M2SR: Cell-based Flu Vaccine and Platform for Infectious Diseases

WVC 2023 Barcelona

19 October 2023

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InVitria

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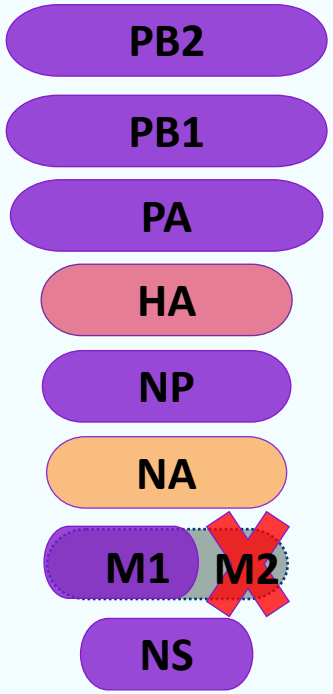
Next Generation COVID/Influenza Vaccines: Key Unmet Needs

- Enhanced breadth of protection (drift/variant strain protection)
- Improved durability
- Enhanced ability to block infection/transmission

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M2SR (M2-deleted Single Replication) Virus – Natural Delivery of RNA to the Site of Infection

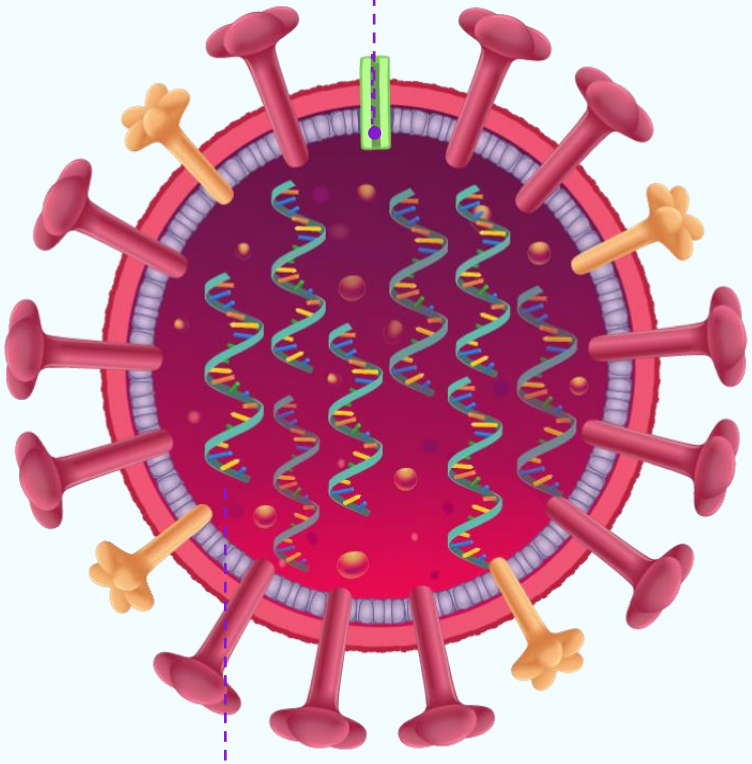
DNA Plasmids Encoding M2SR Genome



M2 Expressing

Production Cell Line

M2 viral matrix protein — essential for virus infection



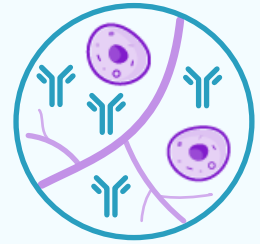
RNA segments with conserved proteins—

M2SR Vaccine

Mobilizing the Entire Immune System



Mucosal



Humoral



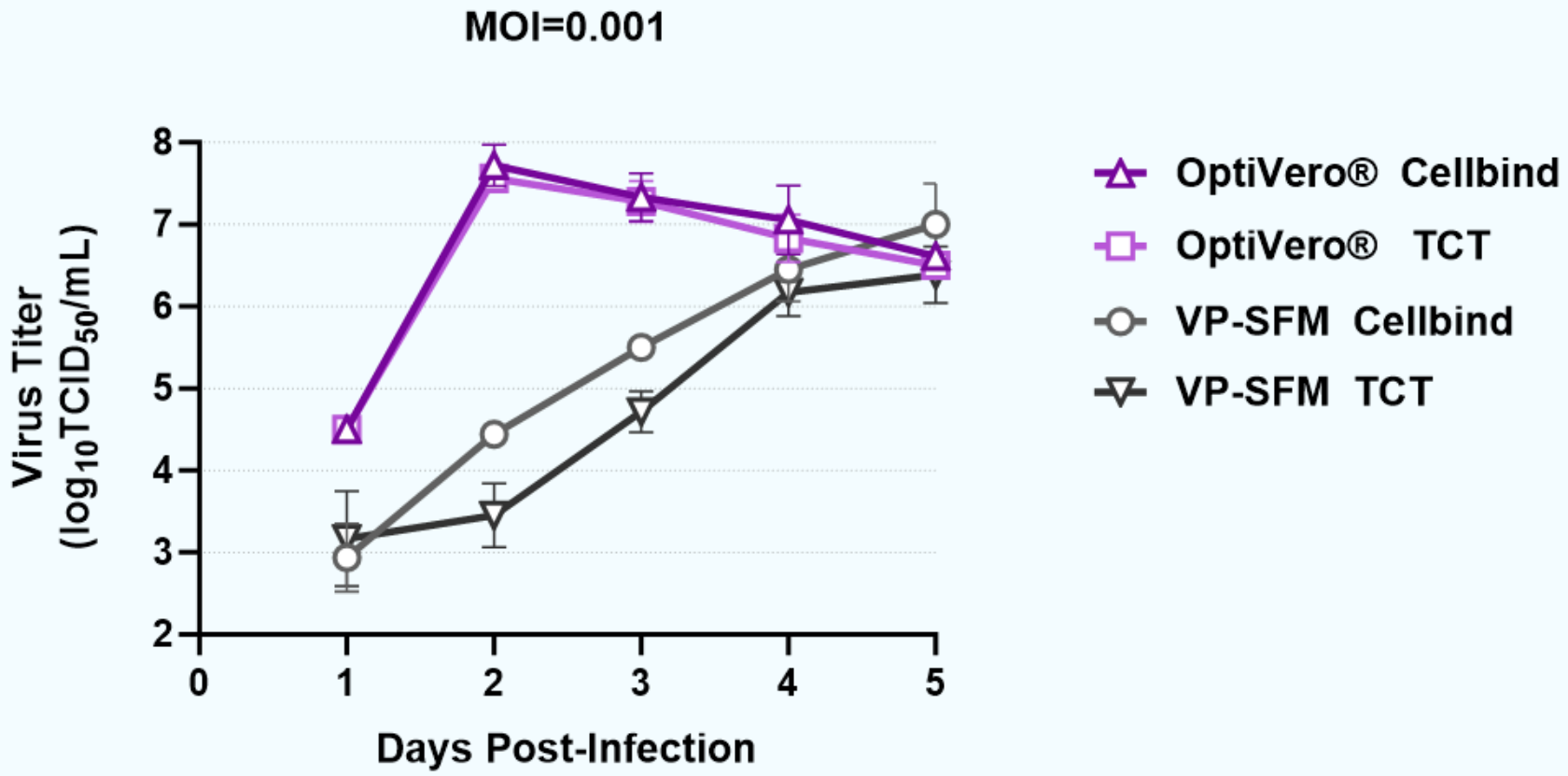
Cellular

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No vaccine virus shedding after vaccination

