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NSF's Finding Health Session

"Vaccinations & Nephrotic Syndrome"

September 26, 2023

Disclaimer

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- Material in this presentation is designed to serve only as a general resource for awareness and discussion purposes. Information provided in this presentation should not be taken as complete, nor acted on without further verification, research, or discussion with your personal physician, nephrologist, and medical team.
- In addition, significant differences exist depending on country, state, medical facilities and individual physicians.
- Opinions expressed in this session and on the following slides represent only those of individuals and not those of NSF, or other related institutions.

Introductions

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Tonight's Agenda

- Vaccine Overview
- Vaccination Timing
- Vaccines and Concerns for Relapse
- Immunosuppression Concerns
- "Tips and Tricks"
- Travel / Exposure Considerations
- Q & A
- Closing & Wrap-Up

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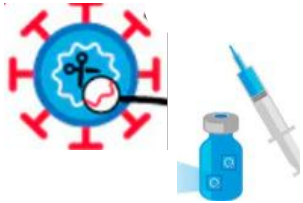
"With his kidney condition, what I know was, whenever he gets sick…the immune system becomes a little active, then he has higher chances of relapse. So with this vaccine, I don't know… it might cause him a relapse because he gets sick."

Vaccine Overview

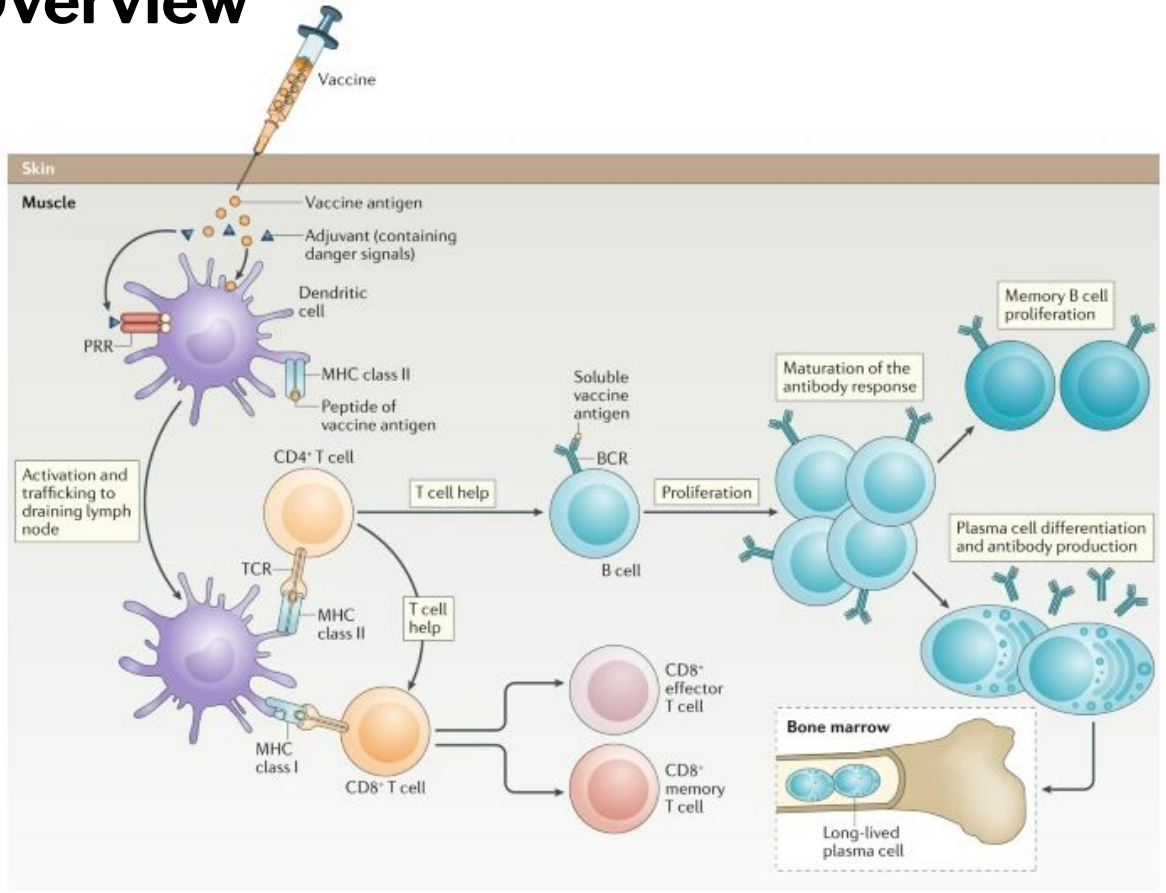


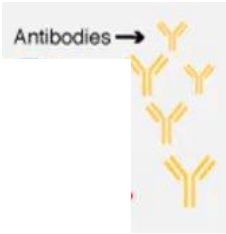
Vaccines contain antigen

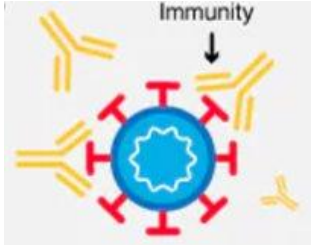
- Weakened live pathogen particles → Live, attenuated vaccines
- Inactivated pathogen
- Bits of exterior surface or genetic material → Non-live vaccines
- Inactivated toxins

https://www.mayoclinic.org
https://www.cdc.gov/vaccines

Vaccine Overview







Pollard AJ et al. Nature Review Immunology 21,83-100 (2021)

