

Update on Vaccines in Long Term Care

Michelle C. Crank, MD
Institute for Asthma & Allergy

MD DHCC ONLINE FALL WORKSHOP

October 17, 2023

Disclaimers

- Federal employee for 10 years at NIH, NIAID with 5 years at the Vaccine Research Center
- No patents, no speaker or consulting fees
- Currently a partner in a private practice for Allergy & Immunology
- Drug companies occasionally bring (variably nutritious) lunches to our office
- My only compensation for use of any vaccine upon which I have worked is the satisfaction that I have helped a fellow human being and/or stamped out disease

NIAID Vaccine Research Center

Commencement Address by President Clinton at Morgan State University, Baltimore, May 18, 1997

"If America commits to find an AIDS vaccine and we enlist others in our cause, we will do it... Today I'm pleased to announce the National Institutes of Health will establish a new AIDS vaccine research center dedicated to this crusade."



Basic Research



Process Development



- AIDS/HIV
- Influenza
- Ebola/Marburg
- RSV
- Malaria
- Tuberculosis
- EID

- West Nile virus, Zika
- Chikungunya
- W/E/V equine encephalitis viruses
- MERS-CoV, SARS, and other CoV
- Nipah and other paramyxoviruses
- EV-D68 and other picornaviruses
- Smallpox



GLP Analysis



Clinical Trials



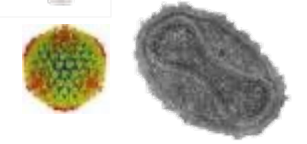
cGMP Manufacturing



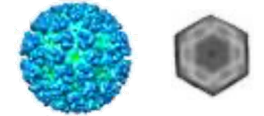
Nucleic acid



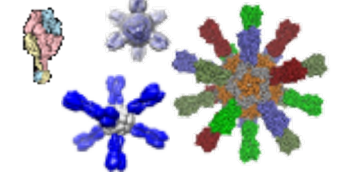
Vectors



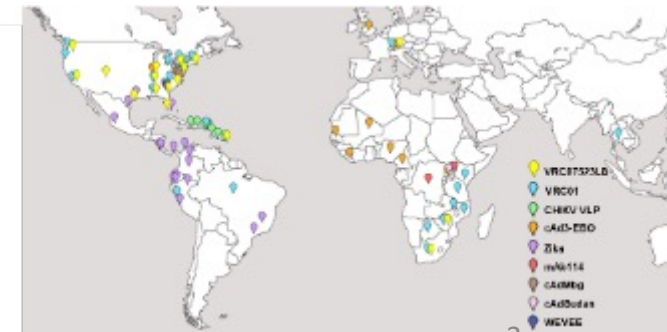
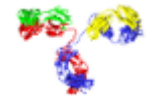
VLPs



Proteins and nanoparticles



Monoclonal antibodies



Outline

- Recent updates to CDC vaccine recommendations for older adults
- Development of RSV vaccines
- Current influenza vaccines & development of universal flu vaccines
- Nutrition and immunity to infections and vaccines

Outline

- **Recent updates to CDC vaccine recommendations for older adults**
- Development of RSV vaccines
- Current influenza vaccines & development of universal flu vaccines
- Nutrition and immunity to infections and vaccines

CDC Vaccine Schedule for Adults

Table 1 See Addendum for new or updated ACIP vaccine recommendations
Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2023

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
COVID-19	2- or 3- dose primary series and booster (See Notes)			
Influenza inactivated (IIV4) or Influenza recombinant (RIV4)	1 dose annually			
Influenza live, attenuated (LAIV4)	1 dose annually			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			For healthcare personnel, see notes
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (see notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PPSV23)	1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)			See Notes
				See Notes
Hepatitis A (HepA)	2, 3, or 4 doses depending on vaccine			
Hepatitis B (HepB)	2, 3, or 4 doses depending on vaccine or condition			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication			

 Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
 Recommended vaccination for adults with an additional risk factor or another indication
 Recommended vaccination based on shared clinical decision-making
 No recommendation/Not applicable

Updates: CDC Vaccine Schedule for Adults

- Influenza
 - **Age 65 years or older:** Any one of quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4) is preferred. If none of these three vaccines is available, then any other age-appropriate influenza vaccine should be used.
 - All persons ages ≥ 6 months with egg allergy should receive influenza vaccine. Any influenza vaccine (egg based or non-egg based) that is otherwise appropriate for the recipient's age and health status can be used.
- COVID-19 (Moderna, Pfizer-BioNTech)
 - All persons ≥ 6 months of age should receive 2023–2024 (monovalent, XBB containing) COVID-19 vaccines as authorized under EUA or approved by BLA.
 - Bivalent mRNA COVID-19 vaccines are no longer recommended in the United States

Updates: CDC Vaccine Schedule for Adults

- Pneumococcal vaccines:
 - **Age 65 years or older who have:**
 - **Not previously received a dose of PCV13, PCV15, or PCV20 or whose previous vaccination history is unknown:** 1 dose PCV15 OR 1 dose PCV20. If PCV15 is used, this should be followed by a dose of PPSV23 given at least 1 year after the PCV15 dose.
 - A minimum interval of 8 weeks between PCV15 and PPSV23 can be considered for adults with an immunocompromising condition,* cochlear implant, or cerebrospinal fluid leak to minimize the risk of invasive pneumococcal disease caused by serotypes unique to PPSV23 in these vulnerable groups.

For guidance on determining which pneumococcal vaccines a patient needs and when, please refer to the mobile app which can be downloaded here: www.cdc.gov/vaccines/vpd/pneumo/hcp/pneumoapp.html

- Shingles:
 - **Age 50 years or older*:** 2-dose series recombinant zoster vaccine (RZV, Shingrix) 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon), regardless of previous herpes zoster or history of zoster vaccine live (ZVL, Zostavax) vaccination.
- Tetanus +diphtheria & pertussis
 - Tdap every 10 years

RSV Vaccine for Adults Age 60+

- May 2023 FDA approved the first vaccines for prevention of RSV-associated lower respiratory tract disease in adults aged ≥ 60 years.
- June 21, 2023, ACIP voted to recommend that adults aged ≥ 60 years may receive a single dose of an RSV vaccine, using shared clinical decision-making.
 - RSVPreF3 (Arexvy, GSK): 1-dose (0.5 mL) adjuvanted (AS01E) recombinant stabilized pre- fusion F protein (preF) vaccine
 - RSVpreF (Abrysvo, Pfizer): 1-dose (0.5 mL) recombinant stabilized preF vaccine

Outline

- Recent updates to CDC vaccine recommendations for older adults
- **Development of RSV vaccines**
- Current influenza vaccines & development of universal flu vaccines
- Nutrition and immunity to infections and vaccines

RSV Disease Burden in Adults

- Seasonal epidemics: winter in the Northern Hemisphere
- Significant morbidity & mortality in adults ≥ 65 years of age
 - Lower Respiratory Tract Disease (LRTD), hospitalization & death
 - 60,000-160,000 hospitalizations annually
 - 6,000-10,000 deaths annually
 - Adults with certain medical conditions or who are residents of long-term care facilities are at high risk of hospitalization

