

Hall, Caroline Breese. "*The Lancet* 375.9725 (2010): 1500-1502.

RESPIRATORY SYNCYTIAL VIRUS (RSV) IN ADULTS

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I have no conflicts of interest to disclose

Let's start with a case.....

60 yo F s/p right single lung transplant for ILD
in 2018.....

Presents with 3 days of SOB, non productive
cough, nasal congestion and wheezing....

Background

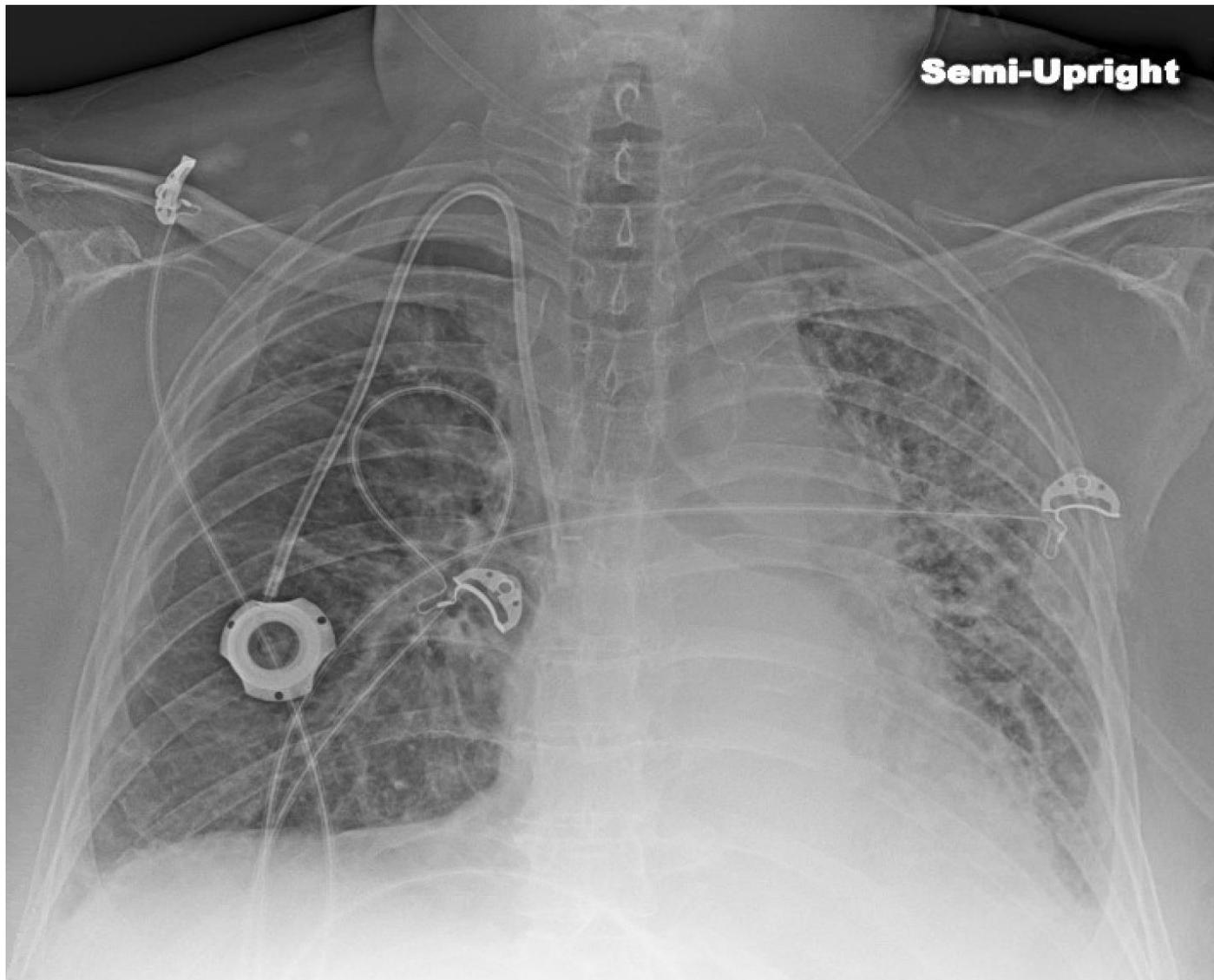
- Well at last surveillance bronchoscopy in Oct except for one small foci of acute cellular rejection, A1
- Scheduled for 6 mo bronchoscopy next week, but noted symptoms that have worsened over past 2 days
- Seen in transplant clinic and noted to be breathless with ~ 35% decrease in her FEV1 by office spirometry
- Sent to ED for evaluation and likely admission

Past Medical/Surgical History

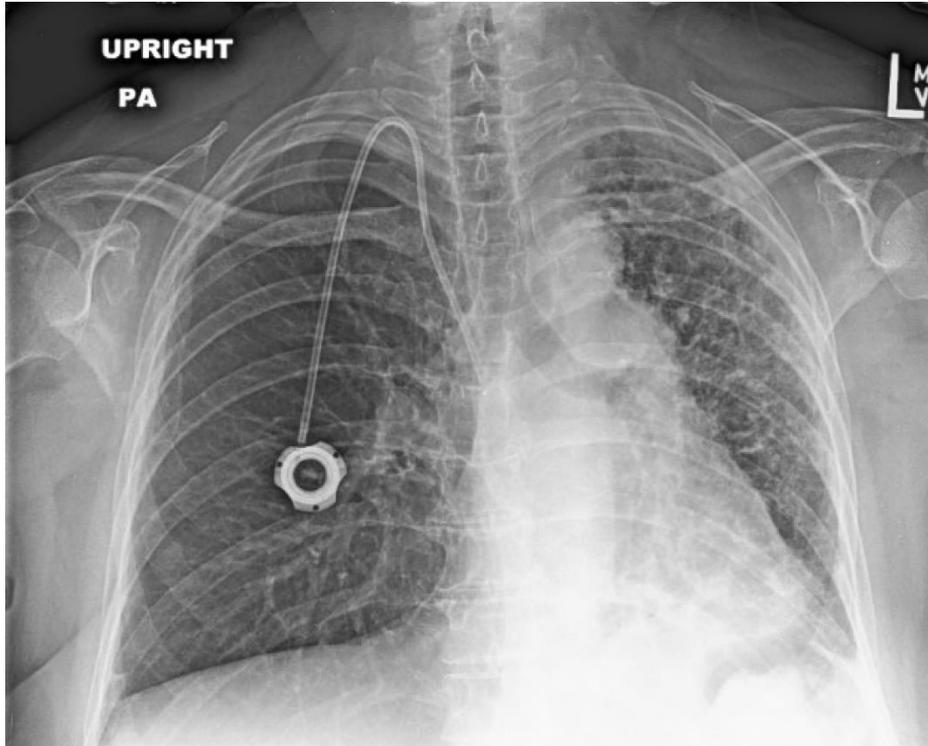
- S/p right lung transplant 2/2014 (CMV ?/-, EBV ?/(-))
- HTN
- GERD s/p fundoplication 2013
- Barrett's esophagus s/p surveillance EGD 2/2016
- DM2

Home Meds

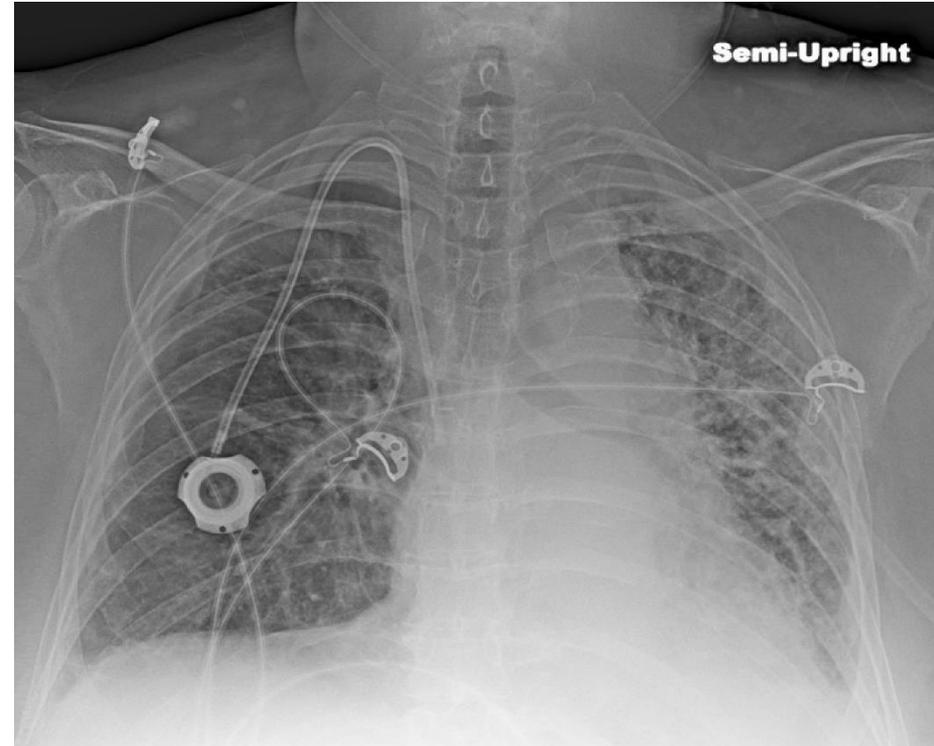
- Abelcet 5 mg/ml inhalation weekly
- Advair 500/50 bid
- Azithromycin 250mg
- Bactrim DS M-W-F
- Cellcept 250mg bid
- Metoprolol 50mg bid
- Prednisone 5mg daily
- Prograf 0.25mg bid
- Valcyte 450 bid
- VFEND 200mg q12



ED CXR



Post-transplant Baseline



ED CXR

Bronchoscopy was performed.....

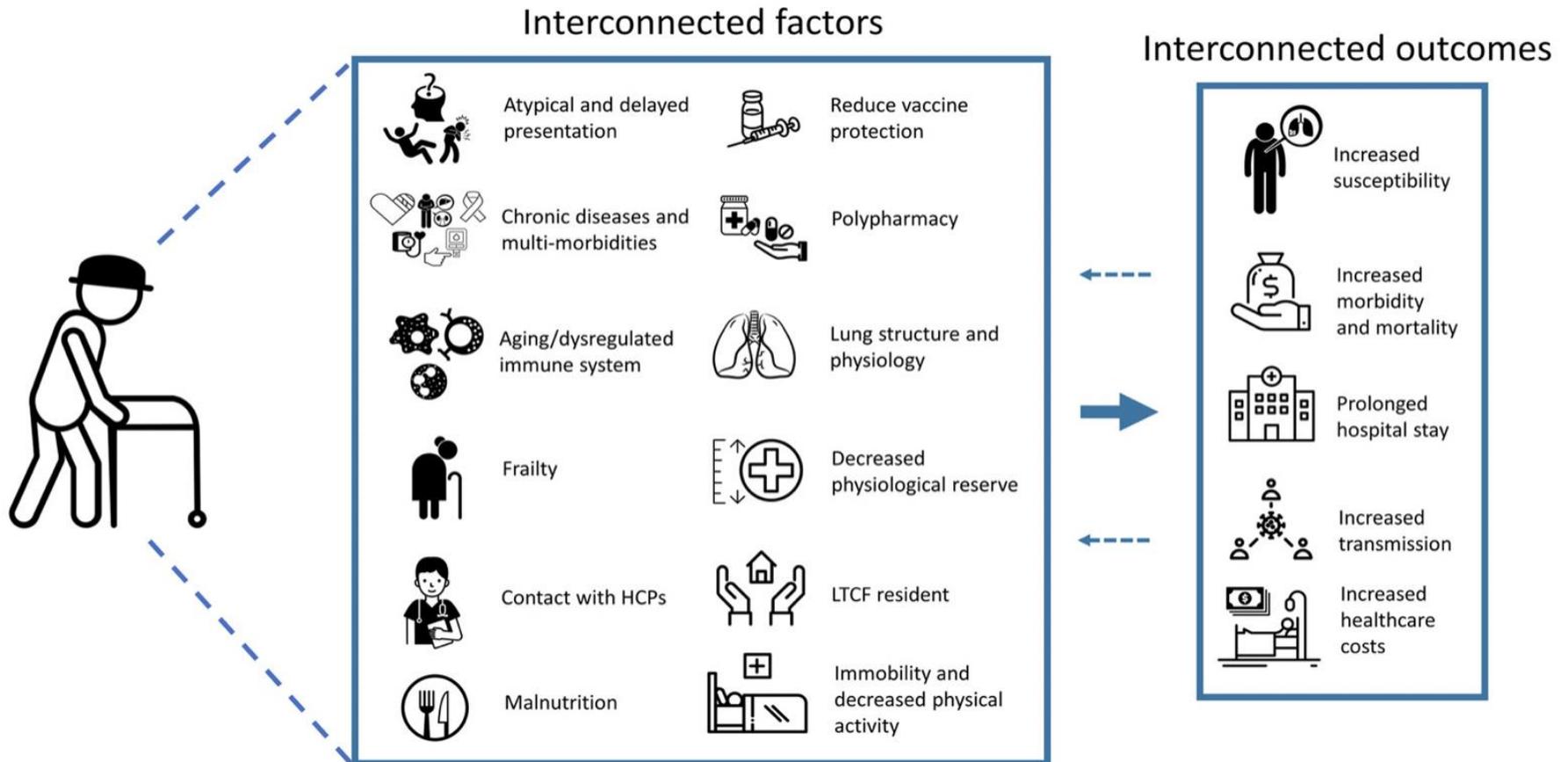
CMV DNA PCR Result	<LLOQ *					
<input type="checkbox"/> CMV DNA PCR Quant nbr	<136.5 H					
<input type="checkbox"/> CMV DNA PCR Log Conv						
BAL Disclaimer					See comment *	
Influenza A PCR					Not Detected	
Influenza B PCR					Not Detected	
Parainfluenza 1 PCR					Not Detected	
Parainfluenza 2 PCR					Not Detected	
Parainfluenza 3 PCR					Not Detected	
Parainfluenza 4 PCR					Not Detected	
Adenovirus PCR					Not Detected	
Coronavirus PCR					Not Detected	
Respiratory Syncytial Virus PCR					Detected * C	
Human Rhinovirus/Enterovirus PCR					Not Detected	
Human Metapneumovirus PCR					Not Detected	
Bordetella pertussis by PCR					Not Detected	
Chlamydomphila pneumo by PCR					Not Detected	
Mycoplasma pneumo by PCR					Not Detected	
HA Macroscopic						