Vaccine Overview

Live attenuated vaccines

- 2 doses
- Long-lasting protection
- Could cause infection in immunocompromised persons

Examples:

- Varicella, MMR
- Rotavirus
- Yellow fever, smallpox

Non-live vaccines

- 3 or more doses
- Protection fades over time; need booster doses

Examples:

- Hepatitis A&B, pneumococcal vaccines

https://www.cdc.gov/vaccines

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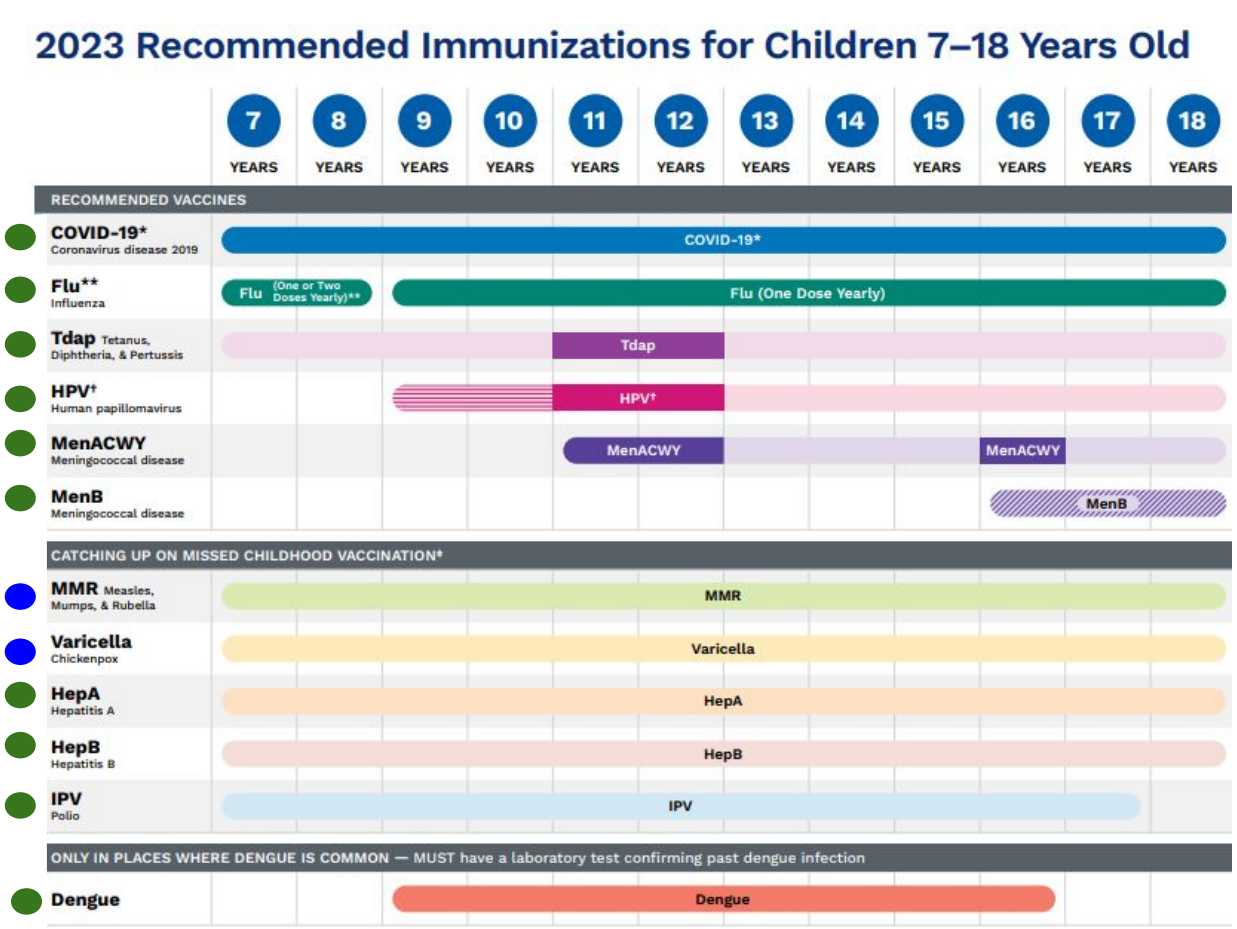
Advisory Committee on Immunization Practices (ACIP)

- Medical and Public Health experts
- 15 voting members + 30 non-voting representatives
- Provide advice and guidance to the Director of CDC

2023 Recommended Immunizations for Children from Birth Through 6 Years Old

primary series

https://www.cdc.gov/vaccines/parents/downloads/parent-ver-sch-0-6yrs.pdf



- Primary series
- Catch-up vaccines
- Booster vaccines
  - ➢ COVID-19
  - ➢ Hepatitis B
  - ➢ Tdap

https://www.cdc.gov/vaccines/schedules/downloads/teen/parent-version-schedule-7-18yrs.pdf

