

RESPIRATORY SYNCYTIAL VIRUS:

Protecting Older Adults at Risk for Serious Complications



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Disclosure

Angela Branche, MD

<i>Research Support</i>	CyanVac, Janssen, Merk, Pfizer
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<i>Consultant</i>	GlaxoSmithKline
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<i>Research Support</i>	Pfizer, Sanofi Aventis, Seqirus, Genentech
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<i>Consultant</i>	Janssen, Merck, Novavax, Sanofi Aventis, Seqirus, Vaxart
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Learning Objectives

After participating in this CME activity, the learner should be able to:

-  Discuss the burden of disease related to respiratory syncytial virus (RSV) infection in adults
-  Identify challenges in diagnosing RSV infection in older adults, particularly in the outpatient setting
-  Identify the factors that place older adults at increased risk for morbidity due to RSV infection
-  Integrate prophylactic vaccinations related to RSV into the routine management of older adults



RSV Background

- First discovered as cause of bronchiolitis in children in 1957
- Found to cause mild infection in young adults as part of family studies
- Not discovered as serious cause of adult illnesses until the 1990s
- Has since been suggested as a cause of serious illness in community dwelling older adults

RSV, respiratory syncytial virus



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Branche AR, et al. *Drugs Aging*. 2015;32(4):261-269.

Overview of RSV Illness

- Common respiratory virus
 - Fourth most common viral pathogen after influenza A and B, and SARS-CoV-2
- Classified into 2 major subtypes—A and B—based on antigenic and genetic analysis
 - One subtype predominates during one season
- Spreads through air via respiratory droplets or direct contact via surfaces → CDC recommends “contact” precautions
- Contagious for 3 to 8 days but immunosuppressed might shed for up to 4 weeks
- RSV infection does not confer long-term immunity → recurrent infections common

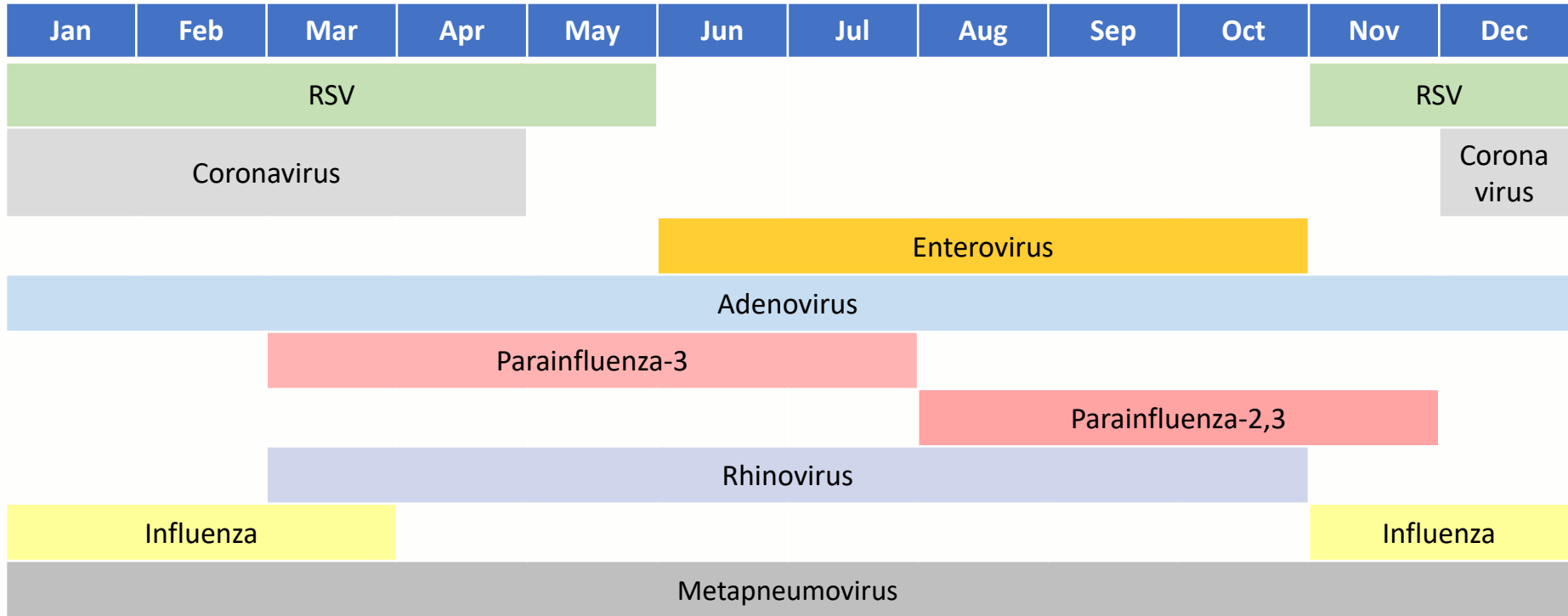
CDC, Centers for Disease Control and Prevention



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Centers for Disease Control and Prevention. December 2020. Accessed July 26, 2021.
www.cdc.gov/rsv/clinical/index.html
Chatterjee A, et al. *Infect Dis Ther.* 2021;10:S5-S16.
Jung HE, et al. *Viruses.* 2020;12(1):102. doi: 10.3390/v12010102.

