



CLL SOCIETY

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# COMMON INFECTIONS WITH CLL: PREVENTION AND TREATMENT

**December 13, 2024**  
9 AM PT, 10 AM MT  
11 AM CT, 12 PM ET



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# SPEAKERS



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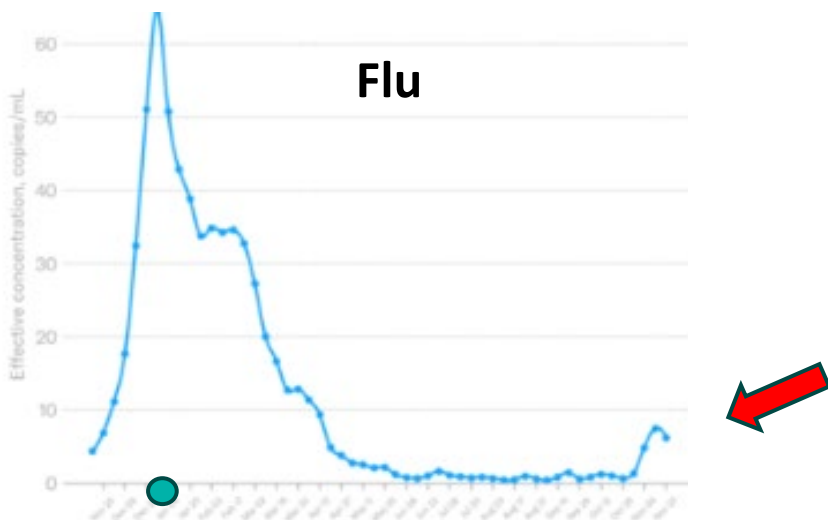
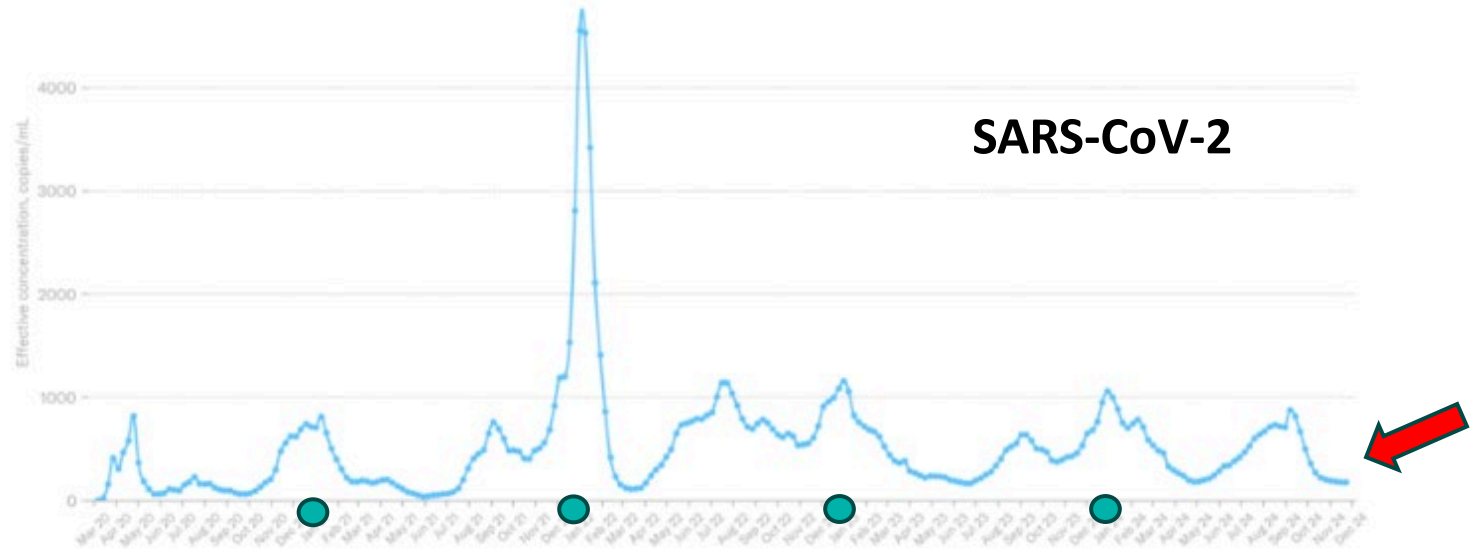
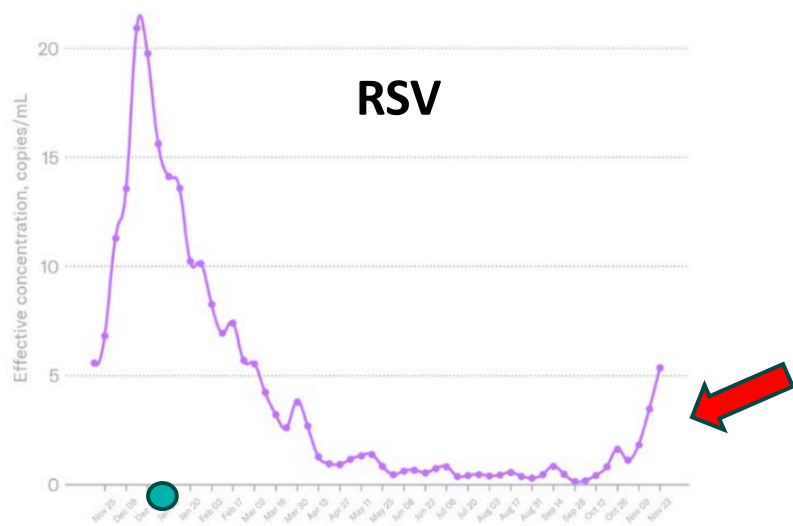
Infectious Diseases Webinar