Chemically-Defined OptiVero Media Improves M2SR Vaccine Virus Production In M2Vero Cells

Bris2007 H3N2 M2SR influenza vaccine virus in M2Vero cells



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Chemically-Defined OptiVERO supplied by

INVITRIA Performance. Defined.

Robust Virus Rescue System in Production Vero Cells for Influenza A and B

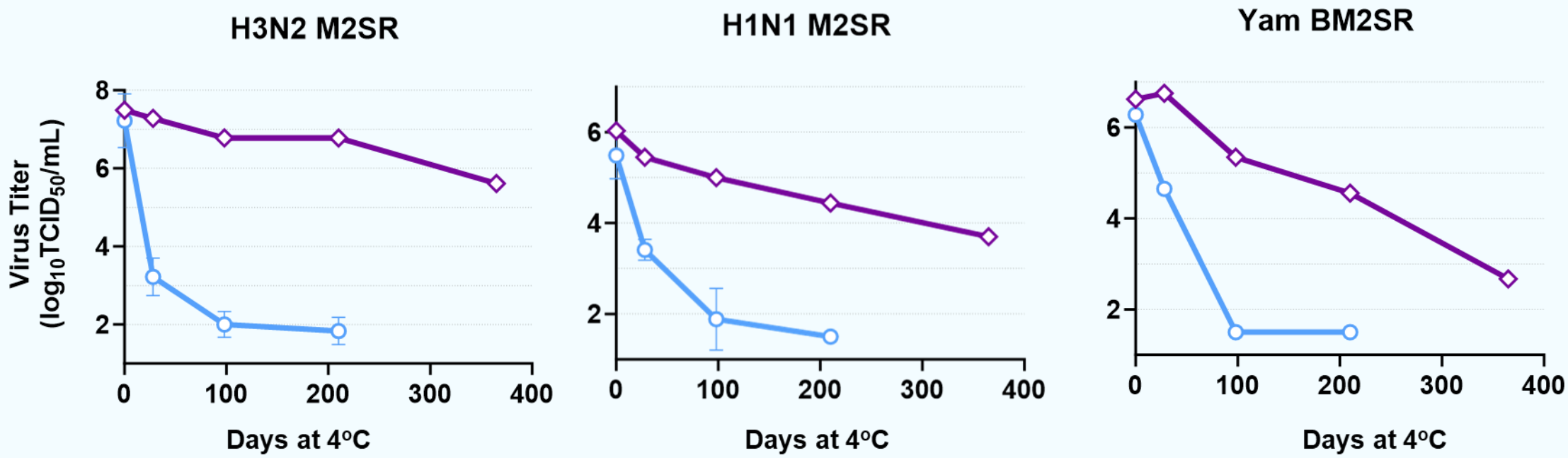
Influenza A M2SR viruses	
H3N2	Brisbane/10/2007 *
	Hong Kong/4801/2014
	Texas/50/2012
	Singapore/INFMH-16-0019/2016 *
	Cambodia/E0826360/2020 *
H1N1	Puerto Rico/8/1934
	Brisbane/59/2007
	California/07/2009
	Massachusetts/15/2013
	Michigan/45/2015
	Montana/50/2015 *
H5N1	Vietnam/1203/2004
H7N9	Anhui/1/2013

Influenza B BM2SR viruses	
	B/Lee/1940
Yamagata	B/Wisconsin/01/2010
	B/California/12/2015 *
Victoria	B/Brisbane/60/2008
	B/Brisbane/46/2015
	B/Colorado/06/2017
	B/Washington/02/2019 *
	B/Austria/1359417/2021

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* GMP banks generated at CDMOs

M2SR Influenza Vaccine Virus Stability at 2-8°C



- **Sucrose Phosphate + Exbumin® rHSA**
- **Sucrose Phosphate Buffer**

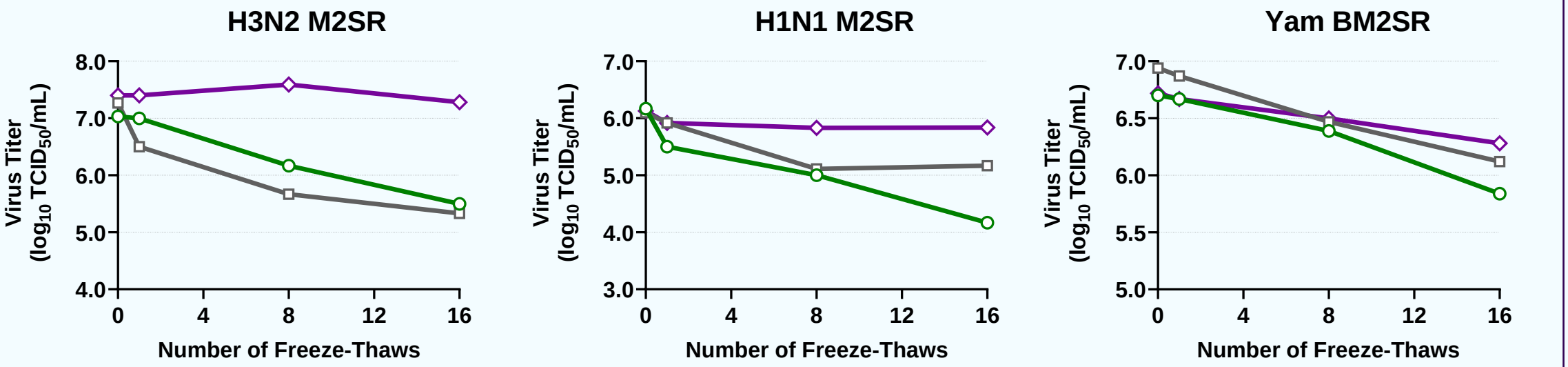
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Exbumin

Recombinant human serum albumin (“rHSA”) supplied by INVITRIA Performance. Defined.