RSV Vaccinology and the Legacy of FI-RSV

Immunizations 1965-1966; Infections Winter of 1966-1967

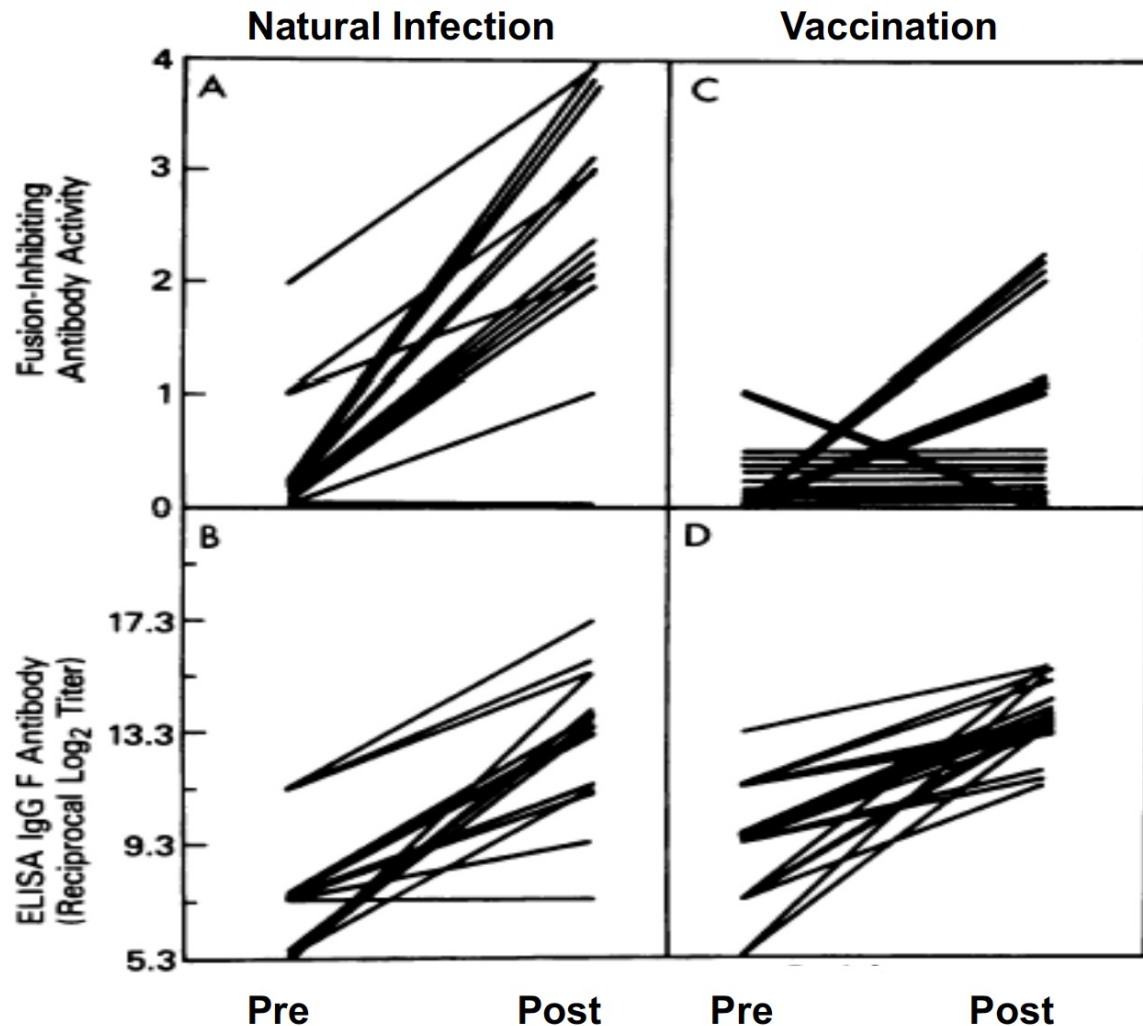
Vaccine	n*	Infected (%)	Hospitalized (%)**	Deaths***
FI- RSV	31	20 (65)	16 (80)	2
FI-PIV-1	40	21 (53)	1 (5)	0

* 1 injection (n=2); 2 injections (n=8); 3 injections (n=21)

** In unpublished 1962/3 trial - 21/54 infected; 10/21 hospitalized

*** 14 and 16 mo. of age; 3 injections starting at 2 and 5 mo. of age.
Both had bacterial pneumonia complicating RSV

FI-RSV: Quantity vs. Quality of Antibody Response



**Fusion
Inhibition**

Dissociation between serum neutralizing and glycoprotein antibody responses of infants and children who received inactivated respiratory syncytial virus vaccine.

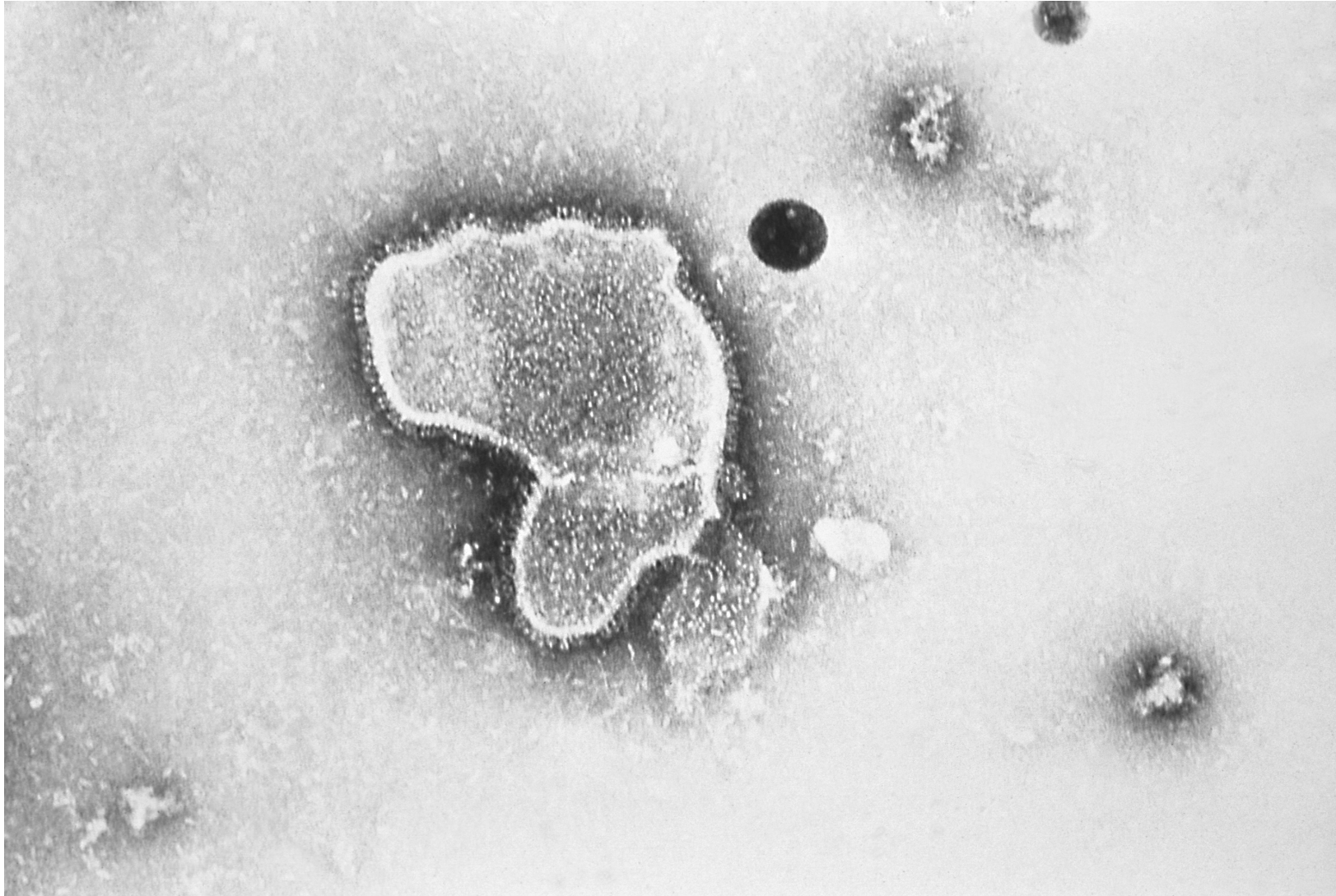
Murphy, Walsh et al JCM 1986; 24:197.