# OUTLINE

- **Respiratory infection “status report” and forecast**
- **General and CLL-specific factors for serious respiratory viral disease**
- **Ways to reduce risk (behavioral, pharmacological)**
- **Virus specifics (prevention and treatment)**
  - RSV
  - Influenza
  - COVID-19
- **Other infectious considerations and risks**
  - Emerging infections (e.g., “bird flu,” mpox, measles)
  - Drug <-> Bug associations (med-specific “opportunistic” infections)



# VIRAL CIRCULATION: WASTEWATER



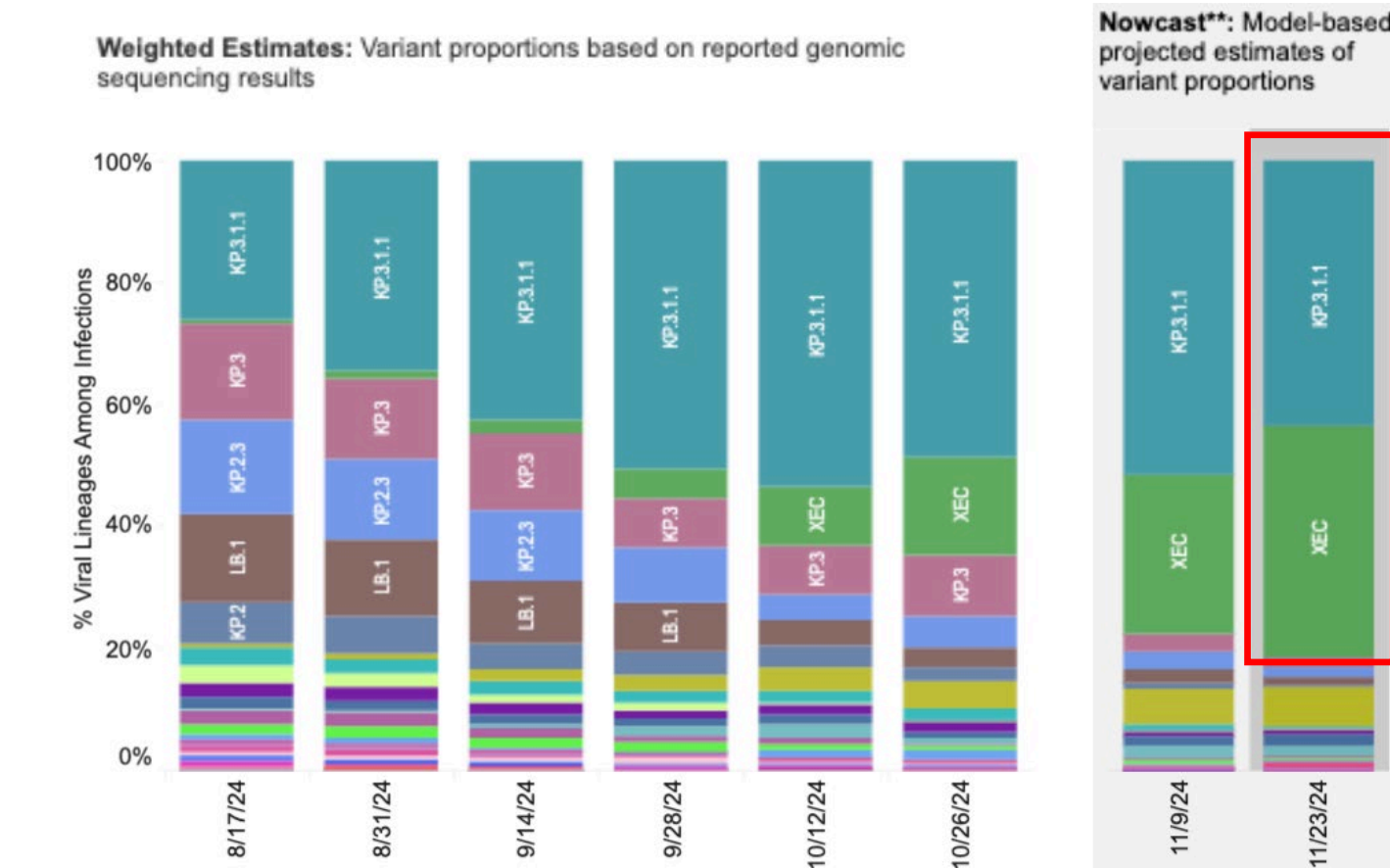
- RSV surging now (Dec-Jan)
- Influenza to surge shortly (Dec-Feb)
- COVID-19...uncertain (?Jan)



Biobot.io

# COVID-19 VARIANT FORECAST

- All Omicron (BA.2) descendants
  - JN.1 most recent “child”
  - KP.2 and KP.3 “grandchildren” → the vaccine targets
- XEC newest member
  - Recombination of two JN.1 children
  - Moderately more immune evasive



LP.8.1 next?