Overlapping Seasonality of RSV with Other Respiratory Viruses



Features of RSV Infection Across the Age Spectrum

Runny nose, decreased appetite, cough, sneezing, fever, wheezing

Infants

Children

Adults

Older Adults

Increased risk for more severe infection

- Bronchiolitis
- Pneumonia



More Than a Disease of Childhood, RSV Poses a Serious Threat to Older Adults

- Annual attack rates in the US¹
 - 2%-10% of older adults within the community
 - As high as 5%-10% of older adults within congregate settings
- Compared with younger adults, older adults with RSV are more likely to become hospitalized and die²
- Disease burden expected to increase due to the aging population (30% increase 2020 to 2050)



RSV in Older Adults and Adults with Chronic Medical Conditions

- Healthy adults with RSV
 - Mild symptoms consistent with upper respiratory tract infection
 - Symptom duration is ~5 days
- Adults at risk for RSV lower respiratory tract infection:
 - Older adults, especially age ≥ 65 y
 - Adults with chronic lung or heart disease
 - Adults with weakened immune system



RSV in Older Adults and Adults with Chronic Medical Conditions (continued)

- RSV infection may exacerbate underlying cardiopulmonary diseases:
 - Asthma
 - Chronic obstructive pulmonary disease
 - Congestive heart failure
- Viral shedding
 - Longer in older adults (and infants) vs other adults



Comorbidities Increase Risk of Hospitalization Among Older Adults Who Develop RSV

Patients with medical claim for RSV diagnosis identified using the Medicare 5% national sample administrative database between July 1, 2011, and June 30, 2015

*Odds ratio >1 indicates that the variable is a positive predictor of hospitalization among patients who were initially hospitalized as compared with patients who were never hospitalized

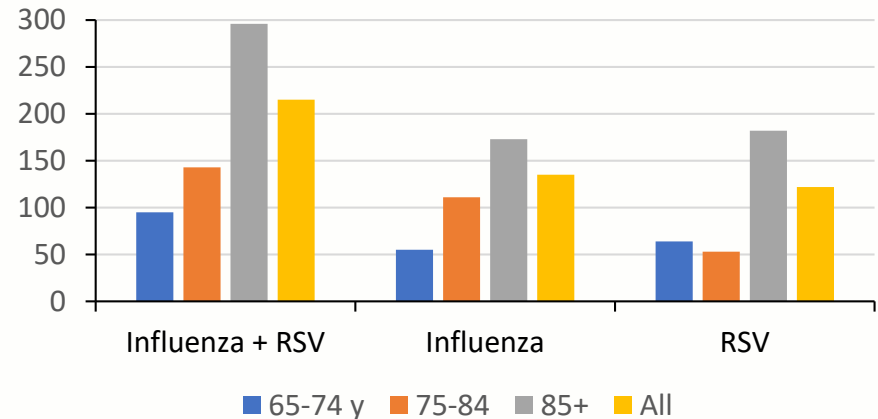
Associated Risk Condition	Odds Ratio (95% CI)*	P Value
Osteoarthritis	0.72 (0.51-1.02)	0.062
High cholesterol	0.75 (0.55-1.03)	0.074
Asthma	0.79 (0.50-1.24)	0.303
Coronary artery disease	1.16 (0.82-1.65)	0.411
Stroke	2.00 (1.02-3.96)	0.045
Congestive heart failure	2.06 (1.40-3.02)	<0.001
Chronic obstructive pulmonary disease	2.12 (1.49-3.02)	<0.001
Solid organ transplant	2.52 (0.88-7.22)	0.085
Stem cell transplant	2.53 (0.21-29.70)	0.461
Chronic kidney disease	4.37 (2.74-6.98)	<0.001
Hematologic malignancy	5.17 (2.02-13.20)	0.001



RSV Is an Important Cause of Cardiorespiratory Hospitalization

- Retrospective analysis for 6 respiratory seasons (2011-2017)
 - Medicare Provider Analysis and Review inpatient claims and Minimum Data Set
- Long-stay (≥ 100 d) residents of long-term care facilities age ≥ 65 y

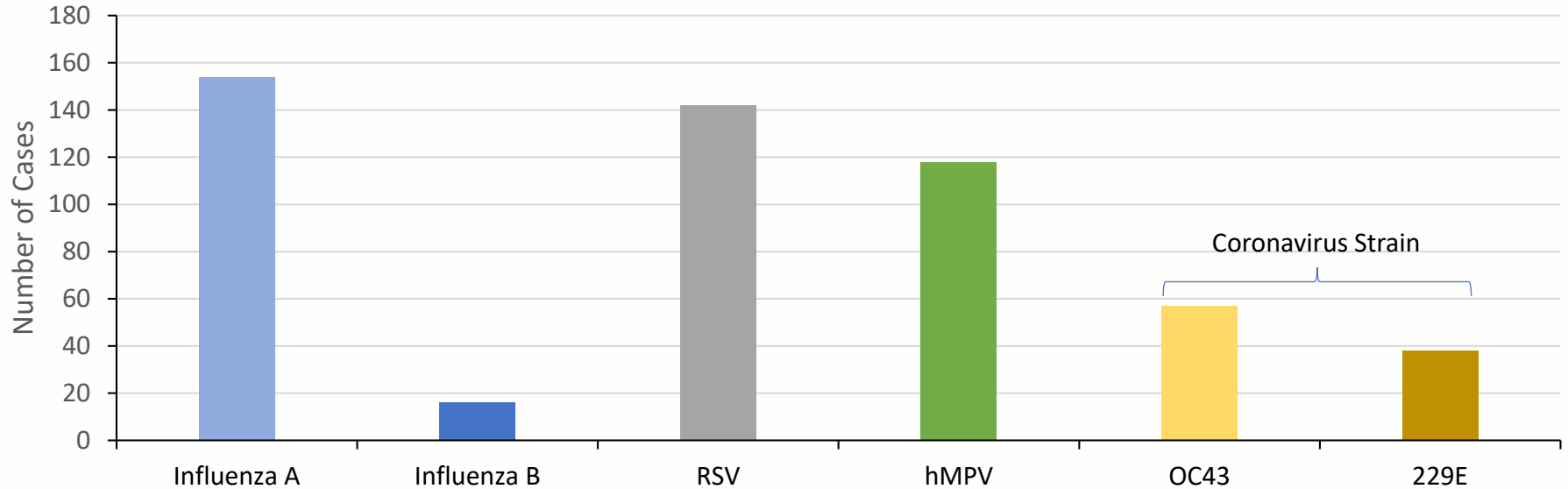
Attributable Cardiorespiratory*
Hospitalization Rate (per 100,000
person-years)