Additional Vaccine: Pneumococcal Vaccine

- Primary series= Pneumococcal conjugate vaccine (PCV)
- Additional= Pneumococcal polysaccharide (PPSV 23)
  - ➢ For 2 years and older
  - ➢ Booster dose after 5 years

Vaccines & Timing

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Advisory Committee on Immunization Practices (ACIP) Guidelines

	Non-live Vaccines	Live-attenuated Vaccines
Not on prednisone	• Safe • Concerned about the ***effectiveness*** of vaccines • The higher the immunosuppression, (probably) the lower the immune response	• Concerned about the ***safety*** of vaccines • Same rationale regarding effectiveness
Low dose prednisone		
High dose prednisone		
Other immunosuppressive medications		

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html

Vaccines & Timing

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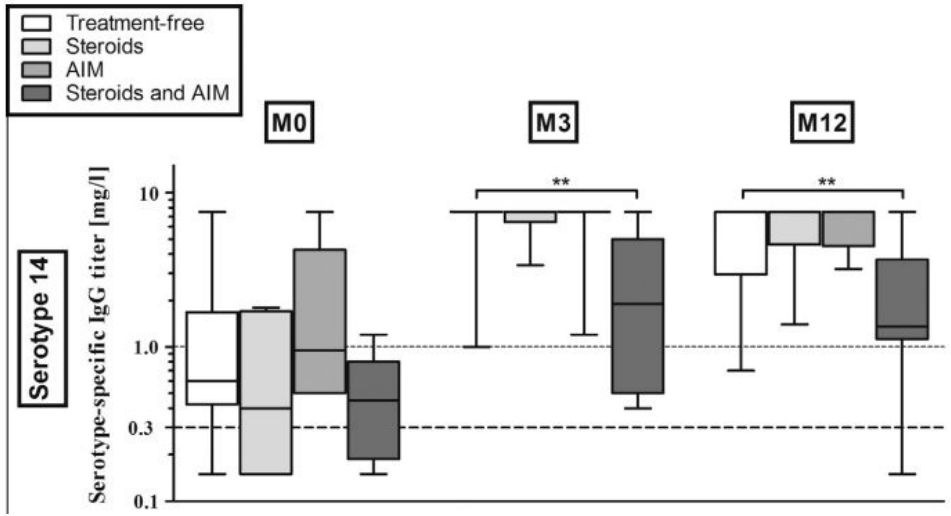
Advisory Committee on Immunization Practices (ACIP) Guidelines

	Non-live Vaccines (Safe. Effective?)	**Live-attenuated Vaccines** (Safe? Effective?)
Not on prednisone		

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html

Response of PCV-13 in Nephrotic Syndrome

- 42 children with nephrotic syndrome (median age 7.7 years)
- In remission□, prednisone□, alternate immunosuppression (AIM)■, prednisone + AIM■



- Achieved protective serotype specific IgG level
- Prednisone + AIM group achieved protective level but lower

← highly protective

← protective

Pittet LF et al. *Vaccine*, 2016 (34):4948-4954

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Vaccines and Concerns for Relapse

Vaccine Attitudes and COVID-19 Vaccine Intention Among Parents of Children With Kidney Disease Or Primary Hypertension

Methods

Atlanta, USA

Dec 2020-Oct 2021

207 Parents of children with kidney disease and primary hypertension surveyed

25 Parents with differing opinions further interviewed

Parental Vaccine Attitudes

Vaccinate child?

- 36% = YES
- 39% = UNSURE
- 25% = NO

Predicators:

- Hesitancy towards general childhood and influenza vaccines
- Lower parental education
- Black race

Influences on Vaccine Attitude

"What do the doctors think?"

- Doctors are trusted sources of info
- Inconsistent info from doctors lead to confusion and hesitancy
- Communication styles that disregard patient values and concerns negatively impact attitudes

Information is key

- Parents desire information specific to their child's kidney condition and health
- Concrete information on benefits vs harm may be important to provide

CONCLUSION: COVID-19 vaccine hesitancy is highly prevalent. Information relevant to kidney patients must be communicated in consistent, empathetic, and health-literacy appropriate manners.

Chia-shi Wang, Rinchen Doma, Adrianna L. Westbrook, et al

@AJKDonline | DOI: 10.1053/j.ajkd.2022.04.011

AJKD

Influenza Vaccination among Children with Nephrotic Syndrome

- **57 parents interviewed**
- **Only ¼ of the children were vaccinated against flu**
- **Concerns of parents:**
  - Safety of vaccine (39.5%)
  - Unaware it is recommended (37.2%)
  - Doctors told them not to vaccinate (11.6%)
  - Forgot (7%)

Klifa et al. BMC Nephrology. 2019

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Do vaccines cause relapses or make protein levels, kidney function worse?