ELISA

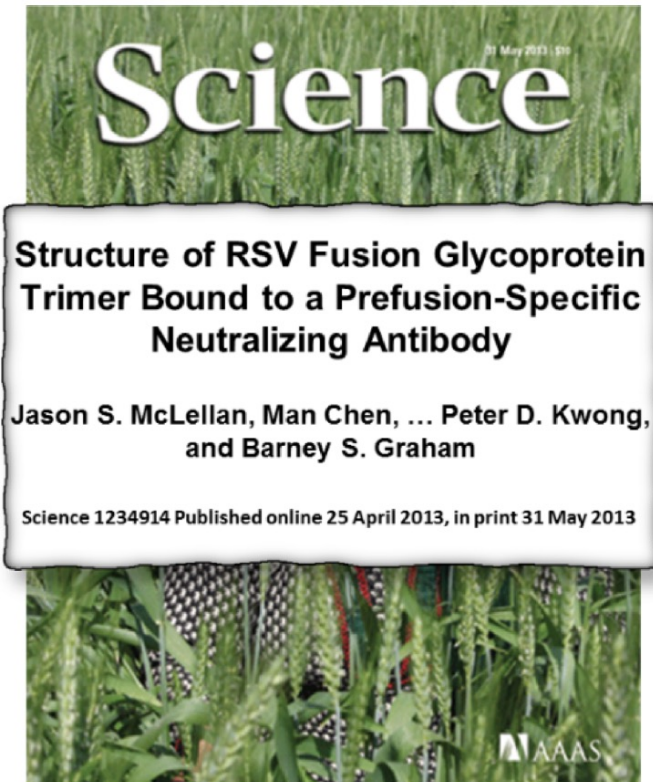
Formalin-inactivated respiratory syncytial virus vaccine induces antibodies to the fusion glycoprotein that are deficient in fusion-inhibiting activity.

