



CLL SOCIETY

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PROTECTING AGAINST INFECTIONS WHEN YOUR IMMUNITY IS IMPAIRED

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Protecting Against Infections When Your Immunity is Impaired

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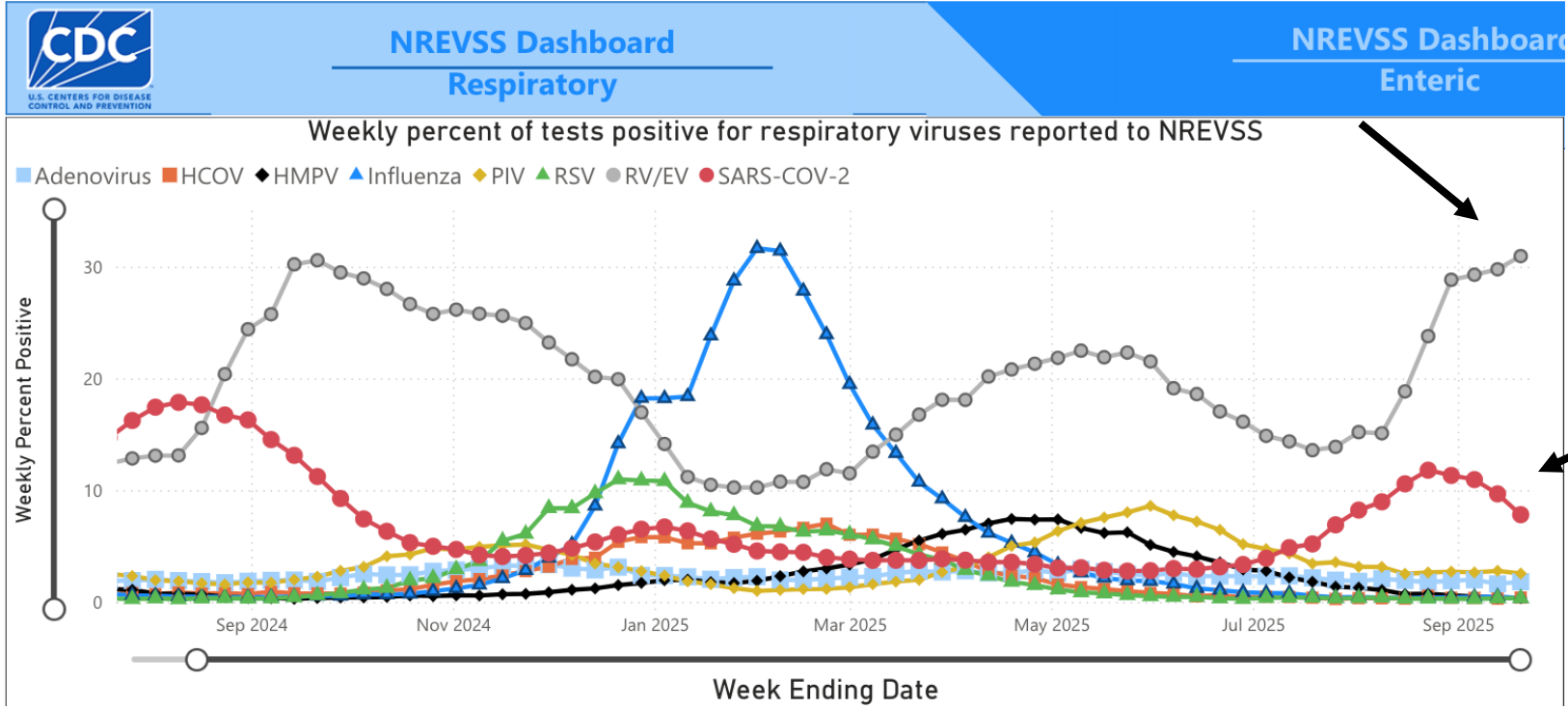
Johns Hopkins University
School of Medicine

Infectious Diseases Webinar

Outline

- Active infection “**status report**” and forecast
- General and CLL-specific **risk factors for infections**
- Brief **immune system review and impact of medications**
- Ways to **reduce risk** (behavioral, pharmacological)
- Updates in respiratory virus **prevention and antiviral advances**