CDC  
Liu et al., 2024



# OTHER: MYCOPLASMA PNEUMONIAE

- Increased in the US this fall, especially in children
- Common bacteria, cause of “walking pneumonia” or “chest cold”
- Spread through respiratory droplets (coughing, sneezing)
- Usually diagnose via PCR of nasal and/or oral swabs
- Note: rising global azithromycin (“Z-pak”) resistance
  - If not improving, may consider second antibiotic such as doxycycline or moxifloxacin

Upsurge of respiratory illnesses among children-Northern China

23 November 2023



Waites et al., 2019



# WHY ARE INFECTIONS MORE COMMON IN PEOPLE WITH CLL?

- Many patients are older, with non-CLL medical conditions
- CLL saps the “good” immune system and supplies a less functional one, particularly lymphocytes (e.g., B cells & their “good” antibodies)
- Treatments for CLL (steroids, chemo, BMT) further impair the immune system in other ways

These make it easier to get infections, harder to fight them off, and reduces impact of preventative vaccines

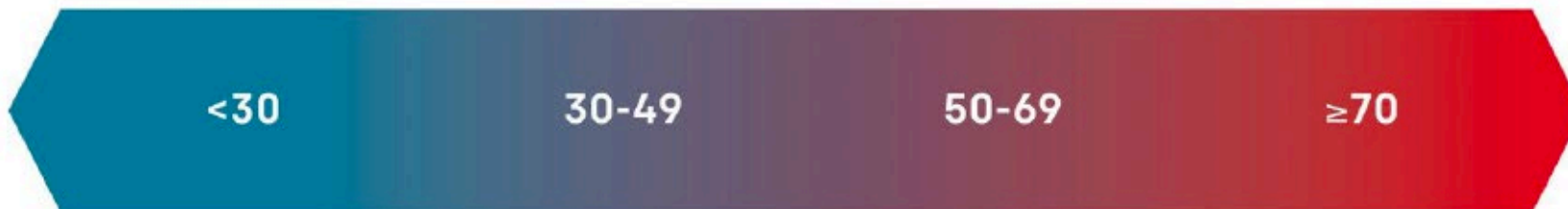


# COVID-19 Risk Continuum

LOWER RISK

HIGHER RISK

Age  
(years)

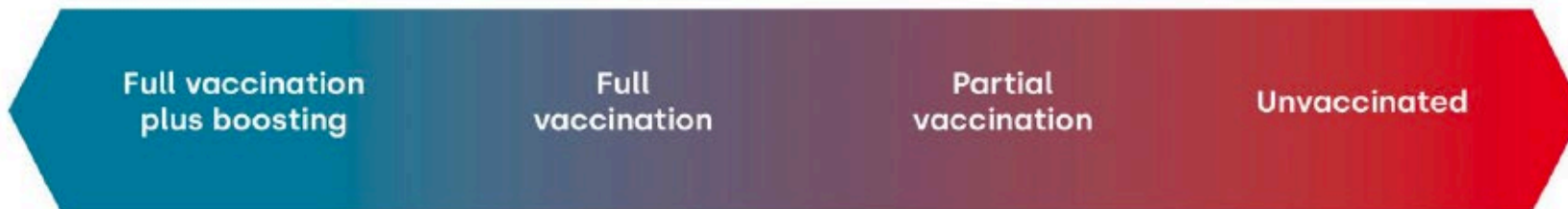


*The most important risk factor is increasing age.*

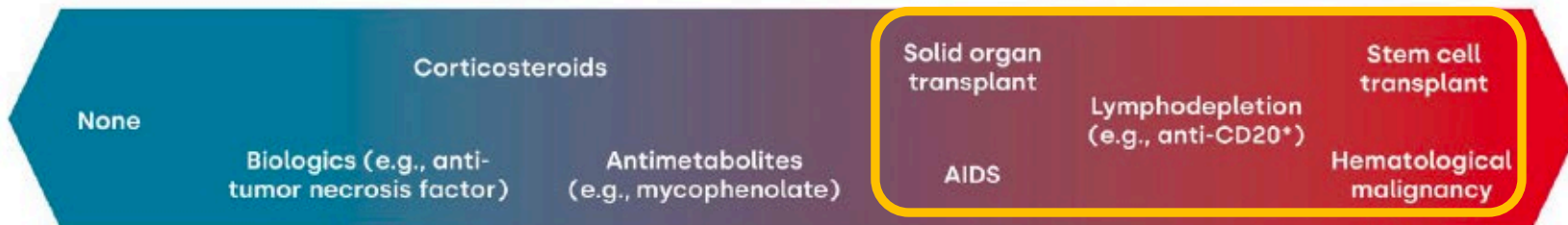
Medical Conditions  
(e.g., diabetes, chronic kidney disease, obesity, lung disease, pregnancy)