Murphy, Walsh et al JCM 1988; 26:1595

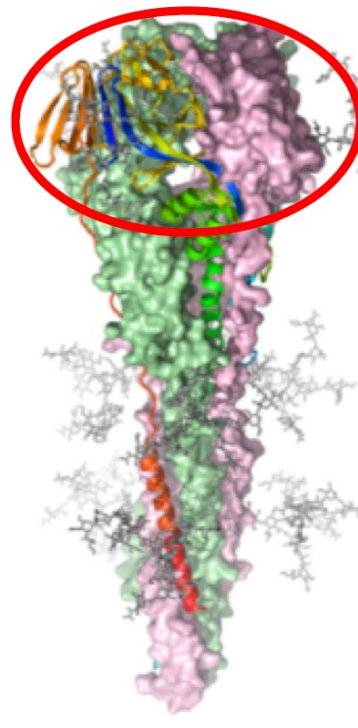
RSV Virus Structure



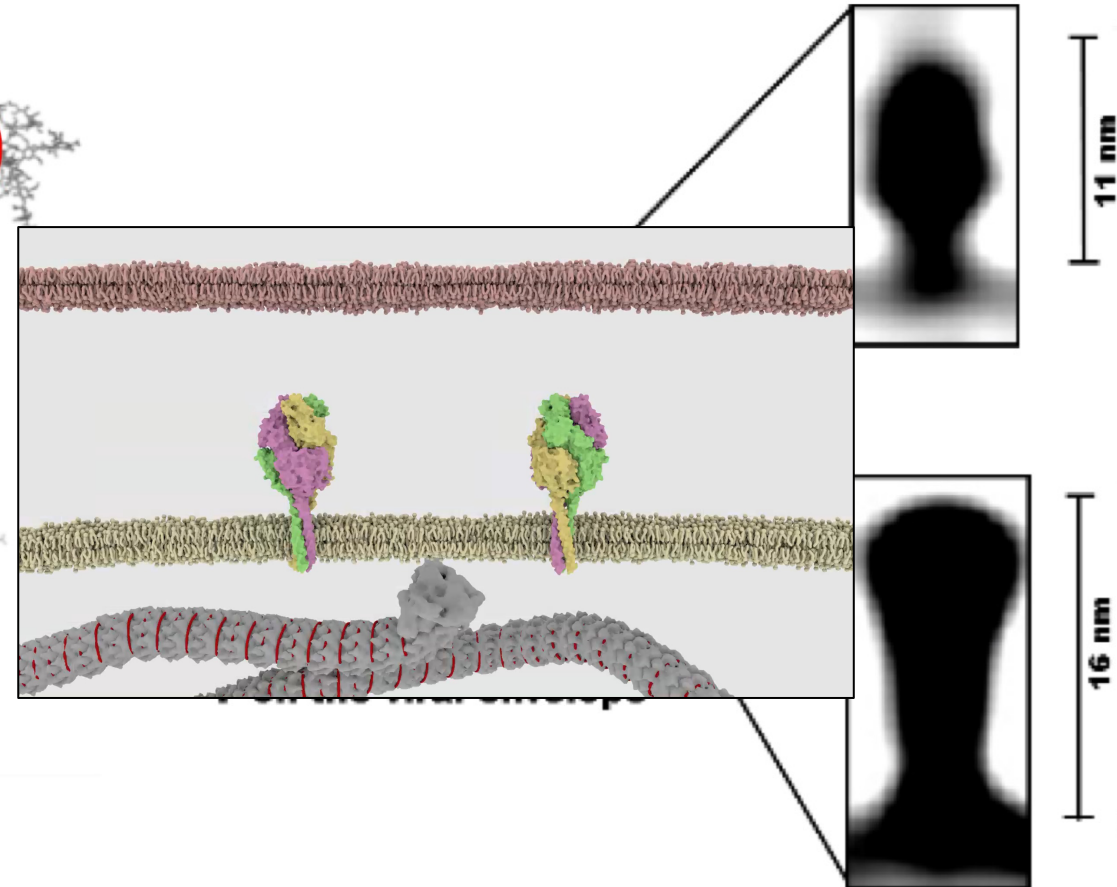
Structure of Prefusion F Glycoprotein



Prefusion

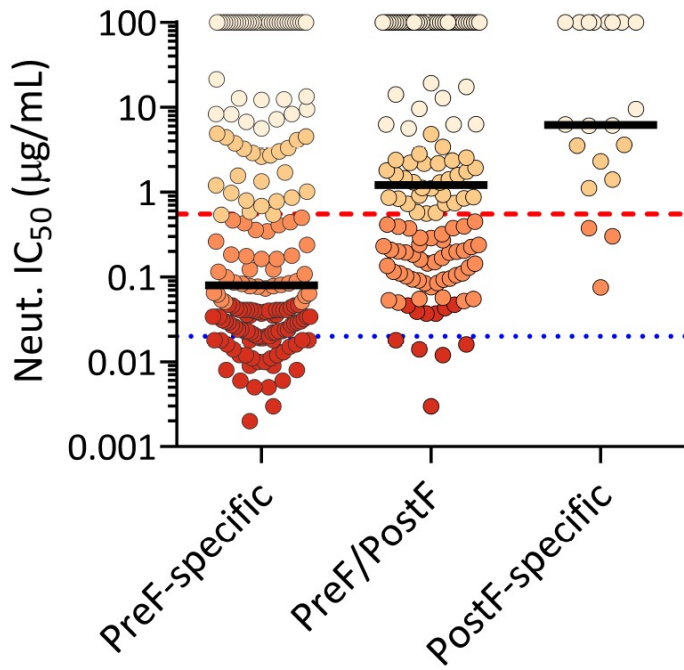


Postfusion



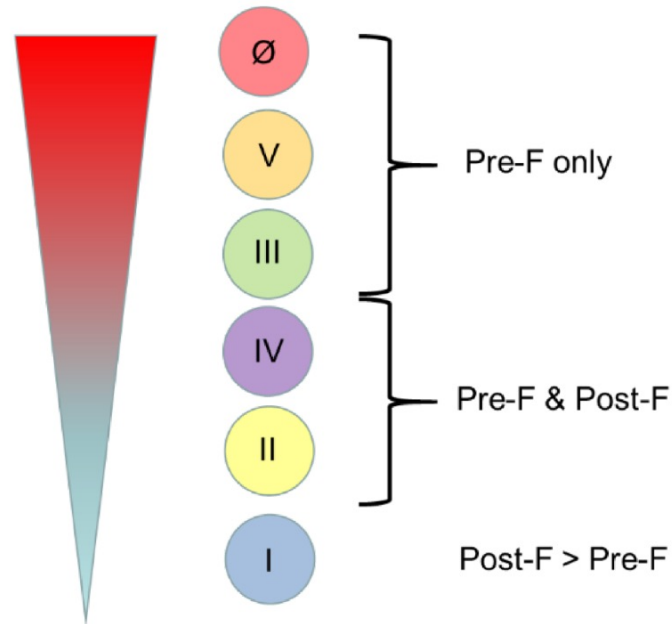
Immunogenicity is Epitope and Conformation Dependent

- High potency ($\leq 0.05 \mu\text{g/mL}$)
- Medium potency (> 0.05 to $0.5 \mu\text{g/mL}$)
- Low potency (> 0.5 to $5 \mu\text{g/mL}$)
- Weak/non-neutralizing ($> 5.0 \mu\text{g/mL}$)

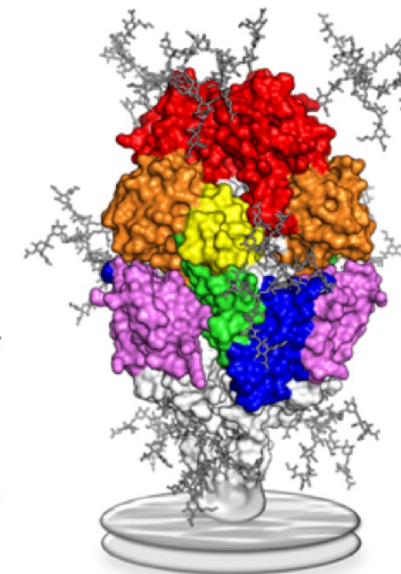


Neutralizing Potency

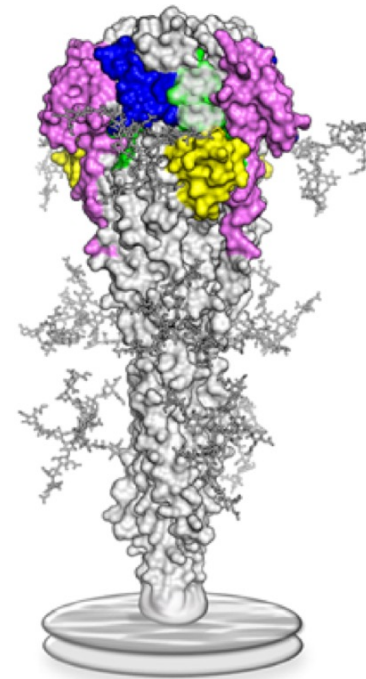
Location



Prefusion RSV F

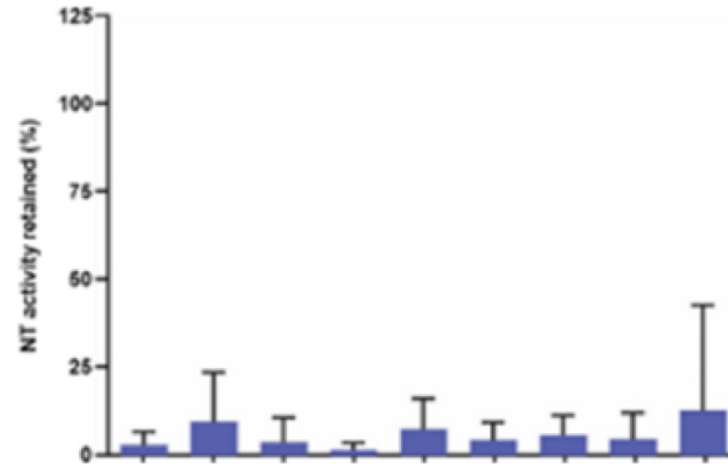
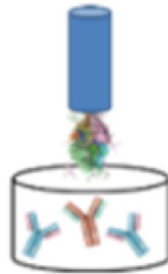


Postfusion RSV F

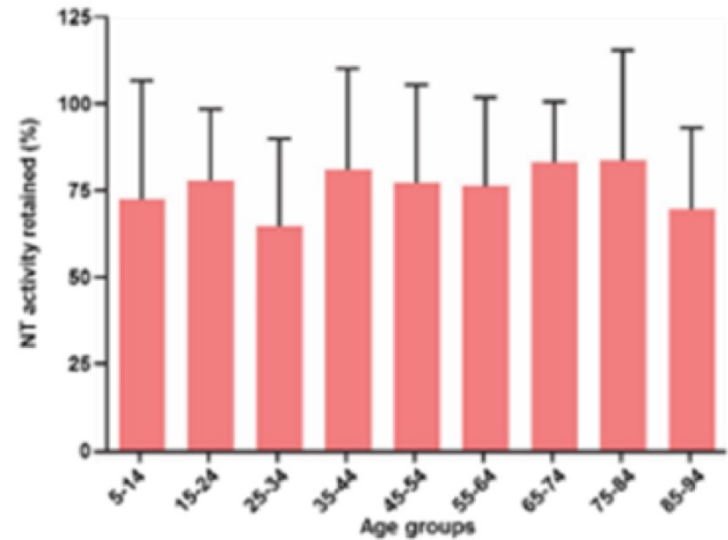
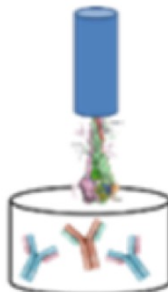


- Site Ø
- Site I
- Site II
- Site III
- Site IV
- Site V

Human Sera Show Epitope-Specific Neutralization



Pre-F
removes
most NT
activity



Post-F
removes a
small fraction
of NT activity

VRC 317 Trial Schema

VRC 317 Study Schema				
Group	Subjects	Dose	Day 0	Week 12
1	15	50 mcg	DS-Cav1	DS-Cav1
2	15		DS-Cav1 + alum	DS-Cav1 + alum
3	20	150 mcg	DS-Cav1	DS-Cav1
4	15		DS-Cav1 + alum	DS-Cav1 + alum
5	15	500 mcg	DS-Cav1	DS-Cav1
6	15		DS-Cav1 + alum	DS-Cav1 + alum
Total	95*	All DS-Cav1 vaccinations are administered with needle and syringe into the deltoid muscle. *Up to 100 subjects may be enrolled if needed to evaluate safety or immunogenicity.		