RSV in adults

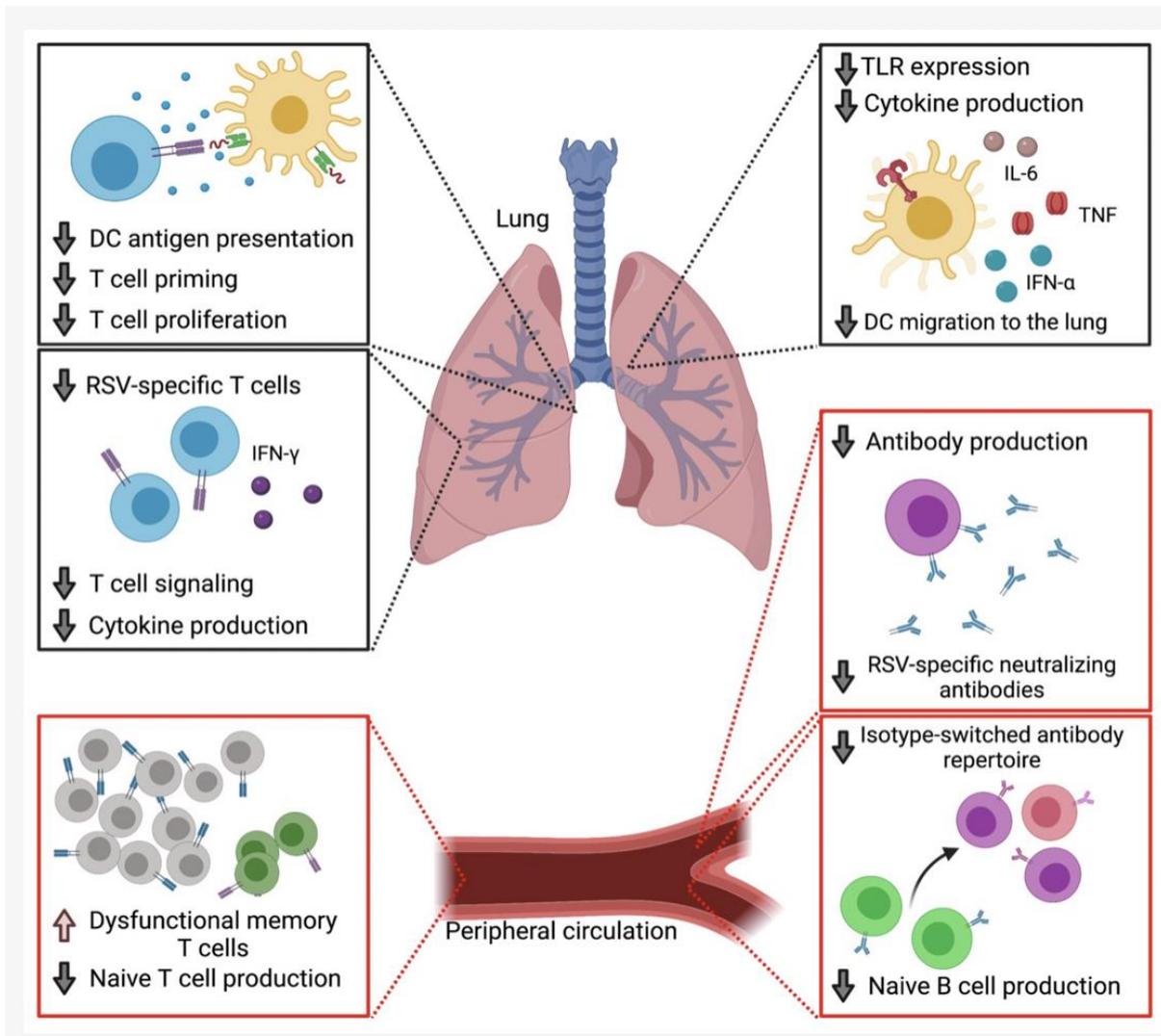
Respiratory Syncytial Virus (RSV)

- First isolated from a chimpanzee with a cold in 1956 and recognized as a leading cause of respiratory infection in infants in the 1960's
- RSV is the leading cause of lower respiratory tract infection in infants and children
 - 58,000-80,000 children younger than 5 years are hospitalized due to RSV infection
 - 100–300 deaths in children younger than 5 years old annually
- Seen mainly in elderly, nursing home residents and the immunocompromised
- Now is the second most common cause of viral pneumonia in adults

Drivers of susceptibility to viral infections in the Elderly



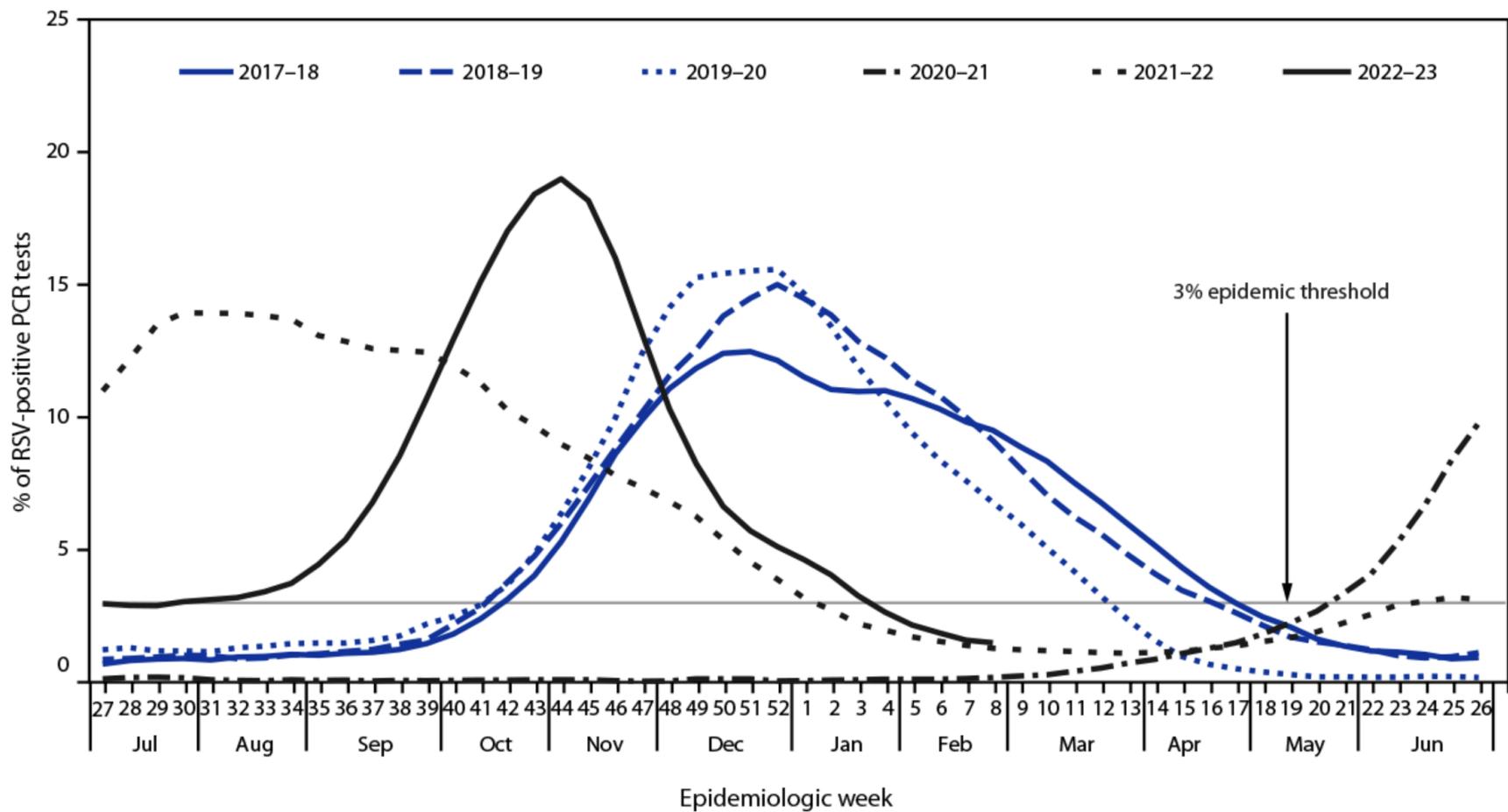
Immune senescence



Respiratory Syncytial Virus (RSV)

- COVID-19 pandemic interrupted seasonal RSV circulation
- Timing and number of incident cases of the 2022–23 fall and winter 2023-2024 support return to pre-pandemic seasonality
- 60,000–160,000 hospitalizations and 6,000–10,000 deaths annually among adults aged ≥ 65 years
- Risk for severe infection
 - COPD, CHF, Asthma, CAD, DM, CKD
 - Residents of long-term care facilities
 - Persons who are frail or of advanced age
 - Highest rates among those aged ≥ 75 years

