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FDA Considerations and Recommendations for the 2024-2025 COVID-19 Vaccine Formula Composition

Vaccines and Related Biological Products Advisory Committee Meeting (6/5/2024)

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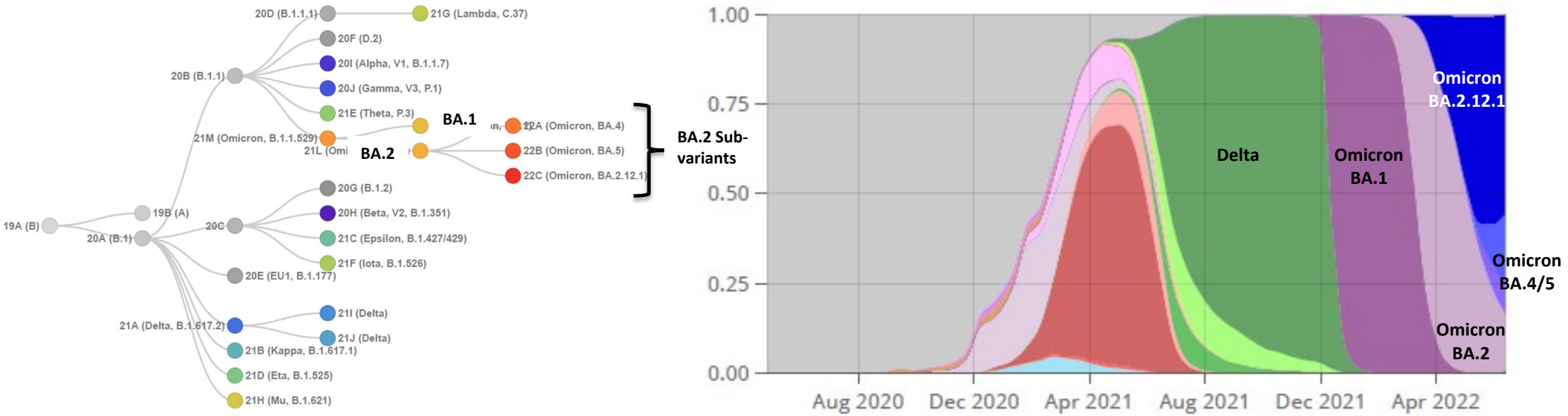
Division of Viral Products/OVRR/CBER/FDA

Background

- The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has previously convened four times to discuss the composition of COVID-19 vaccines for the U.S.
  - April 6, 2022 – Initial discussion about the framework for updating COVID-19 vaccine composition process
    - Agreement that COVID-19 vaccine strain composition decisions should be data driven and there should be evidence to indicate that a proposed modified vaccine composition would likely provide improved effectiveness compared to the current vaccine composition
  - ***June 28, 2022 – Discussion and recommendation to update the COVID-19 strain composition to include a SARS-CoV-2 Omicron component for COVID-19 booster vaccines***
  - January 26, 2023 – Further discussions about the approach to periodic updates of COVID-19 vaccine strain composition
    - Agreement that 1) there should be a periodic assessment by FDA and VRBPAC to reassess the need for an updated composition, 2) updating the strain composition of COVID-19 vaccines would likely be a continuous process, and 3) a late Spring/early Summer target for FDA/VRBPAC review and recommendation seemed reasonable, but this timing would be modified as needed
  - ***June 15, 2023 – Discussion and recommendation to update the COVID-19 strain composition to a monovalent XBB-lineage***

SARS-CoV-2 Variant Situation – June 2022

from https://covariants.org/ using Nextstrain data (https://nextstrain.org/



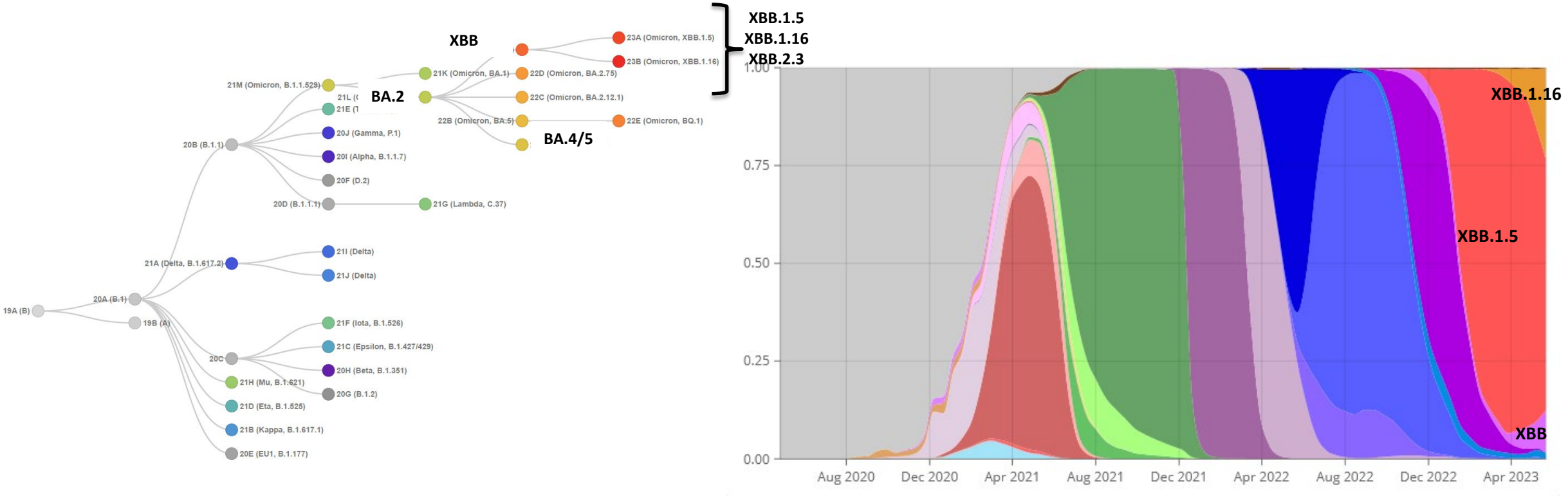
- The Omicron variant had replaced previous SARS-CoV-2 viruses
- Manufacturers had produced and evaluated BA.1 vaccines in clinical trials and were prepared to supply a BA.1 containing vaccine for 2022-2023
- BA.1 was no longer in circulation by June 2022 and was antigenically very distinct from BA.2 derived viruses
- VRBPAC discussion concerned selection of Omicron sub-lineage variants BA.1 versus BA.4/5