*ICD-9-CM codes 390.XX-459.XX; ICD-10-CM codes 100.XX-199.XX; ICD-9-CM codes 460.XX-519.XX; ICD-10-CM codes J00.XX-J08.XX; J12.XX-J99.XX



Viral Pathogens in Hospitalized Patients



229E, Coronavirus strain 229E; hMPV, human metapneumovirus; OC43, Coronavirus strain OC43; RSV, respiratory syncytial virus



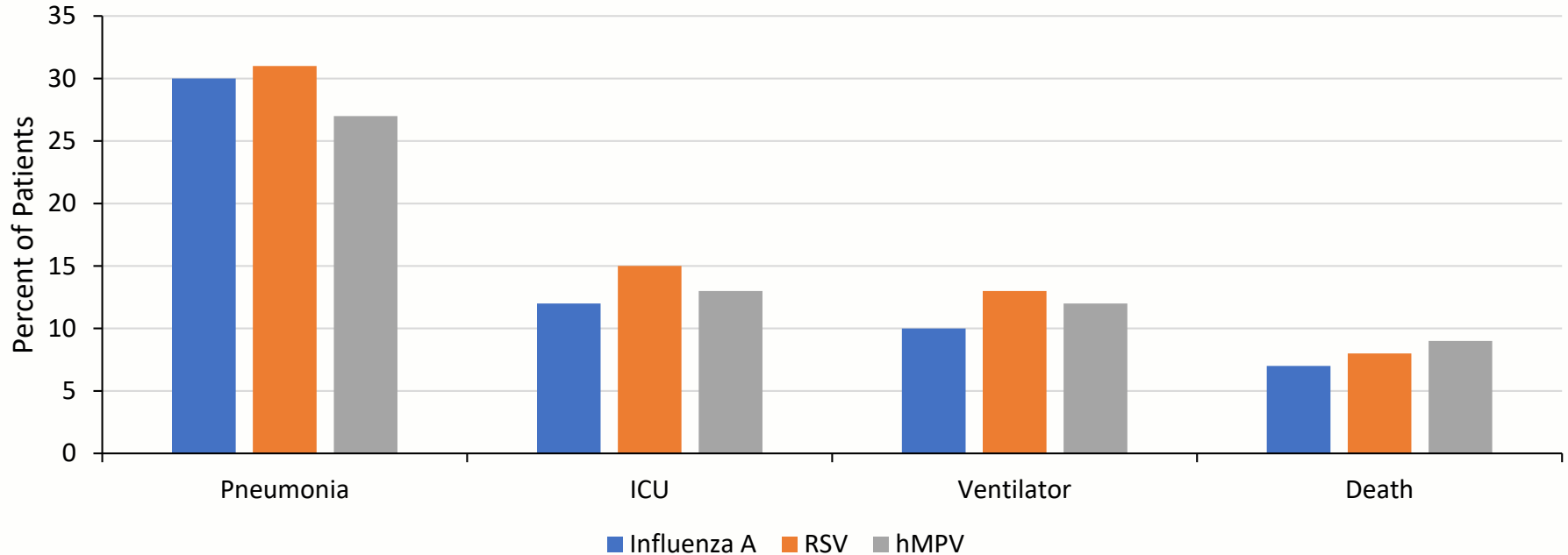
RSV Infection in Older Adults

- Rates of office visits for **RSV vs influenza** were **lower in healthy adults but similar for high-risk adults**
- For hospitalized patients, **RSV and influenza resulted in similar** (next slide)
 - **lengths of stay** (14 vs 8 days)
 - **ICU admission** (15% vs 12%)
 - **mortality** (8% vs 7%)
- RSV accounted for:
 - 11.4% of COPD exacerbations
 - 10.6% of pneumonia admissions
 - 7.2% of asthma admissions
 - 5.4% of CHF admissions

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit



Clinical Outcomes in Hospitalized Patients



hMPV, human metapneumovirus



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Falsey AR, et al. *N Engl J Med.* 2005;352(17):1749-1759.
Walsh EE, et al. *J Infect Dis.* 2013;208(10):1634-1642.