Seasonality of RSV



Adult Hospitalizations with RSV

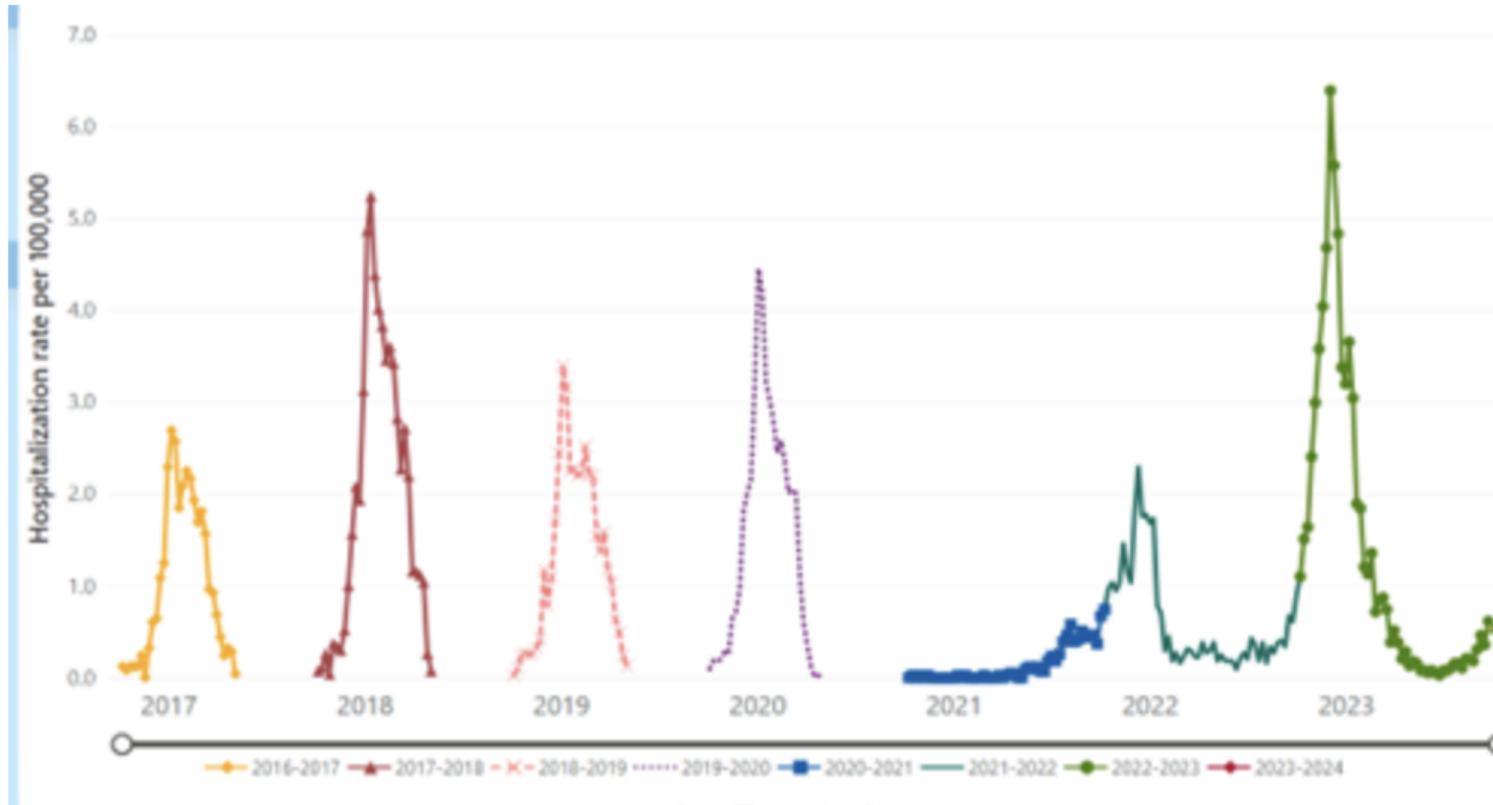
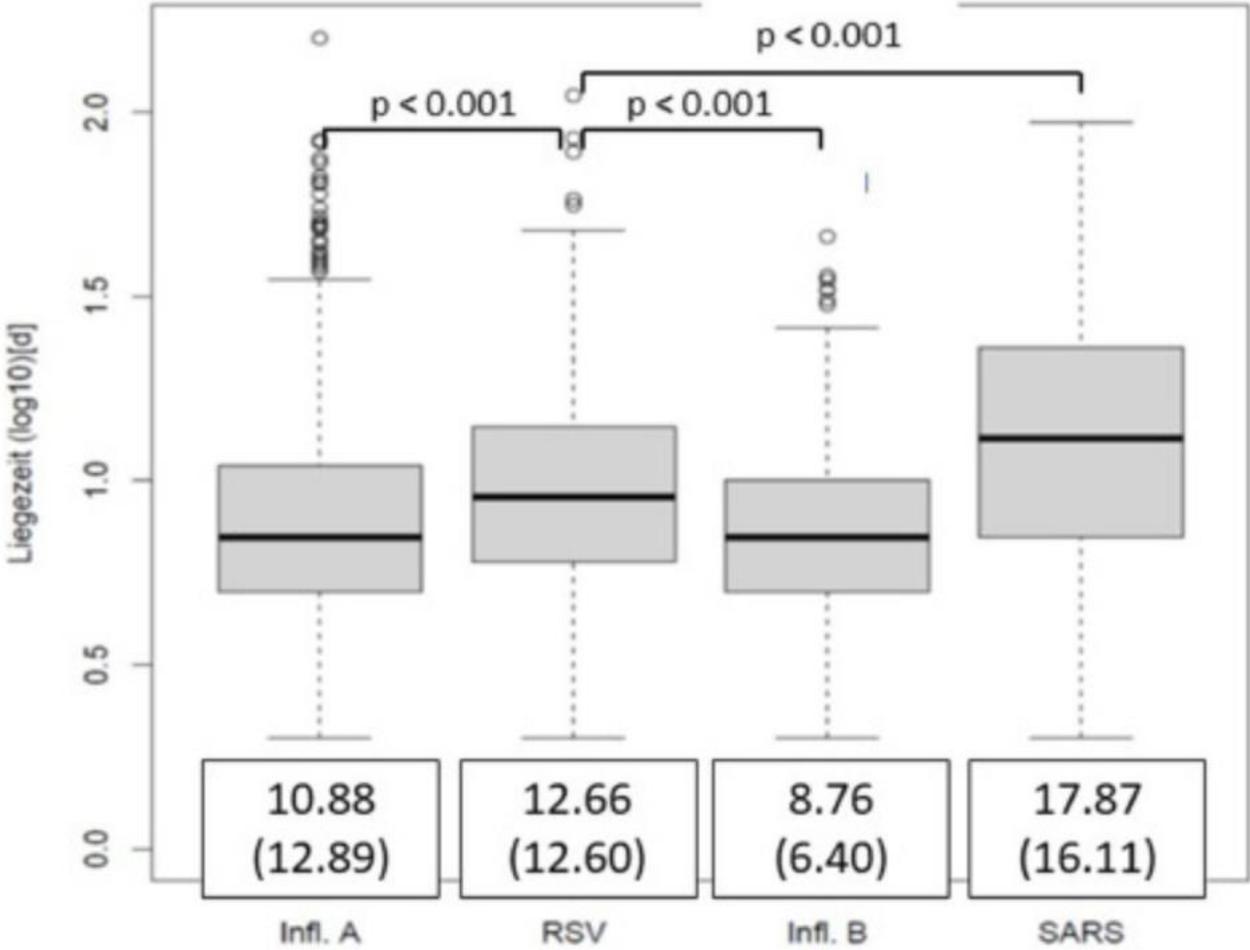


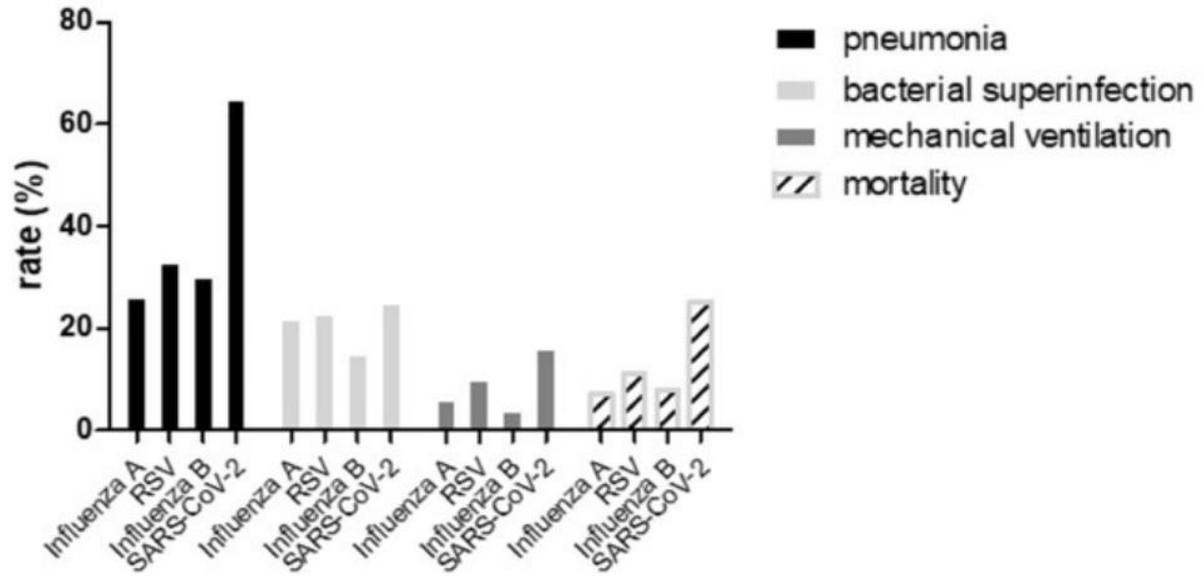
Figure 1 Rates of RSV-Associated Hospitalization for Adults \geq Age 65, all seasons. Source: RSV-NET. Centers for Disease Control and Prevention. (2023, October 25).³

Length of Hospital Stay RSV vs Influenza A/B and SARS-CoV-2



Ambrosch, Andreas, et al. "Focusing on severe infections with the respiratory syncytial virus (RSV) in adults: risk factors, symptomatology and clinical course compared to influenza A/B and the original SARS-CoV-2 strain." *Journal of Clinical Virology* 161 (2023): 105399.

Complications of RSV vs Influenza A/B and SARS-CoV-2



OR (95%CI, p)	Pneumonia	Bacterial superinfection	Mechanical ventilation	Mortality
RSV / Influenza A	1.39 (1.01 - 1.93; 0.035)	1.12 (0.73 - 1.69, 0.60)	1.59 (0.93 - 2.69, 0.05)	1.65 (0.98 - 274, 0.05)
RSV / Influenza B	1.09 (0.77-1.57, 0.60)	1.64 (1.02- 2.64, 0.04)	2.33 (1.15 - 4.96, <0.001)	1.42 (0.78 - 2.61, 0.26)
RSV / SARS-CoV-2	0.27 (0.19-0.38, <0.001)	0.91 (0.59 - 1.38, 0.68)	0.59 (0.35 - 0.98, 0.035)	0.37 (0.23 - 0.59, <0.001)

Ambrosch, Andreas, et al. "Focusing on severe infections with the respiratory syncytial virus (RSV) in adults: risk factors, symptomatology and clinical course compared to influenza A/B and the original SARS-CoV-2 strain." *Journal of Clinical Virology* 161 (2023): 105399.

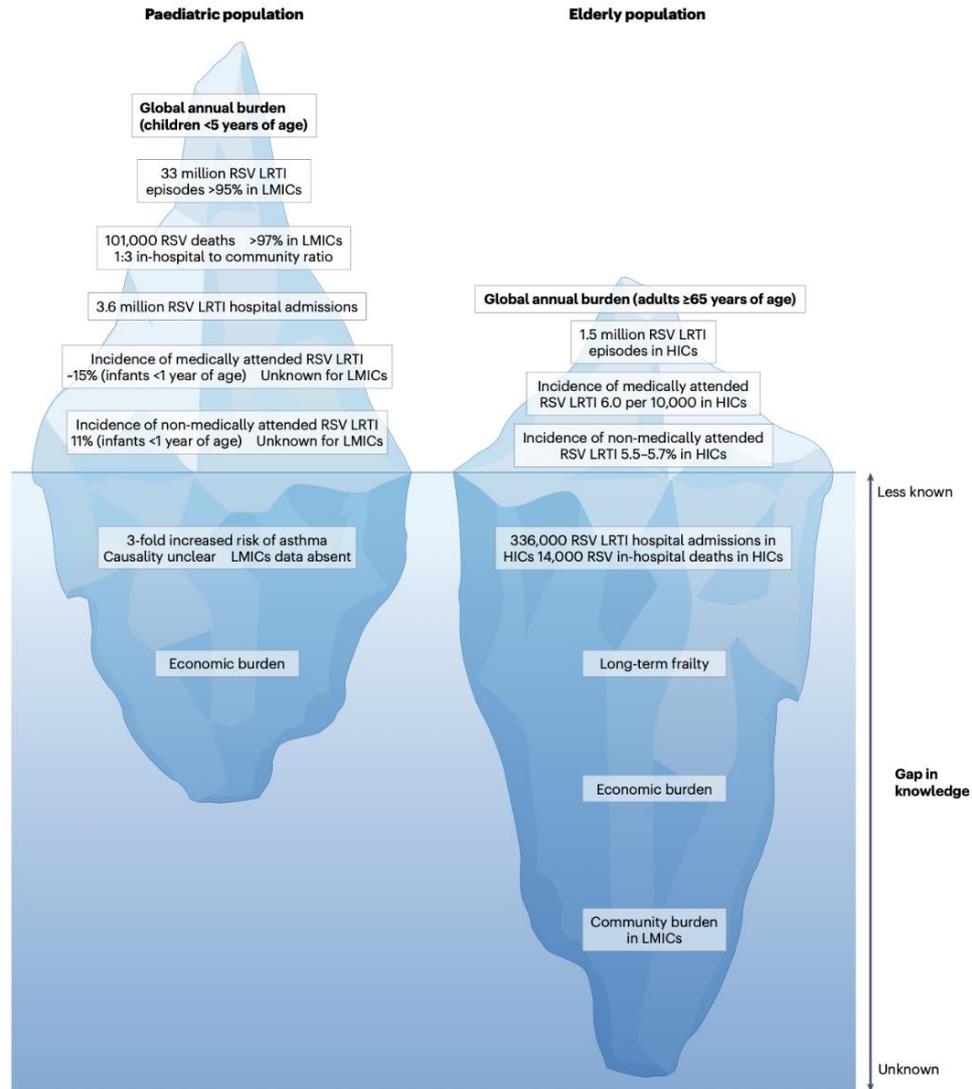
Global Initiative for Obstructive Lung Disease GOLD 2024