Viral Circulation: Wastewater Monitoring



COVID-19 decreasing

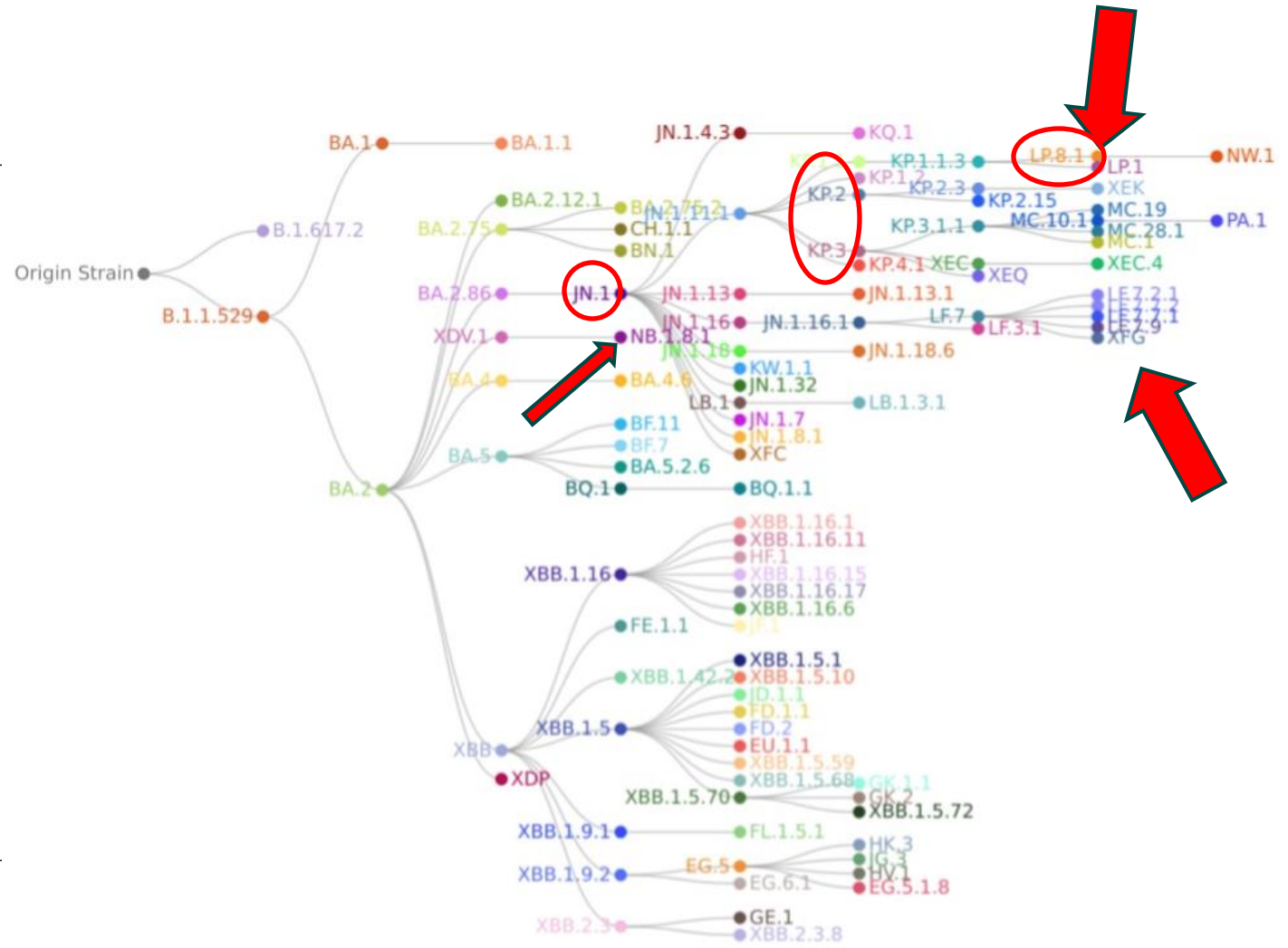
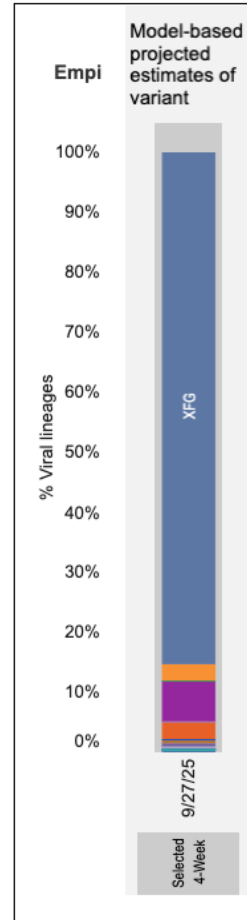
MODERATE

Nationally, the wastewater viral activity level for COVID-19 is currently **moderate**.

Note: enteroviruses particularly common in late summer and early fall

COVID-19 Variant Update and Forecast

- **XFG** overtook LP.8.1 this summer (**NB.1.8.1** present)
- “Grandchildren” of JN.1/KP.2 and “cousins” of LP.8.1 (i.e., 2026 updated vaccine strain)
- Pemivibart (Pemgarda®) mAb appears active against XFG (less active against NB.1.8.1)



Highly Pathogenic Avian Influenza (H5N1, “Bird Flu”)

- No recent human cases and no clear human-to-human transmission
- Ongoing sporadic poultry outbreaks (backyard & commercial), cattle, mammals