Recommendation for 2022-2023 COVID-19 Vaccine Composition

- VRBPAC met on June 28th 2022 to consider whether a change to the current COVID-19 vaccine strain composition was needed
- The committee discussed the evidence supporting:
  - a monovalent (Omicron) or bivalent vaccine (prototype + Omicron)
  - the selection of a specific Omicron sub-lineage (e.g., BA.1 vs. BA.4/BA.5)
- The committee voted to recommend inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the United States
- There was a general preference for a bivalent COVID-19 vaccine containing ancestral and Omicron strains
- On June 30, 2022, FDA notified vaccine manufacturers of FDA's recommendation to develop a bivalent vaccine (Ancestral plus Omicron BA.4/BA.5) as a booster dose to improve protection
  - The first bivalent vaccines from Moderna and Pfizer-BioNTech were authorized for use for individuals 18 years of age and older and 12 years of age and older, respectively, on August 31, 2022

SARS-CoV-2 Variant Situation – June 2023

from https://covariants.org/ using Nextstrain data (https://nextstrain.org/



- XBB-lineage viruses had replaced previous BA.5-derived SARS-CoV-2 viruses
- VRBPAC discussion concerned selection of XBB lineage variants, e.g., XBB.1.5, 1.16, 2.3
- XBB.1.16 and XBB.2.3 each differed from XBB.1.5 by one amino acid in the RBD suggesting antigenic similarity

Recommendation for 2023-2024 COVID-19 Vaccine Composition

- VRBPAC met on June 15th 2023 to consider whether a change to the current COVID-19 vaccine strain composition was needed
- The committee discussed the evidence supporting:
  - an updated XBB-lineage COVID-19 vaccine
  - the selection of a specific XBB-lineage (e.g., XBB.1.5, XBB.1.16, XBB.2.3)
- The committee voted to recommend an update of the vaccine composition to a monovalent XBB-lineage for the United States
- There was a consensus that based on the data presented and other practical considerations, the XBB.1.5 sublineage should be selected for the 2023-2024 COVID-19 vaccine
- On June 16, 2023, FDA notified vaccine manufacturers of their recommendation to "develop a monovalent (XBB.1.5) COVID-19 vaccine for age-appropriate use in potentially eligible populations"
  - Updated XBB.1.5 monovalent mRNA vaccines from Moderna and Pfizer-BioNTech were approved/authorized for use on September 11, 2023
  - Updated XBB.1.5 adjuvanted COVID-19 vaccine from Novavax was authorized for use on October 3, 2023

Major Considerations for Modifying the COVID-19 Strain Composition

- Key questions to be addressed by the agency and the VRBPAC in considering whether to modify the COVID-19 vaccine composition include the following:
  - Have currently circulating SARS-CoV-2 virus variants become, or are they expected to become, dominant and displace earlier virus strains?
  - Are currently circulating SARS-CoV-2 virus variants antigenically distinct from current vaccines?
  - Is there evidence that current vaccines are less effective against new circulating virus variants than against previous strains of the virus?
  - Is there evidence that a candidate vaccine with an updated composition will be more effective against new circulating virus variants and provide an improved clinical benefit?