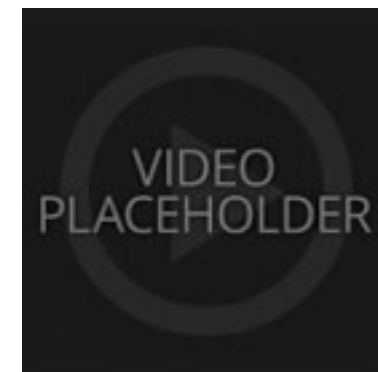
Vaccination Status



Immunosuppression  
(illustrative therapies and conditions – there may be significant variation in risk within each category)



*Sociodemographic factors and non-pharmaceutical interventions affect exposure risk*



Werbel et al., CID, 2023

# GENERAL APPROACHES TO REDUCE INFECTIONS

- Wash hands
- Wear a well-fitted, high-quality mask when indoors
- Minimize interactions with large groups of people, especially:
  - When virus circulation is high
  - Setting is poorly ventilated
- Ensure close contacts around you are (1) vaccinated and (2) let you know if they're feeling ill and/or test before gatherings
- Immunoprophylaxis
  - Vaccines ("active")
  - Preventative antibodies ("passive")
- (Use of pre or post-exposure antiviral drugs)



# HOW DO VACCINES WORK?

- **Show an important piece of a pathogen to your immune system “ahead of time”**
  - Often need to be shown 2+ times to gear up immunity (prime → boost)
- **Stimulates B cells to produce antibody (Ig) and store memory for next encounter**
  - Antibodies will bind and ideally neutralize the pathogen → in enough numbers, this would block infection altogether
- **Builds T cell memory to:**
  - Send alarm signals when encountering pathogen (e.g., CD4 helper T cells)
  - Develop killer T cells to clear and destroy infected cells once an infection begins (e.g., CD8 T cells) → key to prevent severe disease
- **If a person either 1) does not have enough immune cells or 2) the immune cells are weakened by underlying medical issues or medicines → diminish vaccine immunity**
  - May need more or different vaccines (higher dose or with adjuvants)



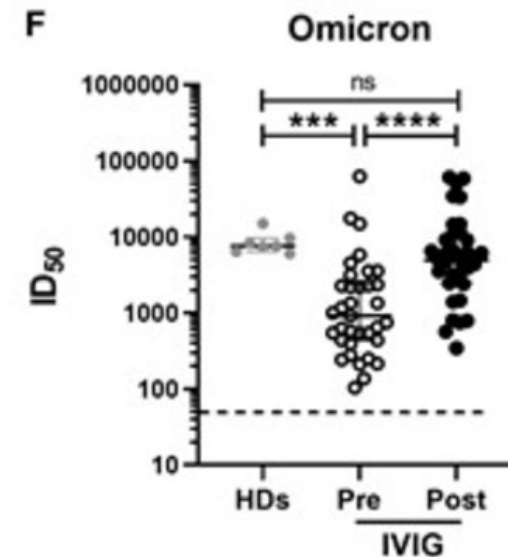
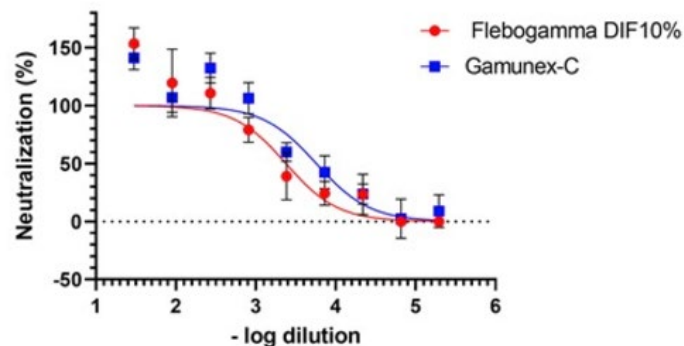
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# CONCEPT OF PASSIVE IMMUNOPROPHYLAXIS

- Best supported for people with hypogammaglobulinemia (IgG <400-600) or “CVID” with impaired vaccine responses (e.g., low flu or pneumococcal antibody titers)
  - Especially if a patient has a history of recurrent sinus or lung infections
- Subcutaneous or intravenous immunoglobulin (IVIg)
  - Usually given every 2-4 weeks
  - Neutralization vs influenza, RSV, COVID-19 (variable)

Influenza A Guangdong-Maonan/SWL1536/2019 (H1N1)



Diez et al., OFID, 2022  
Upsani et al., CID, 2023

# RSV (RESPIRATORY SYNCYTIAL VIRUS)

- A “cold” virus, at least as severe as influenza in older adults
  - Often more wheezing/respiratory, less intense systemic symptoms
  - ~100K hospitalizations, 5-10K deaths per year in adults
    - Especially among elderly, frail, chronic lung disease, diabetes, obesity
  - Leading cause of hospitalization in young children (“bronchiolitis”)
- **Adult RSV Hospitalizations in 2022-2023**
  - Majority were ≥75 yrs, 95% ≥1 condition (COPD, obese, DM, CHF)
  - 5% of hospitalized died → 42% were ≥80 years
  - Worse outcomes with (the rare) SARS2 or influenza coinfection