National Total Cases: 70

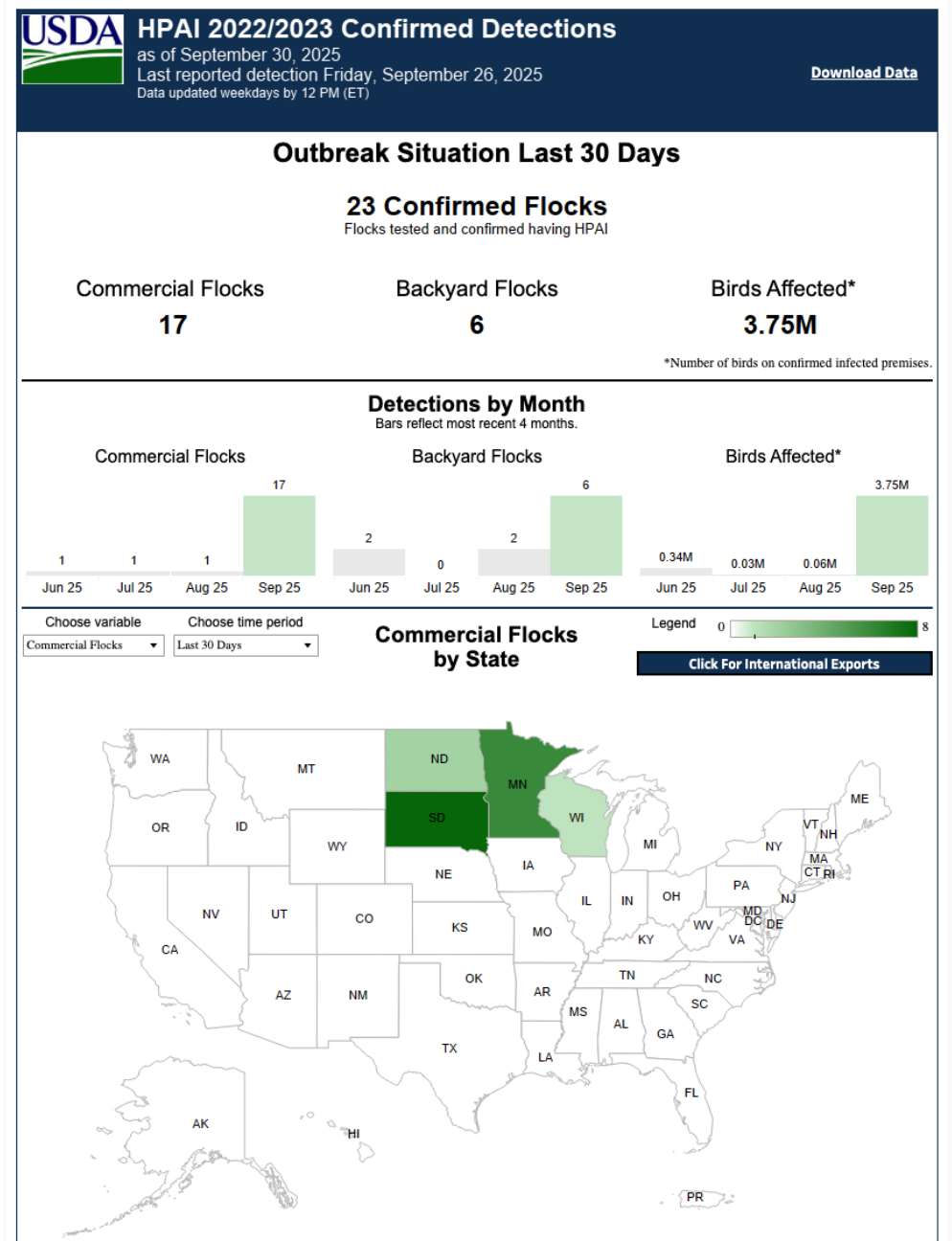
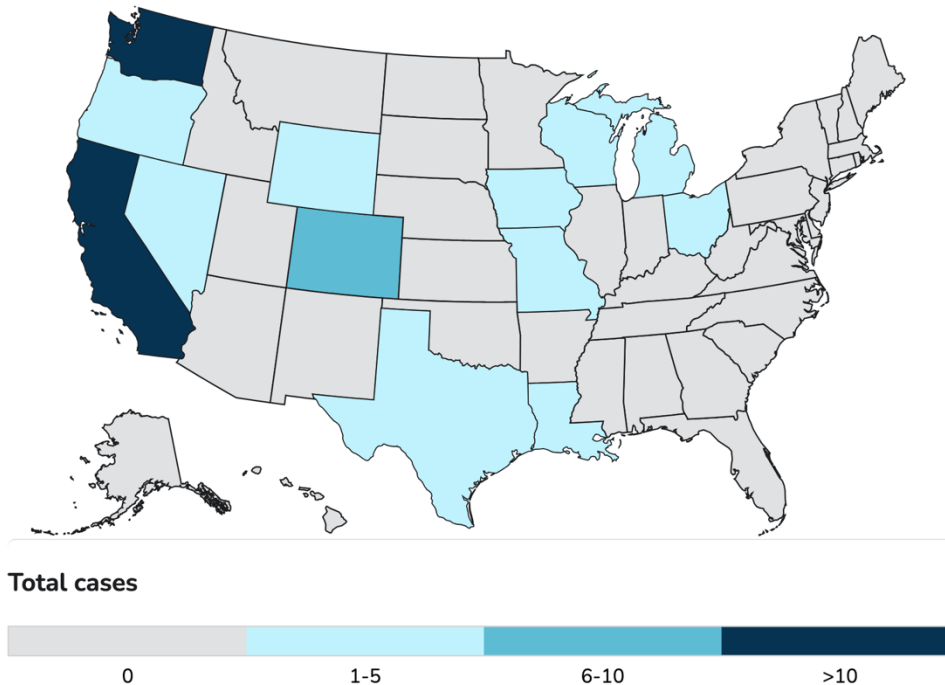
Cases	Exposure Source
41	Dairy Herds (Cattle)*
24	Poultry Farms and Culling Operations*
2	Other Animal Exposure†
3	Exposure Source Unknown‡

