Real World Evidence to Confirm Vaccine Benefit: Updating COVID-19 Vaccines

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Presentation Outline

Process to Support Vaccine Variant Updates

Real World Effectiveness and Variant Epidemiology to Support JN.1 & KP.2 Adapted Vaccines

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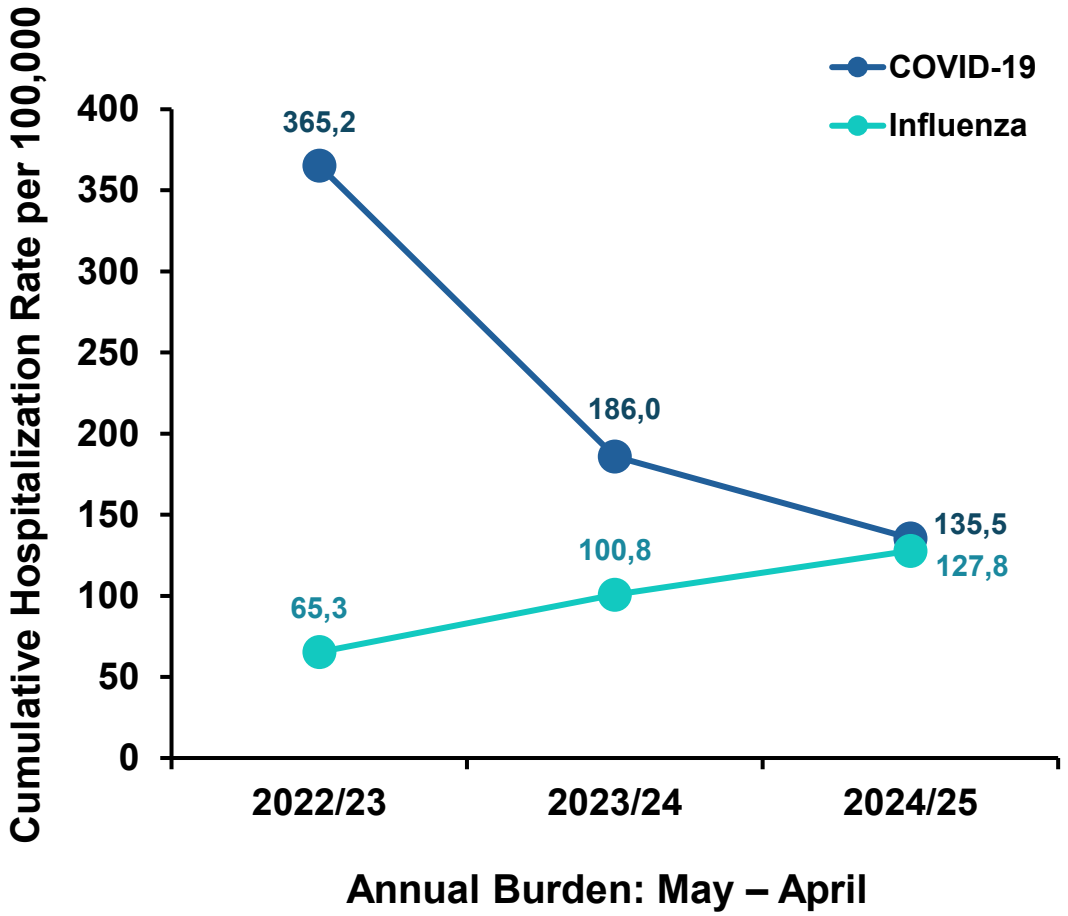
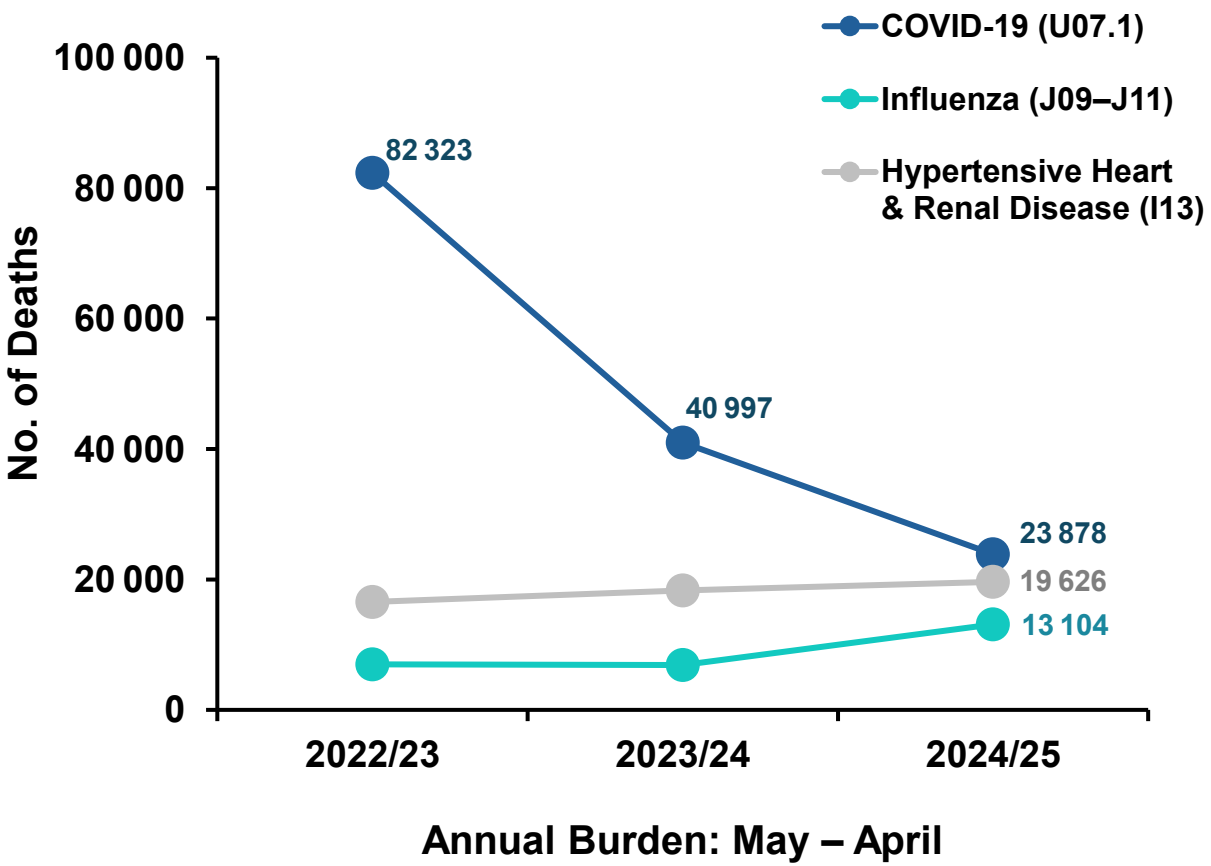
Evidence Supporting 2025-26 LP.8.1. Adapted Vaccine

COVID-19 Still Causes Significant Morbidity and Mortality

Hospitalizations Associated with COVID-19 and Influenza in the US[1]



Deaths due to COVID-19, Influenza, and Hypertensive Heart & Renal Disease in the US[2]

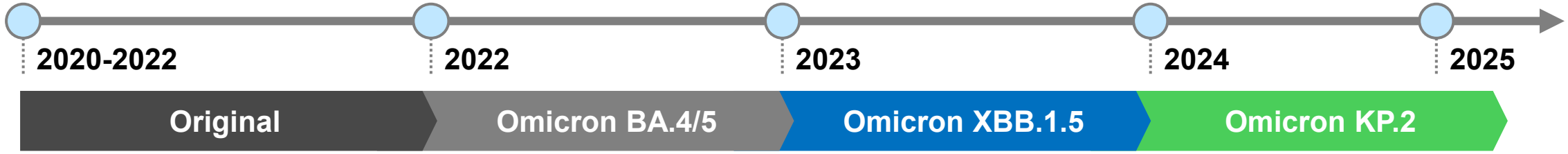


1. Centers for Disease Control and Prevention. Respiratory Virus Hospitalization Surveillance Network (RESP-NET). Available at: https://www.cdc.gov/resp-net/dashboard/index.html. Accessed 14 May 2025.
2. Centers for Disease Control and Prevention. Provisional Mortality Statistics, 2018 through Last Week (CDC WONDER). Available at: https://wonder.cdc.gov/mcd-icd10-provisional.html. Accessed 14 May 2025.

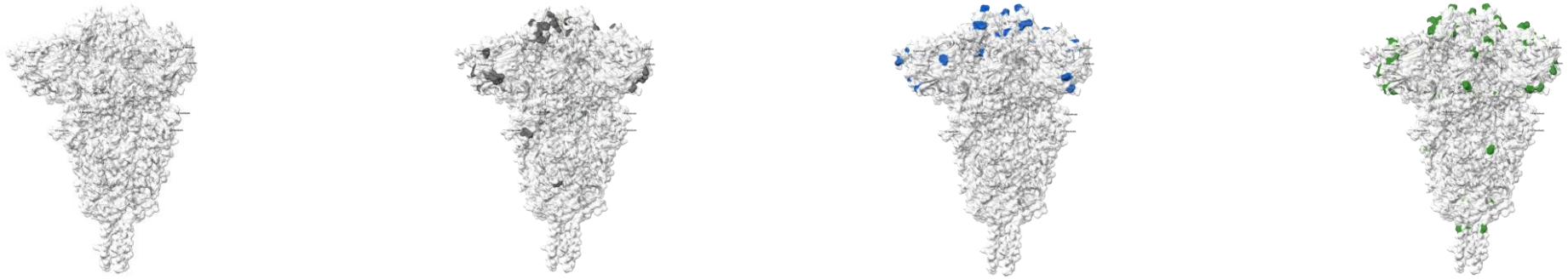
BNT162b2 Safety & Effectiveness Continuously Monitored by Pfizer/BioNTech

- **5 billion doses distributed globally since 2020 authorization**
- **22 clinical studies performed, enrolling >72,000 participants**
  - >10,000 participants ≥ 65 years of age
  - >42,000 participants ≥ 18 to 64 years of age
  - >18,000 participants ≥ 6 months to 17 years of age
- **12 postmarketing safety studies evaluating safety in >60 million individuals**
- **Studies on 5 continents to monitor real-world effectiveness**

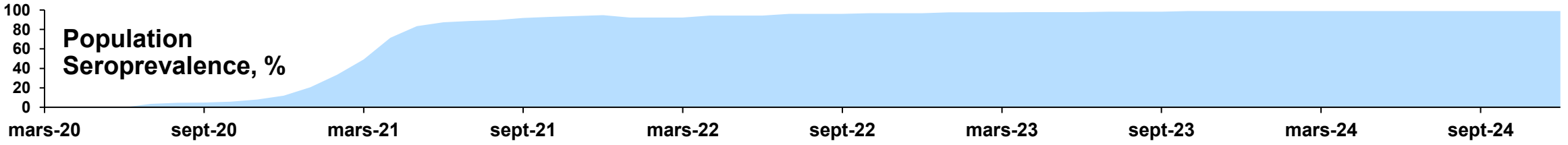
COVID-19 Variant-Adapted Vaccine Approvals Keeping Pace with Virus Evolution