Vaccination for Stable COPD

Figure 3.6

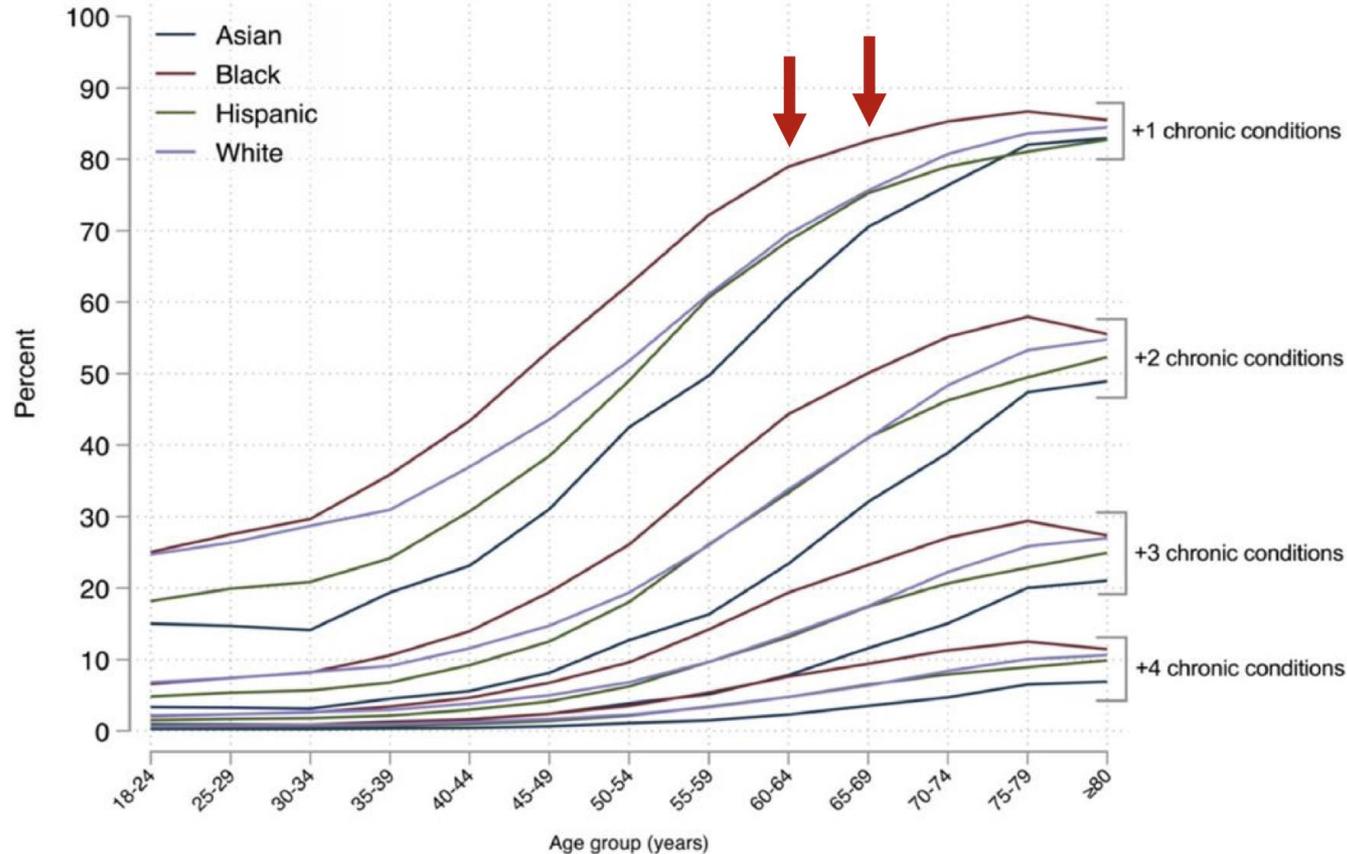
- Influenza vaccination is recommended for people with COPD (Evidence B)
- The WHO and CDC recommends SARS-CoV-2 (COVID-19) vaccination for people with COPD (Evidence B)
- The CDC recommends one dose of 20-valent pneumococcal conjugate vaccine (PCV20); or one dose of 15-valent pneumococcal conjugate vaccine (PCV15) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) for people with COPD (Evidence B)
- Pneumococcal vaccination has been shown to reduce the incidence of community-acquired pneumonia and exacerbations for people with COPD (Evidence B)
- The CDC recommends the new respiratory syncytial virus (RSV) vaccine for individuals over 60 years and/or with chronic heart or lung disease (Evidence B)
- The CDC recommends Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence (Evidence B), and Zoster vaccine to protect against shingles for people with COPD over 50 years (Evidence B)

Respiratory Syncytial Virus (RSV)



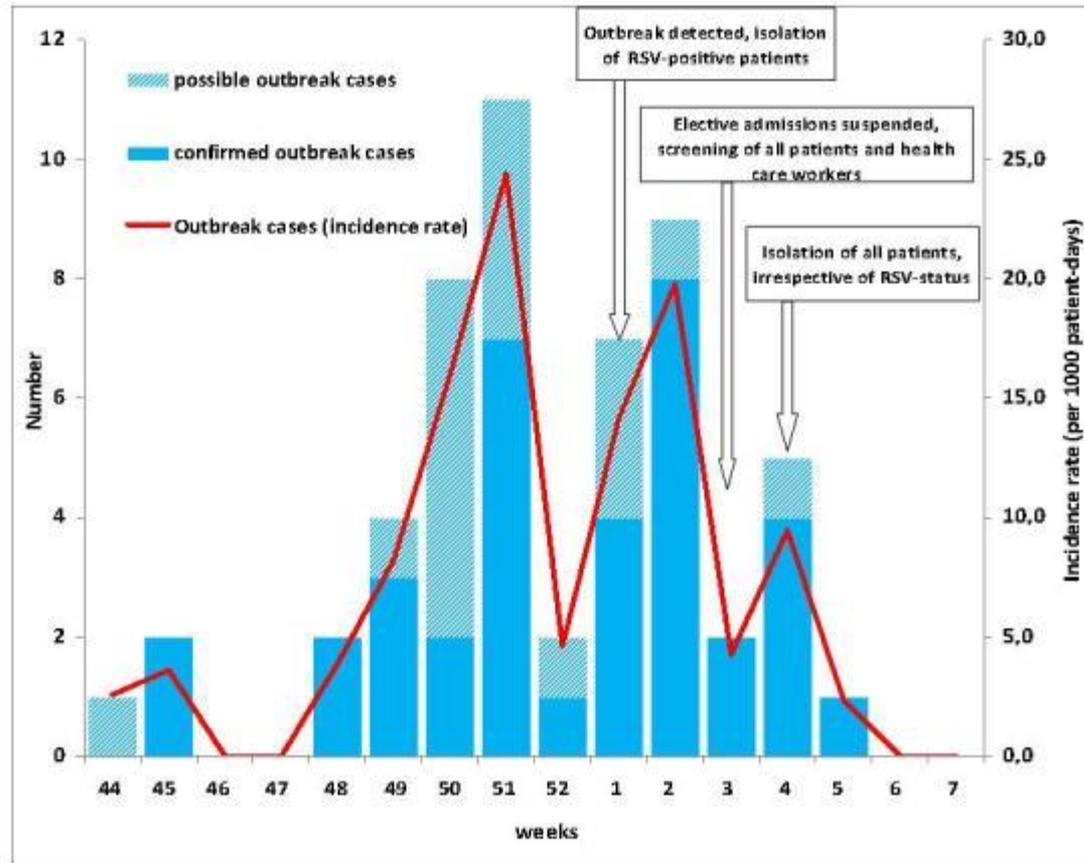
Social Determinates of health: RSV Risk

Number of chronic conditions by age among Asian, Black, Latino/Hispanic, and White adults in the National Health Interview Survey (NHIS), 1999 to 2018



Source: Caraballo C, Herrin J, Mahajan S, et al. Temporal Trends in Racial and Ethnic Disparities in Multimorbidity Prevalence in the United States, 1999-2018. *Am J Med.* 2022;135(9):1083-1092.e14. doi:10.1016/j.amjmed.2022.04.010

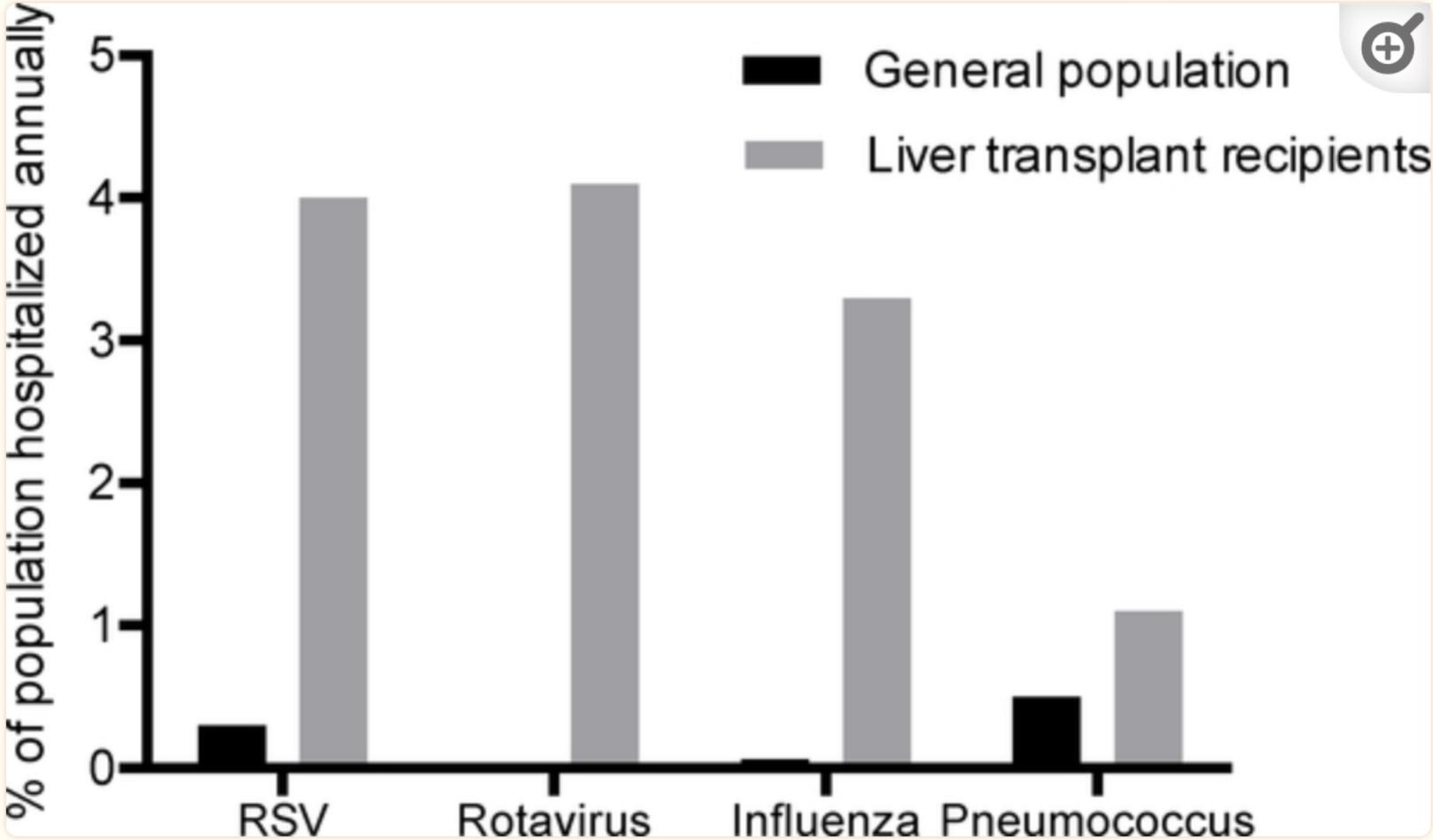
Outbreak on hem/transplant ward (36 confirmed cases, 17 suspected)



Heidelberg, November 2011 to February 2012

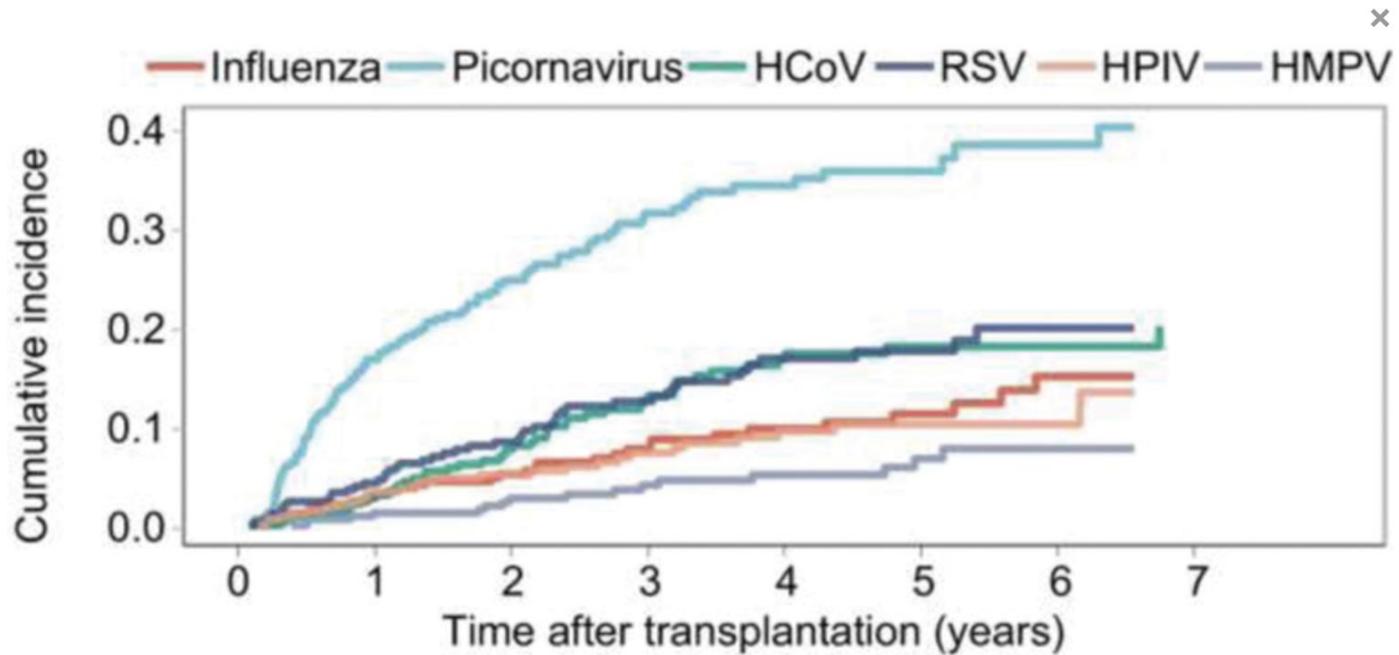
Team, RSV Outbreak Investigation. "Contributing and terminating factors of a large RSV outbreak in an adult hematology and transplant unit." *PLoS currents* 6 (2011).