NOTE: One additional case was previously detected in a poultry worker in Colorado in 2022. Louisiana reported the first H5 bird flu death in the U.S.

*Exposure Associated with Commercial Agriculture and Related Operations

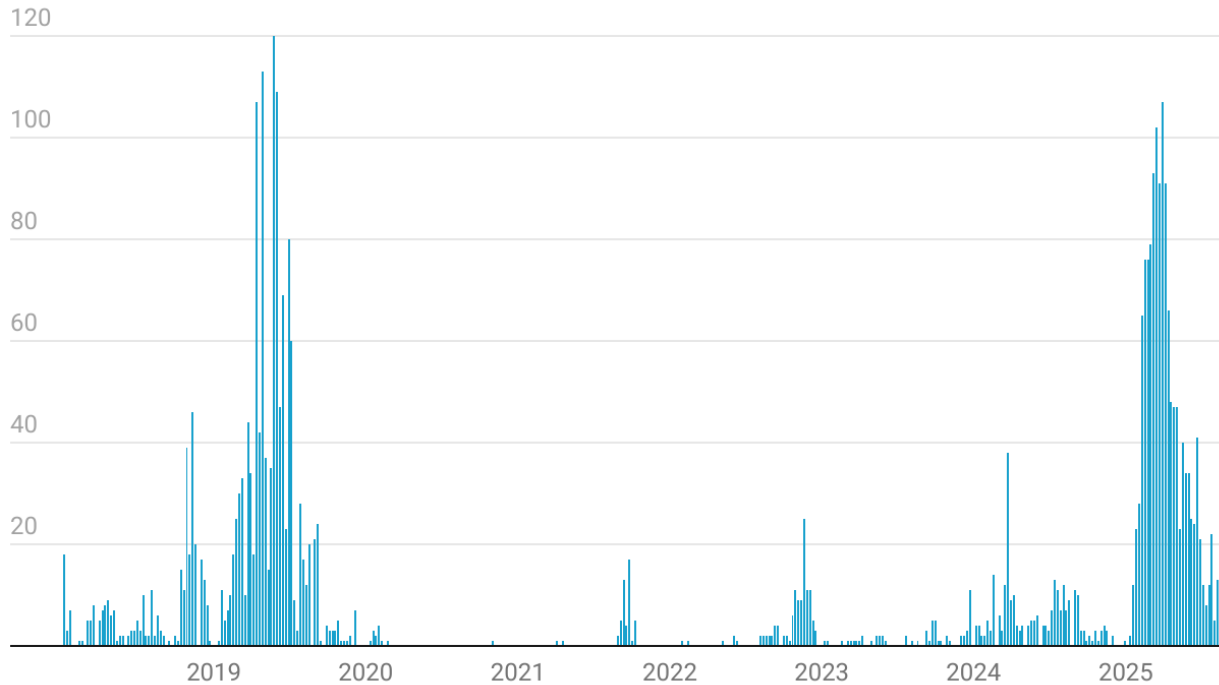
†Exposure was related to other animals such as backyard flocks, wild birds, or other mammals

‡Exposure source was not able to be identified



US Measles Outbreak: Fading, yet not Gone

Weekly measles cases in the U.S.