SARS-CoV-2 Spike Mutations[1]

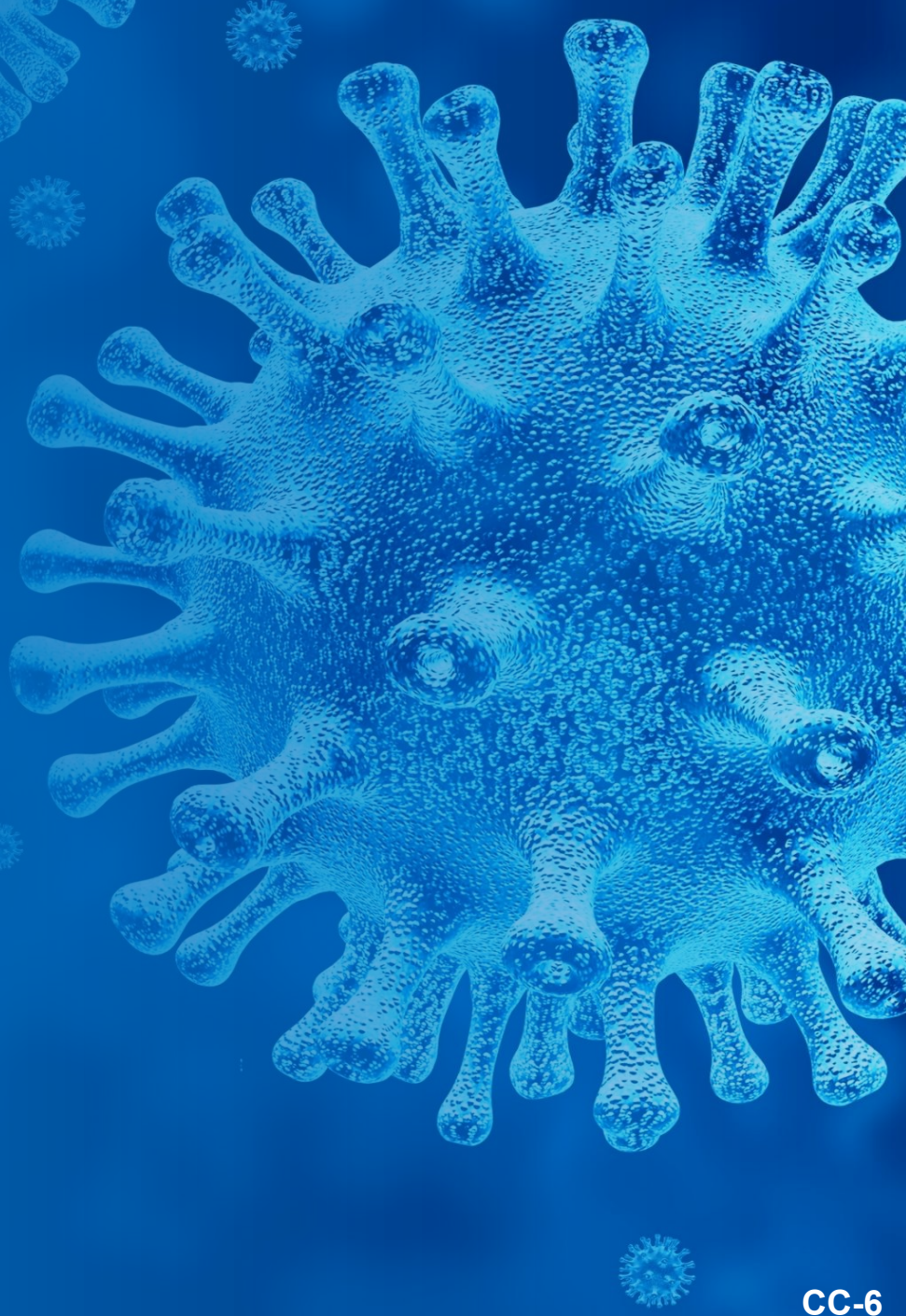


	WT Spike	BA.4/5 Spike	XBB.1.5 Spike	KP.2 Spike
		(**34** mutations relative to WT)	(**17** mutations relative to BA.4/5)	(**38** mutations relative to XBB.1.5)
Vaccine Effectiveness For Hospitalization[2-8]	32-97%	34-76%	32-74%	41-68%

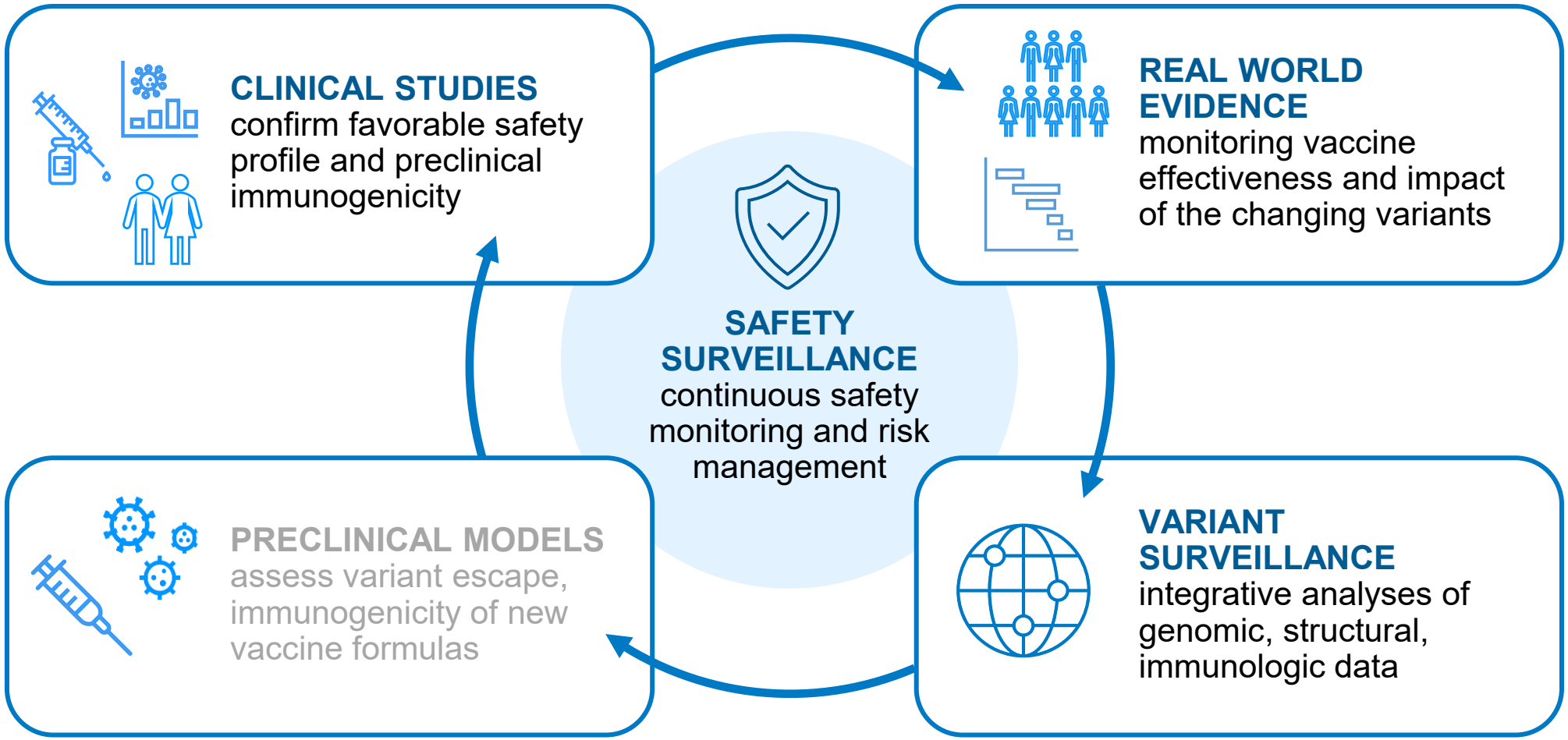


1. Pfizer internal analysis using data downloaded from GISAID - gisaid.org 2. Tartof et al. 2023. DOI: 10.1016/S2213-2600(22)00354-X 3. Tartof et al. 2022. DOI: 10.1016/j.lana.2022.100198 4. Tartof et al. 2023. DOI: 10.1016/S2213-2600(23)00306-5 5. Caffrey et al. 2024. DOI: 10.1016/j.lana.2022.100198 6. Tartof et al. 2024. DOI: 10.1093/ofid/ofae370 7. Pfizer data on file 8. Appaneal et al. 2025. DOI: 10.1038/s41467-025-59344-7

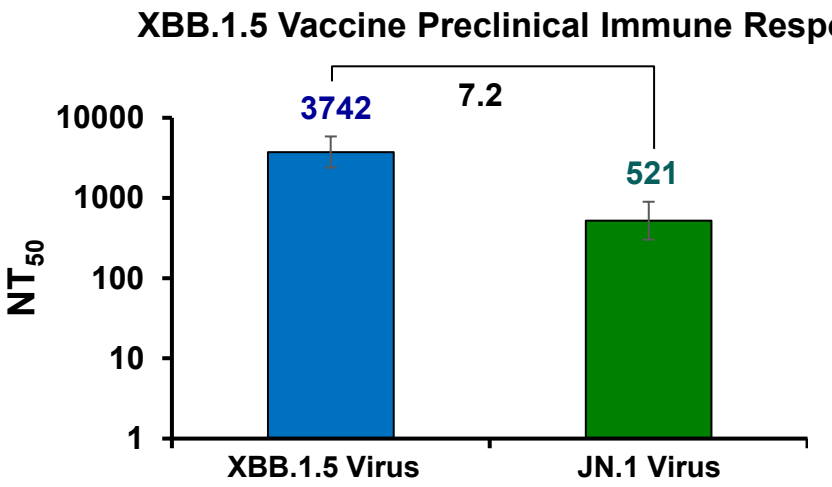
Process Supporting Vaccine Variant Updates