Bacterial Superinfections: Common in Patients With RSV

- Occur in 12.5% of RSV+ infections¹
- In study of 842 winter hospitalizations (N=771)²
 - 348 (41%) had evidence of viral infection
 - Of these,
 - 61% involved viral infection alone
 - 18% of RSV+ patients had confirmed bacterial infection
 - Additional 21% of RSV+ patients had procalcitonin evidence of bacterial infection
 - 90% received antibiotics as part of treatment



RSV Disease Burden in Older Adults May Be Underestimated

- Clinical syndrome results in a broad differential and low index of suspicion results in low clinical diagnosis
- Little motivation to make a diagnosis without targeted therapy
- Likely to be updated with a multiplex test to distinguish SARS-CoV-2, RSV, influenza



RSV Is Challenging to Diagnose, Particularly in Older Individuals

- Clinical symptoms of RSV are nonspecific and can overlap with other viral respiratory infections (eg, influenza and COVID-19) and some bacterial infections¹
 - Adults with reinfection shed virus at titers much lower and for shorter durations than children²
- Most common RSV clinical laboratory tests¹:

Common RSV Clinical Laboratory Tests	Notes
Real-time reverse transcriptase polymerase chain reaction	Most sensitive
Antigen testing	Highly sensitive in children but not in adults
Viral culture	Less commonly used
Serology	Typically used for research purposes

- Some tests can differentiate between RSV subtypes (A and B), but clinical significance unclear¹



Making a Diagnosis of RSV: Antigen-Based Tests

- Dramatically reduced sensitivity in older children and adults
 - Adults have a lower viral load and shorter duration of viral shedding
 - Advanced age and immunosuppression increase duration of viral shedding
- Quick and easy with acceptable performance in young children
- Used widely in clinical practice for children

RSV RADT Accuracy Estimates Based on Population Analysis ^a			
Population (# Studies)	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	P Value for the Joint Model
Children (63)	0.81 (0.78-0.84)	0.96 (0.95-0.98)	<0.001
Adults (4)	0.29 (0.11-0.48)	0.99 (0.98-1.00)	Reference

^a Data for children include results from 59 studies examining exclusively pediatric subjects and 4 mixed studies of adults and children from which data on the pediatric subgroup were available. Data for adults include results from 2 studies examining exclusively adult subjects and 2 mixed studies of adults and children from which data on the adult subgroup were available.



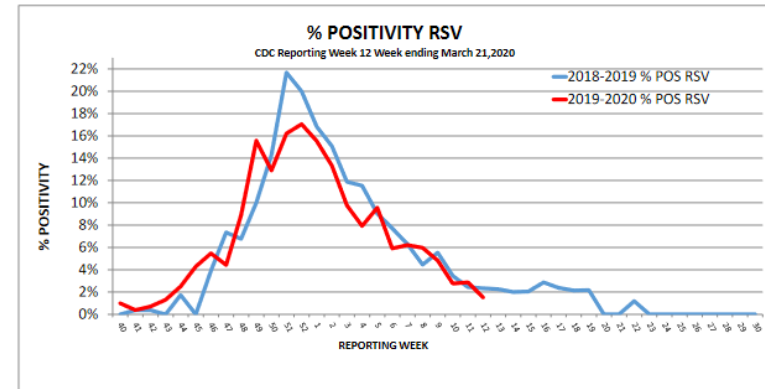
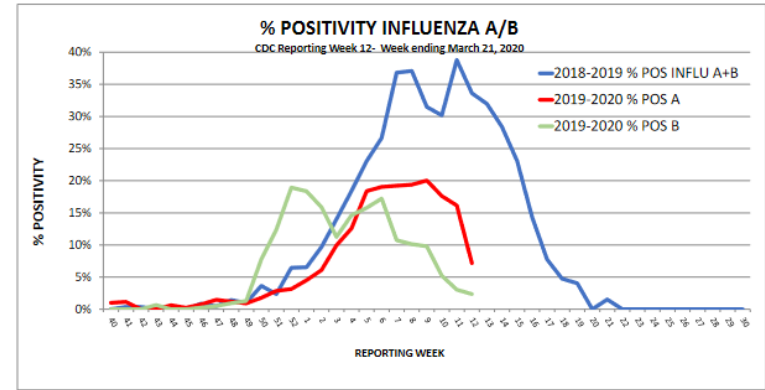
Making a Diagnosis of RSV: Rapid Molecular PCR Tests

- Now more widely available
- Sensitivity >95% for most platforms
- Usually duplexed with influenza testing and results are available within 1 hour
- Shown to reduce the number of ancillary tests, decrease antibiotic use
- Rapid identification of pathogen also informs infection control measures to prevent nosocomial outbreaks in hospitals and skilled nursing facilities



Making a Diagnosis of RSV: Duplexed or Multiplexed Tests

- Primarily driven by influenza
- Temporal peaks of RSV and influenza do not necessarily coincide
- May result in bias and underestimation of RSV cases



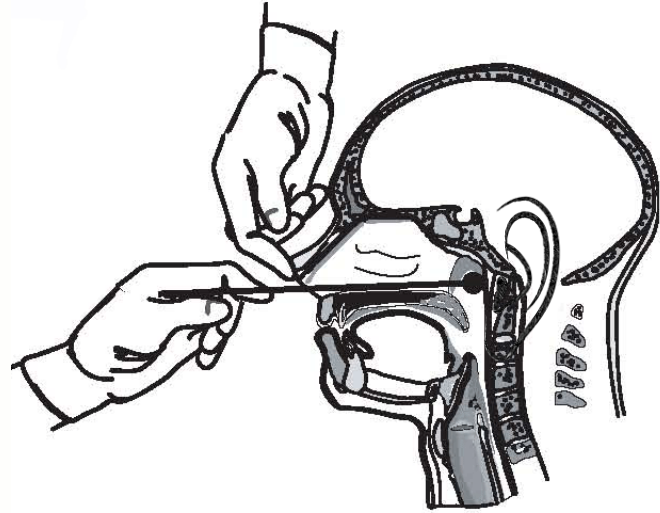
Testing Cost

- One investigation reported a cost of \$170 for 1 respiratory viral panel



Diagnosis of RSV: Sampling Technique

- Sampling yield increased:
 - Utilizing flocked swabs
 - Nose and throat combined
 - Testing sputum