M2SR Influenza Vaccine Virus Stability After Multiple Freeze/Thaw Cycles



- **Histidine Buffer + rHSA Exbumin®**
- **Histidine Buffer**
- **Histidine Buffer + CMC**

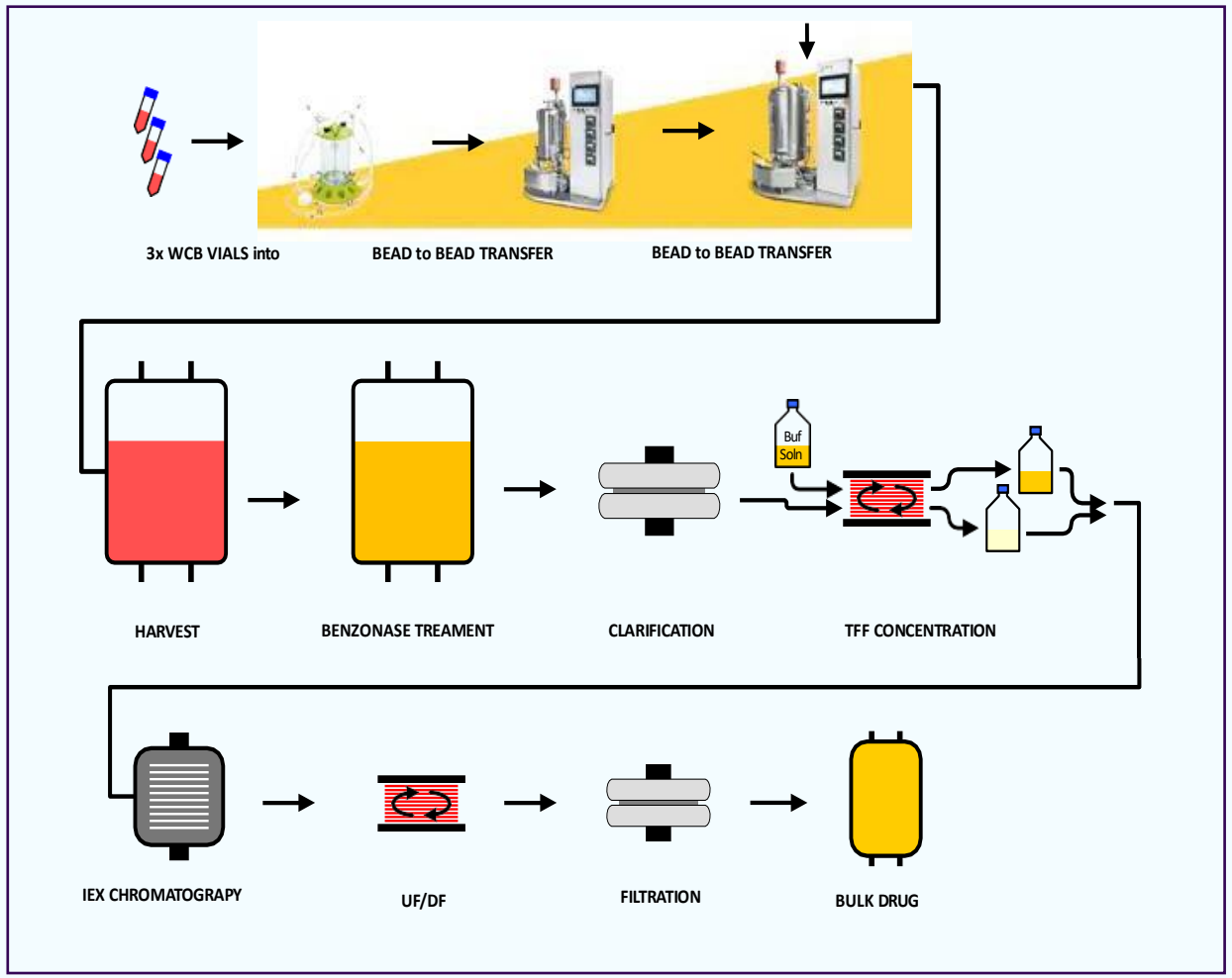
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Exbumin

Recombinant human serum albumin (“rHSA”) supplied by INVITRIA Performance. Defined.

M2SR Vaccine Cell-based Production Process



- GMP clinical trial material for H3N2 produced at 50L scale
- Robust process
- 3 different H3N2 strains
- 3 different CDMOs
- Animal origin free production process

OptiVERO

- Chemically-Defined Media (“OptiVERO”) supplied by

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Performance. Defined.