First Enrollment Feb 21,
2017

After an interim analysis demonstrated significant titers with 1 dose of DS-Cav1, the trial protocol was amended to allow for patients to opt out of their second dose.

RSV Neutralizing Activity Post DS-Cav1 Vaccination

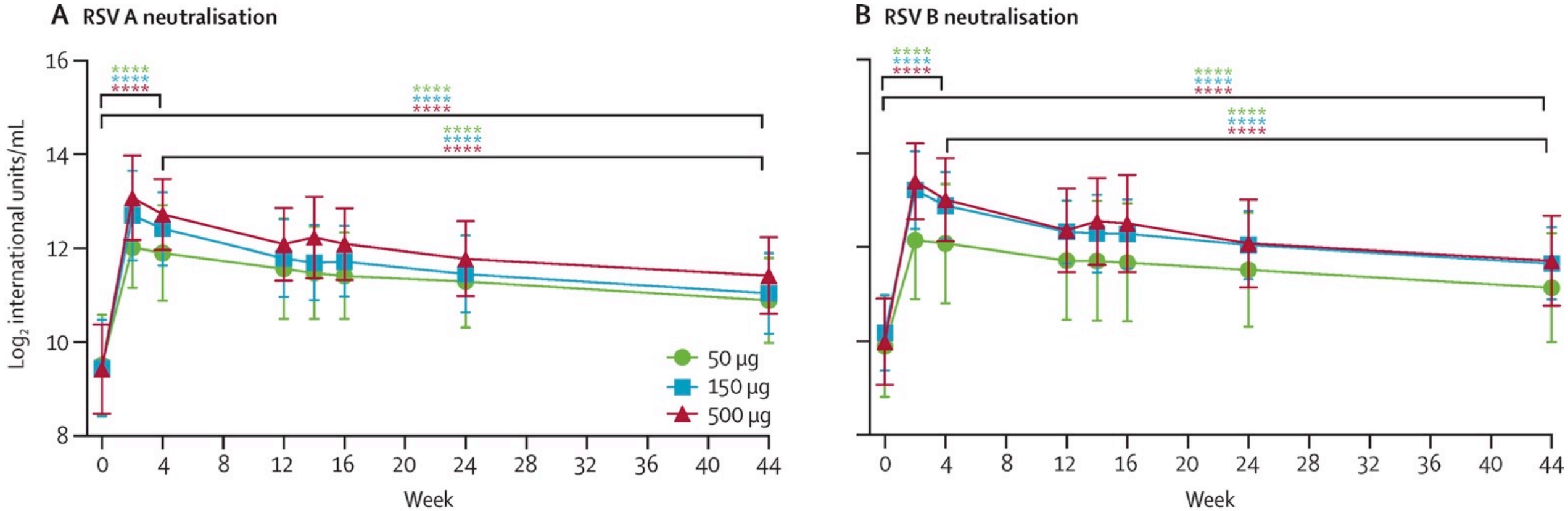


Figure 2

A and B show neutralizing activity in the serum against a reporter RSV A2 virus (RSV A) and RSV B18537 virus (RSV B), respectively at weeks 0, 2, 4, 12, 14, 16, 24, and 44 for participants immunized with 50 µg, 150 µg, or 500 µg of DS-Cav1 (adjuvanted and unadjuvanted groups combined for each dose). Significance determined using Student's t test to compare log fold-change (at specific timepoints) without adjustment for multiple comparisons. Symbols (A, B) represent the mean, and error bars represent the SD. Significance indicated as ****p<0.0001, ***p<0.001, **p<0.01, and *p<0.05.

Efficacy of Approved RSV Vaccines Over 2 Seasons

- GSK (Arexvy) 0.5mL single dose with AS01_E adjuvant
 - 75% in preventing LRTD
 - 78% in preventing medically-attended LRTD
- Pfizer (Abrysvo) 0.5mL single dose without adjuvant
 - 84% in preventing LRTD
 - 81% in preventing medically-attended LRTD

Safety of Approved RSV Vaccines

- GSK (Arexvy) & Pfizer (Abrysvo) were similar
 - Similar reactogenicity & adverse events between vaccine & placebo
 - 3 cases of inflammatory neurologic events with each product
 - Guillain Barre Syndrome, Acute Disseminated Encephalomyelitis
 - Greater number of reports of atrial fibrillation in vaccine vs. placebo
 - Many were in participants with a history of afib

Vaccinate After “Shared Decision Making”

- Patients with chronic medical conditions including:
 - Lung disease
 - Cardiovascular disease
 - Diabetes mellitus
 - Immune suppression (from medications or immune deficiency)
 - Kidney disorders
 - Liver disorders
 - Hematologic disorders
- Frail
- Advanced age
- **Residents of nursing homes or other long-term care facilities**

Summary: RSV

- Stabilized RSV pre-F candidate trimeric subunit vaccine (DS-Cav1) provides a **clinical proof-of-concept for structure-based vaccine** design
- DS-Cav1 subunit vaccine was **safe and well tolerated**
- One vaccination was capable of eliciting a **robust increase in neutralizing activity** that exceeds the increase seen after RSV infection in people in a similar age category
- GSK and Pfizer now each have an approved vaccine for adults aged 60 years and older based upon DS-Cav1 and this vaccine is recommended for older adults with medical problems or living in long-term care facilities with shared decision making