Clinical Syndrome: RSV vs Influenza

Table 1. Baseline Characteristics, Presenting Symptoms, Complications, and Outcomes of 607 Adults Hospitalized With Respiratory Syncytial Virus Infection, 2009–2011

Variable	RSV (N = 607)	Influenza (N = 547)	P Value
Age, y, mean (SD)	75.1 (16.4)	74.7 (16.6)	.650
Male sex	48.6	49.5	.749
Resident of long-term care facility	32.9	30.5	.378
Comorbidity, major systemic (except chronic lung diseases) ^a	74.0	65.8	.003
Chronic lung diseases ^a	35.6	24.1	<.001
Symptom onset to admission, d, mean (SD)	2.6 (2.2)	2.0 (1.7)	<.001
Fever >37.5°C	75.0	94.2	<.001
Cough	87.5	85.7	.513
Sputum production	81.2	72.5	.010
Wheezy breathing and dyspnea	68.9	53.2	<.001
Sore throat	11.8	14.3	.364
Runny nose	25.6	30.2	.214
Pneumonia	42.3	36.7	.006
Lower respiratory complications ^b	71.9	55.6	<.001
Cardiovascular complications ^b	14.3	13.3	.653
Complications, any ^b	80.4	72.8	.002
Bacterial infection, overall ^c	14.8	14.3	.790
Bacterial infection, at presentation ^c	12.5	9.1	.066
Supplemental oxygen therapy	67.9	59.0	.002
Ventilation, noninvasive or invasive	11.1	6.2	.003
30-day mortality	9.1	8.0	.538
60-day mortality	11.9	8.8	.086
Time to death, d, median (IQR)	13 (7–29)	7 (3–13)	.001
Extended care in subacute hospitals	25.2	19.7	.027
Duration of hospitalization for survivors, d, median (IQR)	7 (5–14)	6 (5–11)	.238

- Comorbidity, major systemic (except chronic lung diseases)
- Chronic lung diseases
- Time from symptom onset to admission
- Fever >37.5°C
- Sputum production
- Wheezy breathing and dyspnea
- Pneumonia
- Lower respiratory complications
- Any complications
- Supplemental O₂ therapy
- Ventilation, noninvasive/invasive
- Time to death
- Extended care in subacute hospitals

Why Make a Diagnosis?

Low awareness has resulted in delayed diagnosis and intervention, or ability to distinguish RSV from other potential diseases of concern, eg, COVID

1) Health care utilization associated with RSV for older adults, including antibiotic and diagnostic stewardship

Health care utilization for older patients hospitalized with RSV has been reported to be similar or higher when compared to patients hospitalized with influenza*

	Influenza	RSV
Hospital length of stay (days)	3.6	6
Mechanical ventilation (%)	7.2	16.7
Mean adjusted costs	\$14,519	\$38,828

*Data taken from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, and Agency for Healthcare Research and Quality for 1997 to 2012; data did not differentiate among strains.



Why Make a Diagnosis? (cont)

Low awareness has resulted in delayed diagnosis and gaps in knowledge

- 1) Health care utilization with RSV for older adults, including testing, antibiotics
- 2) **Long-term morbidity and mortality associated with RSV infection in this population**

	Better	Worse	Same	Total
MRC	72 (37.7)	45 (23.5)	74 (38.7)	191
L-B IADL	50 (25.3)	60 (30.3)	88 (44.4)	198
Barthel ADL	74 (37.9)	63 (32.3)	58 (29.7)	195
GFI	80 (52.6)	50(32.9)	22 (14.5)	152

- 13% mortality at 6 months after discharge
- Change in subjects living independently from 40% → 32%

Barthel ADL = Barthel Index for Activities of Daily Living (0-100); GFI = Groningen Frailty Index (0-15) and Mini-Cog instrument;
L-B IADL = Lawton-Brody Instrumental Activity of Daily Living Scale (0-8); MRC = Medical Research Council Breathlessness score (1-5).



Why Make a Diagnosis? (cont)

Low awareness has resulted in delayed diagnosis and gaps in knowledge

- 1) Health care utilization associated with RSV for older adults
- 2) Long-term morbidity and mortality associated with RSV infection in this population
- 3) Risk stratification to inform future vaccine efforts**

	October 2017 – April 2018		October 2018 – April 2019		October 2019 – April 2020	
Age groups	Rochester, NY	New York City	Rochester, NY	New York City	Rochester, NY	New York City
	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
18-49 y	9.95 (6.61-14.98)	8.43 (4.78-14.83)	9.09 (5.92-13.94)	11.94 (7.42-19.20)	7.79 (4.91-12.36)	7.72 (4.28-13.95)
50-64 y	57.50 (43.82-75.45)	47.24 (31.67-70.47)	63.03 (48.62-81.70)	57.08 (39.67-82.13)	40.91 (29.64-56.46)	33.46 (20.80-53.82)
≥65 y	138.20 (114.46-166.86)	212.00 (168.58-266.60)	136.92 (113.30-165.46)	255.56 (207.43-314.86)	139.48 (115.62-168.26)	214.90 (171.16-269.83)