M2SR H3N2 Influenza Vaccine Administered to ~700 Subjects 2 – 85 Years of Age

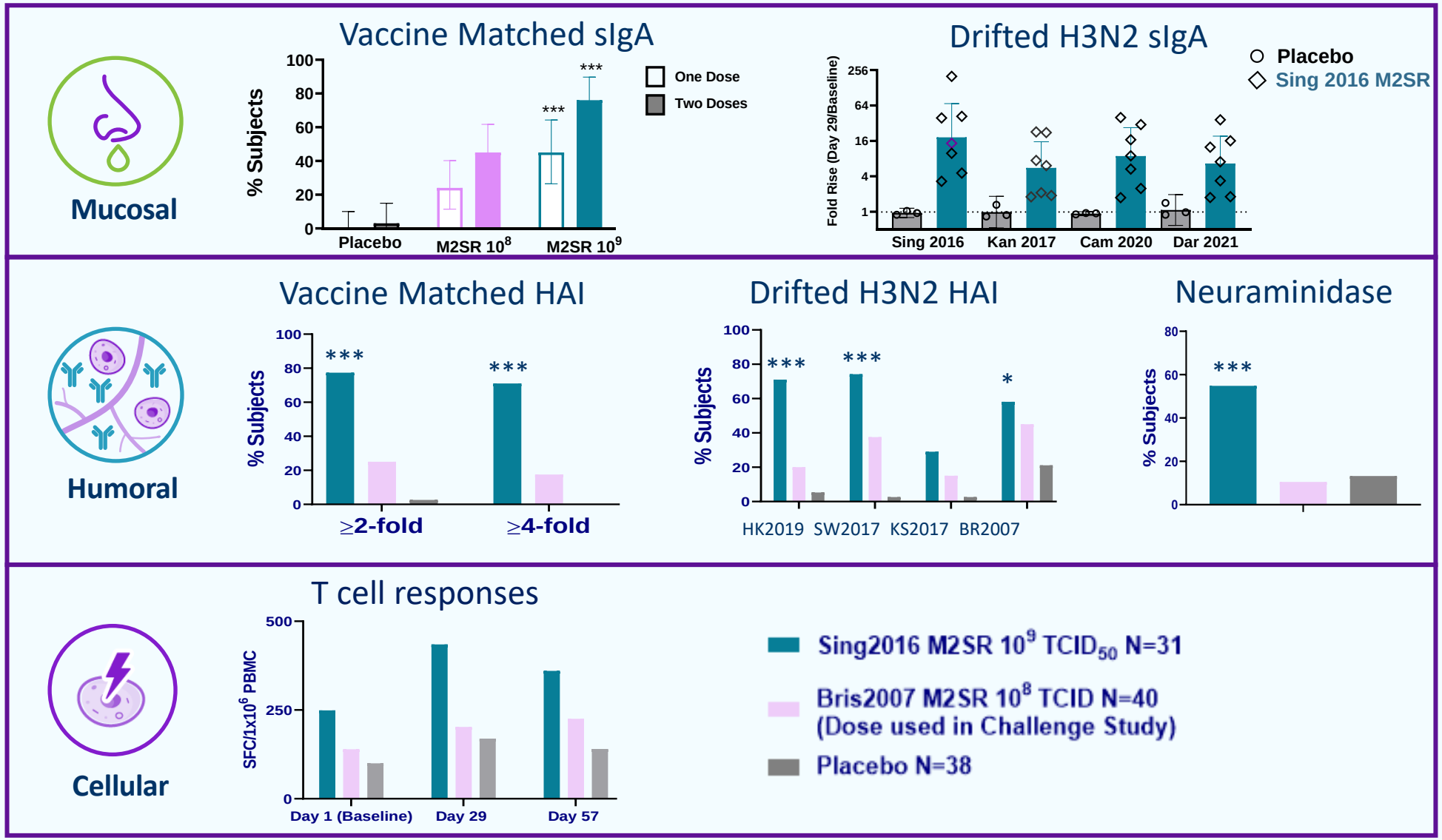
Study #	Phase	Period	Purpose	Country	Vaccine Strain	Dose ($TCID_{50}$)	Population Ages	N (target)
V001	1a	2016-2017	FTIH	US	Bris 2007	10^6 - 10^8	18-49	96
V002	2a	2018-2019	Drifted H3N2 challenge	Belgium	Bris 2007	10^8	18-55	108
17-0012	1b*	2018-2020	Adolescent, safety	US	Bris 2007	10^8	9-17	43
V003	1b	2019-2020	Dose finding & repeat dose	US	Bris 2007 Sing 2016	10^8 - 10^9	18-49	206
V005	1b	2021	Older adult, safety	US	Sing 2016	10^9	50-85	122
20-0009	1b**	2021-2022	Pediatric, safety	US	Sing 2016	10^7 - 10^9	6m-17	(220)
V006	1b	2022	Older adult, safety & concomitant	US	Cam 2020	10^9	65-85	305

M2SR well tolerated at all dose levels across all age ranges tested; no IP-related SAEs

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*conducted by NIH VTEU
**conducted by NIH CIVICs: planned completion in 2023

M2SR H3N2 Broadly-reactive, Multi-faceted Immune Response



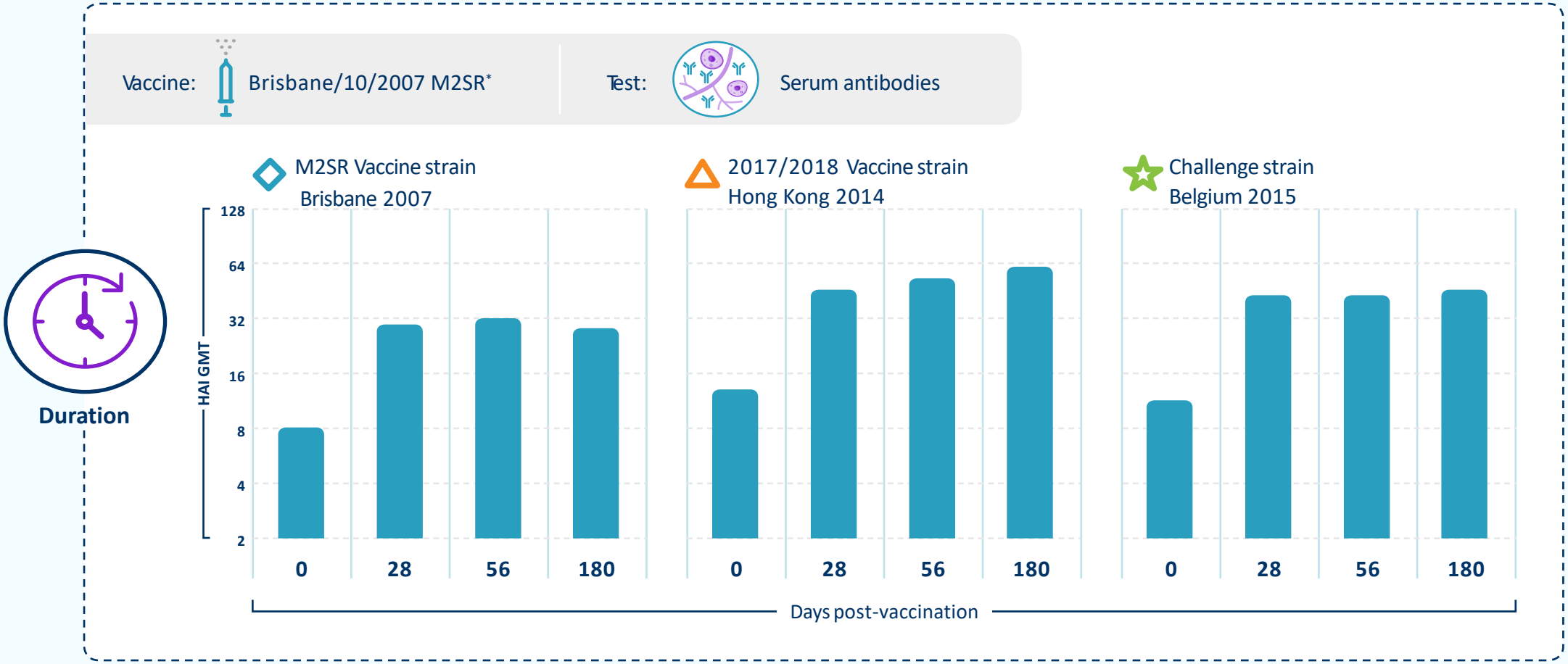
***P<0.001, *P<0.1

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Study V003

Eiden, 2022, JID

Single, Intranasal Dose of M2SR Induces Durable Antibody Response Against H3N2 Matched and Drift Strains in 18-49 Year Olds