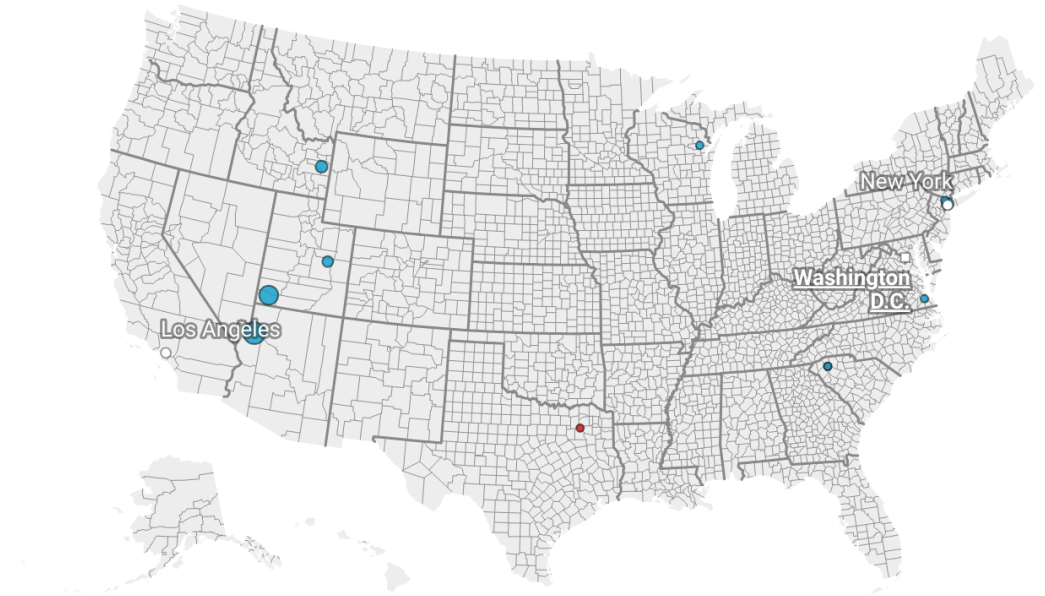


Source: Johns Hopkins University

Worst outbreak in 21st century: 1,522 confirmed cases
94% unvaccinated or unknown status; 55% ≤ 18 yrs
12% hospitalized, 3 confirmed deaths

Where measles cases are now

Imported Local Count 2 8 20



Source: Johns Hopkins University

About 50 cases in past 2 weeks
Mostly in Utah, Arizona, Minnesota
Note: ongoing outbreaks in Canada (Alberta)

(Tentative) Forecasting...

- Current COVID-19 wave likely fading over next 2 weeks, entering lull for a few weeks
- Traditional respiratory virus seasons tends to begin in late October/early November
- Typically starts with RSV (Oct/Nov) → influenza & COVID-19 rise (Nov/Dec) → all peaking together in December and January (climate, holidays, behavior)
- Hence, **now is a good time to get vaccinated** vs RSV, flu, & COVID-19
 - Greatest protection vs flu and COVID-19 are in the first 2-3 months
 - RSV protection might be more durable (see later slides)
 - Be aware the “tail” of flu season stretches out to March-April



Approach to Assessing Infectious Risks in People with CLL

How Infectious Diseases Doctors Judge Risk:

1) Assess “The Net State of Immunosuppression”

- **Sum of immune system impairments** → determines type & severity of immunocompromise → specific infection risk
 - **Extremes of age** (very young or older adults)
 - **Medical conditions** (e.g., diabetes, kidney or liver diseases, poor nutrition)
 - Immunosuppressive **medications** (type, dose, duration)
 - **Specific immune defects** (e.g., low neutrophil counts, low B and T cell counts, hypogammaglobulinemia, splenic dysfunction)
 - Certain **infections** (e.g., HIV, CMV, Measles)
 - **Barrier** defects (e.g., skin, mouth, gut, IV lines, trauma, surgeries)

2) Past and Current Life Exposures Also Matter!

- Influences risks of **new infections** from environment, as well as **reactivation of old infections** from the body
- Daily activities, interactions with others, residence/region
- Ex) environmental exposure → possible infection risks
 - Gardening, camping, birds, wood, mold → fungus
 - Travel, outdoors, animals → ticks, mosquito-borne
 - Food/water, animals, travel, sexual activity → parasites and GI infections
 - Travel or life abroad, health work, prison → tuberculosis

Mapping “Net State of Immunosuppression” to Individuals with CLL

- Often older patients (60+ years of age) with multiple other health issues
- CLL saps the normal immune system, particularly lymphocytes (e.g., B cells & their “good” antibodies)
- Treatments for CLL (steroids, chemo, BMT, CAR-T) impair other parts of the immune system in multiple 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)

<30

30-49

50-69

≥70

The most important risk factor is increasing age.

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

None

1

2

3+

Vaccination Status

Full vaccination
plus boosting

Full
vaccination

Partial
vaccination

Unvaccinated

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

None

Corticosteroids

Biologics (e.g., anti-tumor necrosis factor)

Antimetabolites
(e.g., mycophenolate)

Solid organ
transplant

AIDS

Lymphodepletion
(e.g., anti-CD20*)

Stem cell
transplant

Hematological
malignancy

Sociodemographic factors and non-pharmaceutical interventions affect exposure risk