Solid organ transplant patients and RSV



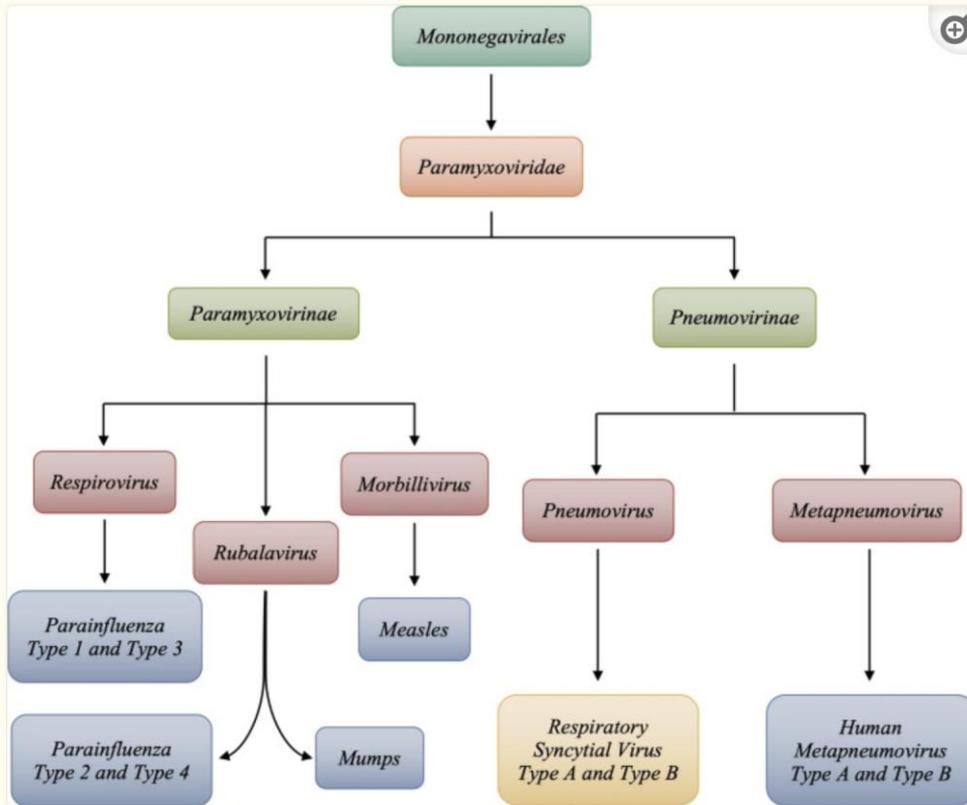
Feldman, Amy G., Evelyn K. Hsu, and Cara L. Mack. "The Importance of Prioritizing Pre and Post Transplant Immunizations in An Era of Vaccine Refusal and Epidemic Outbreaks." *Transplantation* 104.1 (2020): 33.

Risk in lung transplant patients

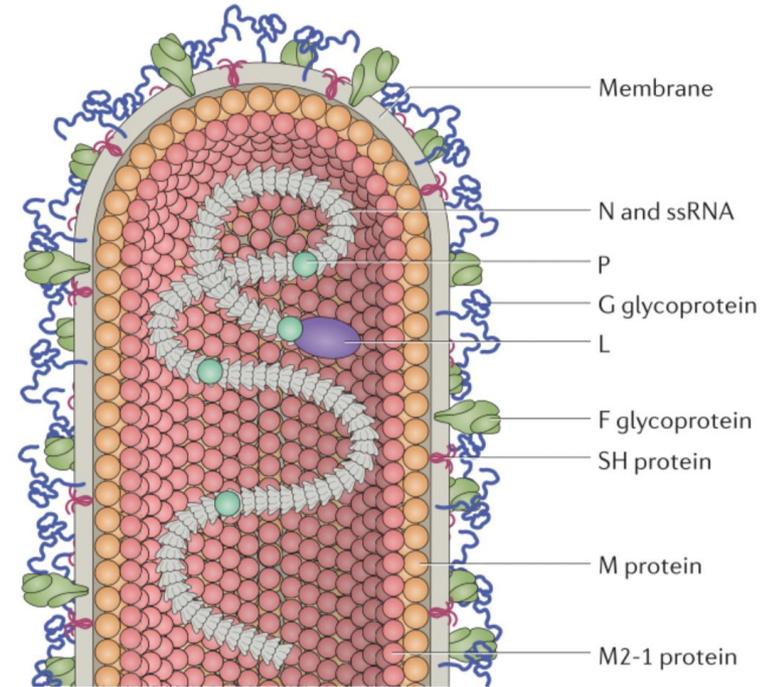


Influenza	334	266	203	143	97	53	30	13	Number at risk
Picornavirus	334	222	153	96	57	30	19	8	
HCoV	334	266	199	137	89	52	32	15	
RSV	334	261	192	130	84	47	24	10	
HPIV	334	264	202	139	91	50	30	13	
HMPV	334	271	209	147	101	57	32	14	

RSV is the most complex member of the Paramyxovirus family



Lineage of Paramyxoviridae and Respiratory Syncytial Virus

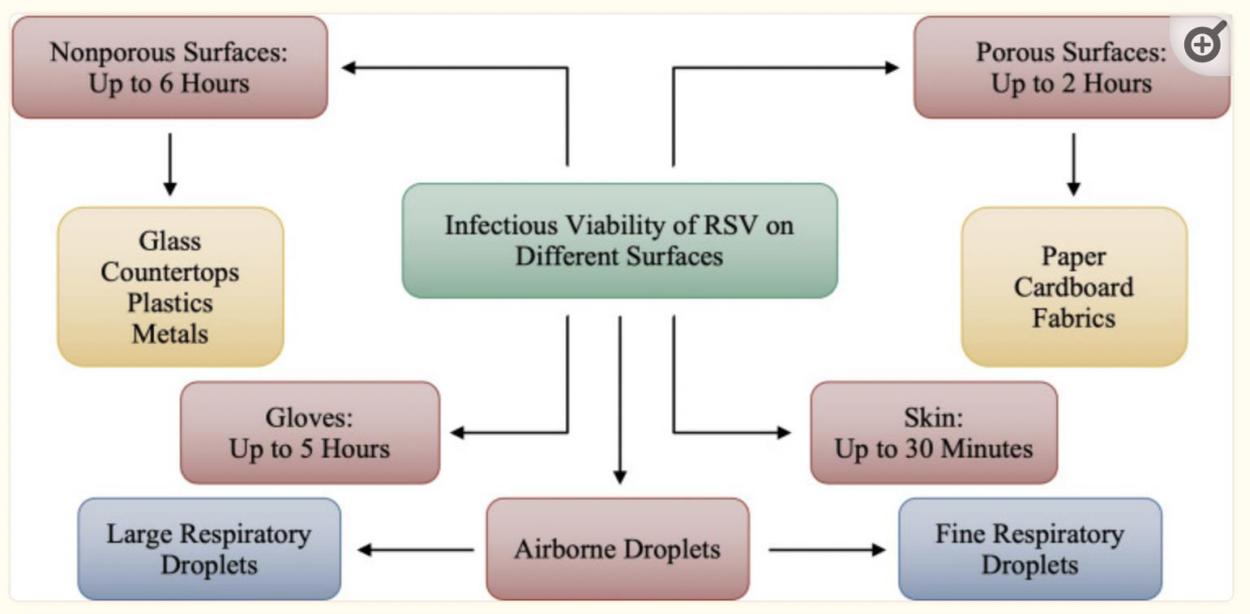


Filamentous enveloped, negative-sense, single-stranded RNA virus

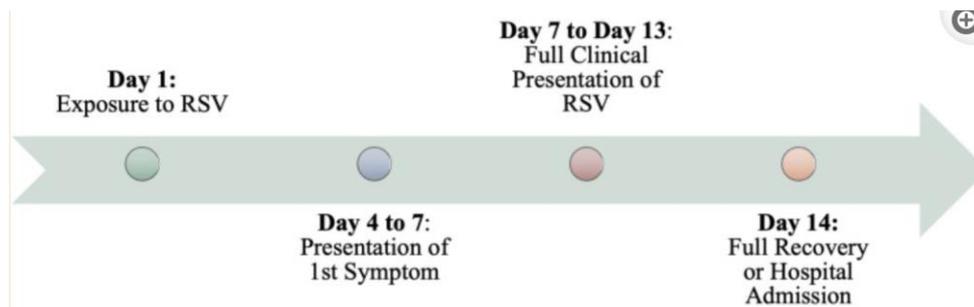


Kaler J, Hussain A, Patel K, Hernandez T, Ray S. Respiratory Syncytial Virus: A Comprehensive Review of Transmission, Pathophysiology, and Manifestation. *Cureus*. 2023 Mar 18;15(3):e36342. doi: 10.7759/cureus.36342.
 Battles, M.B., McLellan, J.S. Respiratory syncytial virus entry and how to block it. *Nat Rev Microbiol* **17**, 233–245 (2019). <https://doi.org/10.1038/s41579-019-0149-x>

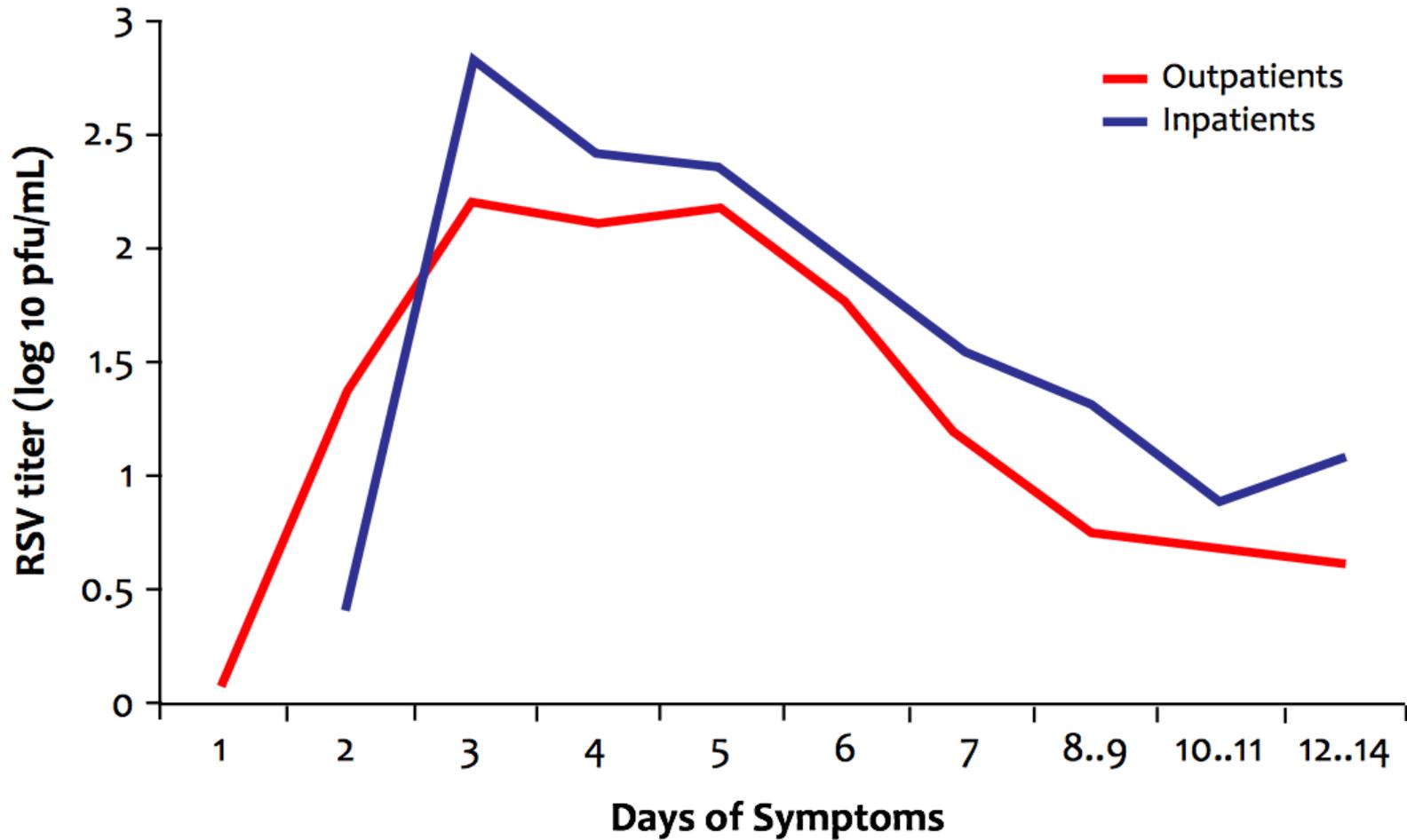
Transmission occurs mainly through large droplet inoculation