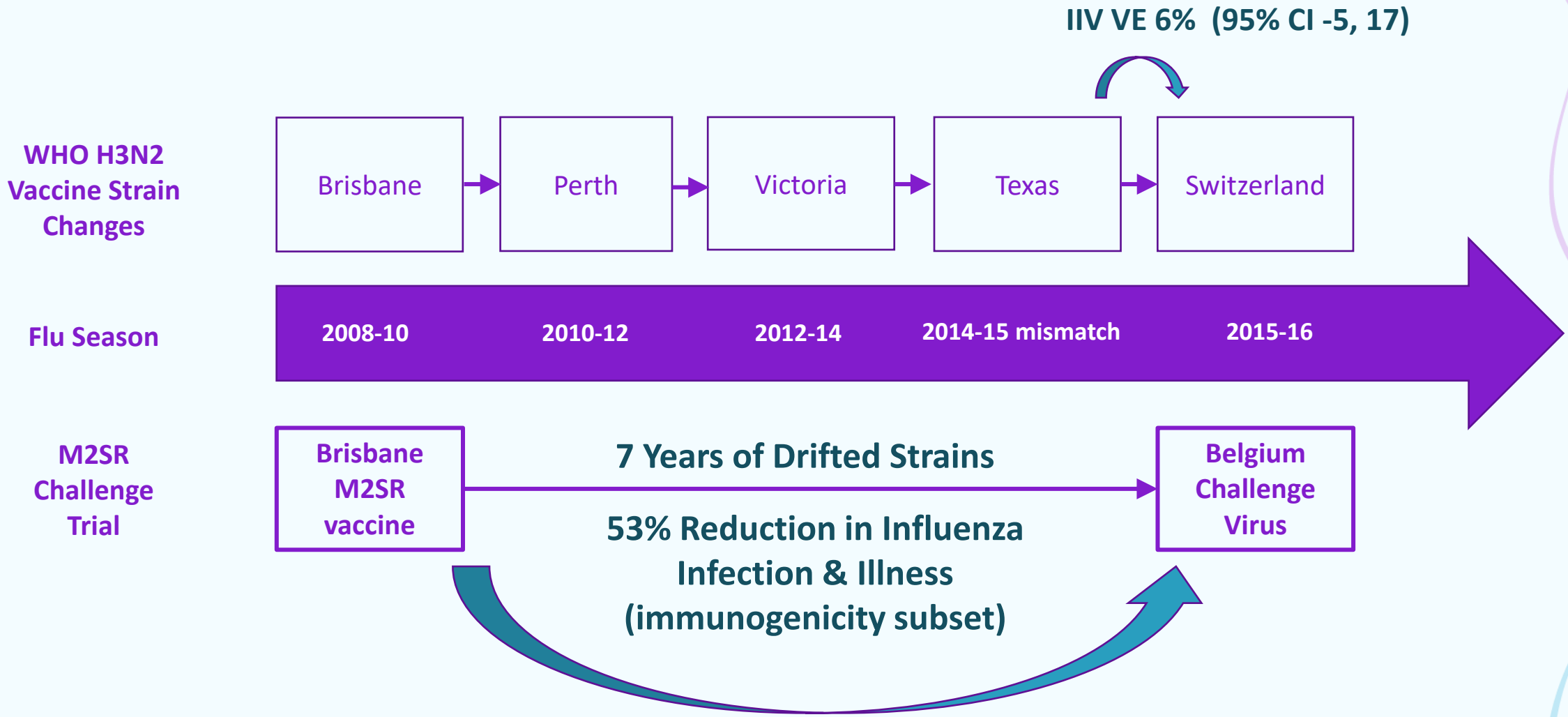


*Subjects that demonstrated serum HAI response, 10/24 (42%).

Study V001

Eiden, 2021, Vaccines

M2SR H3N2 Signals Protection Against Infection & Illness: Even Against Substantially Drifted Strains

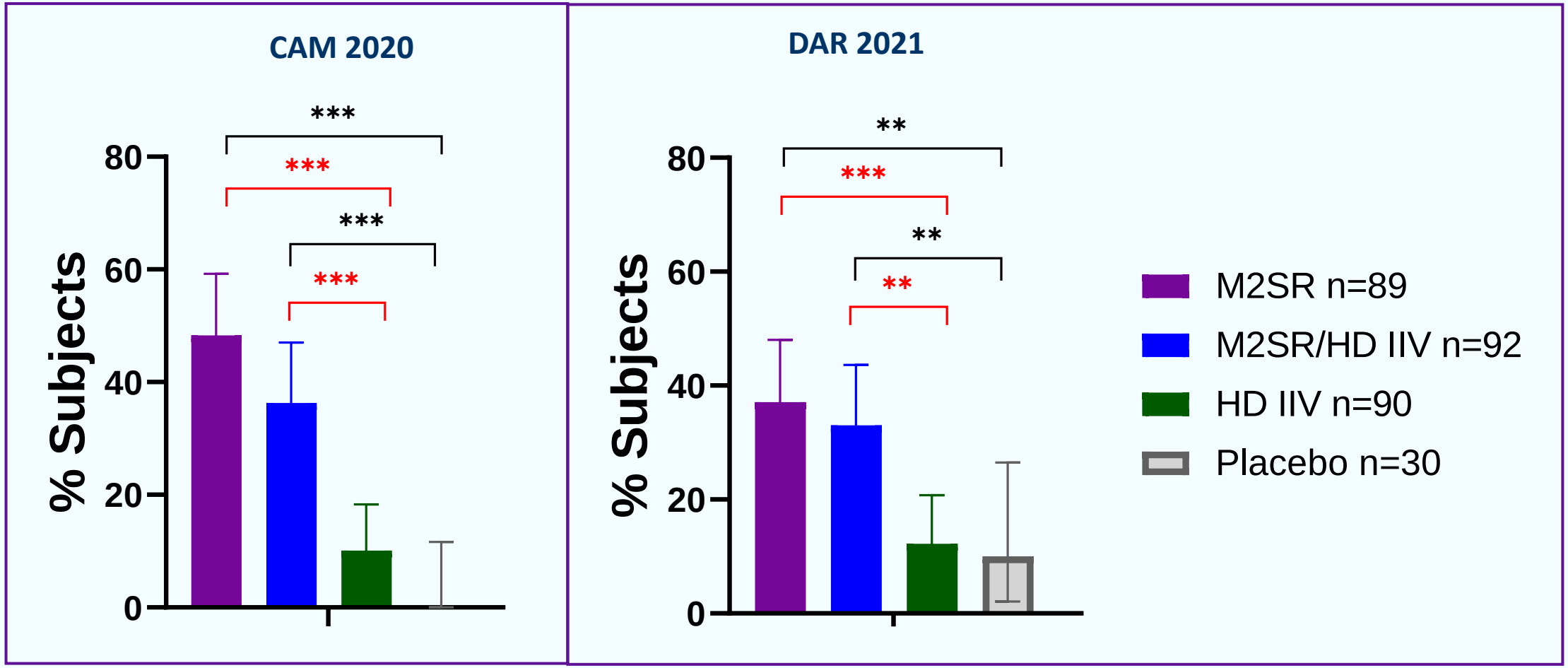


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Study V002

Eiden, 2021, JID

M2SR Generates Significant Mucosal Antibody Responses Against Matched and Drifted H3N2 Viruses in 65-85 Year Olds