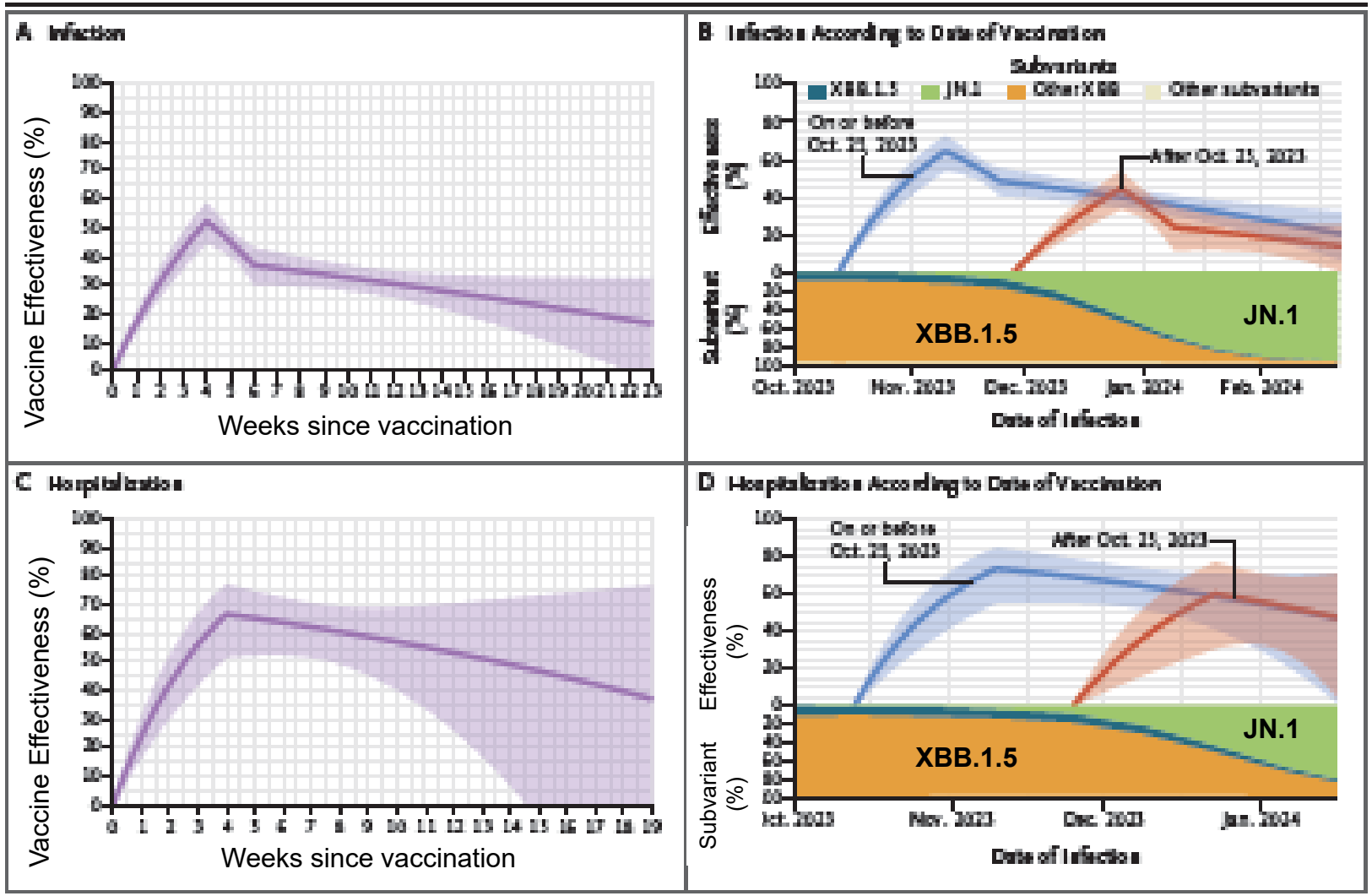
Key Assumptions

- Since broad spectrum, variant-proof vaccines do not yet exist, current Spike-based vaccines will continue to need periodic updating to maintain effectiveness as SARS-CoV-2 continues to evolve
- Since virus neutralization is important for protection, especially for Spike-based vaccines, clinical and nonclinical virus neutralization data are powerful tools that can be used to inform the vaccine composition process
- For vaccines with prior demonstration of efficacy, the data package needed for regulatory review will include comprehensive chemistry, manufacturing, and control data to ensure product quality, in addition to nonclinical data that supports effectiveness of the updated vaccine formulation
    - Clinical data may still be required post-authorization/approval even for vaccines with prior demonstrated efficacy for an ongoing evaluation of the vaccine composition process
- Regardless of the vaccine manufacturing technology, timelines for production and regulatory approval of an updated formulation are constraining and necessitate some manufacturing activities be performed at risk for timely vaccine rollout

Current Effectiveness of Authorized COVID-19 Vaccines and Need for an Updated Composition

- Observational effectiveness data has indicated the effectiveness of the 2023 XBB.1.5 vaccines and strongly supports that updating the composition of the COVID-19 vaccines from the 2022 bivalent vaccine (Original and Omicron BA.4/BA.5) components offered benefit in protection
- Nevertheless, vaccine effectiveness appears to decrease as time since vaccination increases and as new SARS-CoV-2 variants emerge

Effectiveness of XBB Vaccines Over Time



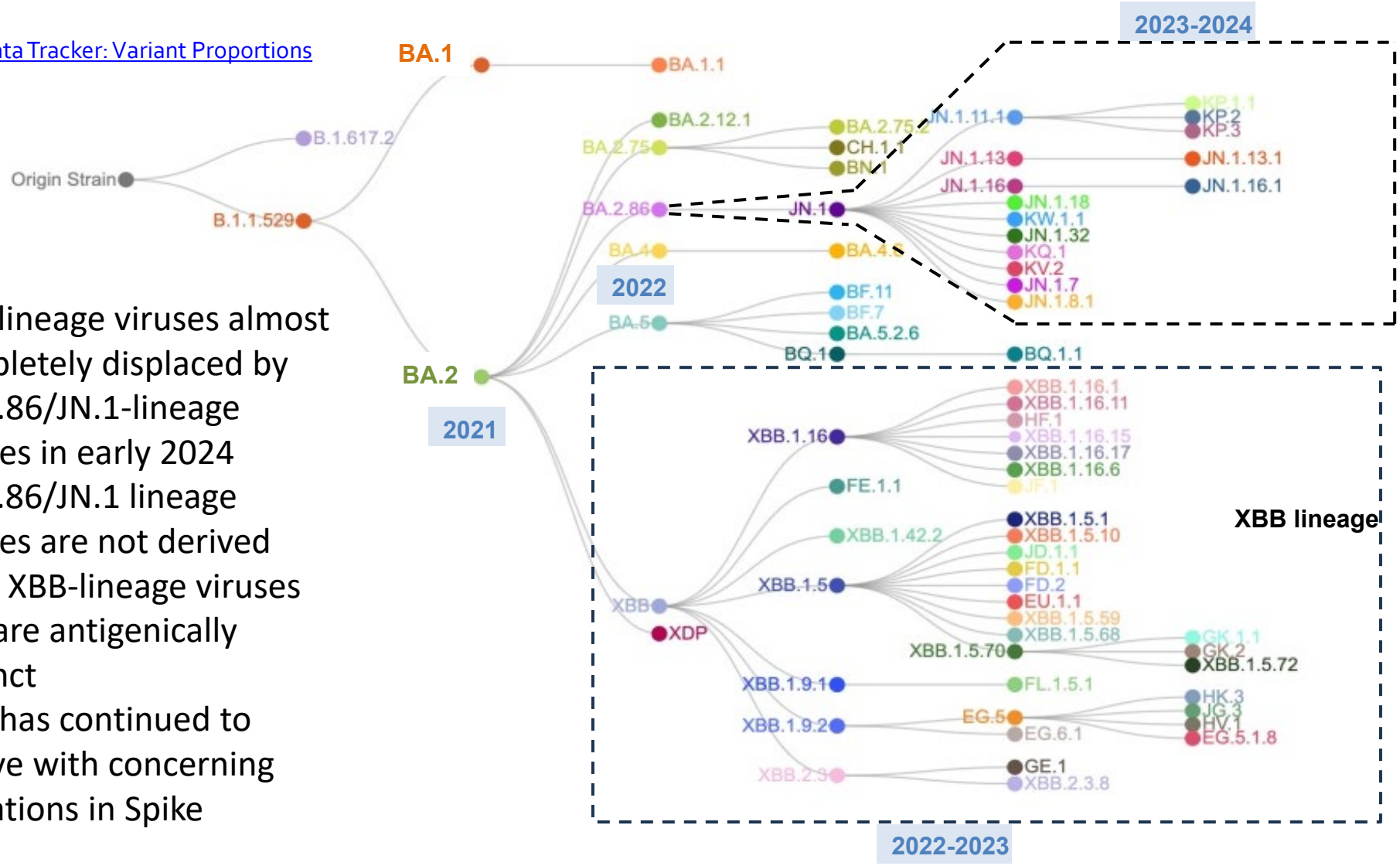
"Durability of XBB.1.5 Vaccines against Omicron Subvariants"