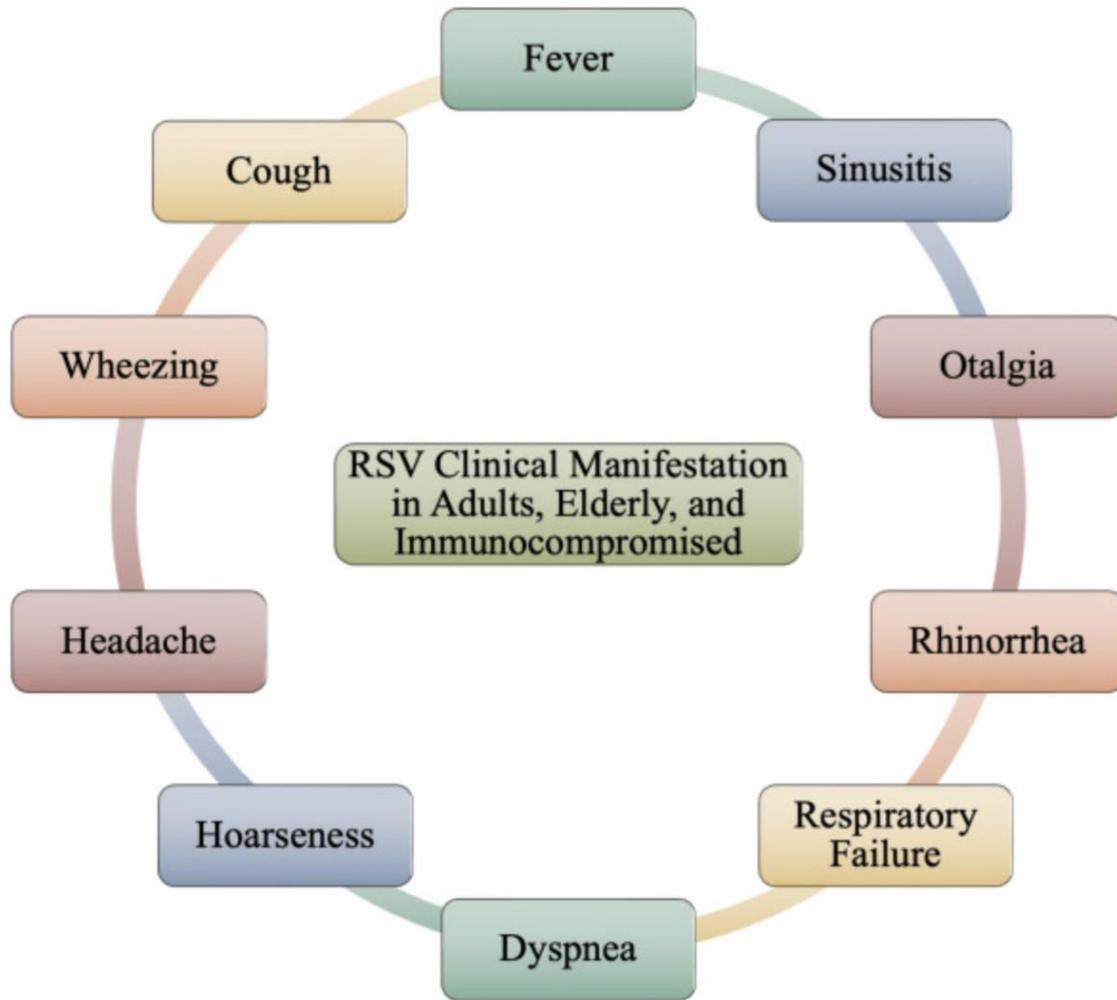
RSV transmission requires close contact with an RSV-infected subject or auto-inoculation to the face (nose, mouth, or eyes) via contaminated fomites or skin



Nasal Shedding in RSV Infected Adults



Clinical Manifestations of RSV in Adults



Complications:

- Pneumonia
- Respiratory Failure
- COPD Exacerbation
- CHF Exacerbation
- Asthma Exacerbation
- Bronchiolitis
- Hypoxemia