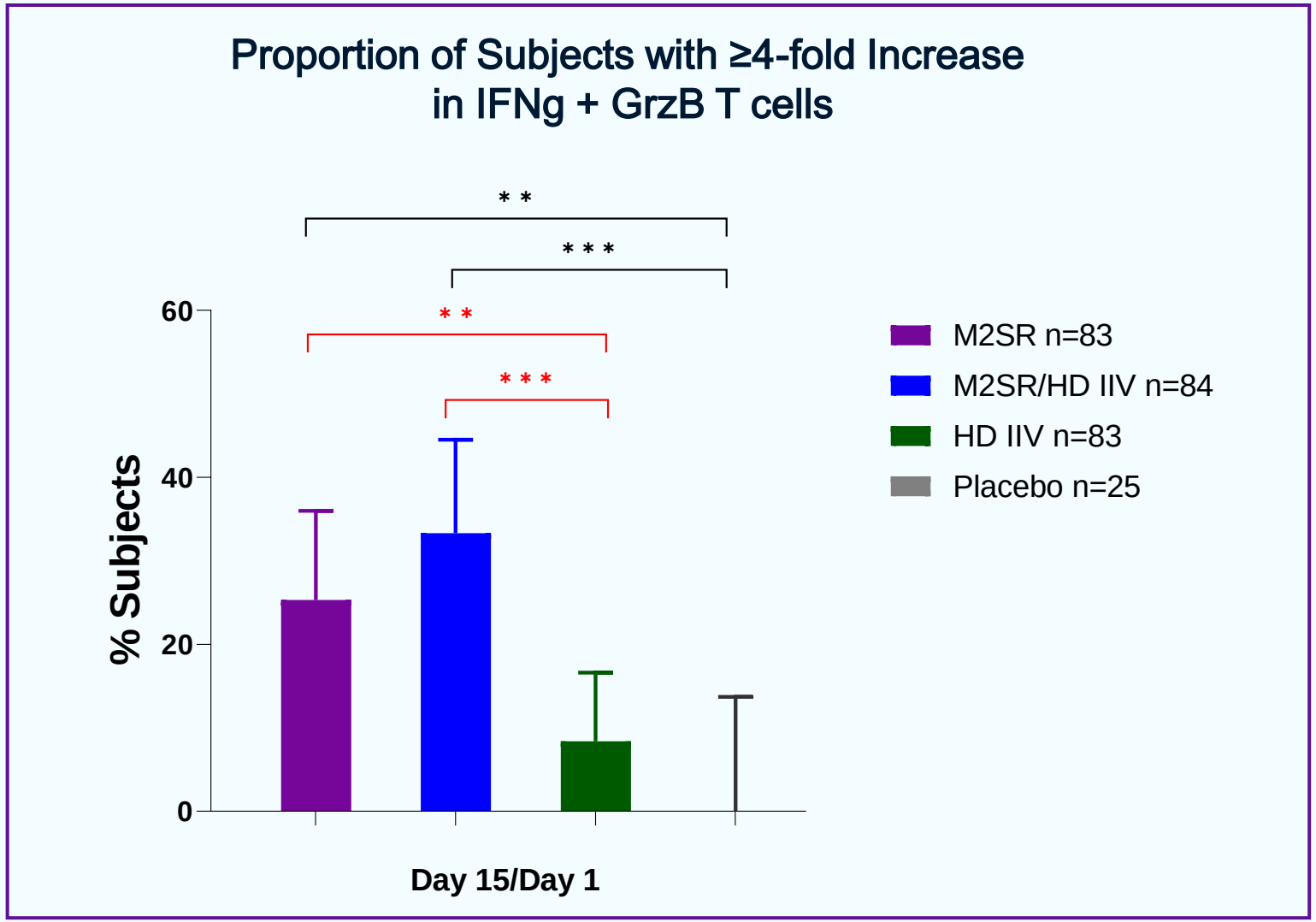
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65-85 year olds