Lin D-Y et al. NEJM
DOI: 10.1056/NEJMc2402779

- Effectiveness of XBB.1.5 vaccines peaked at ~4 weeks and then declined
- XBB.1.5 vaccines were less protective against JN.1 sublineages

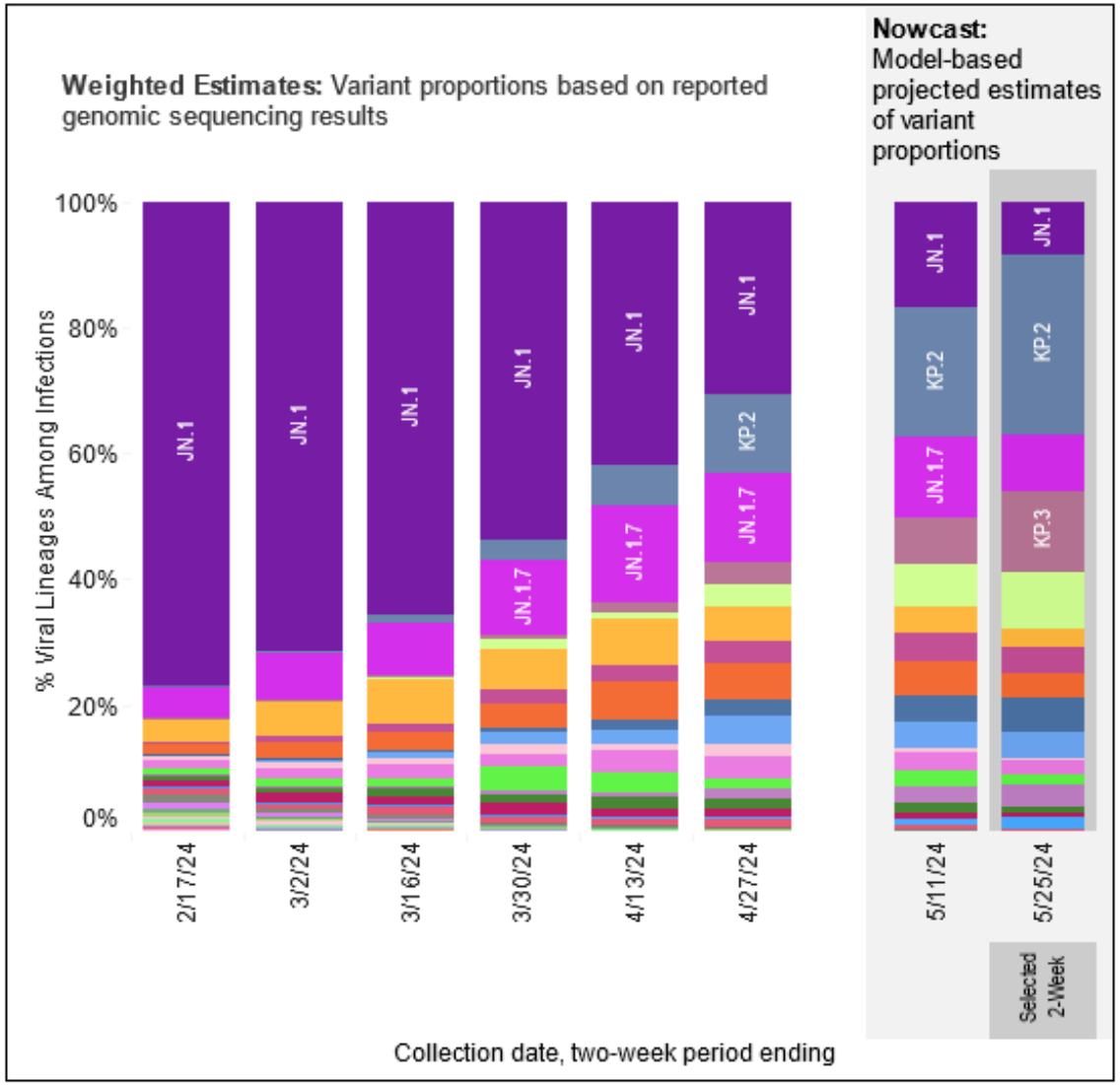
SARS-CoV-2 Surveillance and Genomic Analysis Indicates Continued Evolution and Diversification

CDC COVID Data Tracker: Variant Proportions



- XBB-lineage viruses almost completely displaced by BA.2.86/JN.1-lineage viruses in early 2024
- BA.2.86/JN.1 lineage viruses are not derived from XBB-lineage viruses and are antigenically distinct
- JN.1 has continued to evolve with concerning mutations in Spike