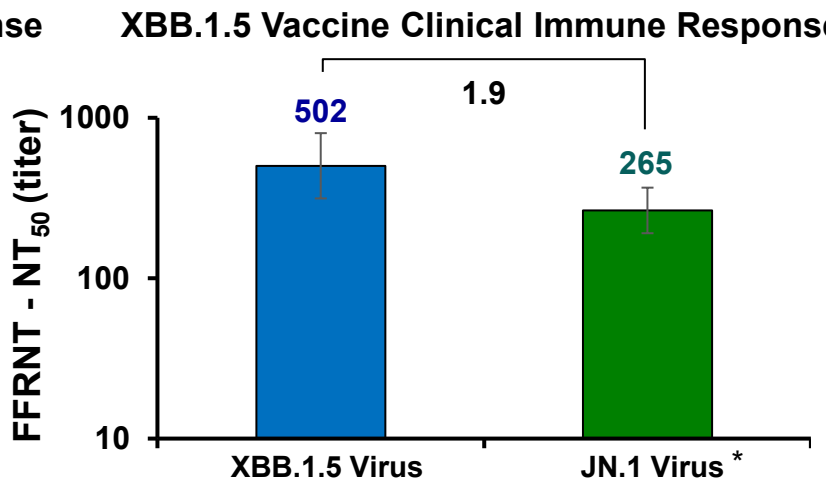


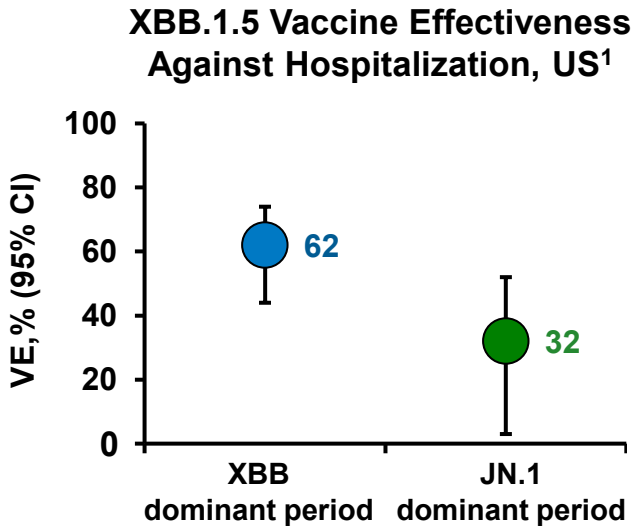
Pfizer/BioNTech's Multifaceted and Continual Process for Variant-Adapted Vaccine Evaluation



Virus Evolution to New Variant Results in Immune Escape; Reducing Vaccine Effectiveness





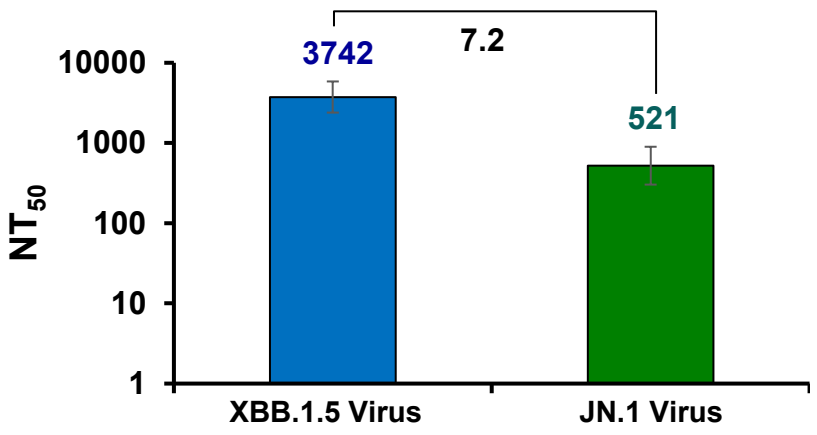


1. Caffrey et al. 2024. DOI: https://doi.org/10.1038/s41467-024-53842-w

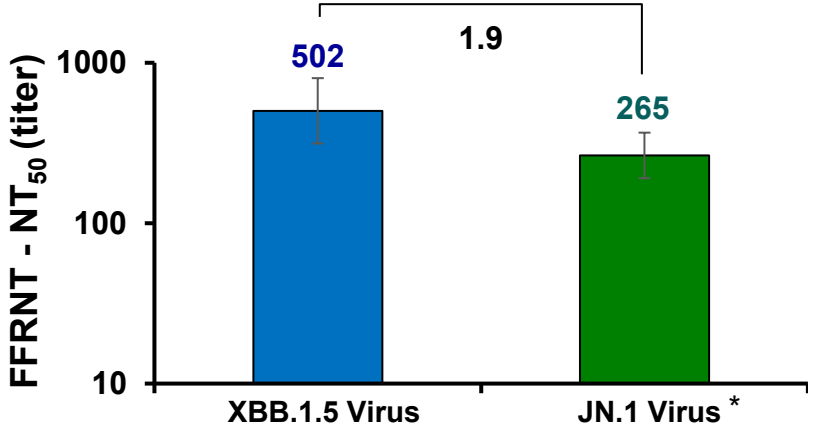
* These data are generated from different subsets of participants in the same study (C4591054 SSA), and samples tested at different times

Virus Evolution to New Variant Results in Immune Escape; Updating Vaccine Provides Benefit

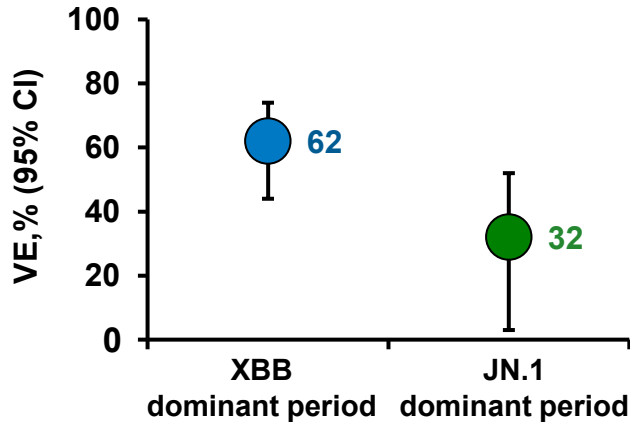
XBB.1.5 Vaccine Preclinical Immune Response



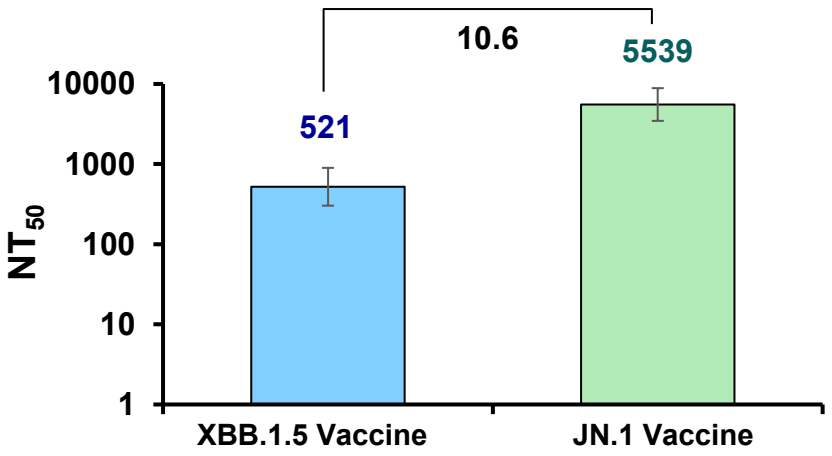
XBB.1.5 Vaccine Clinical Immune Response



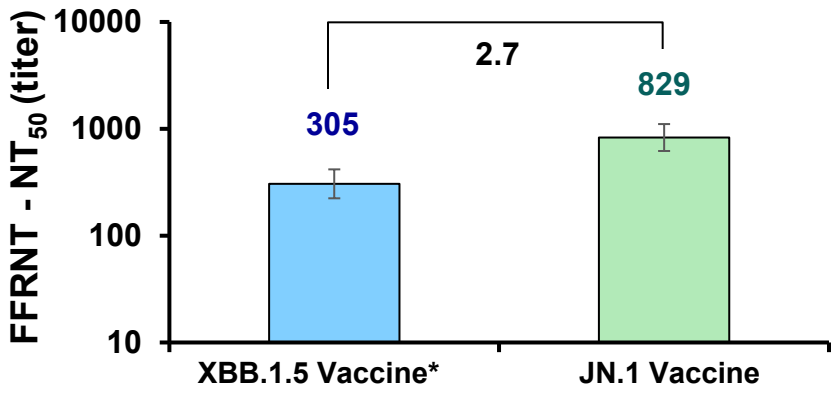
XBB.1.5 Vaccine Effectiveness Against Hospitalization, US[1]



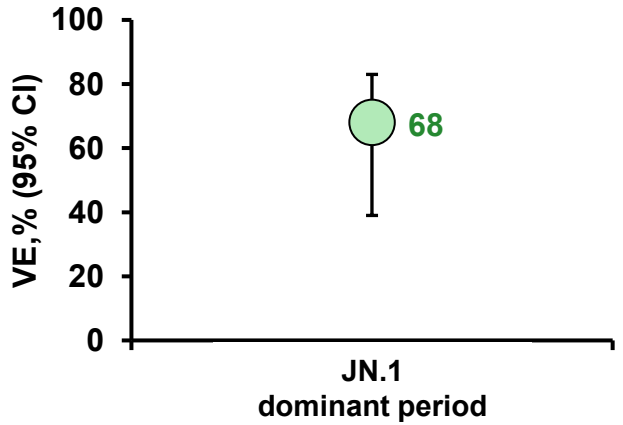
JN.1 Virus Neutralization in Preclinical Study



JN.1 Virus Neutralization in Clinical Study



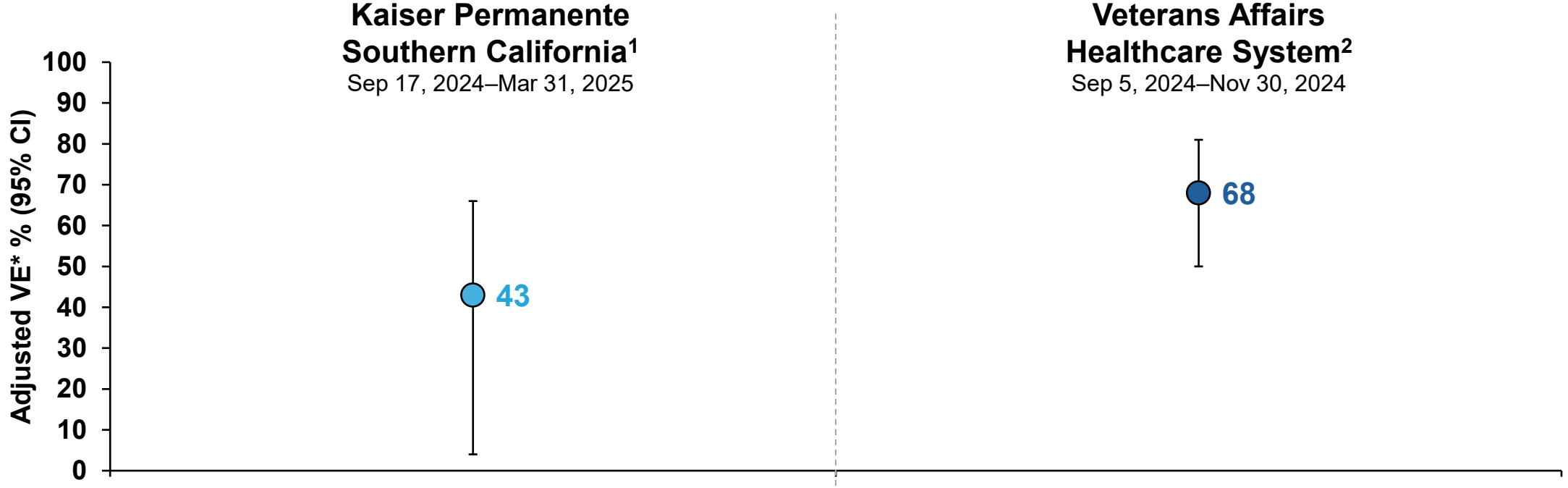
JN.1 Vaccine Effectiveness Against Hospitalization, EU[2]