p<0.01,*p<0.0001

Error bars=95% Confidence Interval

M2SR Elicits Significant T Cell Responses in 65-85 Year Olds



65-85 year olds

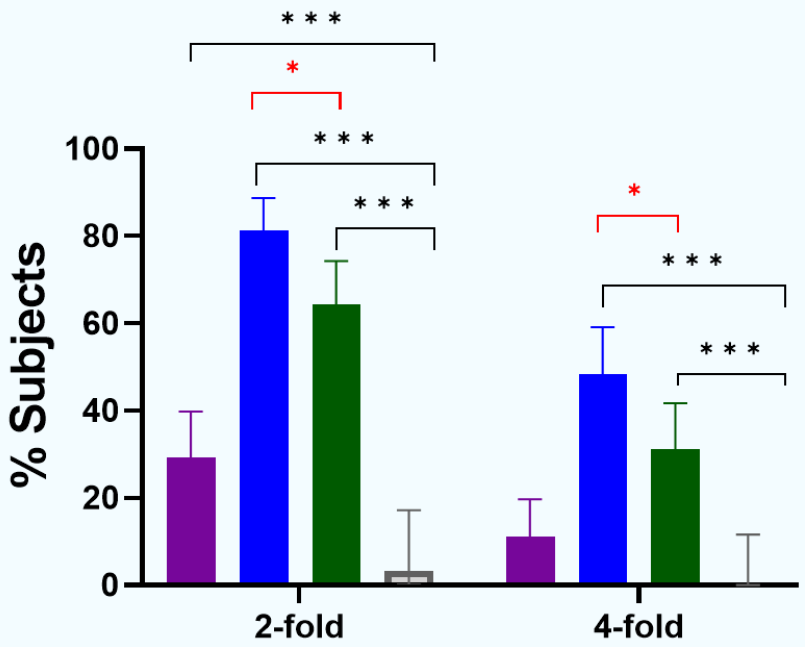
p<0.01,*p<0.0001

PBMCs stimulated with NP peptide pool, Elispot

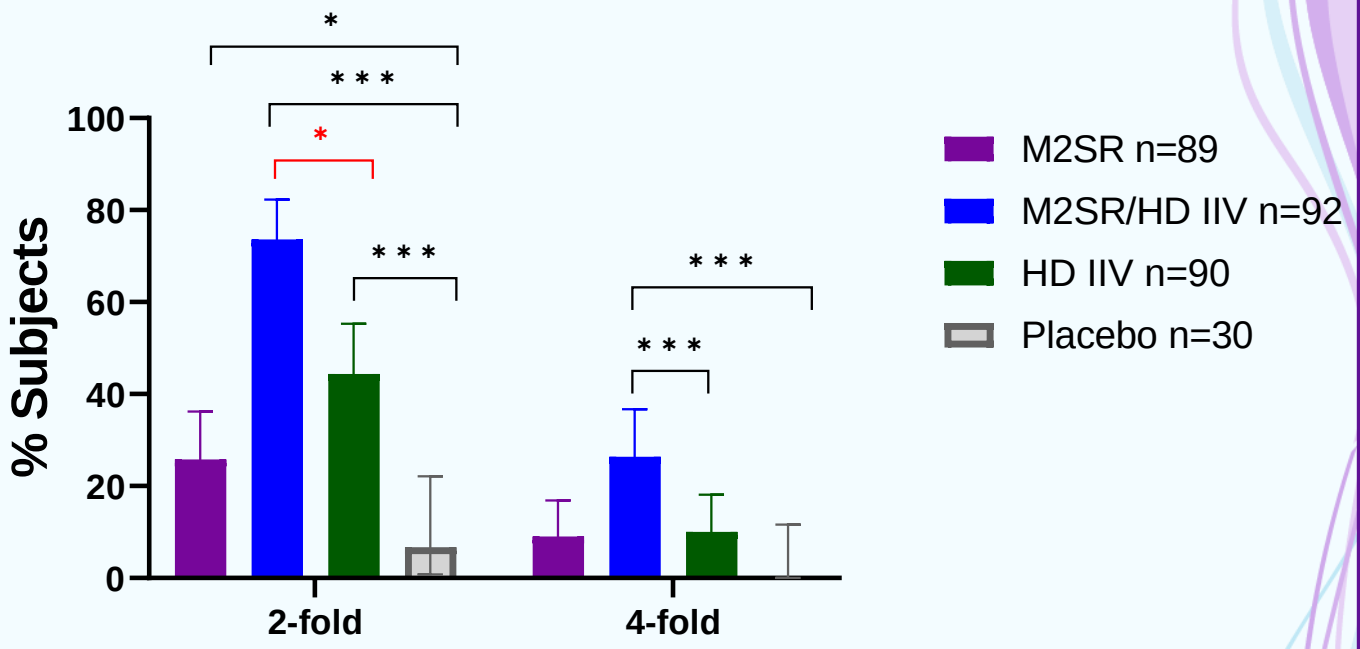
Error bars=95% Confidence Interval

M2SR and M2SR/Fluzone HD Combination Generates Significant Seroconversion Against Cambodia 2020

Proportion of Subjects with ≥2 and ≥4-fold Rise in Cam 2020 HAI Titer 28 Days Post Vaccination