Radiographic appearance of RSV varies widely

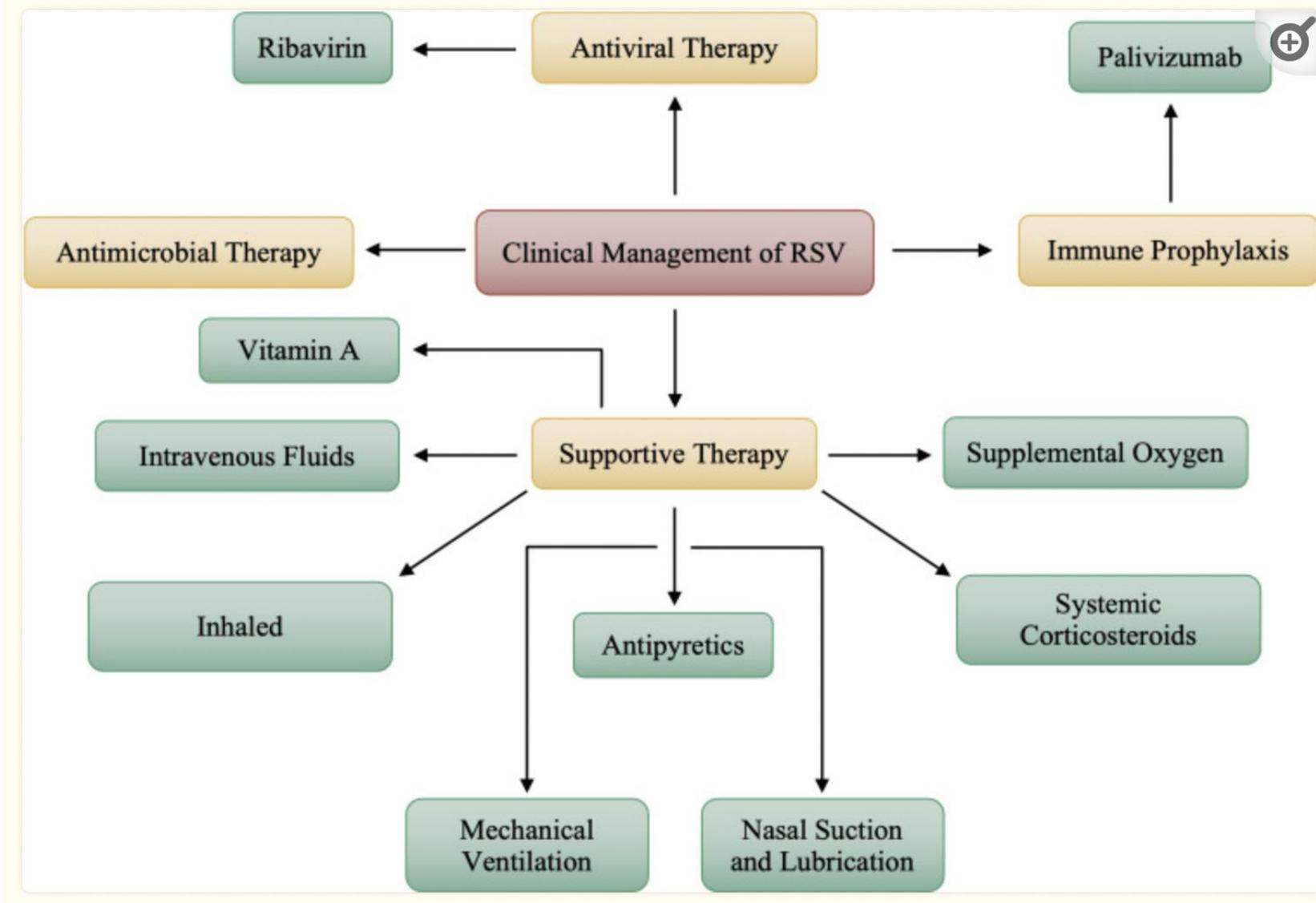


A

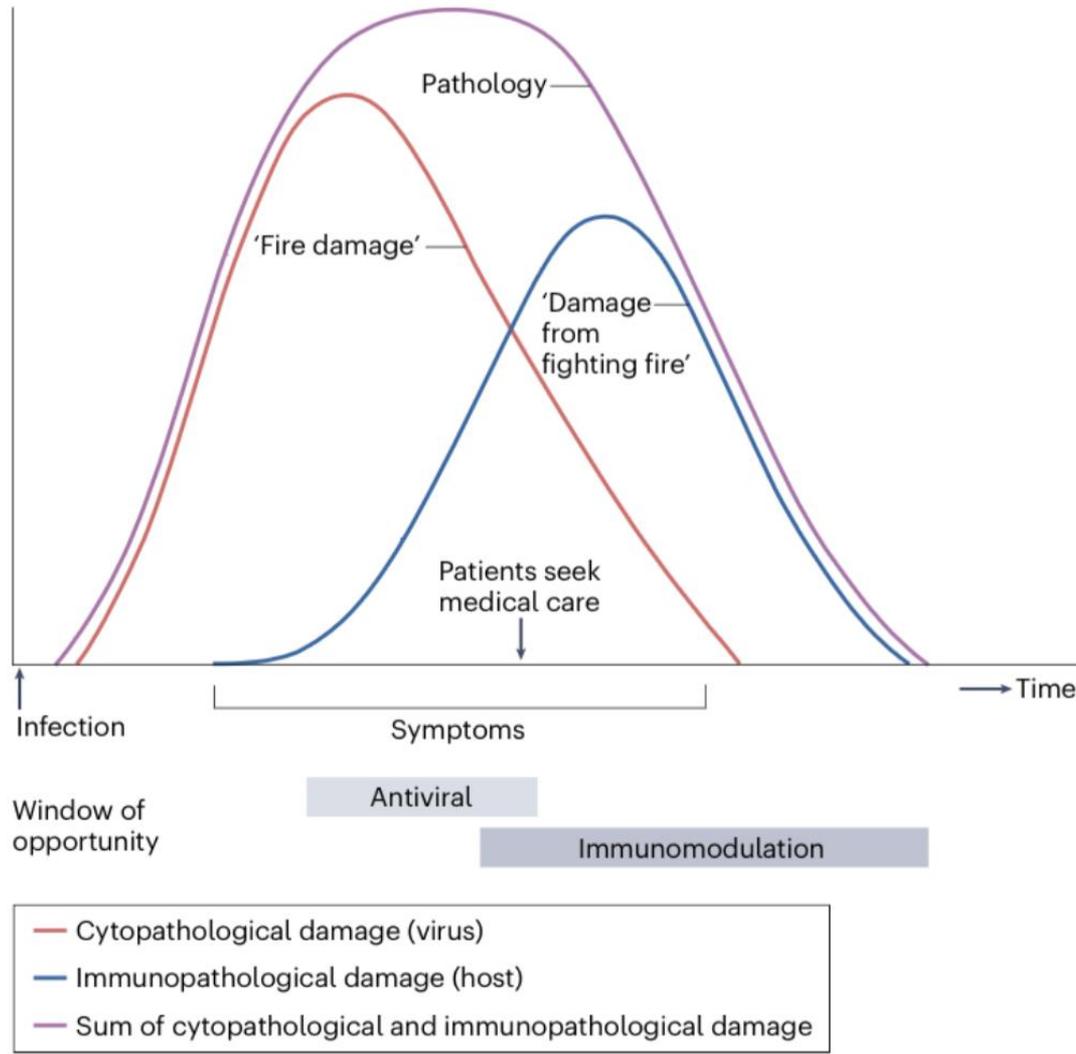


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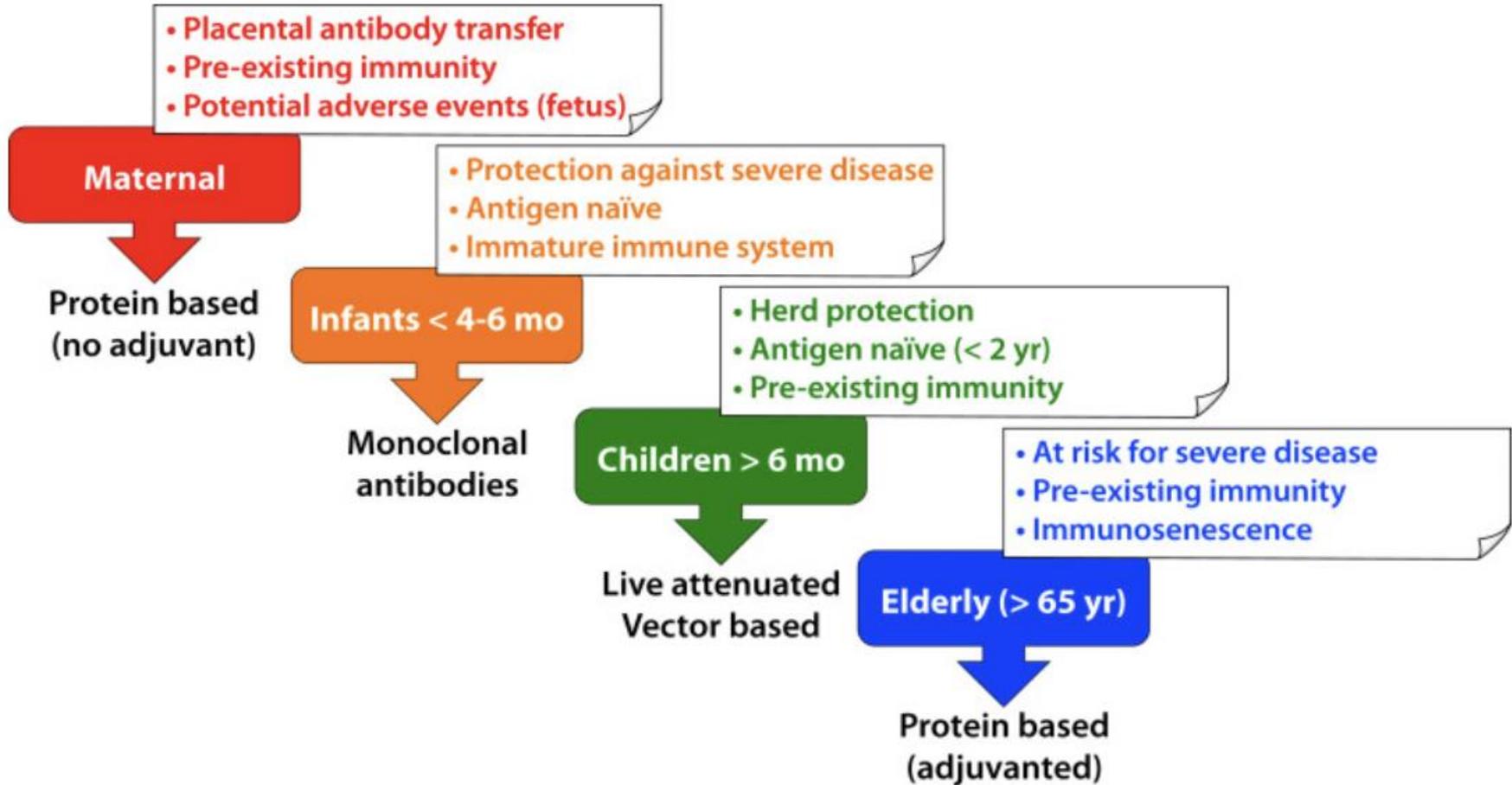
Treatment of RSV in Adults



Respiratory Syncytial Virus (RSV)



Road to RSV Vaccine: Target Populations



Respiratory Syncytial Virus (RSV): Progress!

- US Food and Drug Administration (FDA) approved the world's first RSV vaccine on 3 May, 2023
 - GSK's Arexvy based on phase III clinical-trial data
 - Arexvy reduced the risk of people aged 60 and older developing lower respiratory tract disease from RSV by 82.6% and that of developing severe disease by 94.1%
- Second vaccine was approved on 31 May, 2023
 - Pfizer's Abrysvo based on pivotal phase III clinical trial (RENOIR--RSV vaccine Efficacy study iNolder adults Immunized against RSV disease)
- Monoclonal Antibody nirsevimab received European Medicines Agency (EMA) approval on November 4, 2022 for use in infants

Papi, Alberto, et al. "Respiratory syncytial virus prefusion F protein vaccine in older adults." *New England Journal of Medicine* 388.7 (2023): 595-608.

Falsey, Ann R., et al. "Efficacy and safety of an Ad26. RSV. preF-RSV preF protein vaccine in older adults." *New England Journal of Medicine* 388.7 (2023): 609-620

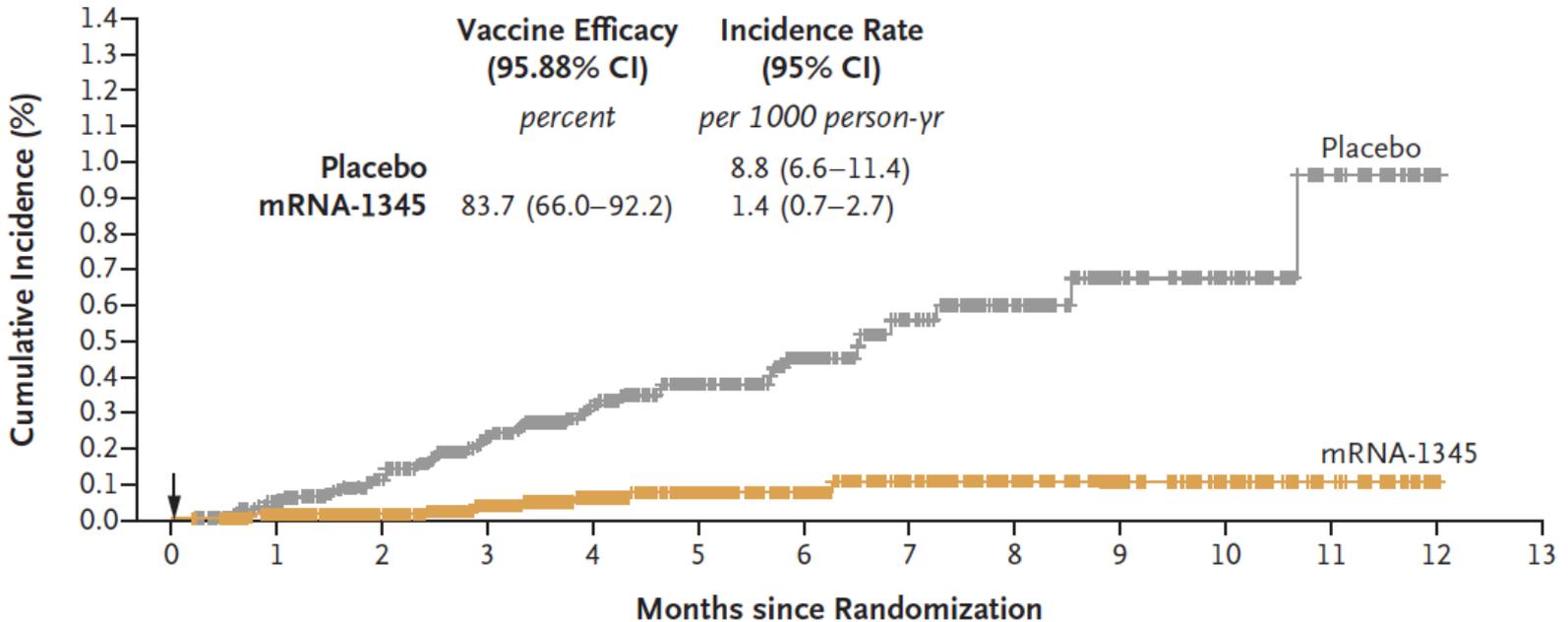
Hammit, Laura L., et al. "Nirsevimab for prevention of RSV in healthy late-preterm and term infants." *New England Journal of Medicine* 386.9 (2022): 837-846.

Respiratory Syncytial Virus (RSV): Progress!

- RSVpreF (Abrysvo) vaccine approved for use during pregnancy
 - Protects infants from RSV-associated lower respiratory tract infection (LRTI)
 - Administration recommended during weeks 32 through 36 of pregnancy
- Feb 12 2024: FDA has granted Priority Review to an application to extend the indication of the adjuvanted respiratory syncytial virus (RSV) vaccine (Arexvy; GlaxoSmithKline) to include adults aged 50 to 59 who are at an increased risk of virus onset

Moderna mRNA-Based RSV PreF Vaccine

A RSV-Associated Lower Respiratory Tract Disease with ≥ 2 Signs or Symptoms



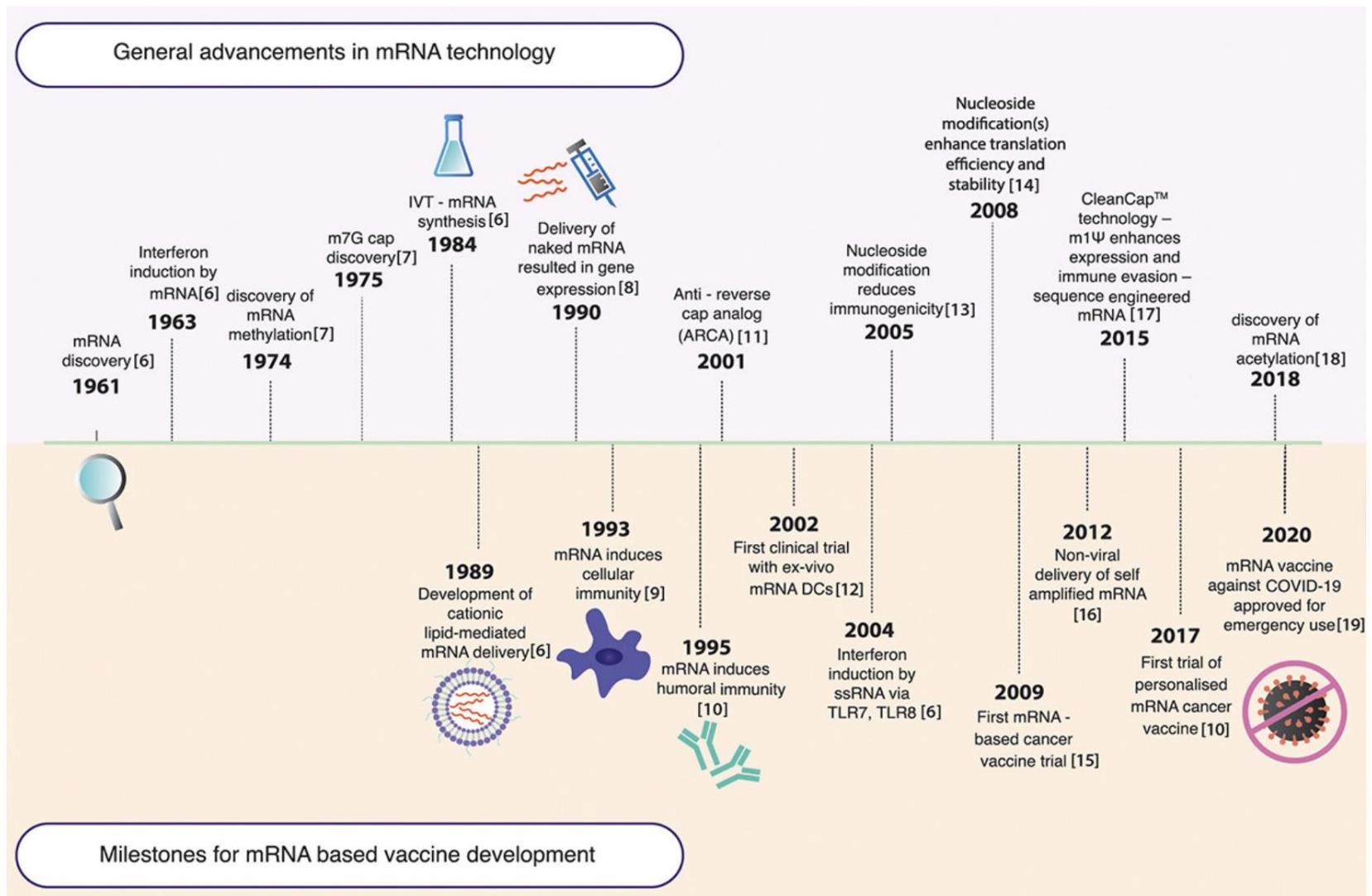
No. at Risk

Placebo	17,516	17,433	14,735	11,275	7866	5314	3657	2384	1682	1058	629	267	43	0
mRNA-1345	17,572	17,514	14,783	11,293	7892	5333	3648	2389	1694	1062	645	273	47	0

