeks for SARS-CoV-2 PCR test to become positive
    - **Antigen test + @ higher titers** (it's contagious!), but **false - in up to half of infected**
  - Ruling in RSV makes a firm diagnosis and dual infection generally is uncommon
  - Multiplex testing identifies virus 40% or more often, can limit other tests
    - Downside: more tests= more false positives, sample dependent
- **In the long-term care setting, having a diagnostic test has huge facility -level implications** in these resource-poor environments: staffing, PPE, time and effort

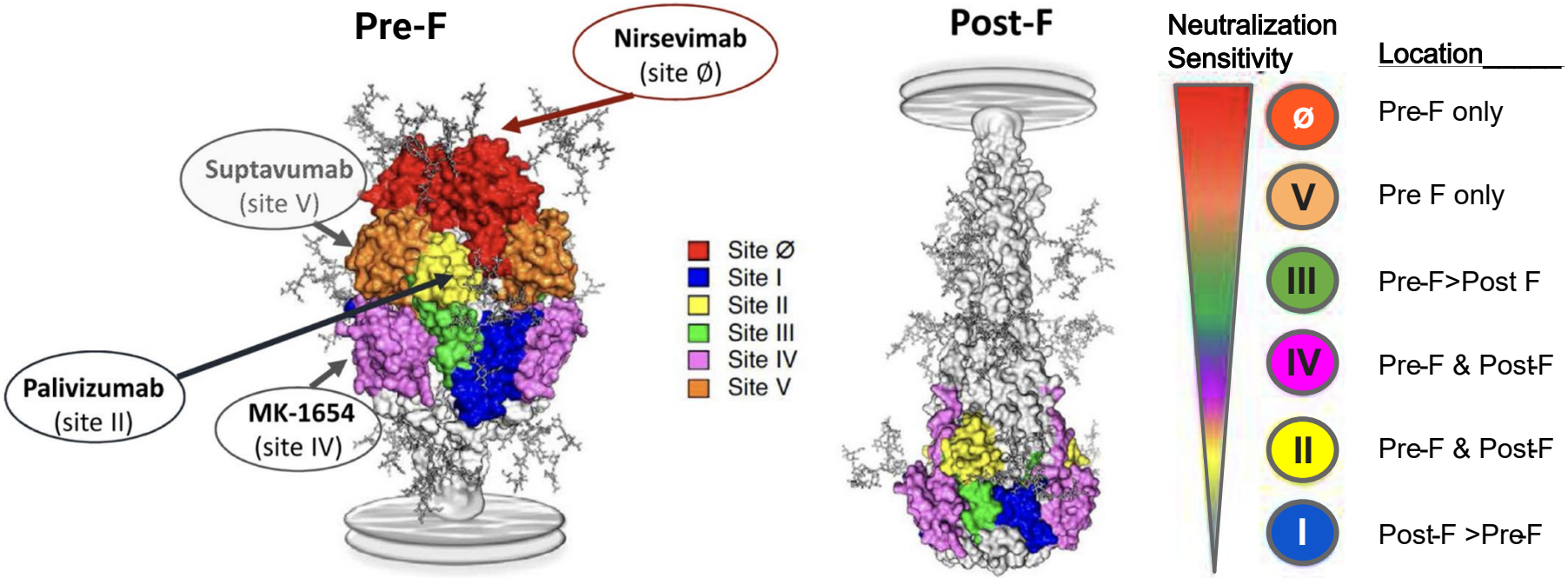
Management of RSV in Older Adults

- **Supportive**
  - Bronchodilators (not FDA approved for this indication)
  - Steroids (especially with COPD) (not FDA approved for this indication)
  - O_2
- Contact precautions
  - Frequent hand hygiene
  - Mask, ideally double mask (hook and loop) and properly fitted
  - Keep high-touch surfaces clean and disinfected
  - Isolate infected patients
- Ribavirin, antibody treatment available not generally used in older adults, and not FDA approved for this indication in older adults

The Path Forward

- RSV is a big deal, but most clinicians caring for adult and older adult patients aren't aware of the implications
- Because there are no meaningful approaches to prevention or intervention, there's little motivation to test or change awareness
- Several vaccines in development, some in phase III now
  - Early failures with RSV vaccine (e.g., enhanced disease in vaccines studies in the 1960s) elevate the importance of safety signals of new vaccines
- Neither monoclonal antibody or antivirals are likely to gain ground any time soon as a therapeutic options for older adults

RSV Sites of the RSV F-protein and mAbs



Adapted from:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7311299/pdf/nihms-1578843.pdf .
Mejias A, et al. Ann Allergy Asthma Immunol. 2020 Jul;125(1):36-46. doi: 10.1016/j.anai.2020.03.017. Epub 2020 Mar 23. PMID: 32217187; PMCID: PMC7311299.

What's in Development: RSV Vaccines for the Elderly

Vaccine Type	Phase 1	Phase 2	Phase 3
Protein based (Inactivated, particle, subunit)	▪ RSV SH Protein (Immunovaccine VIB) ▪ RSV F protein (NIH/NIAID/VRC)	▪ RSV G protein (Advaccine Biotechnology) ▪ RSV F protein (Pfizer)	▪ RSV F protein (RSVPreF3; GlaxoSmithKline)
Nucleic Acid		▪ mRNA-1345 (Moderna)	
Recombinant Vector		▪ MVA (Bavarian Nordic)	▪ Adenovirus (Ad26.RSV.preF, Janssen)

Available at: https://path.azureedge.net/media/documents/RSV-snapshot-07APR2021_HighResolution_NonEditable_PDF_3KgK9PB.pdf.