What the Research Shows: Flu Vaccine

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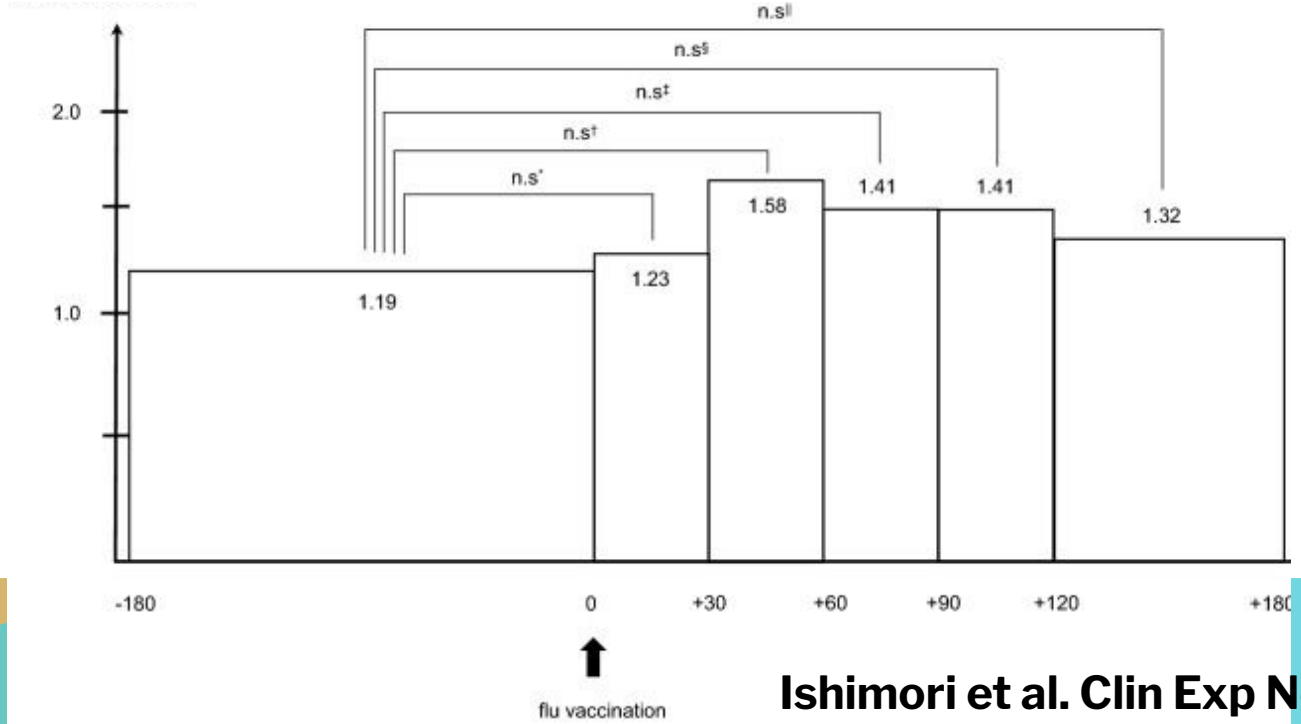
- **Out of 57 children:**
  - 3/42 unvaccinated children developed flu, 2 relapsed within days
  - 1/14 vaccinated children relapsed 2 weeks after vaccination

Klifa et al. BMC Nephrology. 2019

What the Research Shows: Flu Vaccine

- **In 104 children who received a total of 208 flu vaccines:**
  - No difference in relapse rate before or after vaccination



Ishimori et al. Clin Exp Nephrol. 2020

What the Research Shows: Flu Vaccine

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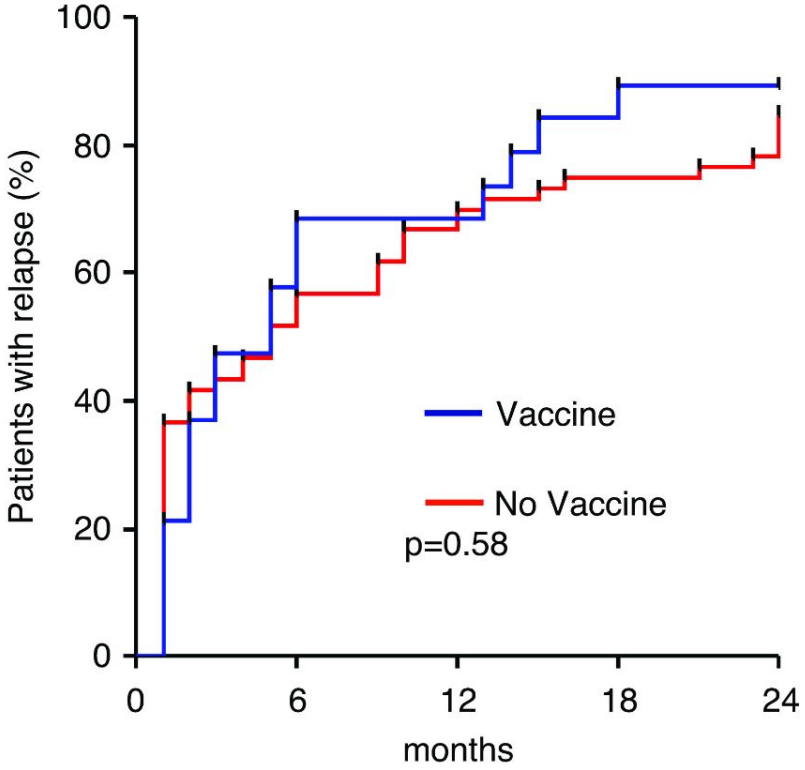
- **In 306 children:**
  - Only 102 children received the flu vaccine
    - 13% of vaccinated children got flu
    - 25% of unvaccinated children got flu
  - Vaccinated children have lower risk for flu (RR: 0.21, 95% CI 0.11-0.38)
  - Vaccinated children have lower risk for relapse
    - Compared to unvaccinated children (RR: 0.22, 95% CI 0.14-0.35)
    - Compared to themselves before vaccination (RR: 0.31, 95% CI 0.17-0.56)