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Werbel et al., CID, 2023

Markers & Contributions to Measles Risk



Factor	Lowest Risk	Highest Risk
Birth Year	Before 1957	After 1957*
Vaccination Status	2 live attenuated pre-immunosuppression	Unvaccinated
Measles Ab Test	Positive	Negative
Immunosuppression	- >2 years since transplant - On 1 or low doses of immunosuppression - Normal lymphocyte counts (e.g., >1000) - On IVIG replacement (if needed)	- <1-2 years since bone marrow transplant - Multiple immunosuppressant medications - Low lymphocyte blood counts - Low immunoglobulins <i>without</i> replacement

*People born in 1960s and 1970s might be at higher risk because:

- Relatively older
- Unlikely natural measles immunity
- Not 2x vaccinated

Immune System Defects: Basic Primer

Immune Cell Type	Function	Deficiency Risks
Neutrophils	Eat/kill pathogens	Bacteria, fungi, some viruses (herpes)
Macrophages	Eat pathogens, signal other cells	Bacteria, fungi, DNA viruses, mycobacteria (TB), parasites
Lymphocytes	B: make antibodies T: signaling (CD4), killing (CD8)	Viruses, bacteria, some fungi
Cytokines, Kinases	Alarm (or cool down) signals	Variable



Meds Knock Down Cells → Raise Risks

Meds	Cells Affected	Notable Infections	Preventative Medication?			
			Herpes	Hep B	Fungi	PJP
Steroids (prednisone)	All Dose [>20 mg] & duration [>2-4 wk] matter	Bacterial skin infections and pneumonia, viral infections, fungal infections, hepatitis B	+	+/-	+/-	+
Anti-CD20+ (obinutuzumab , rituximab)	B cells	Viral infections (herpes, respiratory, hepatitis B), some fungal pneumonia	+	+	+/-	+/-
BTKi (ibrutinib, acalabrutinib, zanabrutinib)	B cells (& off- target neutrophil)	Viral infections (herpes, respiratory), fungal infections	+	+/-	+	+

Bispecific Antibodies (bsAbs, BiTEs)

- **“CAR-T” in a bottle**: best studied for myeloma, now used for lymphomas (epcoritamab, mosunetuzumab, glofitamab)
- Designed to **join and activate a patient’s killer T cells to engage & destroy a patient’s B cells**,
 - Severe longterm **hypogammaglobulinemia (low antibody)** → viruses, pneumonia, sinusitis
- Frequently given with **high dose steroids +/- tocilizumab** (anti-IL6 [alarm cytokine] blocker) to reduce or treat reactions (“CRS”) → **further increases infection risk (all kinds)**

Meds	Cells Affected	Notable Infections	Preventative Medication?				
			Herpes	Hep B	Fungi	PJP	IVIG
bsAb	B cells	Viral infections (herpes, respiratory, hepatitis B), some fungal pneumonia	+	+	+/-	+	+

Example: Putting It Together for HSV (Herpes) & VZV (Shingles)

Overall Infection Risk in Patients with Cancer ^a	Disease/Therapy Examples	Minimum Duration of Antiviral Prophylaxis
Low	Standard chemotherapy regimens for solid tumors	No prophylaxis unless prior HSV episode; if needed, treat during active therapy including periods of neutropenia
Intermediate	- Autologous HCT - Lymphoma - Multiple myeloma - CLL^b - Purine analog therapy (eg, fludarabine)	HSV prophylaxis ^j - Consider during active therapy and possibly longer depending on degree of immunosuppression VZV prophylaxis ^j - Consider for at least 6–12 months after autologous HCT
High	Acute leukemia	HSV prophylaxis during active therapy including periods of neutropenia ^j
	Proteasome inhibitors	VZV prophylaxis during active therapy including periods of neutropenia ^j
	- Alemtuzumab therapy - Allogeneic HCT - GVHD requiring significant escalation of immunosuppression	HSV prophylaxis ^j - Minimum of 2 months after alemtuzumab and until CD4 $\geq$ 200 cells/mcL VZV prophylaxis ^j - Prophylaxis should be considered for at least 1 year after allogeneic HCT

Generally recommend prophylaxis if:

- neutropenia (<500 x >7 dys) and/or severe lymphopenia (<500)
- receiving active treatments for CLL or post BMT/CAR-T
- prior history

Reminder: General Approaches to Preventing Communicable Infections

Norovirus
Enteroviruses
(HFM)