SARS-CoV-2 Variants in the U.S. – Current Proportions



USA

[CDC COVID Data Tracker: Variant Proportions]

WHO label	Lineage #	%Total	95%PI
Omicron	KP.2	28.5%	23.0-34.7%
	KP.3	12.7%	7.8-19.6%
	JN.1.7	9.2%	7.3-11.6%
	KP.1.1	9.2%	6.5-12.8%
	JN.1	8.4%	6.8-10.3%
	JN.1.16.1	5.4%	3.3-8.8%
	JN.1.16	4.2%	2.6-6.8%
	JN.1.13.1	4.0%	2.8-5.7%
	JN.1.11.1	3.9%	2.6-5.9%
	KS.1	3.5%	2.0-6.1%
	JN.1.8.1	2.7%	2.0-3.6%
	KQ.1	2.2%	1.2-4.0%
	KW.1.1	1.7%	0.7-4.2%
	JN.1.18	1.7%	1.1-2.5%
	JN.1.32	1.0%	0.7-1.5%
	XDP	0.6%	0.4-1.0%
	KV.2	0.4%	0.2-0.7%
	GE.1	0.0%	0.0-0.0%
	BA.2	0.0%	0.0-0.1%
	BA.2.86	0.0%	0.0-0.0%
	JG.3	0.0%	0.0-0.0%
	HV.1	0.0%	0.0-0.0%

↑ KP.2
↑ KP.3
↓ JN.1.7
↑ KP.1.1
↓ JN.1
↑ JN.1.16.1
→ JN.16
↓ JN.1.13.1
↓ JN.1.11.1
↑ KS.1

Spike Mutations Associated with Variants Whose Proportions are Increasing

- JN.1-lineage viruses that are increasing in proportion have common amino acid changes in the Spike protein relative to JN.1

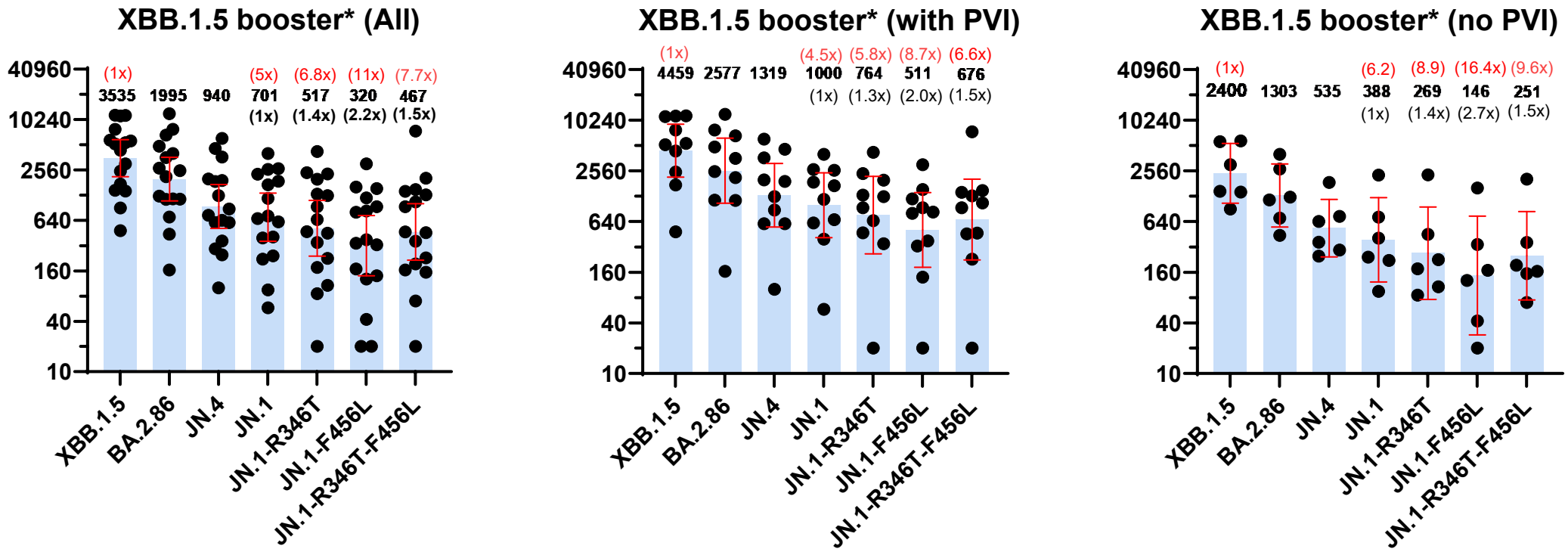
Lineage	RBD Mutation		
KP.2	R346T	F456L	
KP.3		F456L	Q493E
KP.1.1	R346T		
JN.1.16.1	R346T	F456L	
KS.1	R346T	F456L	

- R346T in XBB-lineage viruses and XBB.1.5 vaccines; JN.1, like earlier BA.2, has a 346R
- F456L strongly selected as XBB-lineage viruses evolved, e.g., EG.5.1, HV.1
- R346T and F456L are examples of convergent evolution, presumably conferring an advantage to the virus either in terms of fitness or escape from immunity

Post-Vaccination Human Serology Studies

- Post-vaccination human serology studies are used to evaluate antibody responses generated by the current XBB.1.5 vaccines against more recently circulating virus variants (e.g., JN.1-lineage viruses)
  - Post-vaccination sera are available only from recipients of current monovalent XBB.1.5 vaccines
  - Neutralization titers measured against new variants (e.g., JN.1, KP.2, KP.3, and other JN.1-lineage viruses) can reveal significant immune evasion against these variants compared to the vaccine, but only indirectly suggest similarities or differences among the variants
- Data presented at this VRBPAC by the manufacturers of authorized/approved COVID-19 vaccines, as well as from other studies, indicate that recent virus variants, particularly JN.1-lineage viruses, are more immune evasive to antibodies elicited by prior XBB.1.5 vaccination