Pillie et al., 2015, TID

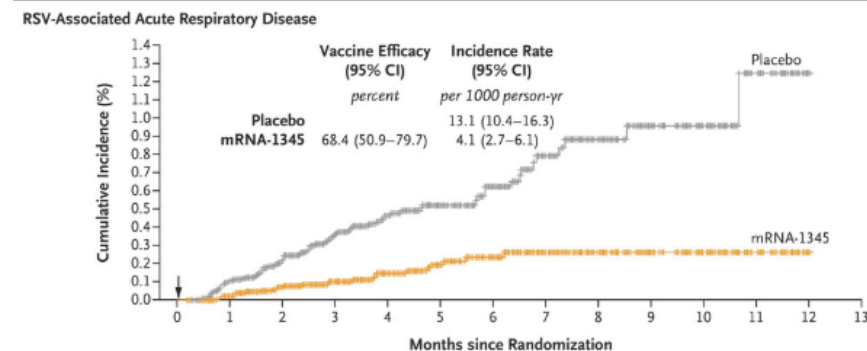
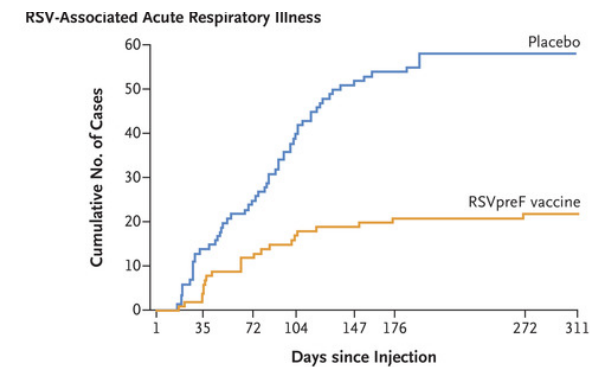
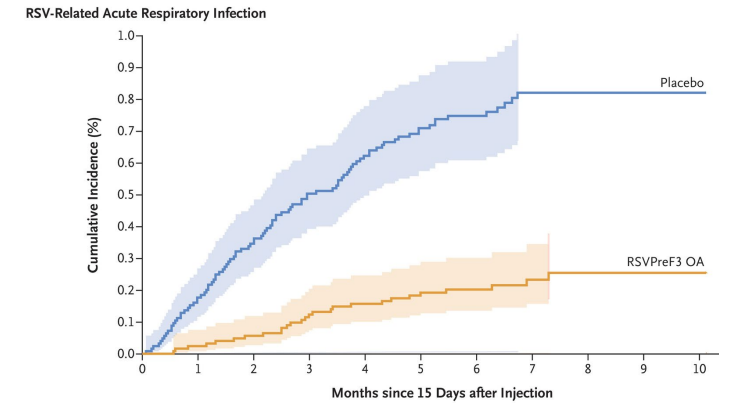
Recto et al., JID, 2024

Havers et al., CDC MMWR, 2023



# RSV VACCINES: A REVOLUTION!

- In older adults, 60-85% effective against disease
  - Studies had many different definitions
- Three vaccines available, all induce high antibodies
  - Arexy (GSK, adjuvanted protein, RSV A)
  - Abrysvo (Pfizer, unadjuvanted protein, A/B)
  - mRESVIA (Moderna, mRNA, A)
- Vaccines are safe
  - Rare instances of Guillain-Barre syndrome
    - ~10/1,000,000 doses
- No published data in CLL
  - Pfizer trial, TBD



# RSV: PREVENTION & TREATMENT

- **Best treatment is prevention**
- **CDC vaccine recommendation for a single RSV vaccine dose**
  - All adults ≥75 years
  - Adults 60–74 years at increased risk of severe RSV (e.g., CLL)
  - CDC did not recommend for younger ages or for a 2<sup>nd</sup> dose
- **Otherwise, for treating confirmed illness**
  - IVIG can be given, especially if known hypogamm/CVID
  - Ribavirin (an antiviral) may be used for high risk to prevent disease progression (OK data), or for very ill persons (poor data)





# INFLUENZA DISEASE

- **10-40 mill. cases/yr (3-12% US), 150-700K hospitalized, 10-50K deaths**
  - Varies based on vaccine uptake, coverage/strain types
  - Vanishingly little COVID-19 during lockdown, now approaching seasonality
- **Mortality in hospitalized immunocompromised patients (including hematological malignancies) can be 10-20%**
  - Secondary bacterial pneumonias (pneumococcal, staph) common
  - Cardiovascular complications such as heart attacks and strokes



CDC

Kodde et al., Inf., 2022

# INFLUENZA TREATMENT

- **Oseltamivir (Tamiflu) can reduce serious outcomes in high-risk people**
  - E.g., extremes of age ( $\geq 65$ ,  $< 2$  yr), immunocompromised, organ disease
    - Note: lower dose with kidney disease
  - Earlier is better - data mixed when given  $> 48$  hours of symptoms
  - Fairly high rate of gastrointestinal side effects (to balance)
  - Rare cases of oseltamivir resistance, may emerge during treatment
- **Approved as post-exposure prophylaxis (PEP) if given  $\leq 48$  hrs of symptoms**
- **Single-dose Baloxavir (Xofluza) also approved for treatment and PEP**
  - May be better for Flu B than oseltamivir?
  - Unclear that combination therapy with oseltamivir adds much
  - Resistance can develop

CDC  
Alonso et al., JCV, 2011  
Van der Vries et al., NEJM, 2018  
Kumar et al., Lancet ID, 2022  
Tramontana et al., EID, 2010