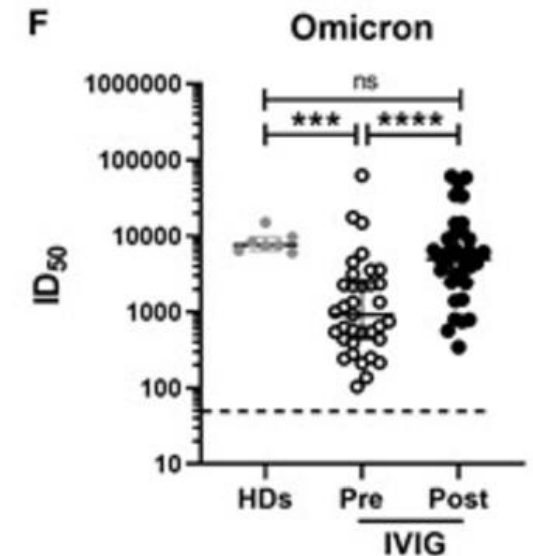
- **Wash hands** (note: hand sanitizer works for most, but not all viruses)
- Minimize interactions with **large groups of people** and wear a well-fitted, **high-quality mask**:
 - When virus circulation is high
 - Setting is poorly ventilated
- Ensure **close contacts** around you are (1) vaccinated and (2) let you know if they're feeling ill and/or test before gatherings
- **Immunoprophylaxis**
 - Vaccines ("active")
 - Preventative antibodies ("passive")
- **Prophylactic medications** (either pre- or post-exposure to infection)

Vaccines: The “How,” “Why,” and Limits

- Vaccines provide a **head start** on seeing some important part of an infection
 - Often need to be shown 2+ times to gear up immunity (prime → boost)
- Stimulates **B cells to produce antibody (Ig)**, store **memory** for a rainy day
 - Antibodies bind and neutralize the invaders
- Builds **T cell memory** to:
 - Send alarm signals when the infection is sensed (“helper T cells”)
 - Develop killer T cells to destroy infected cells → key to **prevent severe disease**
- If a person 1) **does not have enough immune cells** or 2) the **cells are weakened** by underlying medical issues or medicines → vaccine are less **fully** protective
 - May need more or different vaccines (higher dose or with adjuvants)

Add-Ons: Passive Antibody Prophylaxis

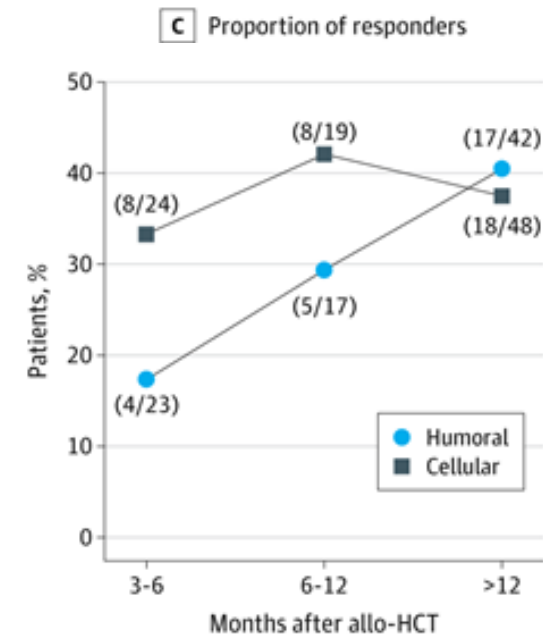
- Either a mix of **donated antibodies** against infection (IVIG) or a high dose of a specific antibody (**monoclonal antibody**; mAb)
- **IVIG** or subcutaneous Ig usually given every 2-4 weeks
 - Best data for people with known hypogammaglobulinemia (low antibody, IgG <400-600) → may be 25-35% people with new CLL diagnosis
 - Especially if history of recurrent sinus or lung infections
- **mAb** usually given every 3-6 months, for high-risk and/or immunocompromised people, to protect against **specific viral infections**
 - Strength = weakness → **very specific** so if a virus changes, could escape drug activity



Recent Developments in Preventing Viral Infections

RSV Vaccines → Data in People with Cancers

- **How good is the immune response after BMT?**
 - Very big range in antibody and T cell responses
 - Worse if: closer to BMT, if on immunosuppressive meds for GVHD, low lymphocyte counts
- **How well do they prevent severe disease?**
 - Decent (40-50%) protection for 1 season in immunocompromised people, worse for BMT
 - Dropped significantly by second season (<10%)
- **Need for a booster?** Very active area of study, limited info
- **Which vaccine is best?** We don't know.
 - Some prefer the adjuvanted vaccine (GSK)
 - No info for mRNA-based vaccine (Moderna)