Post-XBB.1.5 Vaccination Neutralization of Recent SARS-CoV-2 Variants



- XBB.1.5 mRNA booster* - all received 3 ancestral + 1 bivalent +1 XBB.1.5 monovalent
- PVI - postvaccination infections
- ~4.5-6 x drop against JN.1; additional ~2-2.7-fold drop in titer against variants with F456L that may be partially mitigated by R346T
- Sera from Uniformed Services University - healthy adult healthcare workers (military treatment facility); PI: Edward Mitre; Pseudovirus neutralization, unpublished data - Weiss lab, CBER/DVP

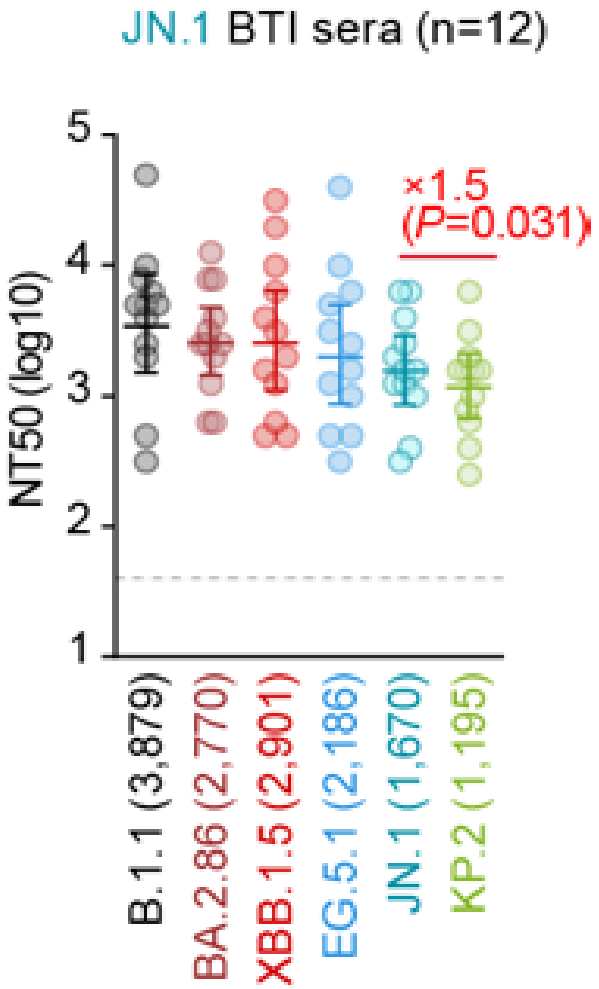
Nonclinical Immunogenicity Studies With New Candidate Vaccines

- Nonclinical immunogenicity studies are used to evaluate immune responses generated by new candidate vaccines (e.g., expressing or containing updated variant Spike components) against antigenically distinct circulating virus variants
- Nonclinical immunogenicity data (neutralizing antibody) can provide an indication of how well antibodies to the Spike of one strain will cross-neutralize other variant strains of SARS-CoV-2 and thus help inform strain selection in combination with other data
- Studies are dependent on COVID-19 vaccine manufacturers producing candidate vaccines at risk and conducting studies to generate the data for evaluation
- Study designs are heterogeneous and do not fully recapitulate human exposure
- Data presented at this VRBPAC by the manufacturers of authorized/approved COVID-19 vaccines indicate that candidate vaccines with updated JN.1-lineage monovalent formulations elicit stronger neutralizing antibody responses against JN.1 and JN.1-descendent viruses than current XBB.1.5 vaccines, but the level of the neutralizing titer varies depending on the variant

Post-Infection Human Serology Studies

- While postvaccination human serology studies are limited to sera available from recipients of current XBB.1.5 vaccines, some serology studies using sera from individuals infected with the more recent JN.1 virus variant have become available
- Data indicate that JN.1 infection elicits higher JN.1-specific neutralizing antibody titers than XBB virus infection
- JN.1 infection also elicits neutralizing antibody titers against JN.1-lineage viruses, including those with concerning Spike mutations, but the titers against the more recent circulating strains of JN.1-lineage viruses appear reduced relative to JN.1
- Caveats include:
  - Limited numbers of JN.1 infected sera for analysis
  - Different exposure histories of subjects
  - Different assays used

JN.1 Post-Infection – Study 1



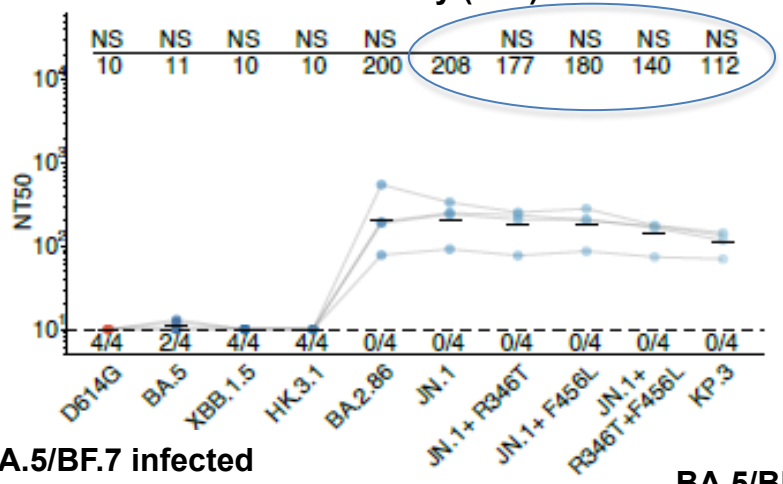
"Virological characteristics of the SARS-CoV-2 KP.2 variant"