# GENERAL INFLUENZA VACCINATION NOTES

- **Many available vaccines, all trivalent, all with some benefit**
  - Standard dose
  - High dose ( $\geq 65$  years [“Fluzone High-Dose”])
  - Adjuvanted ( $\geq 65$  years [“Fluad”])
  - Live attenuated (**NOT** to be given)
- **Better to give late Oct – Nov, protection highest first 3 months**
- **Can be given along with any other vaccine (COVID-19, RSV, etc.)**
  - Usually give only 1 adjuvanted vaccine at a time
- **No need to adjust or time IVIG dosing**
- **Egg allergy is NOT a contraindication to any flu vaccine**
  - Unless known prior flu shot reaction



CDC

# INFLUENZA VACCINATION & CLL

- **Responses are generally worse vs in general population (as low as 10-25% antibody seroconversion)**
  - Vaccination, however, does reduce severe outcomes
  - High dose and adjuvanted vaccines improve responses vs standard dose
- **Anti-CD20 therapies (e.g., rituximab, obinutuzumab) and BTK inhibitors (e.g., ibrutinib, acalabrutinib) particularly impair response**
  - Ideal to wait 3-6 months post rituximab; restart 2 weeks post vaccine
  - But any vaccine better than no vaccine, give in advance of flu season
- **Revaccination needed after BMT (usually 3-6 months)**

Yri et al., Blood, 2011  
Pinana et al., CID, 208  
Sun et al., JAMA Onc, 2016  
Whitaker et al., Vaccine, 2021



# COVID-19 & CLL: CHANGING OUTCOMES

- **Case mortality in early waves (20-30%), particularly if older, frailer**
- **Current risk of severe disease much lower (? 1-5% hospitalized)**
  - Immunity (infection, vaccination), antivirals, improved clinical mgmt
- **Poor understanding of post-COVID conditions (e.g., “Long COVID”)**
  - Early waves: severe lung injury, post-ICU syndromes
  - Middle waves: protracted/prolonged infections
  - Current era: ?

Mato et al., Blood, 2020

Werbel et al., CID, 2023

Visentin et al., AJH, 2023

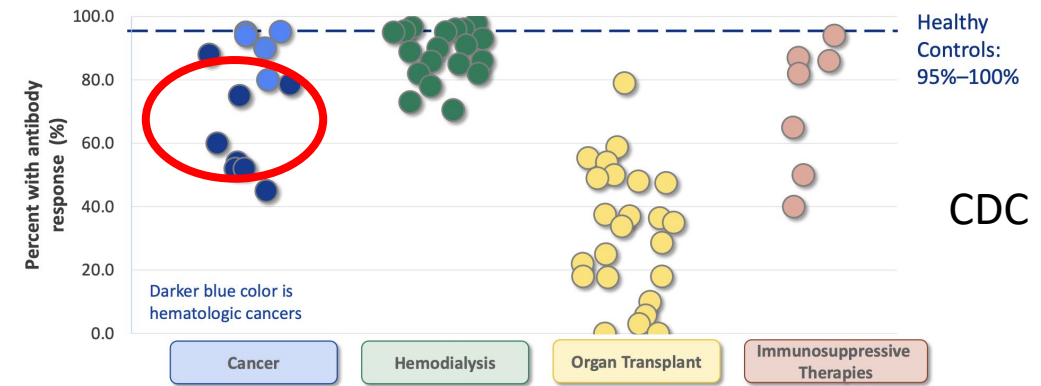
Chatzikonstantinou et al., Leukemia, 2021



# WHY VARIANT IMMUNE EVASION MATTERS FOR PEOPLE WITH CLL

- Many people have poorer immune responses to vaccination
- If cannot block initial infection, some proportion will experience severe disease or difficult-to-clear infections
  - Older CLL patient on anti-CD20 therapy “classic” case for protracted COVID-19
- Loss of monoclonal antibody activity and challenges with certain antivirals limits prevention and treatment options

Percent of subjects with antibody response after two mRNA vaccine doses by immunocompromising condition and study (n=63)



Despite 3+ vaccines, 10-20x higher relative risk of severe Omicron disease in leukemia/BMT