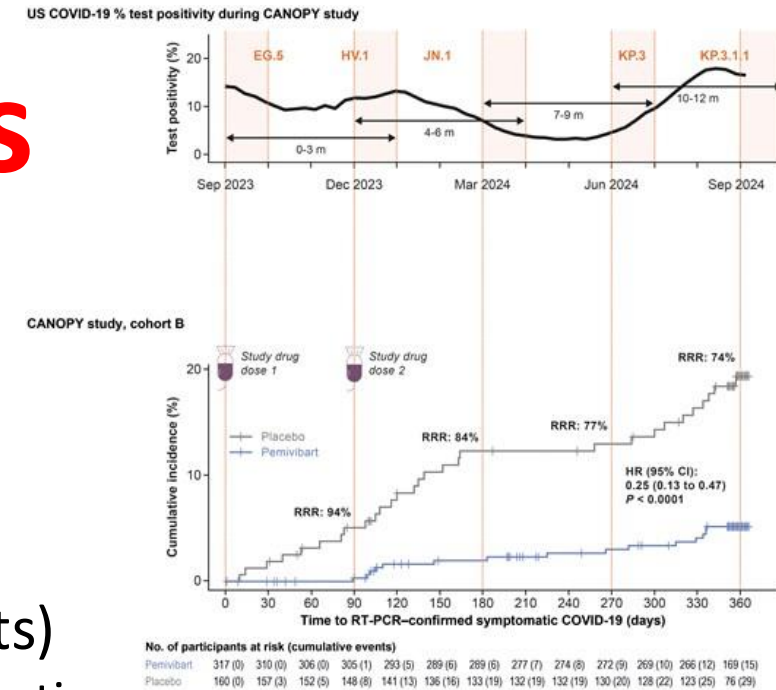
Exciting Antiviral Advances

- **Monoclonal antibodies**

- Pemivibart (Pemgarda™, infusion against COVID)
 - 84% reduction in symptomatic COVID at 6 months
- Clesrovimab (Enflonsia™, infusion against RSV for adults)
 - 60% effective vs RSV requiring medical attn, 84% vs hospitalization

- **Long-acting antivirals**

- CD388 (zanamivir) versus influenza
 - Oseltamivir (Tamiflu™) “cousin”, in clinical trials
 - 60-75% effective vs influenza-like illness over 6 months in healthy unvaccinated adults



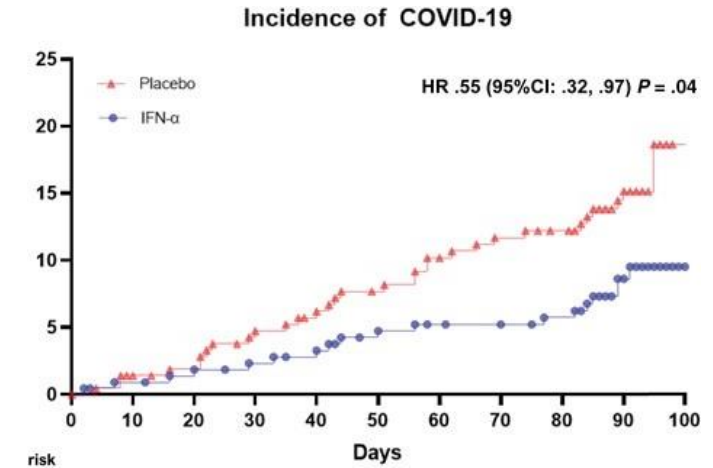
Nasal spray prophylaxis vs COVID-19...?

- **Azelastine**

- OTC “Hay fever” spray, 3x/day vs placebo
- 2% vs 7% COVID; 8% vs 19% all infxns
- **Note:** Took 5x/day x 3 days if pt felt ill (interfere with test results?)

- **Interferon alpha (in people with cancer [9% CLL])**

- Antiviral alarm signal spray, 1x/daily vs saline spray
- 8% vs 14% COVID; 5% vs 5% all other infxns
- **Note:** Mostly early pandemic data



Challenges Related to Shifting US Vaccine Discourse and Policies

- Historically there was high agreement between the US CDC, the ACIP, and major medical societies (IDSA, AAP, ACOG, etc)
- Now **there are conflicting recommendations**, which is confusing
- CIDRAP (U Minnesota) compiling outside expert opinions and data for vaccine guidance via the **Vaccine Integrity Project**
 - <https://www.cidrap.umn.edu/vaccine-integrity-project>
 - <https://www.idsociety.org/ID-topics/special-topics/immunization/>

COVID-19 Vaccine Access

- Moving target and varies by state, pharmacy, and insurance
- **Adults ≥ 65 years and adults ≥ 18 with immunocompromising conditions *should* have both access and insurance coverage** (if in doubt, get an Rx)
- Access and coverage for healthy close contacts or health care workers less certain; e.g., out of pocket, require Rx, attest to a health condition
- Multiple states issuing orders to assure vaccine access, but does not necessarily assure insurance coverage, e.g., West Coast Health Alliance
- Consortium (AHIP) committed to cover COVID-19, flu vax through 2026

Summary

- Respiratory season is on the horizon → **good time to get your RSV, flu, and COVID vaccines**
- **Know your risk (net state of immunosuppression)**: older age, medical conditions, vaccines, immunosuppression intensity
- Certain **medicines have strong links to certain infections**
 - Steroids, BTKi, anti-CD20, BMT, bsAb/BiTE → **prophylactic drugs**
- **Vaccine immunity is lower in people with CLL, but critical**
 - Role of passive immunoprophylaxis (**antibody add-ons**)
- Several important advances on the horizon, stay informed



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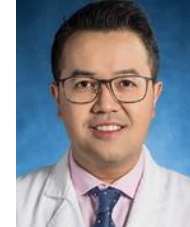


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Emerging Pathogens of Concern in Immunocompromised Persons



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AUDIENCE Q&A



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