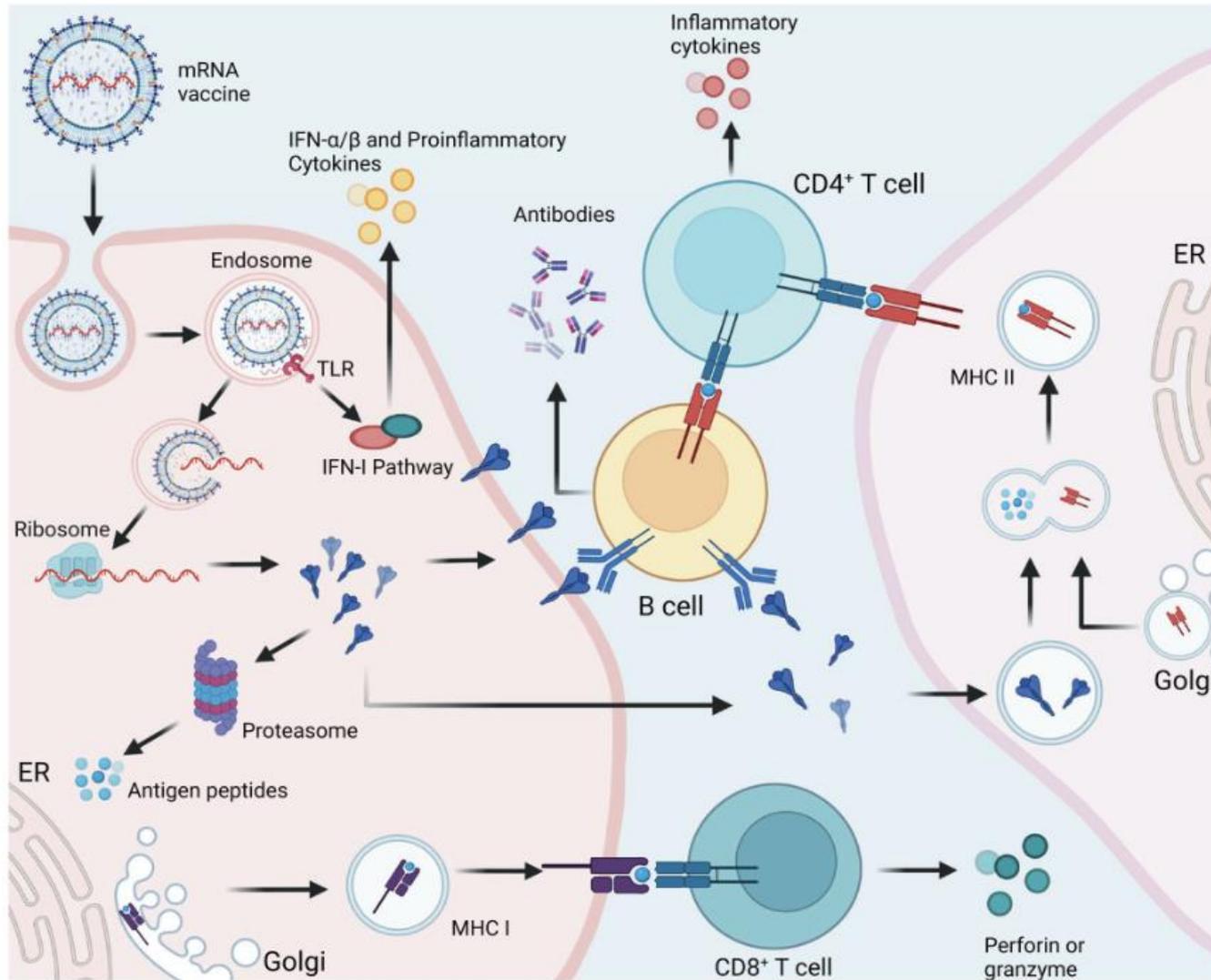
“mRNA-1345 demonstrated vaccine efficacy of 83.7% against RSV lower respiratory tract disease, defined by 2 or more symptoms in older adults”

But concerns about efficacy of about 63% after 8.6 months in preventing RSV-related respiratory disease, down from 84% at 3.3 months

mRNA vaccine explained



mRNA vaccine explained



Side Effects of RSV mRNA vaccinations

- Most common side effects: pain, redness, and swelling where the shot is given, fatigue, fever, headache, nausea, diarrhea, and muscle or joint pain, all usually mild
- Serious neurologic events, including Guillain-Barré syndrome (GBS) and other inflammatory neurologic events, were reported after RSV vaccination in clinical trials
 - 1 to 2 cases among 15,000 to 20,000 participants which is higher than the background rate for GBS among adults ≥ 60 years of age of 1.85 to 2.66 cases per 100,000 people per year

Vaccine mixup: Incorrect RSV shots given to 128 pregnant women and 25 babies, CDC says



Emilee Coblentz
USA TODAY

Published 9:46 p.m. ET Feb. 16, 2024 | Updated 9:46 p.m. ET Feb. 16, 2024

- Nirsevimab (Beyfortus, Sanofi, and AstraZeneca) is only recommended for infants and some young children at increased risk for severe RSV disease
- RSV vaccines (Pfizer Abrysvo, GSK Arexvy) are NOT approved for use in infants or young children
- Pfizer (Abrysvo) is the **only** RSV vaccine recommended for pregnant people. **The GSK RSV vaccine (Arexvy) is NOT approved for use during pregnancy.**

Key points for RSV vaccine hesitancy

Model component	Key points
Complacency	<ul style="list-style-type: none">• RSV contributes to 177,000 hospitalizations and 14,000 deaths among adults ≥ 65 years annually in the United States, with elevated risk among those with comorbid chronic disease.• Hospitalization for RSV results in similar lengths of stay, rates of use of intensive care and mortality as influenza A, with 23% of older adults requiring a higher level of care after discharge.
Confidence	<ul style="list-style-type: none">• Clinical trials of subunit RSV vaccines have reported adverse effects similar in frequency and severity as other available vaccines, with most reactions being mild/moderate and of short duration.• Guillain-Barré syndrome (GBS) will be closely monitored in postmarketing surveillance studies. It is currently unknown how rates of GBS following vaccination compare with natural infection with RSV.• Current RSV vaccines contain a stabilized form of the preF glycoprotein antigen, which mounts a more effective immune response than the vaccine trialed in the 1960s.
Convenience	<ul style="list-style-type: none">• The adjuvanted RSV vaccine has demonstrated a duration of protection spanning at least 2 respiratory virus seasons following a single dose.• Coadministration with influenza vaccines has been found to be safe and effective, with the Advisory Committee on Immunization Practices in the United States advising that coadministration with a number of other vaccines is also acceptable.• Uptake by the public can be enhanced if pharmacy scope, access to publicly funded supply and remuneration are optimized to make RSV vaccination conveniently accessible through community pharmacies.

RSV Vaccine CDC Working Group Conclusions

Domain	Question	Work Group Judgements	
		Pfizer	GSK
	Adults aged ≥65 years		
Public Health Problem	Is RSV of public health importance?	Yes	
Benefits and Harms	How substantial are the desirable anticipated effects?	Moderate	Moderate
	How substantial are the undesirable anticipated effects?	Small	Small
	Do the desirable effects outweigh the undesirable effects?	Favors intervention	Favors intervention
	What is the overall certainty of the evidence profile?	Moderate	Moderate
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Yes/Probably yes	
	Is there important variability in how patients value the outcomes?	Important variability/Probably important variability 	
Acceptability	Is the intervention acceptable to key stakeholders?	Yes/Probably yes	
Feasibility	Is the intervention feasible to implement?	Yes/Probably yes	Yes/Probably yes
Resource Use	Is the intervention a reasonable and efficient allocation of resources?	Probably yes	Probably yes
Equity	What would be the impact on health equity?	Probably increased/Probably no impact	

RSV Vaccine CDC Working Group Conclusions

- Pfizer's bivalent RSVpreF and GSK's adjuvanted RSVPreF3 vaccines both have demonstrated significant efficacy against lower respiratory tract illness caused by RSV among older adults over at least two seasons
- Trials were underpowered to show efficacy in the oldest adults and in adults who are frail
- Trials were underpowered to show efficacy against RSV hospitalization
- Efficacy against symptomatic illness may indicate efficacy against more severe disease
- RSV vaccination has the potential to prevent considerable morbidity from RSV disease among older adults, particularly in those with chronic medical conditions and those who are frail (e.g., long-term care facility residents)

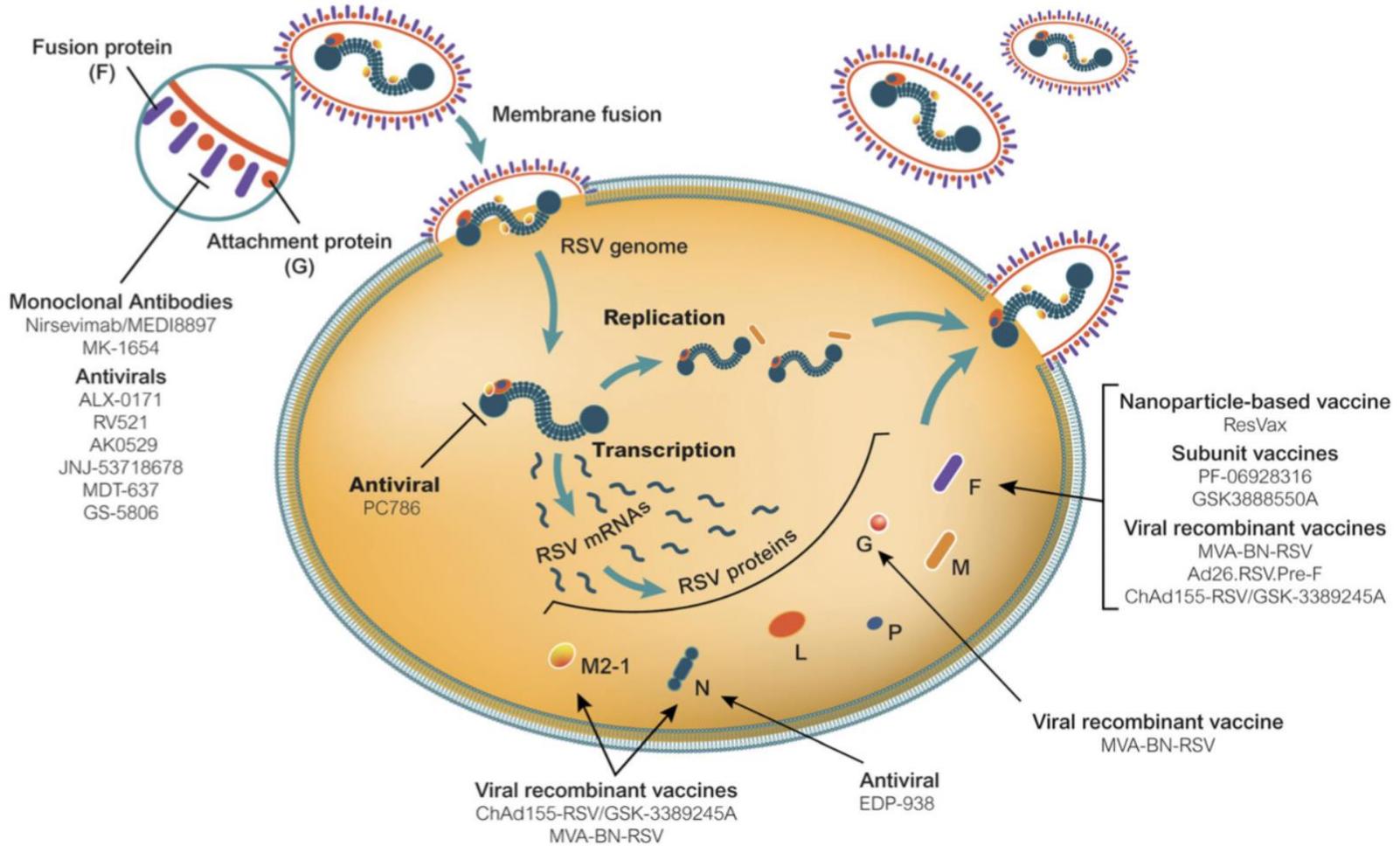
RSV Vaccine CDC Working Group Conclusions

- Cases of inflammatory neurologic events have been reported within 42 days after vaccination with each RSV vaccine
- Clinical trials were not sufficiently powered to determine whether the small number of cases occurred due to random chance
- Whether there is an increased risk of GBS or other inflammatory neurologic events from RSV vaccination is not known at this time
- Post-licensure surveillance for both safety and vaccine effectiveness will be critical

Comparative Costs of RSV Vaccines and Treatments

Preventive measure	Name	Single dose price (USD)
Vaccines	RSV Vaccine RSVPref3 (Arexvy, GSK)	280 ^a
	RSV Vaccine RSVPreF (Abrysvo, Pfizer)	320 ^a
	Influenza vaccines	18-20 ^b
	COVID-19 vaccines	115–130 ^b
Monoclonal antibodies	Palivizumab (Synagis, AstraZeneca)	1600 (50-mg dose) ^c
		3000 (100-mg dose) ^c
	Nirsevimab (Beyfortus, AstraZeneca/Sanofi)	495 ^d

The Future?



Questions?

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