1. Caffrey et al. 2024. DOI: https://doi.org/10.1038/s41467-024-53842-w 2. Volkman et al. *ESCMID*, 2025. Vienna, Austria.
* These data are generated from different subsets of participants in the same study (C4591054 SSA), and samples tested at different times

KP.2-Adapted Vaccine Provides Effectiveness Against Hospital Admission

REAL WORLD EVIDENCE
monitoring vaccine effectiveness and impact of the changing variants

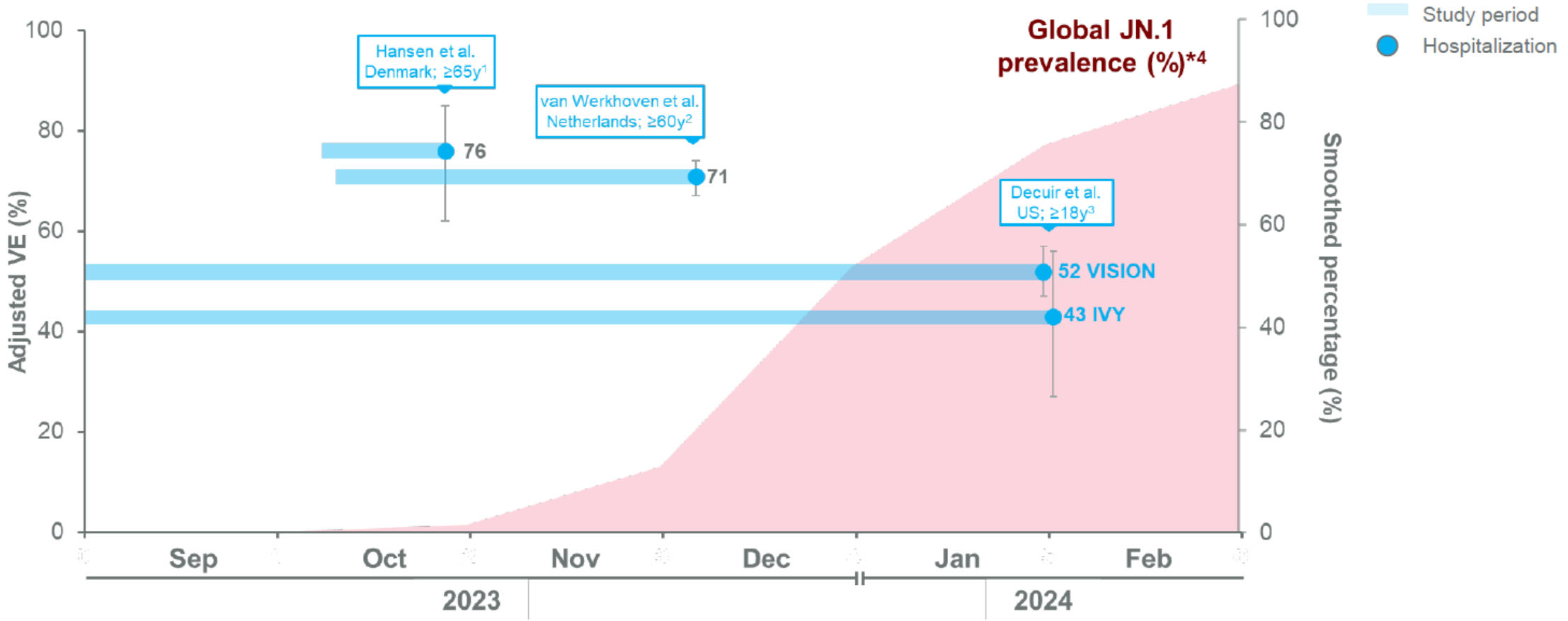


	Kaiser Permanente Southern California[1]	Veterans Affairs Healthcare System[2]
Design	Test-negative case-control	Test-negative case-control
Population	≥18y with ARI diagnosis and SARS-CoV-2 PCR test	≥18y with ARI diagnosis and SARS-CoV-2 PCR or RAT test
Median (IQR) age	53y (35 to 71)	68y (56 to 76)
Median (IQR) time since dose	88d (54 to 121)	30d (21 to 43)
Number of cases (%)	3,039 (5.1%)	7,224 (16.2%)

1. Pfizer data on file.
2. Appaneal, H.J. et al. Early Effectiveness of the BNT162b2 KP.2 Vaccine against COVID-19 in the US Veterans Affairs Healthcare System. Nature Communications. 2025. DOI: https://doi.org/10.1038/s41467-025-59344-7

ARI, acute respiratory infection; CI, confidence interval; d, days; IQR, interquartile range; PCR, polymerase chain reaction; RAT, rapid antigen test; VE, vaccine effectiveness; y, years.
Vaccine Effectiveness (VE) Estimates are compared to no receipt of any 2024–2025 Covid-19 vaccine.

Need to Carefully Consider Biases, Confounding and Effect Modification in Phase 4 VE

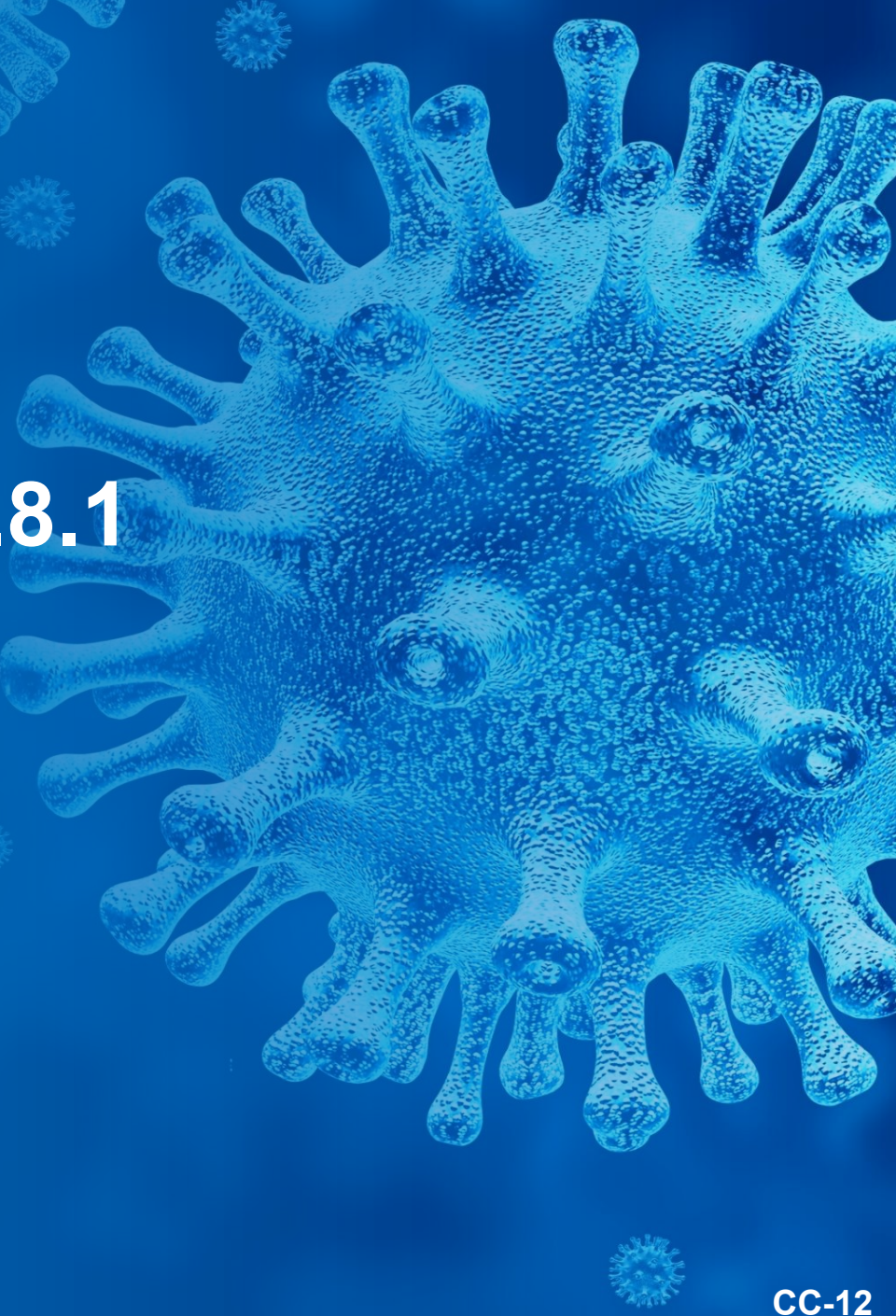


The results summarized on this slide are derived from studies with different designs and limitations, please refer to the preceding slides for design and limitation details.