Why Make a Diagnosis? (cont)

Low awareness has resulted in delayed diagnosis and gaps in knowledge

- 1) Health care utilization associated with RSV for older adults
- 2) Long-term morbidity and mortality associated with RSV infection in this population
- 3) Risk stratification to inform future vaccine efforts**

Age-groups	Incidence Rate	Incidence Rate	Rate Ratio (95% CI)
	COPD	No COPD	
18-49 years	24.87	7.83	3.18 (0.99-10.17)
50-64 years	204.76	32.25	6.35 (2.00-20.11)
≥65 years	1077.36	80.32	13.41 (4.29-41.98)
Age-groups	Diabetes	No Diabetes	
18-49 years	65.39	5.86	11.16 (3.45-36.13)
50-64 years	116.77	34.79	3.36 (1.06-10.63)
≥65 years	501.82	77.93	6.44 (2.06-20.17)
Age-groups	CHF	No CHF	
20-39 years	295.23	8.88	33.23 (10.14-108.90)
40-59 years	485.84	25.87	18.78 (5.92-59.55)
60-79 years	688.58	90.24	7.63 (2.43-23.93)

CHF, congestive heart failure



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Branche A, et al. Unpublished data. 2021.

RSV: Management

- Symptomatic management is the mainstay of current therapy for most adults
 - Steroids*, especially for patients with underlying lung disease
 - Humidified oxygen
 - Bronchodilators*
- Select immunocompromised patients
 - Steroids*
 - Ribavirin*
 - IgIV/RSV Ig/Palivizumab*
 - Experimental therapy

*Not approved by the US Food and Drug Administration for RSV infection in older adults



An Ounce of Prevention...

- Preventing RSV infection is better than acute treatment because
 - There is no approved medication for acute treatment of RSV infection in older adults
 - Antivirals generally work best early in the disease course, not in hospitalized patients



Take-Home Lessons from the COVID-19 Pandemic

- Older adults who contract a viral respiratory infection are particularly susceptible to poor health outcomes, including death
- General preventive measures, including proper masking and social distancing, are effective in reducing viral spread
- People find lifestyle changes to prevent infection difficult to follow long-term
- Vaccination helps
 - prevent the spread of infection
 - reduce infection severity