Ishimori et al. Sci Rep. 2021

What the Research Shows: Flu + Others

- **In 140 children & young adults:**
  - 19 patients received flu, polio, meningococcal vaccines
  - No differences in relapse



Subject at Risk					
Vaccine	19	8	8	3	2
No Vaccine	61	29	20	16	13

Angeletti. Clin J Am Soc Nephrol. 2021

What the Research Shows: COVID

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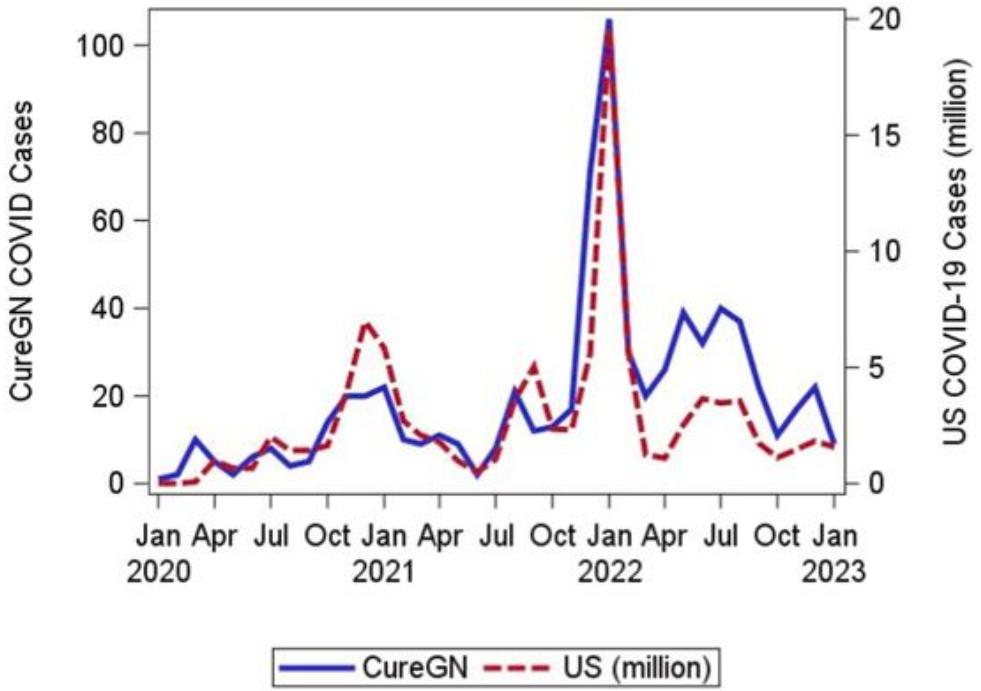
- In Hong Kong, newly diagnosed glomerular disease was tracked and there was no increase in rate of diagnosis after vaccines

- In Canada, there was no increase in relapse among 1,105 patients with glomerular disease after first dose
  - There was an association of increased risk of relapse after the second dose (not controlled)
  - Of the 24 patients who relapsed, 4 required a change in medication, none required a biopsy

Cheng et al. Nephrol Dial Transplant. 2023
Canney et al. J Am Soc Nephrol. 2022

What the Research Shows: COVID

- **Among 2,055 adults and children with nephrotic syndrome**
  - 722 (35%) were infected with COVID
    - 92 (13%) were hospitalized
    - 3 (<1%) died
  - 1,407 (68%) received at least one dose of vaccine