*GISAID – hCoV19 variants.[4]

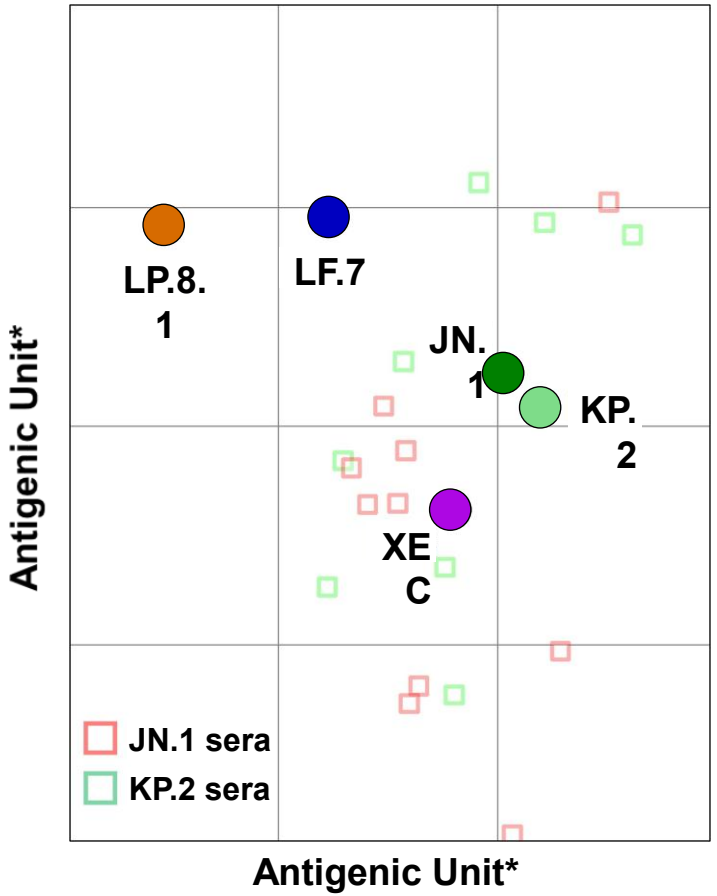
ED, emergency department; GISAID, Global Initiative on Sharing All Influenza Data; IVY, Investigating Respiratory Viruses in the Acutely Ill; RWE, real-world evidence; UC, urgent care; VE, vaccine effectiveness; VISION, Virtual SARS-CoV-2, Influenza and Other Respiratory Viruses Network. 1. Hansen CH et al. *Lancet Infect Dis* 2024;24:e73–e74; 2. van Werkhoven CH et al. *Euro Surveill* 2024;29:2300703; 3. DeCuir J et al. *MMWR Morb Mortal Wkly Rep* 2024;73:180–188; 4. GISAID. https://gisaid.org/hcov19-variants/ (accessed April 2024).

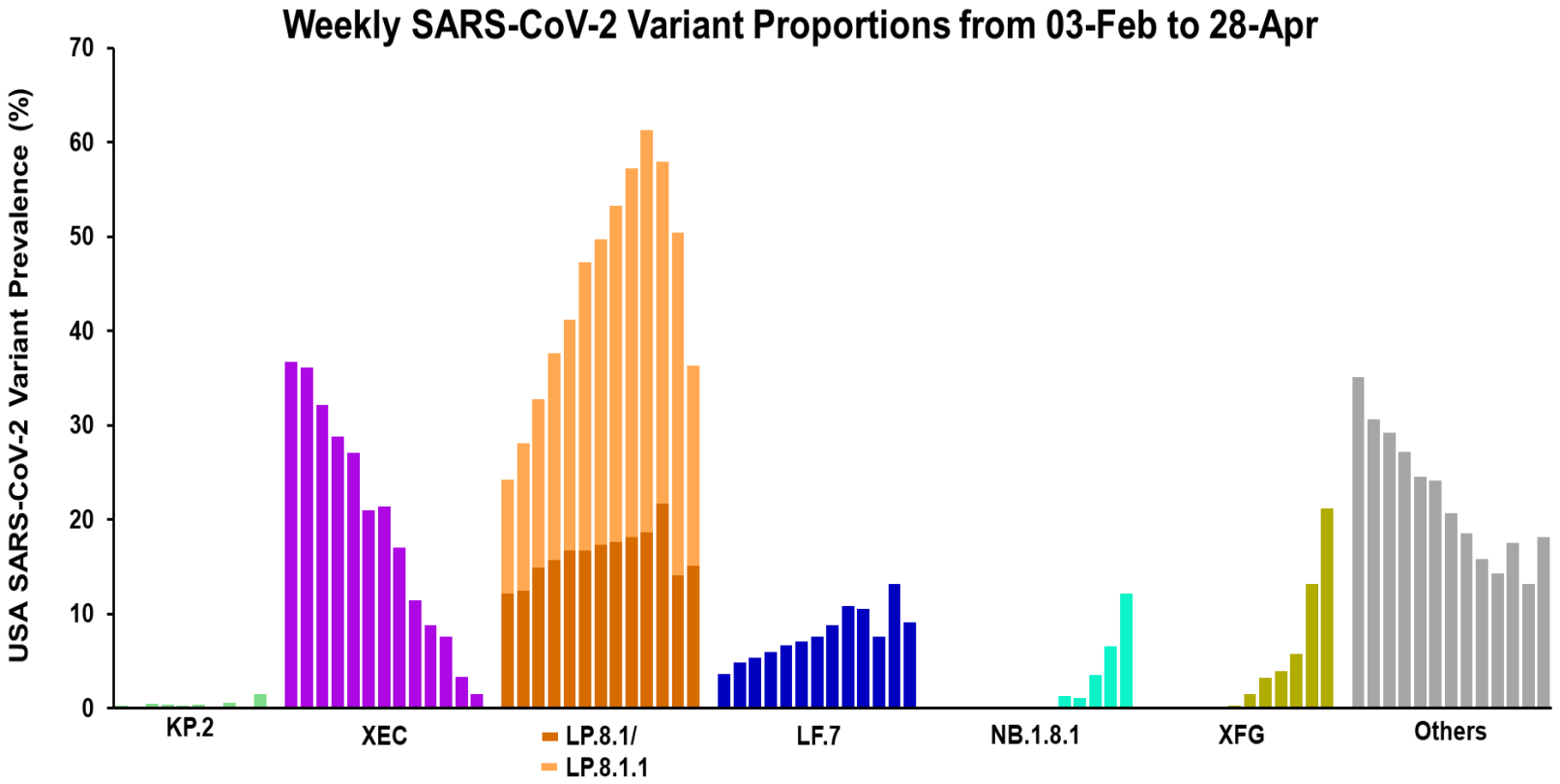
Evidence Supporting 2025-26 LP.8.1 Adapted Vaccine



Recent JN.1 Subvariants Exhibited Greater Antigenic Drift & LP.8 Emerged as the Dominant Variant in Spring 2025

VARIANT SURVEILLANCE
integrative analyses of genomic, structural, immunologic data





*Each box represents 1 antigenic unit = 2-fold difference in neutralization titer.
Antigenic map generated in Racmacs package in R using 2000 optimizations, with the minimum column basis parameter set to "none."
Generated from pseudovirus neutralization titers elicited by JN.1- and KP.2-adapted vaccines administered as a primary series to naïve mice.

After Licensure and Recommendation of LP.8.1-Adapted Vaccine, Focus on Rapidly Generating VE

U.S. FOOD & DRUG ADMINISTRATION

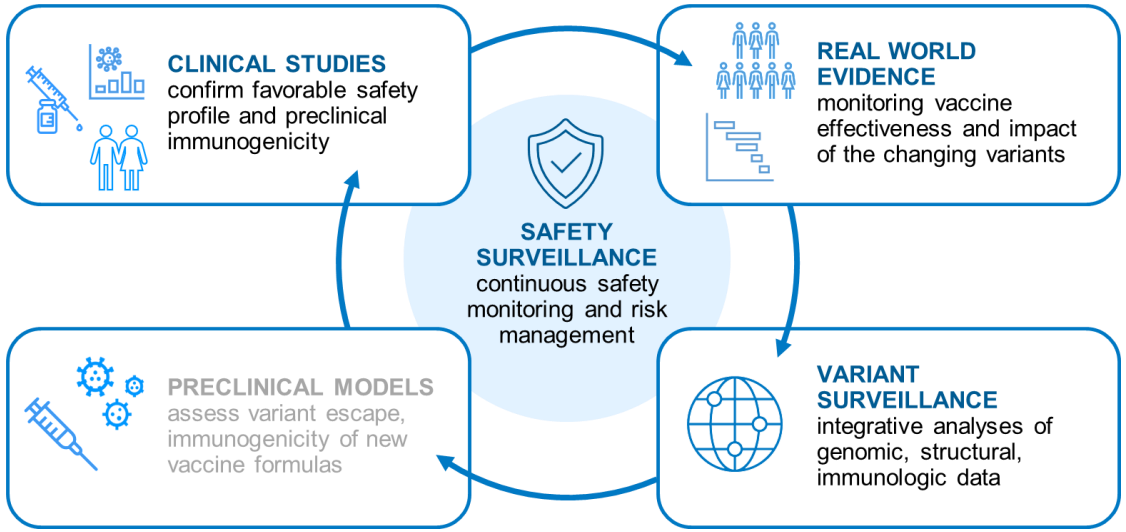
Home / Vaccines, Blood & Biologics / Resources for You (Biologics) / Industry (Biologics) / COVID-19 Vaccines (2025-2026 Formula) for Use in the United States Beginning in Fall 2025

COVID-19 Vaccines (2025-2026 Formula) for Use in the United States Beginning in Fall 2025

Based on the totality of the evidence, FDA has advised the manufacturers of the approved COVID-19 vaccines that to more closely match currently circulating SARS-CoV-2 viruses, the COVID-19 vaccines for use in the United States beginning in fall 2025 should be monovalent JN.1-lineage-based COVID-19 vaccines (2025-2026 Formula), preferentially using the LP.8.1 strain.

FDA will continue to monitor the safety and effectiveness of the COVID-19 vaccines and the evolution of the SARS-CoV-2 virus.

- Early Ph4 VE results in Q1
- Updated VE in Q2
- Ongoing variant surveillance a& preclinical studies to support strain selection for 2026-27



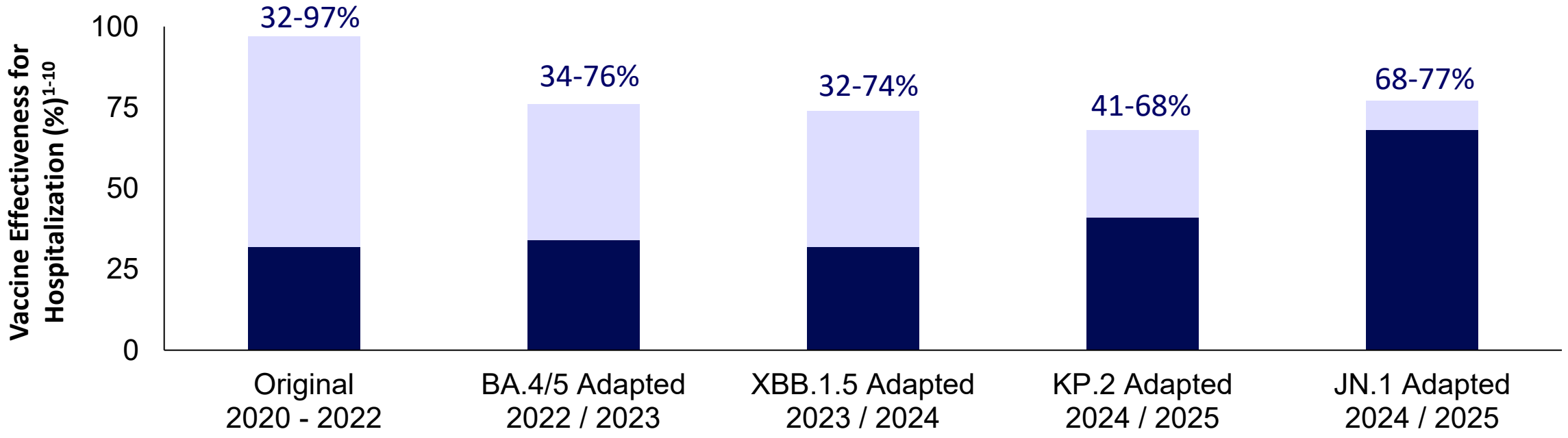
Conclusions

- Evidence supports consistent benefit of seasonal updates to vaccine formulas for antigenically divergent variants
- Annual process to develop variant-adapted vaccines begins and ends with real world vaccine effectiveness studies
- Integrating multiple types of preclinical, clinical and post-licensure VE data – each with their limitations – enables rapid access to updated COVID-19 vaccines