Agrawal et al., Lancet, 2022



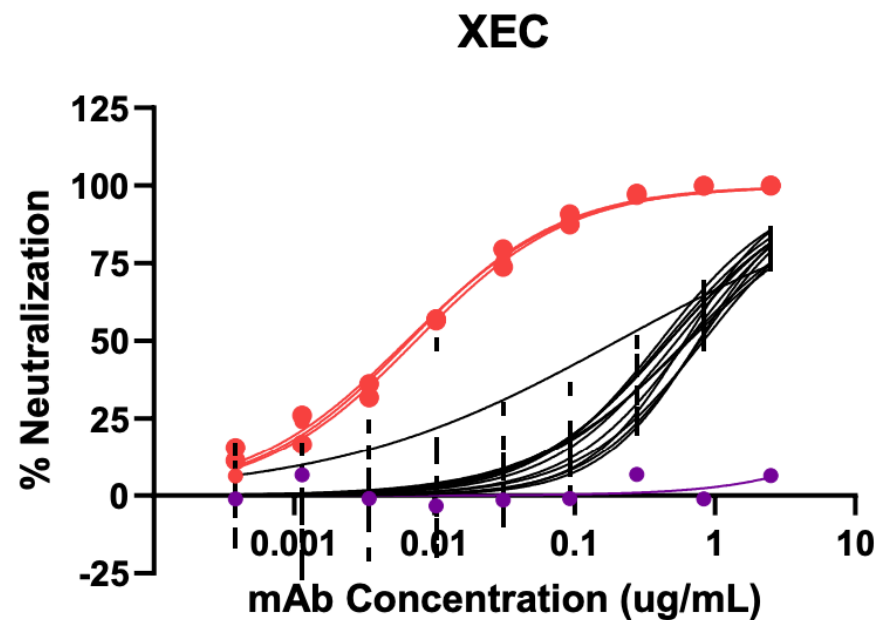
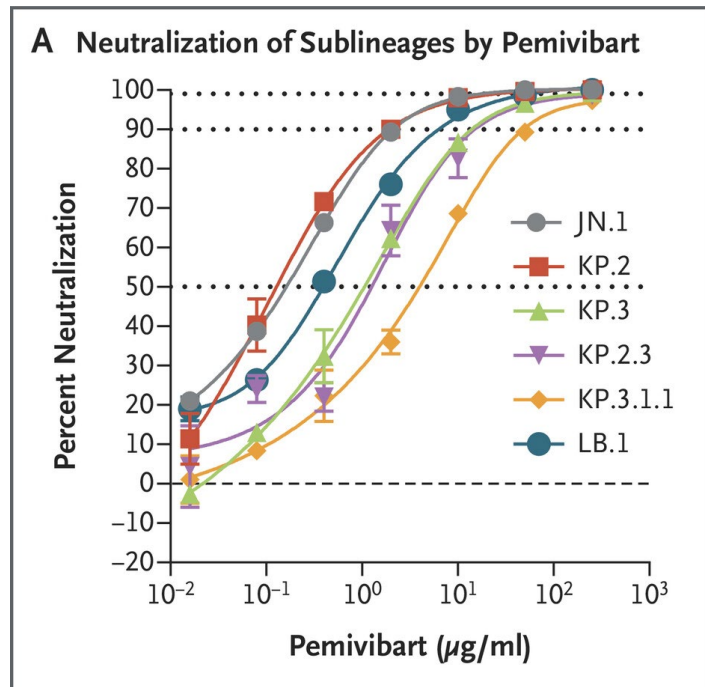
# UPDATED COVID-19 VACCINE RECOMMENDATIONS

- **Persons  $\geq 65$  and/or immunocompromised to receive 2 doses of any updated vaccine, separated by 6 months (minimum interval 2 months)**
  - There is flexibility to permit repeated boosting
- **No recommendation for one vaccine over another**
  - Antibody levels tend to be highest with Moderna vaccines
  - Side effects tend to be less with the Novavax vaccine
- **For those with recent infection, can consider waiting 3-4 months until next vaccination**

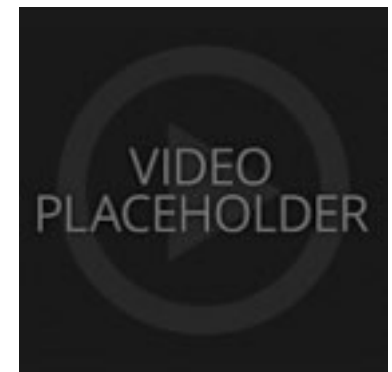


# COVID PASSIVE IMMUNOPROPHYLAXIS: MONOCLONAL ANTIBODIES vs VARIANTS

- When mAbs work, they work (~70% lower risk of disease), but variants outsmart them
- Uncertain whether current mAb (Pemivibart, Pempgarda) remains highly active vs KP.3.1.1/XEC



Wang et al., NEJM  
Yao et al., medrxiv (Preprint)  
Power et al., medrxiv (Preprint)





# TREATMENT: CHOOSING THE RIGHT ANTIVIRAL

	Route	Effectiveness	Patient Considerations	Major Issues	Other Notes
<b>Remdesivir</b> (Veklury®)	IV 3 days, daily	+++	Mild ↑liver enzyme	<b>Logistics</b>	FDA-approved, inc for infants >28 days  ≤7 days of sx onset
<b>Nirmatrelvir/ Ritonavir</b> (Paxlovid™)	Oral 5 days, twice daily	+++	Not recommended for advanced liver or kidney disease	<b>Drug-drug interactions</b>	½ dose N if GFR 30-59  ≤5 days of sx onset  GI sx, rebound?
<b>Molnupiravir</b> (Lagevrio™)	Oral 5 days, twice daily	+	No dose change for renal or liver disease	<b>Lower effectiveness</b>	?Mutagenicity ≠ <18yr; + contraception  ≤5 days of sx onset



FDA Fact Sheets  
NIH Treatment Guidelines

# KNOW/FIND PAXLOVID™ INTERACTIONS!

- Talk to a pharmacist & your doctors
- Make a plan before an acute illness
- Resources
  - Liverpool Drug Interactions
  - Ontario COVID-19 Science Table
  - NIH Treatment Guidelines

## Prescribe Alternative COVID-19 Therapy

For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.