Wang et al. Am J Kidney Dis. 2023

What the Research Shows: COVID

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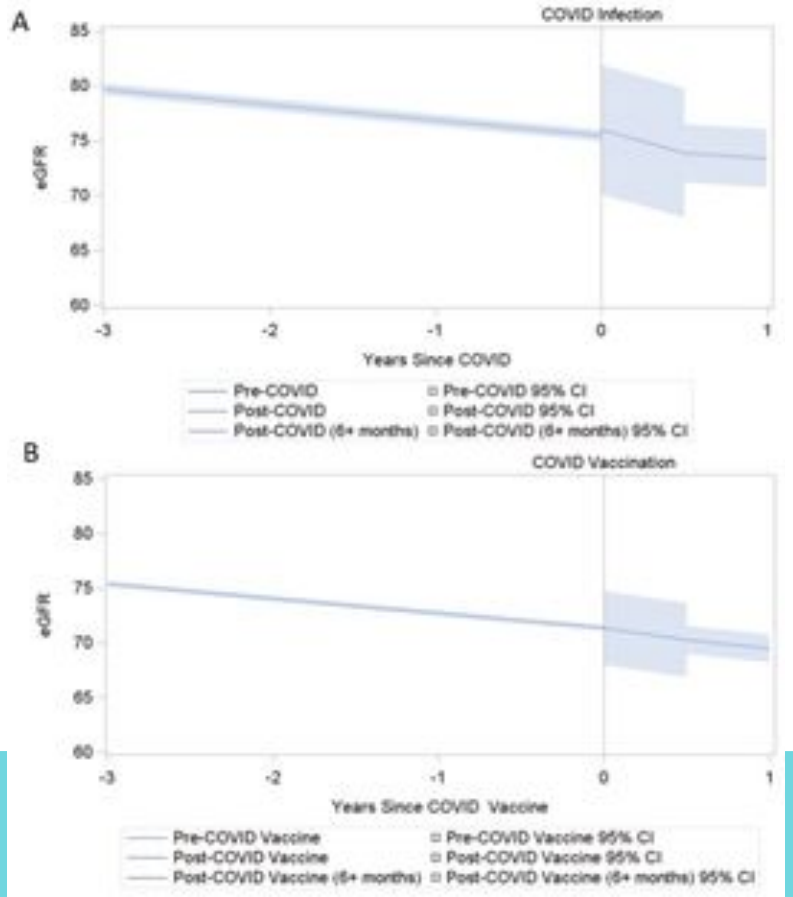
- Vaccination did not affect kidney function
- COVID infection was associated with a 35% increase in risk of worsening proteinuria (HR 1.35, 95% CI 1.01-1.80)
- Vaccination was not associated with worsening proteinuria (HR 1.02, 95% CI 0.79-1.33)



Wang et al. Am J Kidney Dis. 2023

How Immunosuppressed am I?

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High-level

Receiving Immunosuppressive Medications

-mycophenolate, cyclosporine, tacrolimus, rituximab

-daily steroids >20 mg / day or >=2 mg/kg/day for > 14 days

-(especially when taken in combination)

Concern that “Active” Nephrotic Syndrome (i.e. in relapse) may also impair response to vaccination

How Immunosuppressed am I?

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Low-level

Receiving Immunosuppressive Medications (i.e. “low dose”)

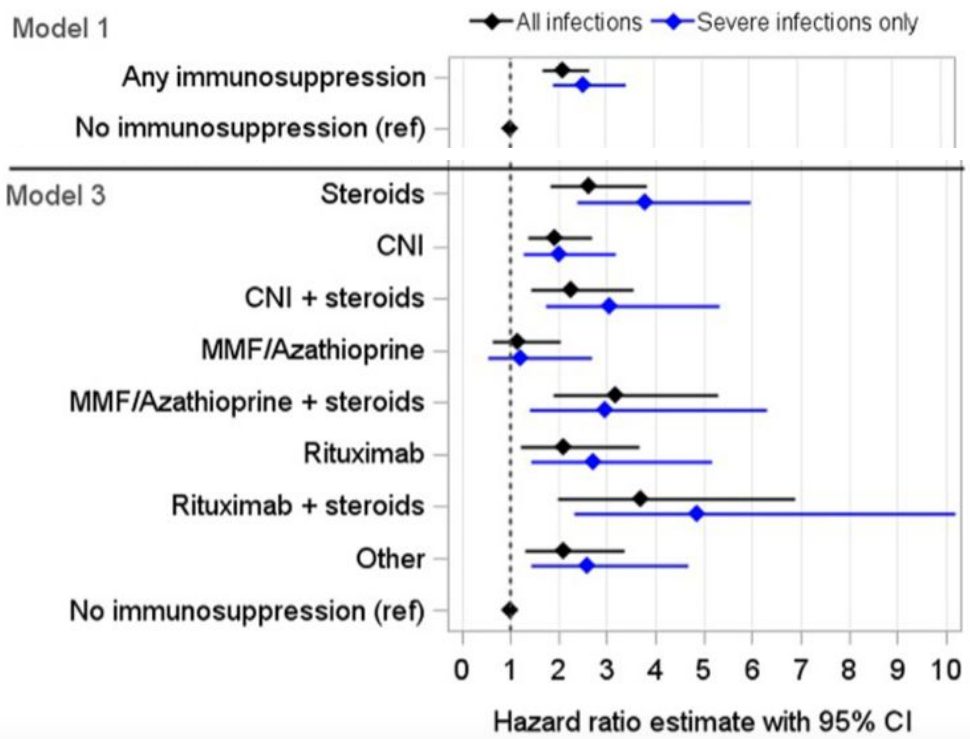
- alternate day steroids or daily steroids < 20 mg/day, or short duration < 14 days

Table 3. Immunosuppression Exposure Over Follow-up,[a] Percent Follow-up Time[b]

	Total (N = 2,388)
Follow-up time (y), median (IQR)	3.2 (1.6-4.6)
0 medications	69.0%
1 medication	
Steroids only	5.1%
CNI only	9.1%
MMF only	3.9%
Rituximab only	2.7%
Azathioprine only	0.7%
Cyclophosphamide only	0.1%
2 medications	
Steroids + CNI	3.5%
Steroids + MMF	1.4%
Steroids + rituximab	1.0%
Steroids + cyclophosphamide	0.3%
Other 2 drug combinations	1.9%
3 medications	
Steroids + CNI + rituximab	0.4%
Steroids + CNI + MMF	0.4%
Other 3 drug combinations	0.3%
4 drug combinations	0.1%

(Glenn, Kidney Medicine, 2022)