EXTRA SLIDES

Real-World Evidence Supports COMIRNATY's Continued Effectiveness

Real-World Evidence Shows Consistent Effectiveness Across Multiple Seasons and COMIRNATY Formulations

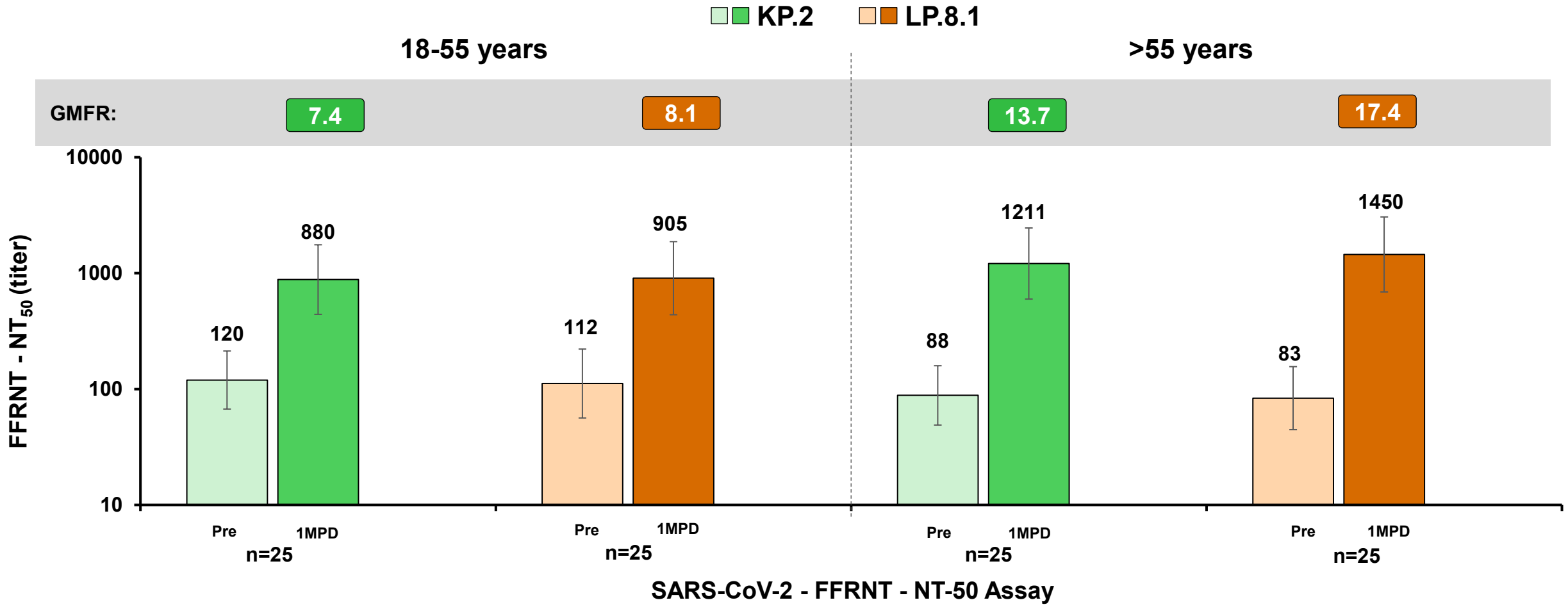


RWE: Real-world evidence; 1. Tartof et al. 2023. DOI: 10.1016/S2213-2600(22)00354-X 2. Tartof et al. 2022. DOI: 10.1016/j.lana.2022.100198 3. Tartof et al. 2023. DOI: 10.1016/S2213-2600(23)00306-5 4. Caffrey et al. 2024. DOI: 10.1016/j.lana.2022.100198 5. Tartof et al. 2024. DOI: 10.1093/ofid/ofae370 6. Pfizer data on file. 7. Appaneal et al. 2025. DOI: 10.1038/s41467-025-59344-7; 8. Hansen et al. Lancet Infect Dis . 2025 Jul 29:S1473-3099(25)00380-9. 9. Pfizer data on file, submitted to ID Week 2025; 10. Volkman, H, et al. Presented at Congress of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 12 April 2025 in Vienna, Austria.11. Wiegand et al. Vaccine. 2025 Mar 7:49:126808. Seasonal period defined October 2023 – April 2024; Annual period defined September 2023 – August 2024. ICU: Intensive care unit

Clinical Trial: KP.2-Adapted Vaccine Elicits Robust Neutralizing Responses Against KP.2 and LP.8.1 Variants

CLINICAL STUDIES confirm favorable safety profile and preclinical immunogenicity

Evaluable immunogenicity population – KP.2 Adapted Vaccine



All participants were ≥18 years old; vaccine naïve or vaccine experienced with last COVID-19 vaccine being administered at least 150 days prior to enrollment.
GMFR = Geometric Mean Neutralizing Titer Fold Rise; Pre = pre-vaccination; 1MPD = 1-month post-vaccination; FFRNT = fluorescent focus reduction neutralization test

Strengths and limitations of RWE

Strengths

Population
May include broad and heterogeneous patient population[1]

Sample size
Can address questions that require large patient populations or long follow-up, including the identification of rare AEs[1]

Vaccine impact
Can estimate burden of COVID-19 in a population and potentially measure impact of vaccination[2]

Outcomes
Can potentially be used to study a broad range of endpoints, ranging from asymptomatic to severe infections[2]

Limitations

Population
May be biased if unvaccinated and vaccinated participants have considerably different demographic and clinical characteristics[3]

Prior exposure
Residual protection from prior doses or infection might make it challenging to interpret VE[3]

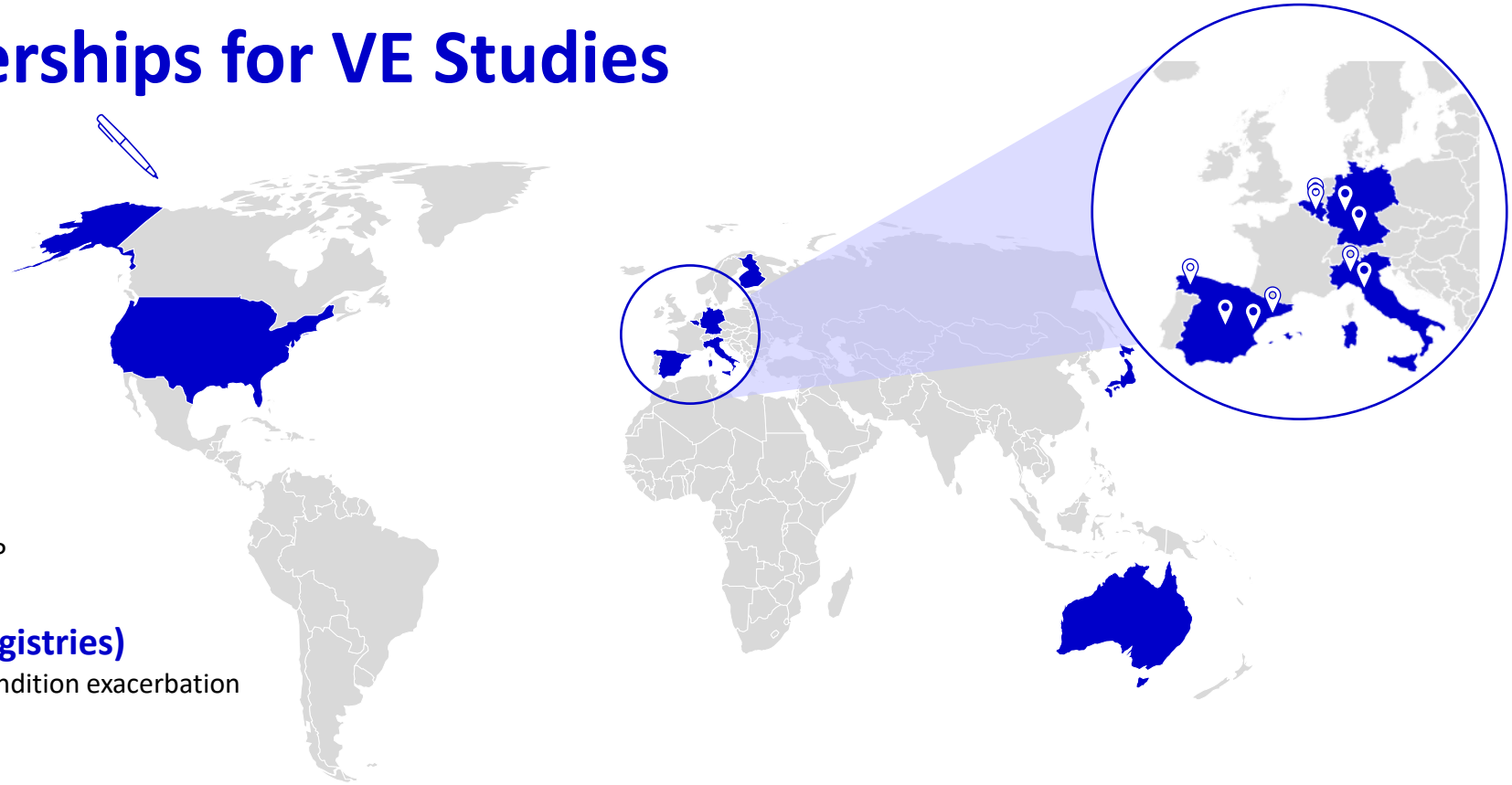
Misclassification
Misclassification of exposure and outcomes[2]

Confounding factors
Potential for residual and unmeasured confounding due to differences in patient-level and community-level factors (e.g., age, health status, healthcare-seeking behavior)[2,4]

AE, adverse event; RWE, real-world evidence; VE, vaccine effectiveness.

1. Garrison LP Jr et al. *Value Health* 2007;10:326–335; 2. World Health Organization. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1 (accessed April 2024); 3. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-24/COVID-07-Britton-508.pdf (accessed April 2024); 4. Tartof SY et al. *Lancet Infect Dis* 2022;22:1663–1665.