Protein-based Vaccine Elicits Robust Immune Response in Elderly

- RSVPreF3 contains recombinant subunit pre-fusion RSV antigen combined with adjuvant
- Vaccine was well tolerated in Phase 1/2 studies in young and older adults
- At one month post-immunization, elicited robust humoral and cellular immune response
  - 10-fold increase in RSV-A neutralizing antibodies
  - >12-fold increase in RSVPreF3 IgG antibodies
- Phase 3 trial (AReSVi 004) started in 2021 to include up to 1650 adults ≥60 years with 3-year follow-up
  - Interim results expected in second half of 2022

Schwarz TF, et al. *J Infect Dis*. 2021;jiab317.
Presented at IDWeek 2020 (Abstract 119). https://www.gsk.com/en-gb/media/press-releases/gsk-starts-phase-iii-rsv-candidate-vaccine-programme-for-older-adults/.

Early Signs of Success with Vector-based Vaccine in Elderly (CYPRESS Study)

- Phase 2b study randomized 5782 individuals ≥65 years to receive Ad26.RSV.preF vaccine or placebo
- Primary endpoint: First occurrence of RT PCR-confirmed RSV-mediated lower respiratory tract disease according to any of 3 case definitions:
  1. ≥3 symptoms of lower respiratory tract infection (LRTI)
  2. ≥2 symptoms of LRTI
  3. ≥2 symptoms of LRTI or ≥1 symptoms of LRTI plus ≥1 systemic symptom
- Vaccine efficacy for each case definition was 80% (definition 1), 75% (definition 2), and 69.8% (definition 3)
- Vaccine elicited a robust humoral and cellular immune response
- A phase 3 trial (EVERGREEN) is underway

Presented at IDWeek 2021 (Abstract LB14). https://www.contagionlive.com/view/cypress-trial-rsv-vaccine-older-adults-elicits-robust-immune-response.

Maximizing Protection in the Elderly: Co-Administration of RSV and Flu Vaccines

- Phase 2a, double-blind, placebo-controlled study of 180 adults ≥60 years
- Participants randomized to receive:
  - Ad26.RSV.preF plus Fluarix on Day 1 and placebo on Day 29
  - Placebo plus Fluarix on Day 1 and Ad26.RSV.preF on Day 29 (control)
- Co-administration had an acceptable safety profile and showed no evidence of interference in immune response.
- Results are compatible with simultaneous seasonal vaccination with both vaccines

Sadoff J, et al. *J Infect Dis*. 2021;223:699-708.

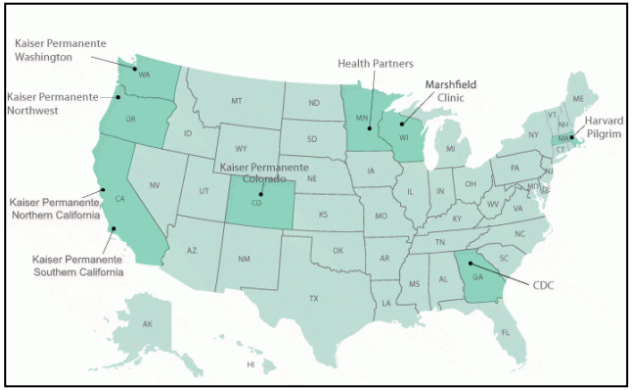
Vaccine Safety

- No vaccine is 100% safe..nothing is
  - Vaccines can cause injection site pain, sore arm, redness, fever
  - Nearly all vaccine side-effects are **very mild**
- The risk of serious adverse event from disease is *far* greater than from vaccination
- We are at far greater risk of an adverse outcome from riding in a car, crossing the street, choking on food..than from a vaccine

Vaccine Safety Monitoring

- **Extensive safety monitoring**
  - Post-licensure manufacturer monitoring
  - Vaccine Adverse Event Reporting System (VAERS) and FDA
  - Vaccine Safety Datalink by CDC

- **The system works…**
  - Vaccines found to be extremely safe
  - Most safety issues are of limited clinical significance



Vaccine Safety Datalink Sites

Tau N, et al. *Ann Intern Med*. 2020;173(6):445-449.

Things That Provoke Doubt in Patients

- Follow invalid contraindications to immunization
  - Low-grade fevers
  - Mild illness
- Providing reading material rather than recommending
- Clinical team providing different recommendations
- Not giving a strong and clear recommendation

American Academy of Pediatrics: Countering Vaccine Hesitancy. Accessed at: https://publications.aap.org/pediatrics/article/138/3/e20162146/52702/Countering-Vaccine-Hesitancy.

Reminder, for the Majority of People

Start with a strong, consistent**presumptive** recommendation:

"I recommend the flu vaccine."

Rather than the participatory approach:

"Do you want to get a flu vaccine?"

Opel DJ, et al. *Pediatrics*. 2013;132(6):1037-1046.

WHO: 10 Threats to Global Health in 2019

1. Air pollution and climate change
2. Noncommunicable chronic disease
3. Global influenza pandemic
4. Fragile and vulnerable settings
5. Antimicrobial resistance
6. Ebola and other high-threat pathogens
7. Weak primary health care
8. **Vaccine hesitancy**
9. Dengue
10. HIV

Summary

- RSV: is under-recognized for its importance in older adults
- Altered presentation but indistinguishable clinically from other important causes of URI and LRTI
- Awareness will increase as the clinical value of multiplex testing gains acceptance and is further established as a tool for:
  - Antimicrobial stewardship
  - Diagnostic stewardship
  - Improving workforce and resource stability in under-resourced environments
- We need an approach for primary prevention (vaccination!)
  - Vaccine recommendation fatigue is felt by both clinicians and patients
  - Do not take it personally!
  - Keep the conversation going

RESPIRATORY SYNCYTIAL VIRUS

Recognizing and Mitigating Risk in Vulnerable Adults

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