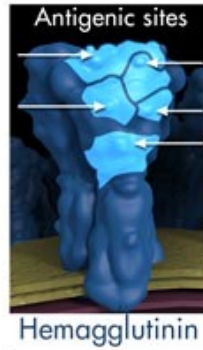
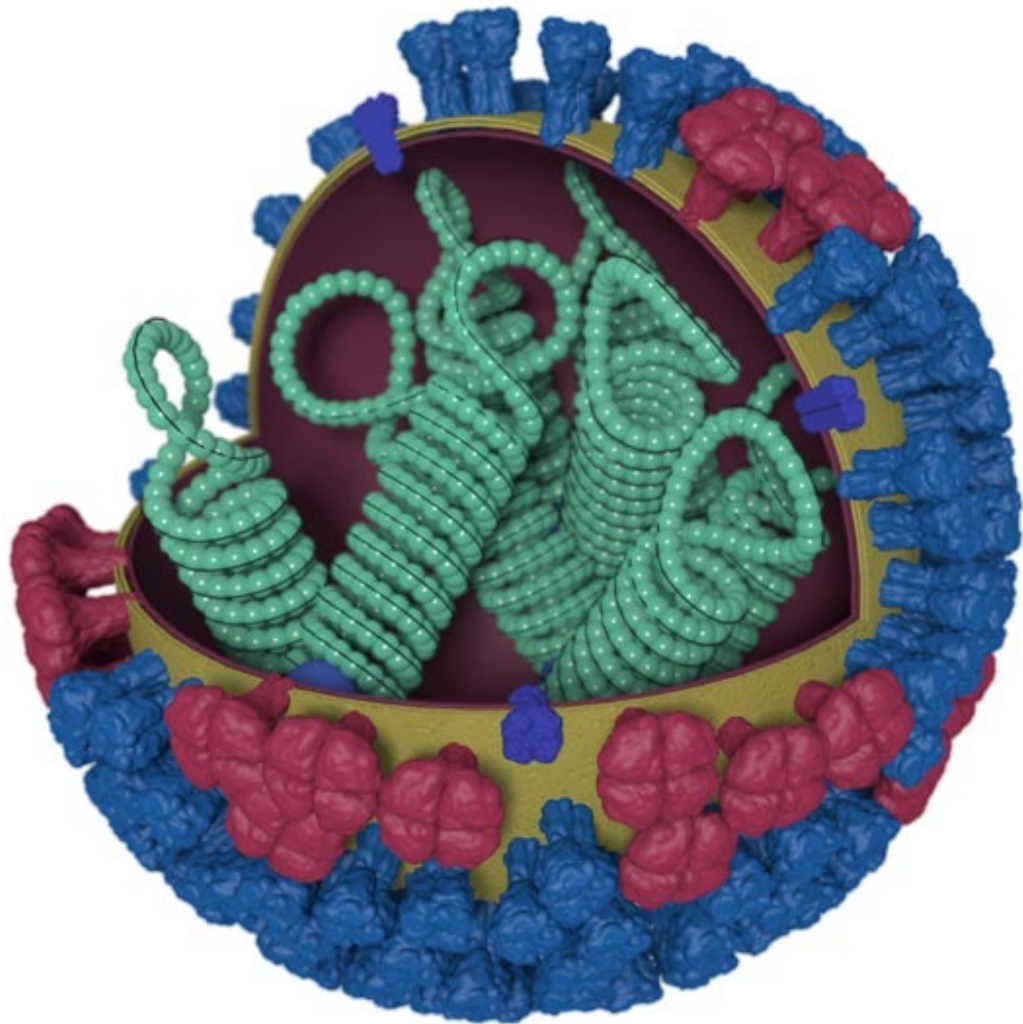
Outline

- Recent updates to CDC vaccine recommendations for older adults
- Development of RSV vaccines
- **Current influenza vaccines & development of universal flu vaccines**
- Nutrition and immunity to infections and vaccines

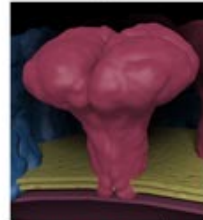
Global Burden of Influenza

- 3-5 million annual cases of severe illness globally
- 2017-18 cases in U.S. similar to 2009 pandemic year (~7.7%)
- 290,000 to 650,000 annual deaths globally
- HIC - most influenza deaths occur in elderly
- Conventional vaccine has marginal efficacy
- LMIC – higher overall severity of disease
- Mortality greatest in children under 5 (28,000 - 111,500 associated with ALRI)

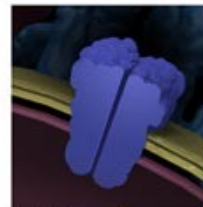
Influenza Virus



Hemagglutinin



Neuraminidase



M2 ion channel



Ribonucleoprotein

- RNA virus (Orthomyxoviridae) Enveloped
- Types A, B, & C
 - A: birds, mammals (humans)
 - B: humans, ferrets
 - C: pigs, dogs, humans
- Hemagglutinin binds sialic acid on epithelial cells:
 - α -2,6 in mammals
 - α -2,3 in birds
- Allows virus to enter cells
- Neuraminidase cleaves sugar residues to facilitate release of viral particles
- M2 allows release of viral RNA into cells

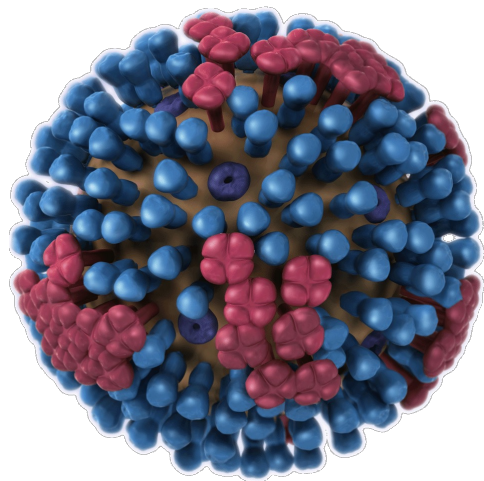
Need For a Universal Influenza Vaccine



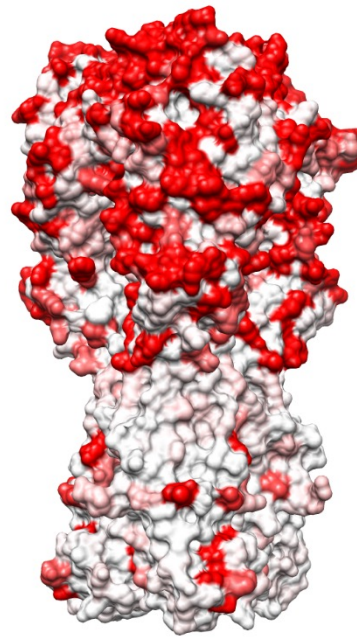
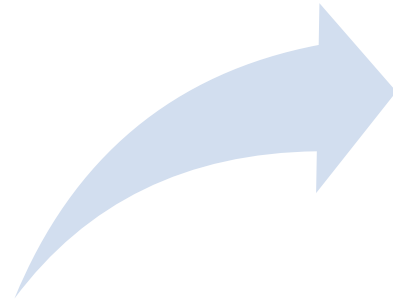
Current Influenza Vaccines:

- Use 1940's technology of inactivated virus grown in chicken eggs
- Only 50-60% effective in good years
- Need to be reformulated every year to match circulating Flu strains
- Not effective against new pandemic strains