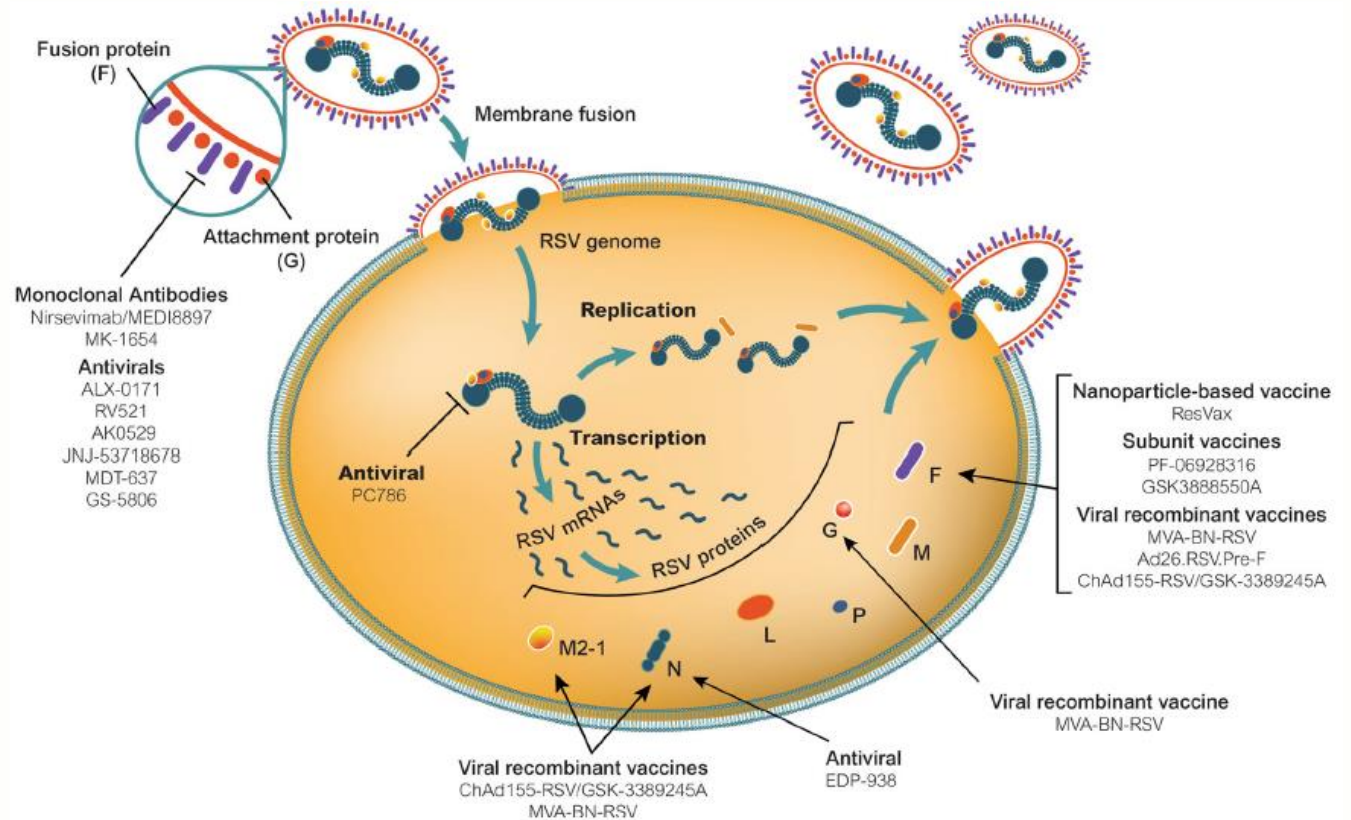


General RSV Prevention Measures

- Perform frequent hand hygiene
- Masking
 - Double mask
 - Hook and loop
 - Properly fitted
- Cover coughs and sneezes
- Stay home when sick
- Avoid those who are sick
- Keep high-touch surfaces clean and disinfected
- Isolate infected patients in health care settings



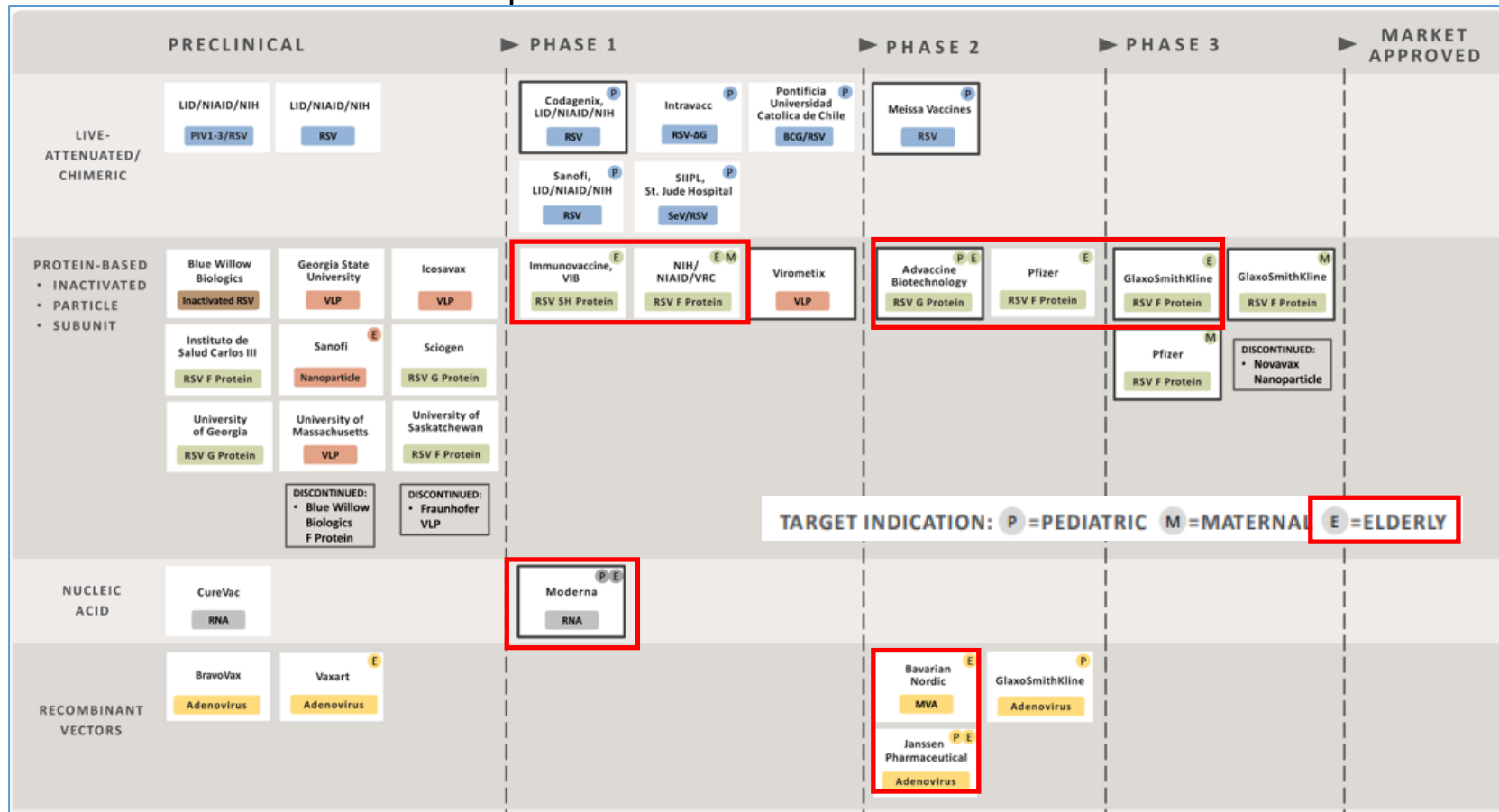
Treatment Targets



F, fusion protein; G, attachment glycoprotein; L, large viral polymerase; M, matrix protein; M2-1 protein, transcription factor; N, nucleoprotein; P, phosphoprotein