Infection Risk and Immunosuppression



(Glenn, Kidney Medicine, 2022)

Table 6. Vaccination of Persons With Chronic Inflammatory Diseases on Immunosuppressive Medications

Vaccine	Planned Immunosuppression		Low-level Immunosuppression[a]		High-level Immunosuppression[a]	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
Haemophilus influenzae b conjugate	U	Strong, moderate	U	Strong, low	U	Strong, low
Hepatitis A	U	Strong, moderate	U	Strong, low	U	Strong, low
Hepatitis B	U	Strong, moderate	U	Strong, low	U	Strong, low
Diphtheria toxoid, tetanus toxoid, acellular pertussis; tetanus toxoid, reduced diphtheria toxoid; tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U	Strong, moderate	U	Strong, low	U	Strong, low
Human papillomavirus	U: 11–26 y	Strong, moderate	U: 11–26 y	Strong, low	U: 11–26 y	Strong, very low
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, moderate	U	Strong, moderate	U	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, very low	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–live	U[b]	Strong, moderate	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–varicella–live	U[b]	Strong, low	X	Weak, very low	X	Strong, very low
Meningococcal conjugate	U	Strong, moderate	U	Strong, moderate	U	Strong, low
Pneumococcal conjugate (PCV13)	R[c]	Strong, moderate	U: <6 y R: ≥6 y[c]	Strong, low strong, very low	U: <6 y R: ≥6 y[c]	Strong, low strong, very low
Pneumococcal polysaccharide (PPSV23)	R: age ≥2 y	Strong, low	R: age ≥2 y	Strong, low	R: age ≥2 y	Strong, very low
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong, moderate	U	Strong, moderate	U	Strong, low
Rotavirus–live	U	Strong, moderate	X	Weak, very low	X	Weak, very low
Varicella–live	U[b]	Strong, moderate	X[d]	Weak, very low	X	Strong, moderate
Zoster–live	R: age 50–59 y[e] U: age ≥60 y	Weak, low strong, low	R: age 50–59 y[e] U: age ≥60 y	Weak, very low Strong, very low	X	Weak, very low

Timing of Vaccination

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IDSA Recommendations

- Inactivated vaccines > 2 weeks before immunosuppression begins
- Live Vaccines > 4 weeks before immunosuppression begins
- No clear recommendation when to vaccinate effectively after end of immunosuppressive therapy
  - reasonable to wait 4 weeks after high dose steroids
  - > 6 months for rituximab
- If easily managed disease with periods off immunosuppression, consider timing vaccines when in disease remission
- If difficult to control disease, consider vaccination when on lower dose immunosuppression
- Discuss risks and benefits with your nephrologist

What about the Flu Shot?

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- Annual Inactivated Influenza Vaccine (IIV) is recommended for immunocompromised individuals > 6 months of age
  - (not live-attenuated influenza vaccine)
- Likelihood of a protective antibody response on high-dose steroids or rituximab is unclear

Risk Factors for Poor Vaccine Response

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- Higher “total” immunosuppression - potentially lower vaccine response
- Rituximab worse than MMF worse than azathioprine
- Vaccination on low dose steroids or alternate day probably better than daily / high dose steroids
- Possibility that being actively nephrotic *(i.e. high levels of proteinuria) may impair vaccine response
    - unclear if vaccination during remission is more effective
    - some evidence for pneumococcal vaccination (PPSV23) effectiveness while under immunosuppression
    - need to way the risks of delaying vaccination

When to get the Flu vaccine to maximize protection

Takes ~ 2 weeks after getting vaccinated to be fully protected

CDC recommends flu vaccination in Sep/Oct

Some people get vaccinated in July / August- typically not recommended if you can wait for the annual vaccine to be available

Protection is then highest, and declines each month

Risk of Flu infection from time of vaccination

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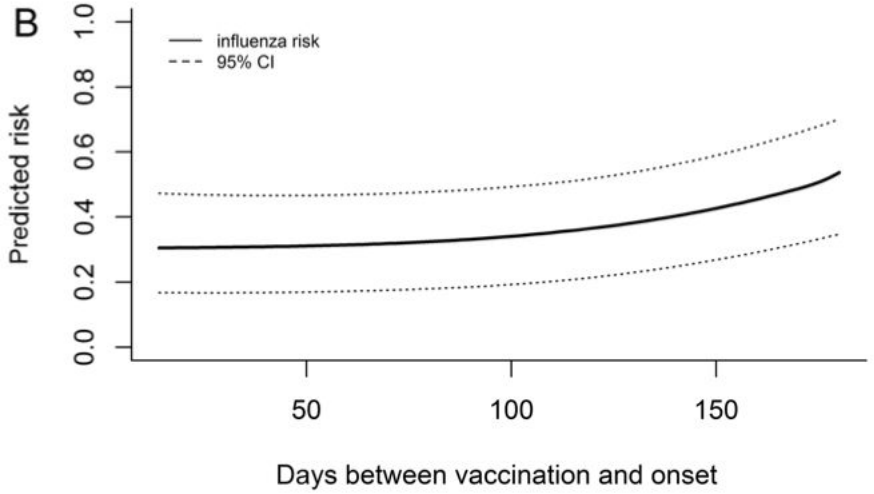
Data from 2011-2015

N=8,201 individuals from gen pop.