Viral Protein Structure Informs Vaccine Design



Influenza virus



Hemagglutinin (HA)
surface
glycoprotein

■ = mutations

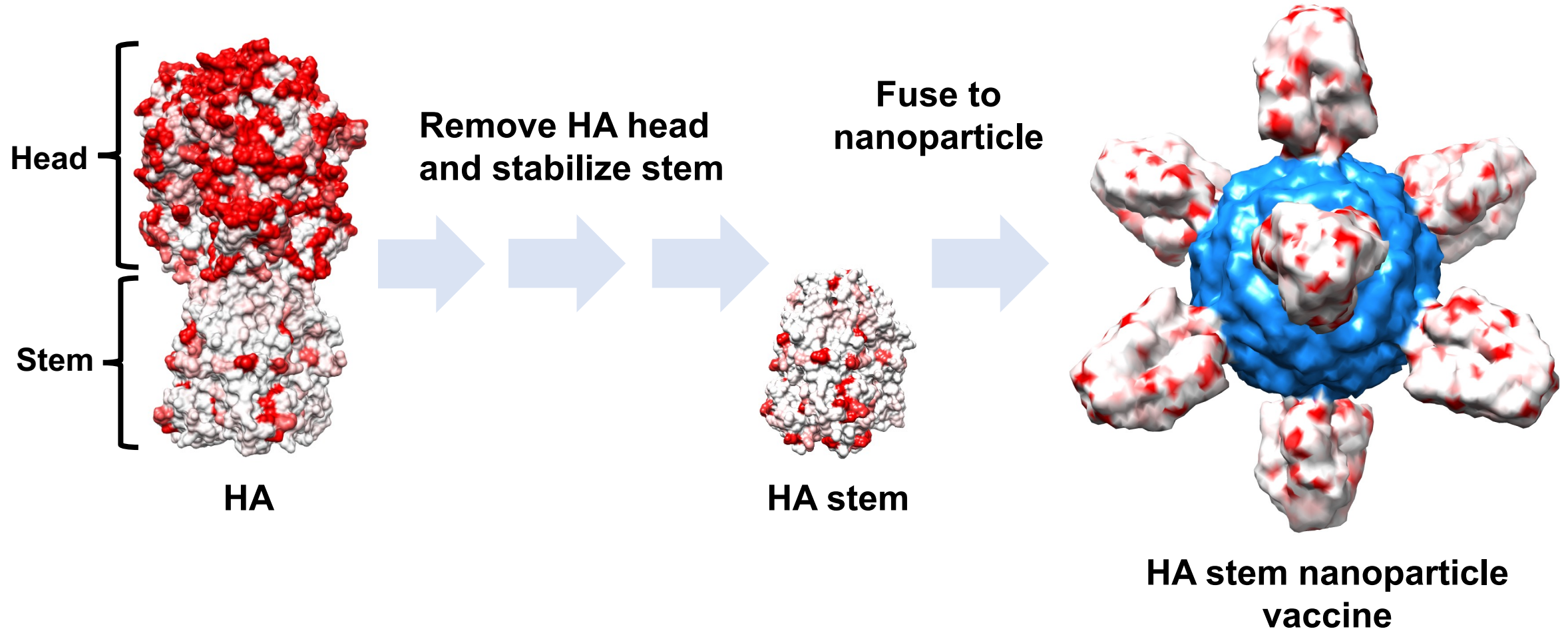
Head:

- High mutation rate
- Targeted by current vaccine

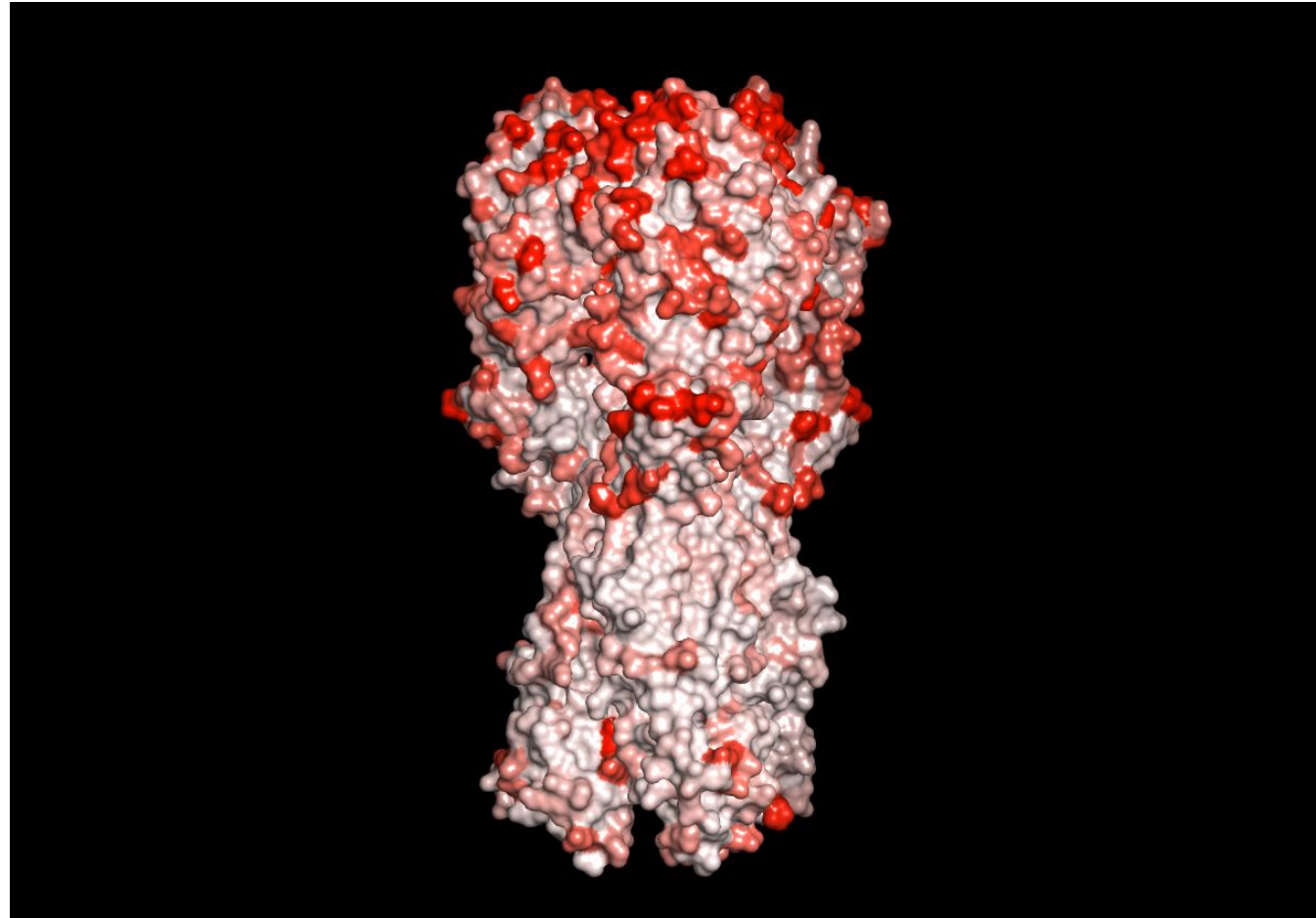
Stem:

- Low mutation rate
- Great target for a universal vaccine

Engineering a Universal Influenza Vaccine



Designing an Influenza HA Stem Vaccine



Phase I Clinical Trial completed at the VRC, NIAID, NIH showed the vaccine led to broad antibody and B cell immunity

Summary: Influenza

- Current influenza vaccines are based on decades old technology and must be updated annually
- 2023 recommendations from the CDC were updated to remove restrictions on administration of influenza vaccines produced in eggs to egg allergic individuals
- Many technologies are currently in the vaccine development pipeline, several past Phase 1 trials, to improve upon breadth and durability of immune responses to influenza vaccines
- Until one of these candidates has been successful in large Phase 3 efficacy studies, current influenza vaccines are the best defense against seasonal influenza
- Adults aged 65 years and older may receive a high-dose influenza vaccine

Outline

- Recent updates to CDC vaccine recommendations for older adults
- Development of RSV vaccines
- Current influenza vaccines & development of universal flu vaccines
- **Nutrition and immunity to infections and vaccines**