RSV Vaccines in Development for Older Adults

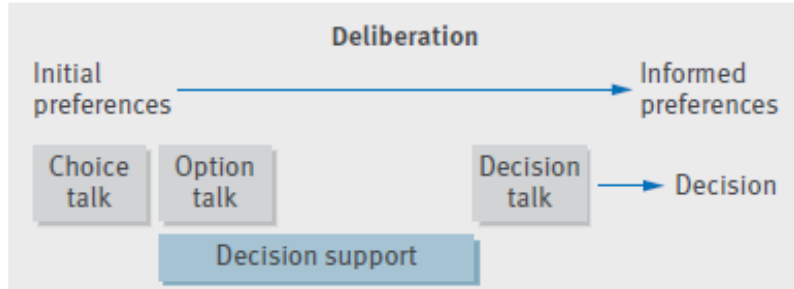


RSV Vaccines in Development Targeting Older Adults

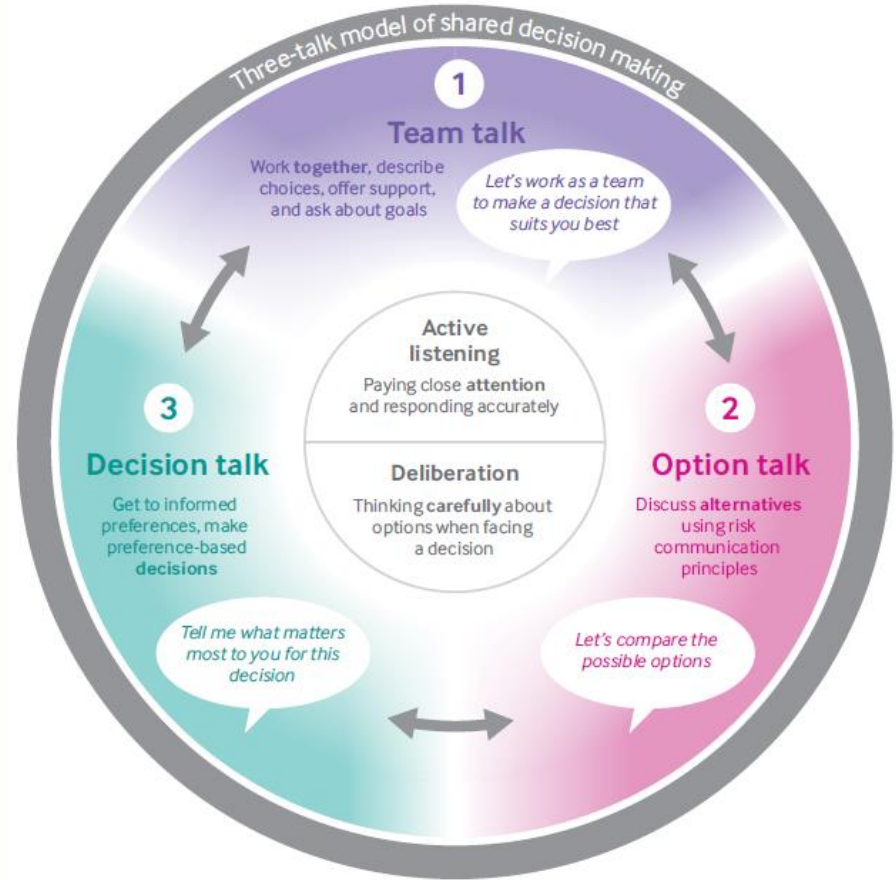
Platform	Phase	Formulation/Antigen	Results
mRNA-1777	1	mRNA Prefusion RSV F	Neutralizing antibodies; RSV F-specific serum antibodies; RSV-specific CD4 and CD8 T cells
VXA-RSVf	1	Vector-based RSV F	N/A
PanA d3-RSV	1	Vector-based RSV F, N, M2	RSV-specific IgG and IgA; T cell-mediated IFN- γ
Ad26.RSV.Pre-F	2	Vector-based Prefusion RSV F	Ongoing
MVA-BN-RSV	2	Vector-based RSV F, G, N, M2	Well tolerated; neutralizing antibodies; T cell-mediated IFN- γ
MEDI-7510	2	Subunit Postfusion RSV F + GLA-SE	RSV F-specific IFN- γ ; did not meet primary endpoint
GSK3844766A	3	Subunit Prefusion RSV F + AS01	Ongoing
ResVax	3	Particle-based RSV F trimers	Acceptable safety and tolerability; RSV-specific serum IgG; neutralizing antibodies; did not meet primary endpoint



Shared Decision-Making



Consider that a strong recommendation from a clinician is the single most effective strategy to vaccine acceptance.



Strategies for Increasing Uptake of Immunizations in Older Adults

Educate

- Place signs and information in waiting area, examination rooms
- Risk vs benefits – keep it simple
- Ask if there are concerns

Be persistent

- Don't stop exploring the barrier(s)
- Don't stop offering

Consider affordability

- Determine insurance coverage
- Public health department

Provide incentives

- Mug, pen
- Certificate

Make access easy

- Give immunizations as part of visit
- Work collaboratively with pharmacists, other local healthcare professionals

Make it a team effort

- Involve office staff
- Involve other healthcare professionals

Enlist a local champion

- Civic or business leader; celebrity



Resources

- [American Academy of Family Physicians](#)
- [Centers for Disease Control and Prevention](#)
- [Immunization Action Coalition](#)
- [Institute for Vaccine Safety](#)
- [National Center for Immunization and Respiratory Diseases](#)
- [National Institute of Allergy and Infectious Diseases](#)



Questions & Answers



https://academic.oup.com/ajcp/article/152/Supplement_1/S142/5567817 laboratory test cost