Priority Research Partnerships for VE Studies



USA

- **Kaiser Permanente***
  >200 sites in Southern California
  VE against critical illness, hospitalization, ED, UC, DOP

- **Veterans Affairs (VA) Administration**
  ~1,500 sites nationwide
  VE against hospitalization, ED, UC, Long COVID, risk factors, DOP

- **RAVEN (Claims Data Linked to State Vaccine Registries)**
  VE against hospitalization, ED, UC, Long COVID, DOP, chronic condition exacerbation

Europe

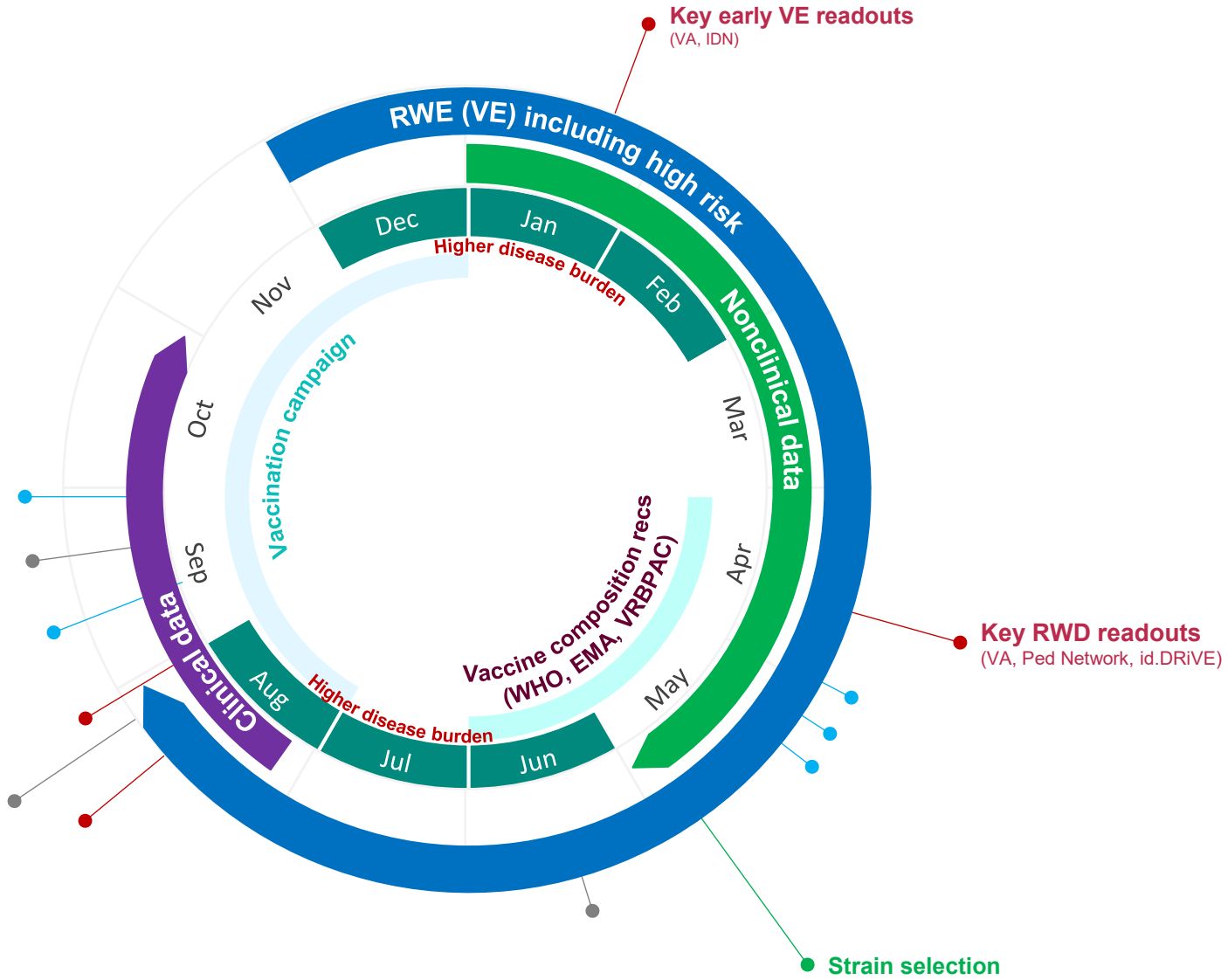
- **id.DRIVE**
  24 sites across Europe
  VE against hospitalization/ICU/death/DOP

Australia

- **Queensland**
  VE against ED/hospitalization/death/DOP
  Publications expected: Q325

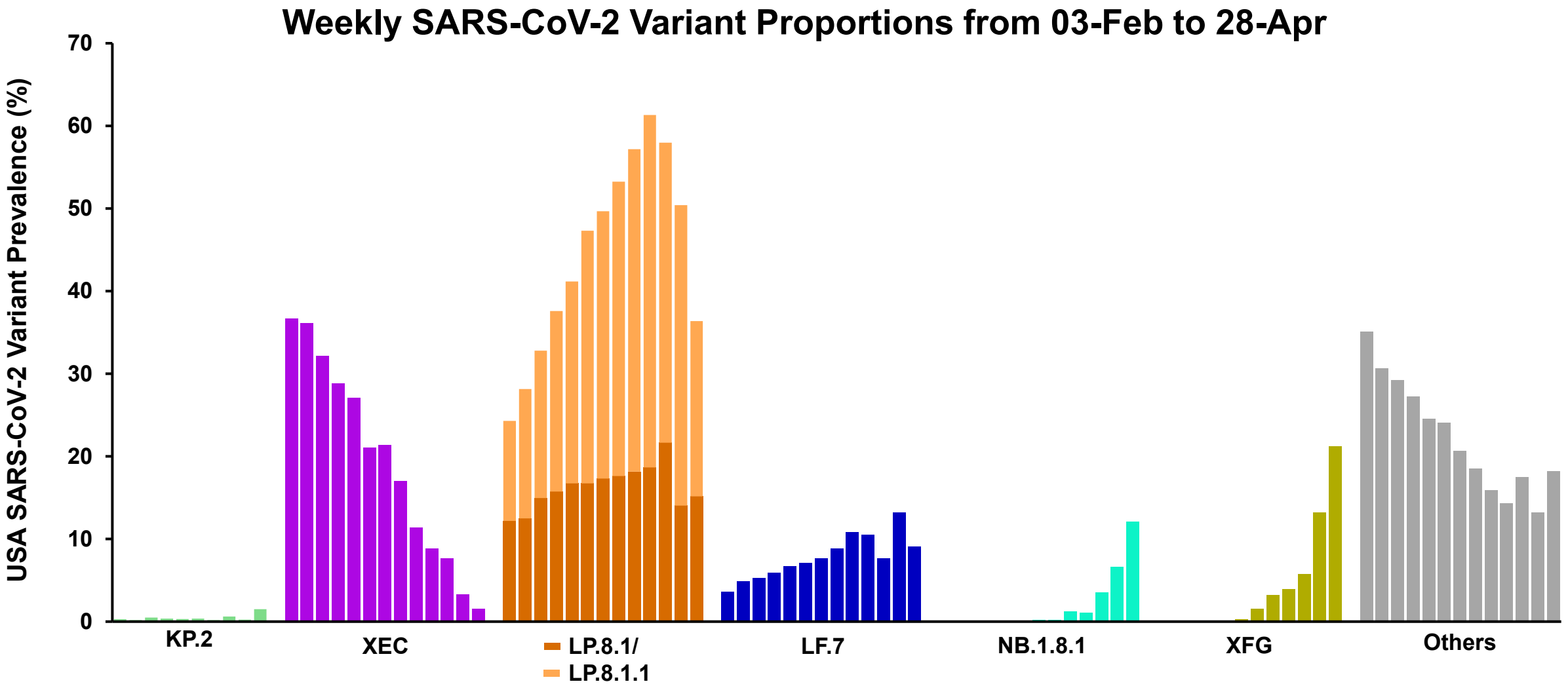
*KPSC no longer available as a site after 2024–25 season, recommendation to replace this gap with another IDN

Key Data Generation Cycle - Comirnaty®



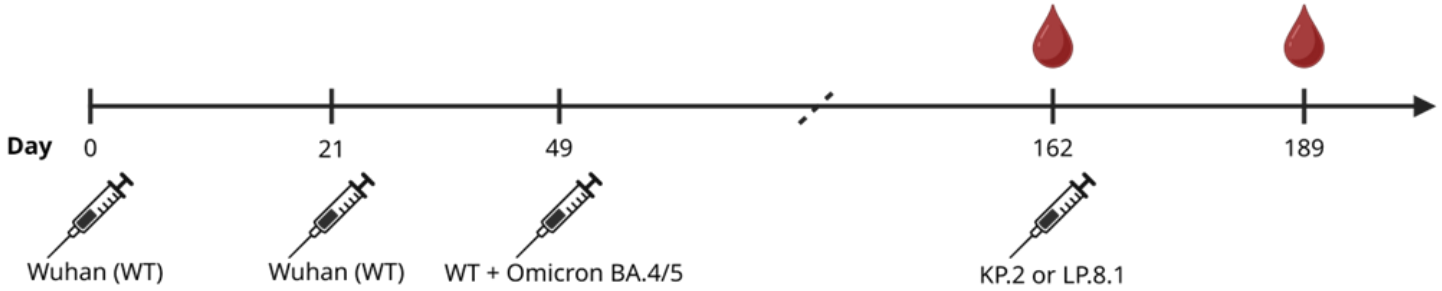
*Medical education plan includes regular materials (slides, webinars, videos, etc) on disease burden, studies, educational materials, RWE, country interactions, regulatory updates, advisory boards, etc

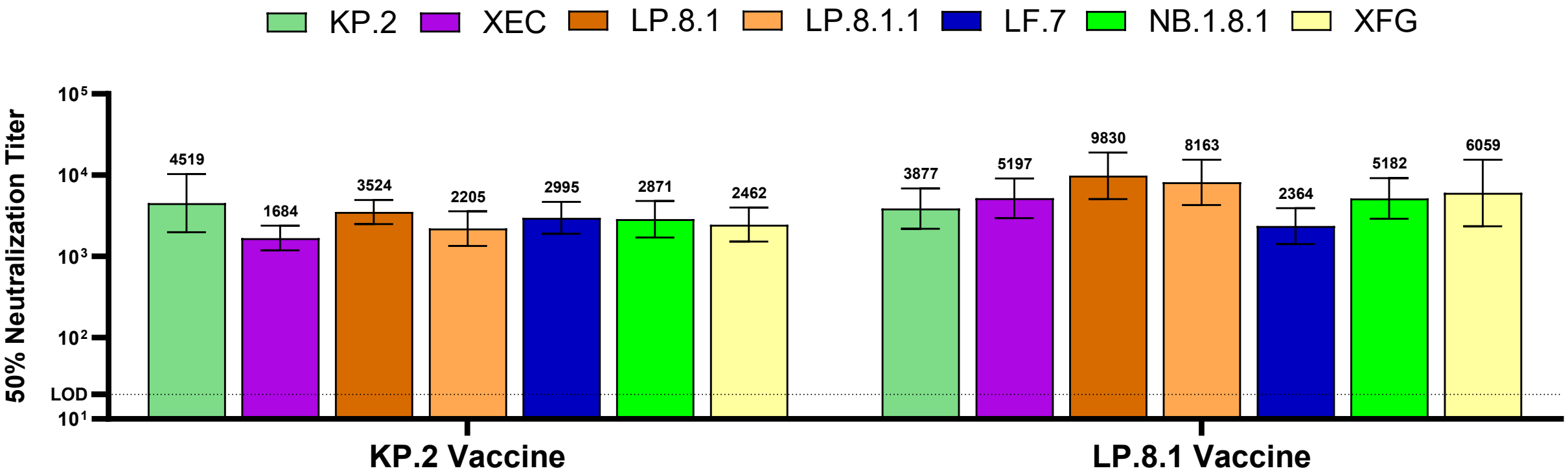
LP.8.1 is Dominant Variant; Emerging Variants Rise in Prevalence



Source: GISAID - gisaid.org; data accessed/analysed/plotted within Pfizer, as of May 11, 2025. Each individual labelled variant includes all subvariants including those with the same Spike protein amino acid sequence. Each bar represents 1 week's variant prevalence data.