Vaccine Immunity and Nutrition

- Studies on vitamins, minerals, and other nutritional supplements and their role in immunity and vaccine responses are primarily observational and/or retrospective
- Many studies have identified vitamins A, D, C, E, B6, and B12, folate, zinc, iron, copper, and selenium as useful in promoting immunity to infection and responses to vaccines
- Unfortunately, in many cases there are contradictory studies showing no role for these micronutrients in immunity—**more studies are needed**
- Observational and retrospective studies have limitations, importantly they do not prove causality between supplementation and improved immune responses
- Obesity and advanced age have both been conclusively shown to have a negative impact on the immune response to multiple vaccines, including influenza

CDC Vaccine Schedule for Adults

Table 2 Recommended Adult Immunization Schedule by Medical Condition or Other Indication, United States, 2023

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 percentage and count		Asplenia, complement deficiencies	End-stage renal disease, or on hemodialysis	Heart or lung disease; alcoholism ^a	Chronic liver disease	Diabetes	Health care personnel ^b	Men who have sex with men
			<15% or <200 mm ³	≥15% and ≥200 mm ³							
COVID-19		See Notes									
IIV4 or RIV4 or LAIV4		1 dose annually					Contraindicated		Precaution		1 dose annually
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td or Tdap booster every 10 years									
MMR	Contraindicated ^c	Contraindicated	1 or 2 doses depending on indication								
VAR	Contraindicated ^c	Contraindicated		2 doses							
RZV		2 doses at age ≥19 years				2 doses at age ≥50 years					
HPV	Not Recommended ^c	3 doses through age 26 years			2 or 3 doses through age 26 years depending on age at initial vaccination or condition						
Pneumococcal (PCV15, PCV20, PPSV23)		1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)									
HepA				2, 3, or 4 doses depending on vaccine							
HepB	3 doses (see notes)	2, 3, or 4 doses depending on vaccine or condition									
MenACWY		1 or 2 doses depending on indication, see notes for booster recommendations									
MenB	Precaution	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations									
Hib		3 doses HSCT ^c recipients only				1 dose					

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
 Recommended vaccination for adults with an additional risk factor or another indication
 Recommended vaccination based on shared clinical decision-making
 Precaution—vaccination might be indicated if benefit of protection outweighs risk of adverse reaction
 Contraindicated or not recommended—vaccine should not be administered.
 No recommendation/Not applicable

*Vaccinate after pregnancy.

a. Precaution for LAIV4 does not apply to alcoholism. b. See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. c. Hematopoietic stem cell transplant.

In Final Summary...

- The National Foundation for Infectious Diseases (NFID) completed a survey in 2023 about attitudes of Americans toward receiving various available vaccines.
 - Healthcare professionals are the primary and most trusted source of information about flu vaccines.
 - Among US adults age 60 years and older who do not plan to get an RSV vaccine, one of the top reasons cited (27%) was that they have not been advised to get an RSV vaccine (respondents were asked to select all that apply)
 - 40% of those at higher risk for pneumococcal disease (including those 65 years and older, adults who currently or ever smoked tobacco, and those who have or ever have had diabetes, asthma, COPD, heart disease, stroke, or kidney disease) have been advised to get a pneumococcal vaccine
 - Among those who have been advised to get vaccinated, the majority (79%) have received a pneumococcal vaccine
 - Among those who do not plan to get a pneumococcal vaccine, the top reason cited (38%) was that they have not been advised to do so

In Final Summary...

ADVISE YOUR PATIENTS TO BE VACCINATED.

(for once) THEY ARE LISTENING.

Selected References

1. Ruckwardt TJ, Morabito KM, Phung E, et al. Safety, tolerability, and immunogenicity of the respiratory syncytial virus prefusion F subunit vaccine DS-Cav1: a phase 1, randomised, open-label, dose-escalation clinical trial. *Lancet Respir Med* 2021; 9 (10): 1111-1120.
2. Crank MC, Ruckwardt TJ, Chen M, et al. A proof of concept for structure-based vaccine design targeting RSV in humans. *Science* 2019; 365(6452): 505-9.
3. Widge, A et. al. An influenza hemagglutinin stem nanoparticle vaccine induces cross-group 1 neutralizing antibodies in healthy adults. *Sci Transl Med*. 2023 Apr 19;15(692):eade4790. doi: 10.1126/scitranslmed.ade4790.
4. Andrews, SF et. al. An influenza H1 hemagglutinin stem-only immunogen elicits a broadly cross-reactive B cell response in humans. *Sci Transl Med*. 2023 Apr 19;15(692):eade4976. doi: 10.1126/scitranslmed.ade4976.
5. Calder PC. Nutrition and immunity: lessons for COVID-19. *Eur J Clin Nutr*. 2021 Sep;75(9):1309-1318. doi: 10.1038/s41430-021-00949-8. Epub 2021 Jun 23. PMID: 34163017; PMCID: PMC8220366.
6. Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients*. 2020 Jan 16;12(1):236. doi: 10.3390/nu12010236. PMID: 31963293; PMCID: PMC7019735.
7. Shaikh SR, MacIver NJ, Beck MA. Obesity Dysregulates the Immune Response to Influenza Infection and Vaccination Through Metabolic and Inflammatory Mechanisms. *Annu Rev Nutr*. 2022 Aug 22;42:67-89. doi: 10.1146/annurev-nutr-062320-115937. PMID: 35995048.
8. Scott D, Painter, Inna G, Ovsyannikova, Gregory A, Poland, The weight of obesity on the human immune response to vaccination, *Vaccine*, Volume 33, Issue 36, 2015, Pages 4422-4429, ISSN 0264-410X, <https://doi.org/10.1016/j.vaccine.2015.06.101>.

Resources for Further Information

1. CDC-INFO Contact Center

The CDC-INFO contact center is supported by CDC and provides public health-related information, including vaccination information, for health-care providers and the public, 24 hours a day, 7 days a week. Contact [CDC-INFO online](#) at any time. To contact CDC-INFO by telephone, call between 8 am to 8 pm Eastern Time Monday through Friday at [English and Spanish]: 800-232-4636; telephone [TTY]: 800-232-6348.

NIAID VRC Viral Pathogenesis Lab (2019)



NIAID VRC Clinical Trials Program (2019)



Ingelise Gordon
Clinical Operations Manager

Sarah Plummer
Chief, Clinical Development Unit

Martin Gaudinski
Medical Director

Grace Chen
Deputy Chief

Julie Ledgerwood
Chief, Clinical Trials Program



Nina Berkowitz
Team Lead,
Protocol Operations



Charla Andrews
Preeti Apte
Alison Beck
Eugenia Burch
Maria Burgos Florez
Cristina Carter
Emily Coates
Pam Costner
Josephine Cox
Jennifer Cunningham

Aba Eshun
Carmencita Graves
Mercy Guech
Cynthia Starr Hendel
Somia Hickman
Renunda Hicks
LaSonji Holman
Kate Houser
Rebecca Lampley
Brenda Larkin

Lam Le
Floreiz Mendoza
Laura Novik
Mark O'Callahan
Abidemi Ola
Iris Pittman
Ro Rothwell
Jamie Saunders
Ellie Seo
Sandra Sitar

Stephanie Taylor
Cora Trelles Cartagena
Olga Trofymenko
Olga Vasilenko
Xiaolin Wang
Wil Whalen
Alicia Widge
Pernell Williams
Galina Yamshchikov