Kaku Y et al. bioRxiv
https://doi.org/10.1101/2024.04.24.590786

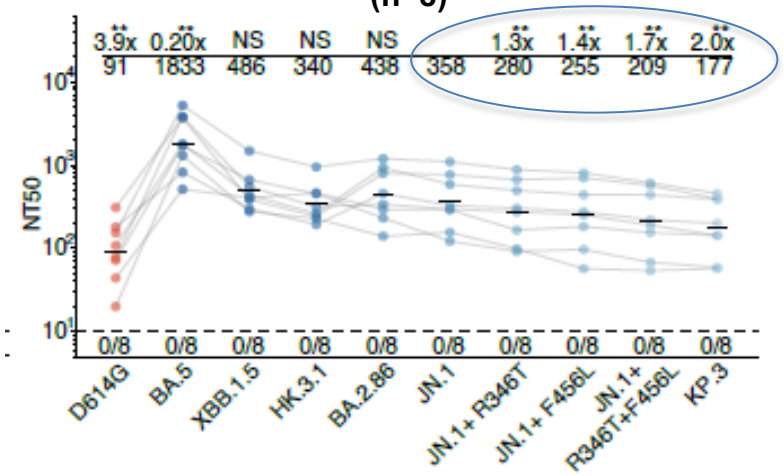
- 12 individuals who had been infected with JN.1 (one 2-dose vaccinated donor, two 3-dose vaccinated donors, two 7-dose vaccinated donors and seven donors with unknown vaccine history of JN.1 infected subjects
- Lower neutralization titers against KP.2 compared to JN.1

JN.1 Post-Infection – Study 2

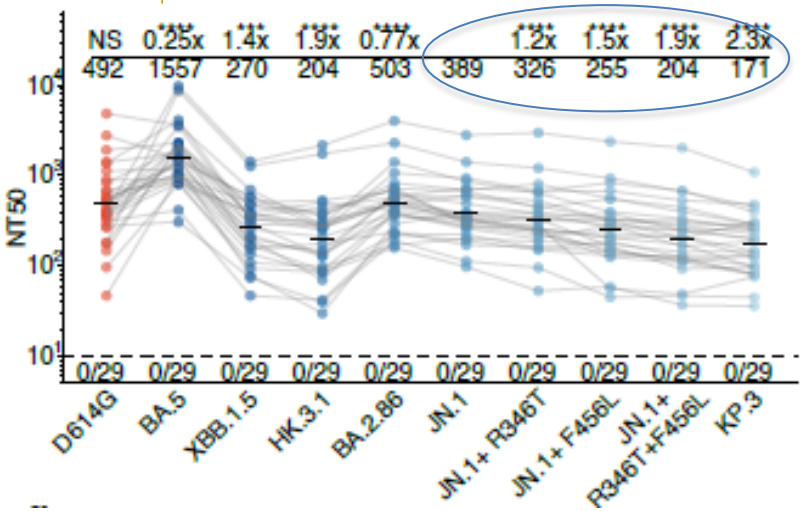
JN.1 infection only (n=4)



Vaccinated/ BA.5/BF.7 infected and JN.1 sequential infection (n=8)



BA.5/BF.7 and JN.1 sequential infection (n=29)

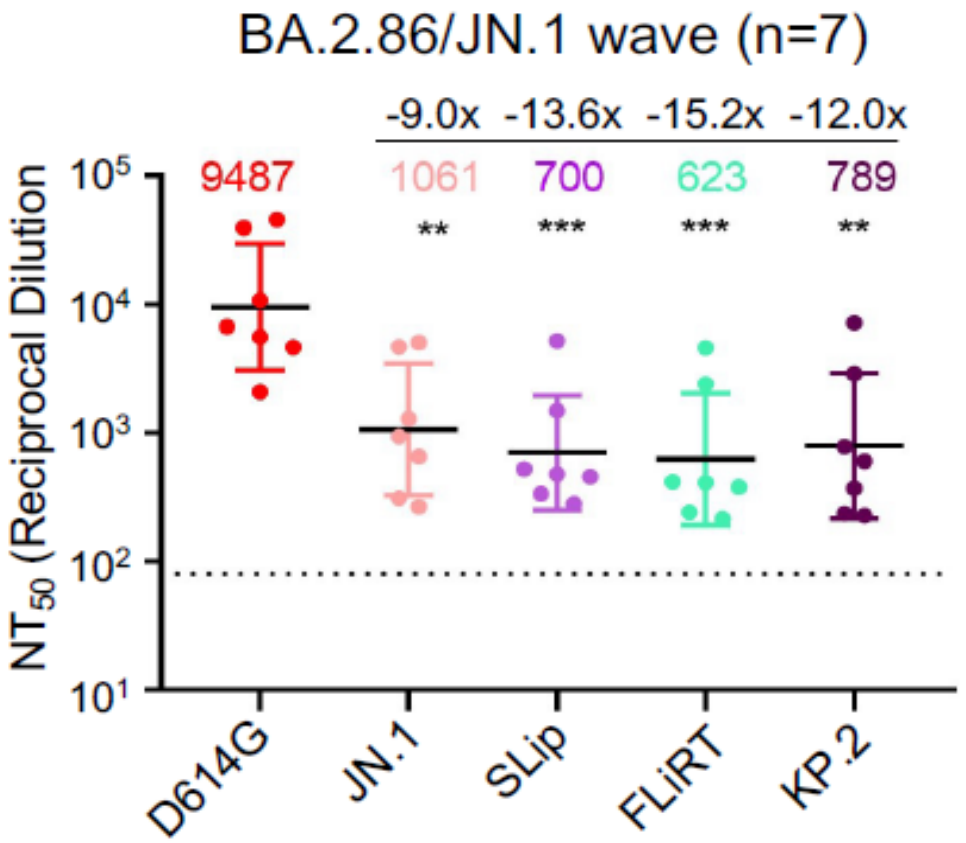


"Humoral immunogenicity comparison of XBB and JN.1 in human infections"

Jian F et al. bioRxiv
https://doi.org/10.1101/2024.04.19.590276

- 3 cohorts of JN.1 infected subjects
- R346T and F456L result in reduced neutralization titers