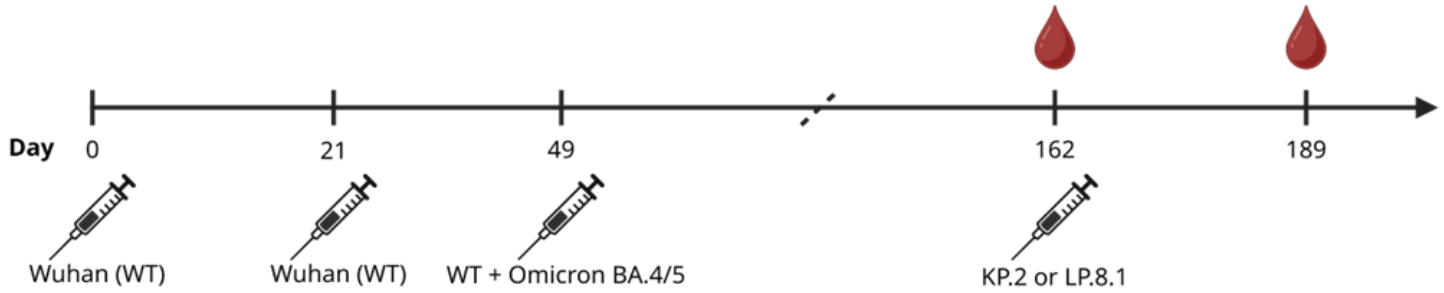
LP.8.1 Vaccine Elicits Broadly Cross-Reactive Neutralizing Responses in Vaccine-Experienced Mice

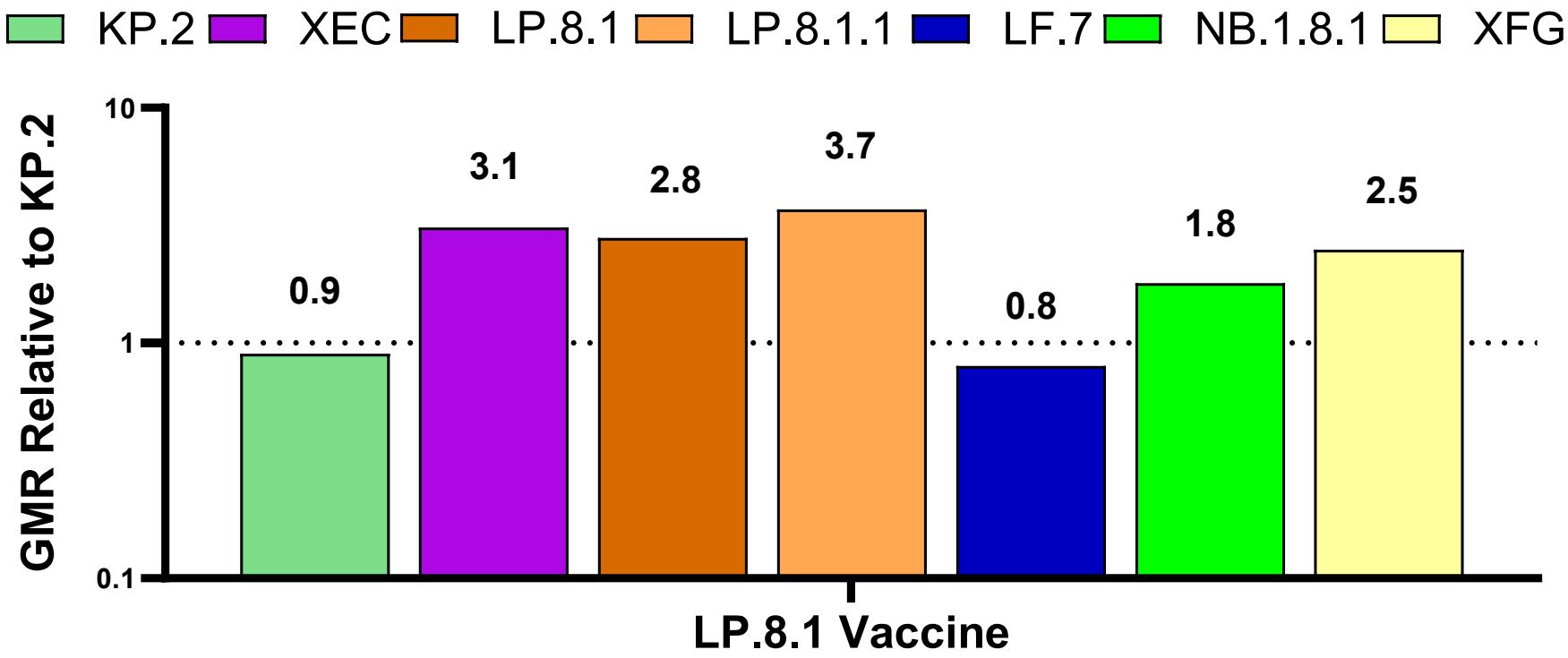




Neutralization titers measured by pseudovirus neutralization assay.
N = 10 mice per vaccine group. Vaccine dose 0.5 μg.

LP.8.1 Vaccine Elicits Improved Neutralization Compared to KP.2 Vaccine in Vaccine-Experienced Mice





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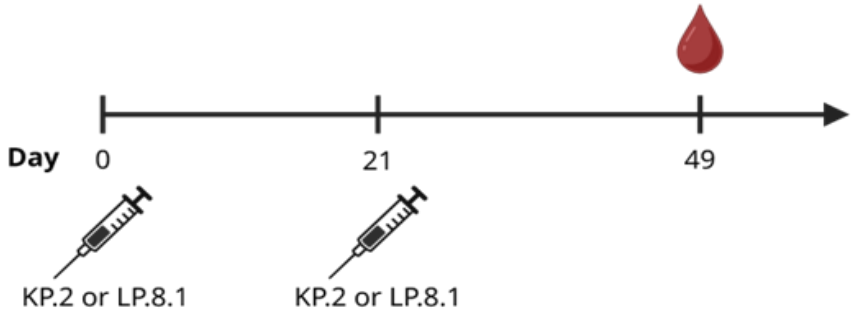
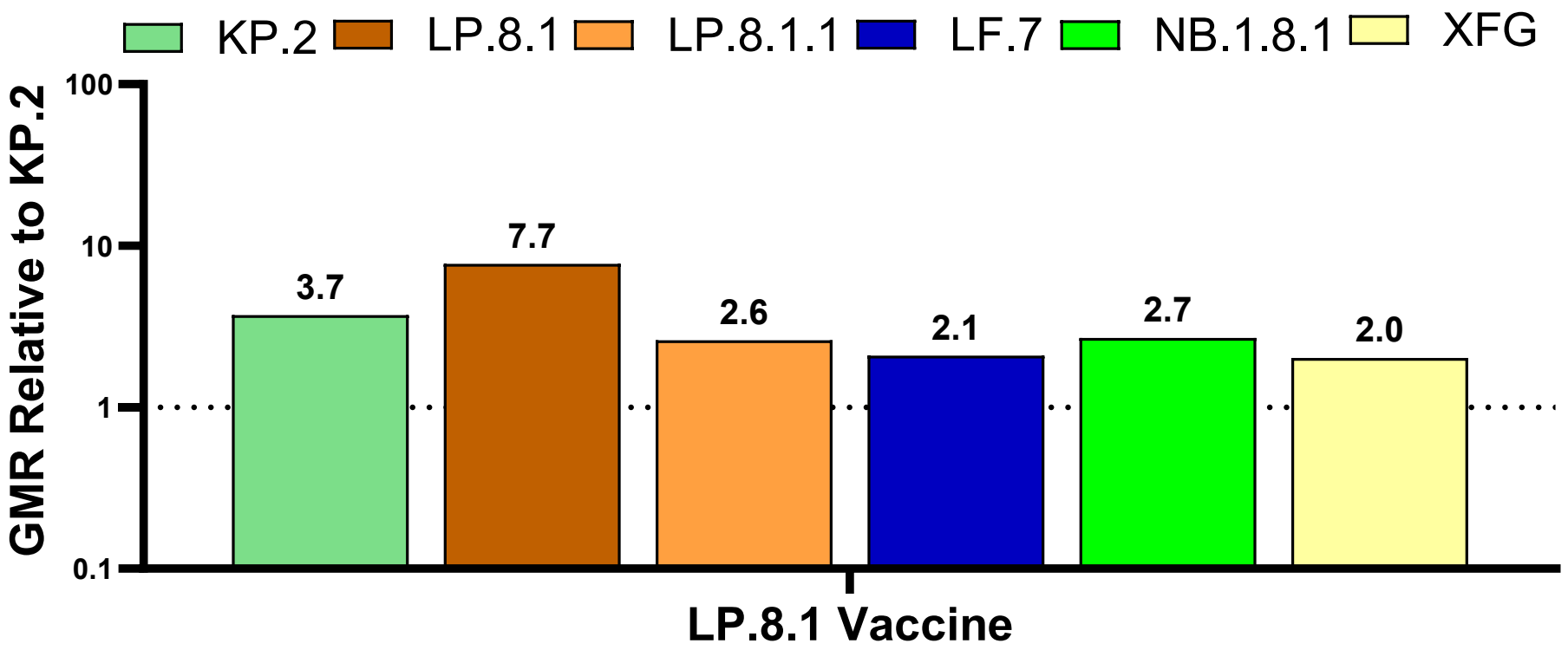
GMR = Geometric Mean Ratio of 50% neutralization titers.
N = 10 mice per vaccine group. Vaccine dose 0.5 μg.

LP.8.1 Vaccine Elicits Improved Neutralization Compared to KP.2 Vaccine in Vaccine-Naïve Mice





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