### Anticonvulsants

- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

### Anti-infectives

- Glecaprevir/pibrentasvir
- Rifampin
- Rifapentine

### Immunosuppressants

- Voclosporin

### Cardiovascular

- Amiodarone
- Clopidogrel<sup>a,b</sup>
- Disopyramide
- Dofetilide
- Dronedarone
- Eplerenone
- Flecainide
- Ivabradine
- Propafenone
- Quinidine

### Neuropsychiatric

- Clozapine
- Lurasidone
- Midazolam (oral)
- Pimozide

### Pulmonary

#### hypertension

- Sildenafil
- Tadalafil
- Vardenafil

### Miscellaneous

- Bosentan
- Certain chemotherapeutic agents<sup>c</sup>
- Ergot derivatives
- Lumacaftor/ivacaftor
- St. John's wort
- Tolvaptan

# INFECTIOUS DISEASES “ROUNDUP”



# EMERGING THREATS: “BIRD FLU”

- **Highly pathogenic avian influenza (HPAI, H5N1, “bird flu”)**
  - Widespread in US livestock, wild fowl, presumably other animals
  - >50 US cases in humans, mostly mild conjunctivitis; one severe case in adolescent
  - Historical mortality >50% for HPAs; uncertain why differing now
  - Immediate risk reported as low, but existential outbreak risk is high
- **Avoid direct contact with birds, dead or alive. Do not consume raw milk**
- **Get your flu shot: unlikely to prevent infection, but may reduce severity**
- **Early treatment with oseltamivir if infected, post-exposure prophylaxis if exposed**
- **Some strains might show lower sensitivity to oseltamivir**
  - Could consider combination treatment with baloxavir in confirmed case and/or higher-dose oseltamivir (treatment or PEP)



CDC

# OTHER EMERGING THREATS

- **Mpox (formerly monkeypox)**

- Relative of smallpox, can cause severe disease in immunocompromised persons
  - Spread mostly through close physical contact
- Two clades: widespread Clade II outbreak in 2023 vs only 1 confirmed Clade I case in US
- Two-dose JYNNEOS inactivated vaccination recommended if higher-risk sexual activity in past 6 months, or if known recent exposure
  - Antiviral therapy (TPOXX) does not appear to work well

- **Measles**

- Highly contagious: 16 outbreaks in the US in 2024, 280 cases, 70% kids  $\leq 19$  years
- Ensure healthy close contacts in your life are vaccinated
- Cannot get MMR vaccine if actively heavily immunosuppressed
  - Can consider 1-2 years post BMT if off immunosuppression, signs of immune recovery
  - Not recommended if on anti-CD20 drugs like rituximab
  - Space 8+ months from IVIG
- Post-exposure prophylaxis with IVIG

CDC

Pergam et al., BBMT, 2019



# CLL DRUG & “BUG” ASSOCIATIONS

- **Steroids (e.g., prednisone) → almost any infection (dose-related)**
  - Prevention with acyclovir (herpes, shingles), bactrim (pneumocystis [PJP])
- **Anti-CD20 (e.g., rituximab, obinutuzumab) → viral infections, recurrent bacterial sinusitis/pneumonia, hepatitis B**
  - Role for IVIG, prevention with acyclovir, hepatitis B screening
- **BTK inhibitors (e.g., ibrutinib, acalabrutinib) → fungal infection (molds, pneumocystis [PJP])**
  - Prevention with bactrim, sometimes antifungal drugs (“XXX-azole”)

**Note: First 1-2 years post bone marrow transplantation are high risk for many infections, especially in setting of graft-versus-host disease**

Ghez et al., 2018  
Rogers et al., Leukemia, 2020  
Agudelo Higueta et al., 2024



# SUMMARY

- **It is respiratory infection season, now (RSV -> Flu -> COVID [hard to predict])**
- **Risks for serious infections relate to age (in particular), medical conditions, vaccination, and immunosuppression (steroids, BTKi, anti-CD20, BMT)**
- **Prevention is the best treatment for respiratory infections**
  - We do have antivirals, which should be used early in disease
- **Vaccine immunity is lower in people with CLL: imperfect, yet important**
  - The time to get vaccinated is now!
  - And/or to complement with IVIG
- **Several emerging infectious threats, including H5N1 (“bird flu”)**
  - Reinforces importance of vaccines and expert treatment teams if infected





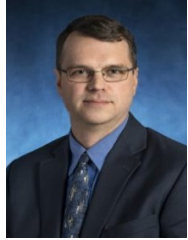
Transplant Research Center

# Johns Hopkins Transplant Research Center



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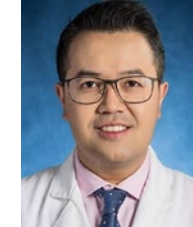


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# Emerging Pathogens of Concern in Immunocompromised Persons



Emerging Pathogens at the  
Transplant Research Center

[www.emergingpathogens.jhmi.edu](http://www.emergingpathogens.jhmi.edu)



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# COMMON INFECTIONS WITH CLL: PREVENTION AND TREATMENT

William Werbel, MD, PhD

Assistant Professor  
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Infectious Diseases

Johns Hopkins University  
School of Medicine



Infectious Diseases Webinar

# AUDIENCE Q&A



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