JN.1 Post-Infection – Study 3

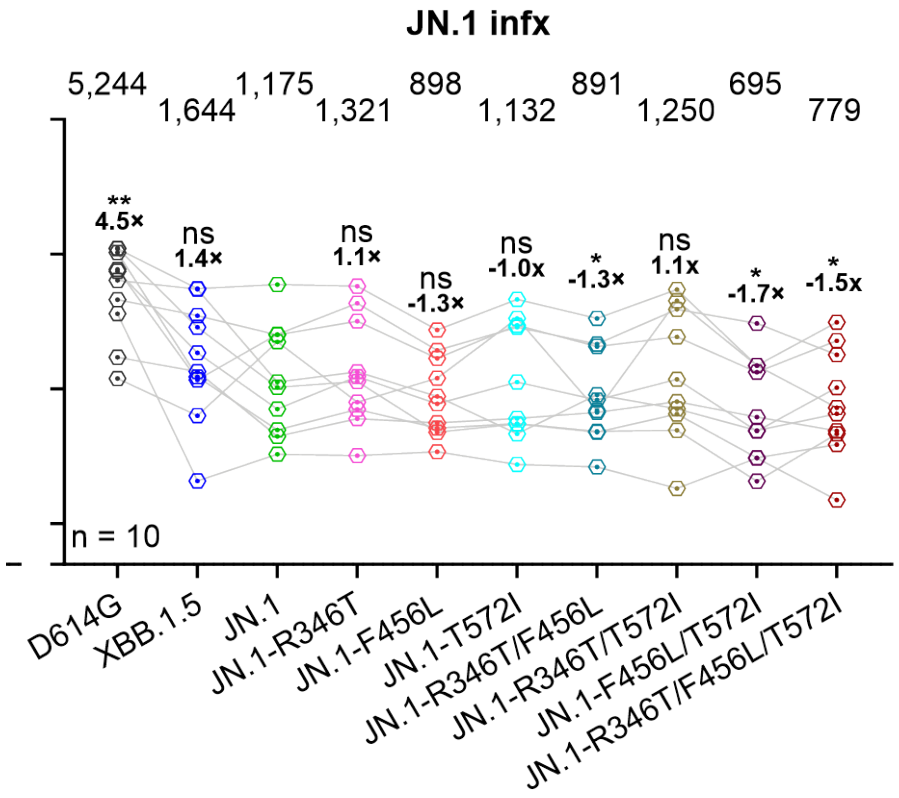


"Characteristics of JN.1-derived SARS-Cov-2 subvariants Slip, FLiRT, and KP.2 in neutralization escape, infectivity and membrane fusion"

Li P Q et al. bioRxiv
https://doi.org/10.1101/2024.05.29.595020

- 7 sera samples from BA.2/JN.1 infected subjects
- Slip - F456L; FLiRT – F456L & R346R

JN.1 Post-Infection – Study 4



"Recurrent SARS-Cov-2 spike mutations confer growth advantages to select JN.1 sublineages"

Wang Q et al. bioRxiv
https://doi.org/10.1101/2024.05.29.596362

- 10 sera samples from JN.1 infected cohort
- F456L is a major driver of antibody evasion

Summary

- By several measures, including increased escape from antibody neutralization and waning protection, current COVID-19 vaccines appear less effective against currently circulating variants (e.g., JN.1-lineage viruses) than against previous strains of virus
- Manufacturers of authorized/approved COVID-19 vaccines have been evaluating updated candidate vaccines “at risk” and are prepared to provide an updated vaccine for 2024-2025
  - Manufacturing timelines may be impacted by the final choice of vaccine antigen

Summary – 2

- Nonclinical data from three different vaccine manufacturers indicate that updated monovalent JN.1-lineage formulations elicit stronger neutralizing antibody responses against JN.1-descendent lineage viruses than current monovalent XBB.1.5 vaccines
- Serology data from JN.1-infected individuals also indicates improved neutralizing antibody responses against JN.1-descendent lineage viruses compared to sera from XBB-infected infected individuals, but the neutralizing antibody responses appear to be reduced by recent amino acid mutations in many JN.1-lineage viruses
- The totality of available evidence indicates that a monovalent JN.1-lineage vaccine is warranted for COVID-19 vaccines (2024-2025 Formula) to be used in the U.S. to more closely match currently circulating SARS-CoV-2 viruses
  - The diversity of JN.1-lineage viruses complicates the specific strain selection decision

Future Directions for the COVID-19 Vaccine Composition Process

- Updating the SARS-CoV-2 strain composition of COVID-19 vaccines will be a continuous process
- Ideal timing for a vaccine composition decision remains elusive
  - SARS-CoV-2 continuous to evolve without a well-defined seasonality
  - Vaccine production timelines differ depending on the manufacturing technology
  - Uncertainty remains regarding the optimal timing for vaccine administration
  - Trade-offs are inevitable in the timing of the vaccine composition decision
- Many challenges for composition recommendation remain, including:
  - A limited amount of critical nonclinical and clinical data is available at the time composition recommendations must be made
  - How differences in neutralization titer relate to clinical outcomes is still poorly understood
  - Current nonclinical models imperfectly reflect human populations receiving vaccines
  - Human postvaccination and post-infection serology panels are not available for distinct populations (e.g., pediatric, adult, and elderly) who may respond differently to vaccination and/or infection

Voting Question for the Committee

1. For the 2024-2025 Formula of COVID-19 vaccines in the U.S., does the committee recommend a monovalent JN.1-lineage vaccine composition?

Please vote “Yes” or “No” or “Abstain”

Discussion Topic for the Committee

- Based on the evidence presented, please discuss considerations for the selection of a specific JN.1 lineage strain (e.g., JN.1, KP.2, etc.) for COVID-19 vaccines (2024-2025 Formula) to be used in the U.S.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