Decline in flu vaccine effectiveness of 7-11% per month

Effectiveness close to 0 by 5-6 months post vaccination

Possibly less effective in patients with glomerular disease



Flu seasons 2010-2019

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Influenza Season	Start Date*	End Date*
2010-11	11/24/2010	4/13/2011
2011-12	2/1/2012	6/6/2012
2012-13	11/7/2012	4/10/2013
2013-14	11/27/2013	5/21/2014
2014-15	11/12/2014	4/8/2015
2015-16	2/4/2016	4/24/2016
2016-17	12/14/2016	4/19/2017
2017-18	12/6/2017	4/18/2018
2018-19	12/12/2018	4/17/2019

What about live vaccines?

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- MMR, rotavirus, varicela, yellow fever, oral typhoid, BCG, live attenuated influenza vaccine
- 8 studies, most case reports or observational studies, 1 prospective clinical trial in 29 children who received varicella vaccine on corticosteroids (Furth et al, 2003). Found to be safe / effective - no relapses or adverse events reported
- Overall, evidence is lacking - therefore, live vaccines generally not recommended for immunosuppressed patients
- Discuss risk / benefits with your providers

HPV Vaccine

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- Cause cervical cancer and anogenital warts
- Risk is increased in later stages of CKD and after kidney transplantation
  - For kidney transplant recipients, there is a 3-6 times risk for cervical cancer, 10 times risk for anal cancel, and a 31-100 times risk for cancer of the vulva.
  - Incidence of HPV-associated cancers in patients on dialysis is 16 times higher than the general population
- Study of HPV response from 2008 to 2012
- 57 girls aged 9–21 years old with CKD (*n*=25), on dialysis (*n*=9)
- Response was excellent in all CKD and dialysis patients, but lower (~60%) for transplant patients

Meeuwis. Am J of Transplant. 2015
Han. J of Investigative Med. 2020

Duration of immunity

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- Varies by vaccine
  - measles and varicella considered lifelong
  - mumps wanes for everyone
  - flu and COVID mutate quickly and antibody wanes quickly so seasonal revaccination with new strains necessary to maintain protection
- Some boosters are recommended specifically for NS
  - PPSV23 - adult pneumococcal vaccine
    - NS higher risk of infection by encapsulated organisms
  - HBV if low titers and starting rituximab

What about travel?

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- Often there are vaccines recommended prior to international travel which are not part of the normal childhood vaccine schedule
  - These depend on destination country
- Recommend discussing which additional vaccines may be indicated with your local ID or travel medicine clinic
  - Often salmonella vaccine is recommended
    - Salmonella is an encapsulated organism (higher risk for NS) and is one of the leading causes of fever in the returning traveler
    - There are both live attenuated and inactivated salmonella vaccines available, NS patients should receive the inactivated vaccine if indicated

Vaccinating Household Contacts

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Critically important to provide a "cocoon" of protection

- Household contacts can safely receive inactivated vaccines
- Healthy immunocompetent household contacts can also receive live attenuated vaccines
  - MMR, rotavirus, varicella, zoster, others
  - Note- immunocompromised persons should avoid changing diapers for infants 4 weeks after rotavirus vaccine and avoid any skin lesions following varicella vaccination
  - Shedding risk from vaccinated classmates household contacts is very low

Exposure to active disease

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Contact your doctor as soon as you know there has been an exposure

- Risk will depend on the nature of the exposure
  - e.g. >5 minutes indoor face to face play with someone later diagnosed with chicken pox vs had lunch with grandparent with shingles who kept lesions covered
- There are medications we can give to lower risk of severe infection when we know about an exposure early enough
- Exposed child may also need to isolate

How to bring up concerns around vaccination with my nephrologist?

- Don’t wait until the very end of your visit to discuss vaccines
  - Ok to start the visit with an agenda
- If possible, have questions and concerns formulated ahead of time, ok to write them down or send them via EMR before your visit
  - e.g. “What is my chance of responding to this vaccine?” or “What is my risk of getting the disease after vaccination?”
- Be ok with uncertainty when “best” evidence is lacking
- Frame the discussion using risk vs. benefit and risk of delay

Trusted Sources and References

- (Review paper) Vaccines and nephrotic syndrome: efficacy and safety, Pediatr Nephrol. 2022 Dec 13 : 1–14.
- (guideline) 2013 Infectious Disease Society of America Clinical Practice Guideline for Vaccination of the Immunocompromised Host
- Websites of CDC, ACIP, AAP, NKF, ASN, ASPN

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Q & A

Closing & Wrap-Up

- Thank you!

- Upcoming Opportunities:
  - NSF **Backpacks of Hope** - *Now taking last minute applications*

  - NSF **Peer CONNECTIONS** Event - “Fall Fun”
    - Saturday, October 14th @ 10am PST

  - **Camp NSF 2023**
    - Saturday, November 18 - Monday, November 20

Closing & Wrap-Up

- Feedback and suggestions welcome - email us!
  dana@nephroticsyndromefoundation.org
  or andi@nephroticsyndromefoundation.org

- Requests or suggestions for future Finding Health topics?

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Thank you for being here!
Your involvement & participation helps all of us!