Proportion of Subjects with Rise in Cam 2020 NAI Titer 28 Days Post Vaccination

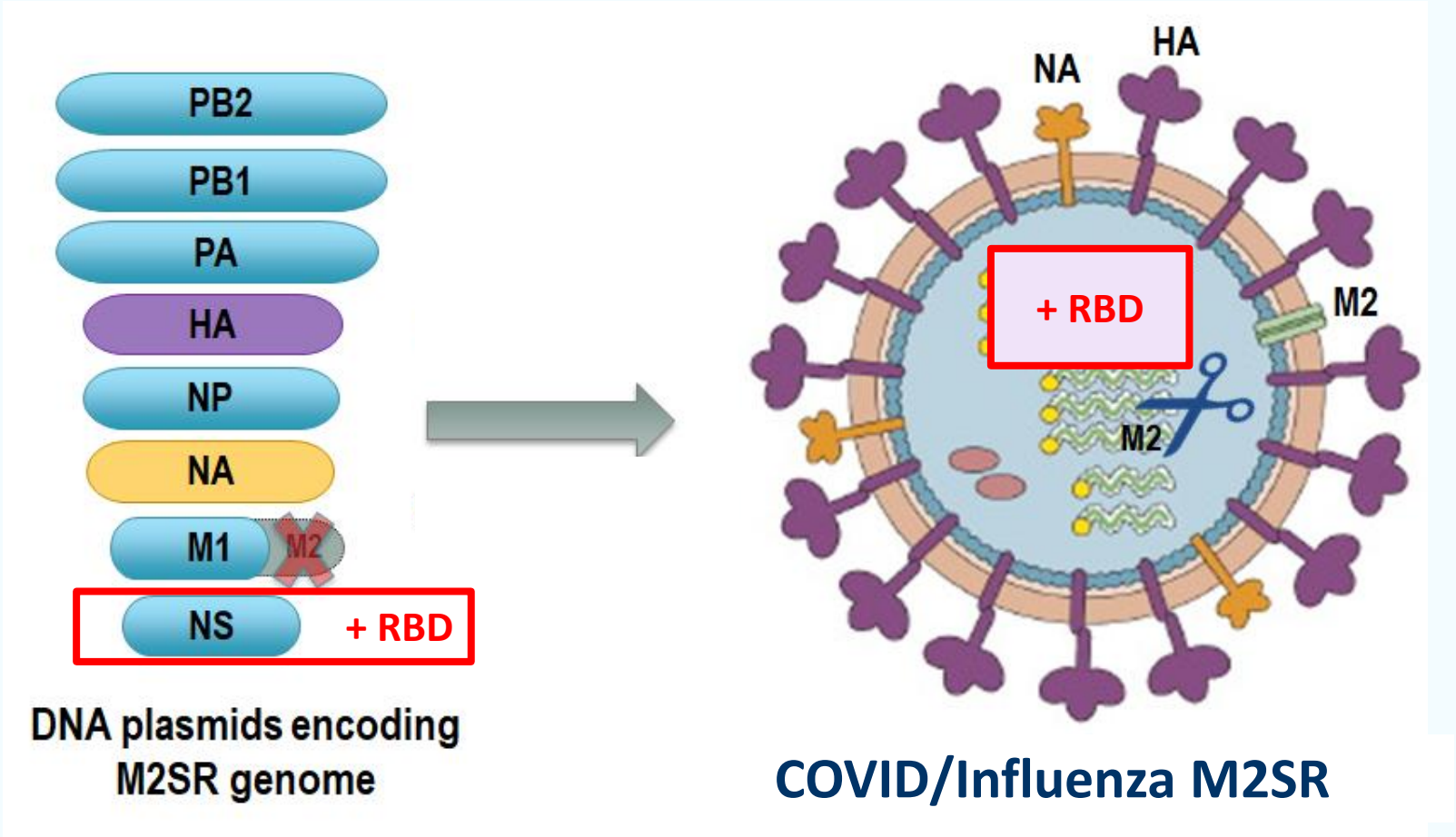


65-85 year olds

*p<0.05, ***p<0.0001
Error bars=95% Confidence Interval

M2SR COVID/Influenza Dual Vaccine Candidate

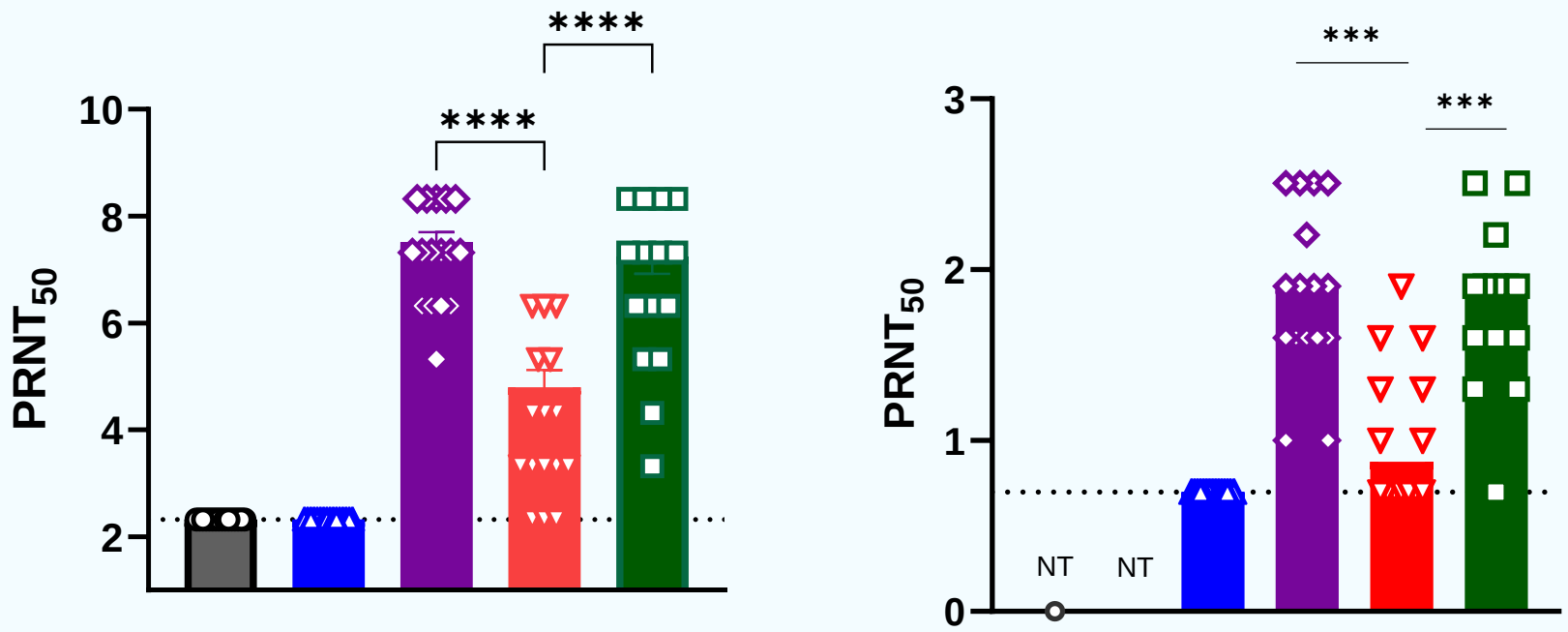
RBD=Receptor Binding Domain of Wuhan SARS-CoV2 inserted into influenza genome



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M2SR SARS-CoV2 (Wuhan RBD) Elicits Neutralizing Antibodies Against Wuhan and Omicron 4/5 SARS-CoV-2 Virus

Plaque Reduction Neutralization Titers After Two Doses



***P<0.005

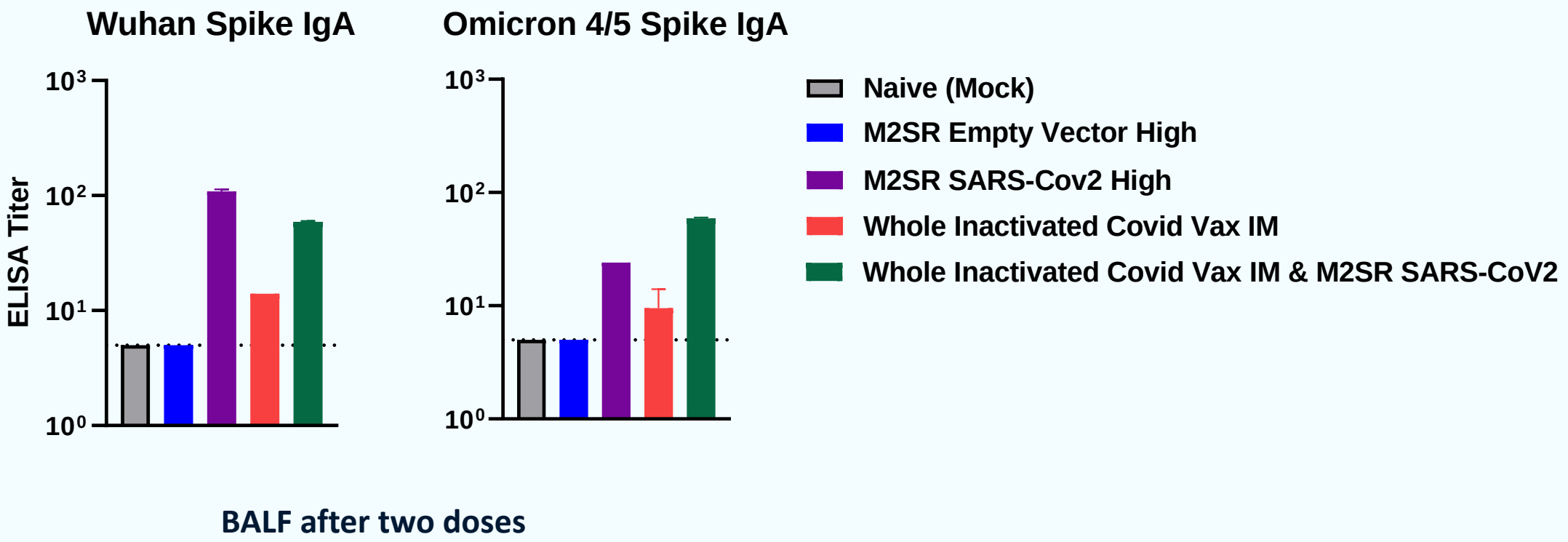
- Mock
- M2SR Empty Vector
- M2SR SARS-Cov2
- Whole Inactivated Covid Vax IM
- Whole Inactivated Covid Vax IM & M2SR SARS-CoV2



n=16/group

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M2SR SARS-CoV2 Expressing Wuhan RBD Elicits IgA Antibodies Against Wuhan and Omicron Spike in Lung



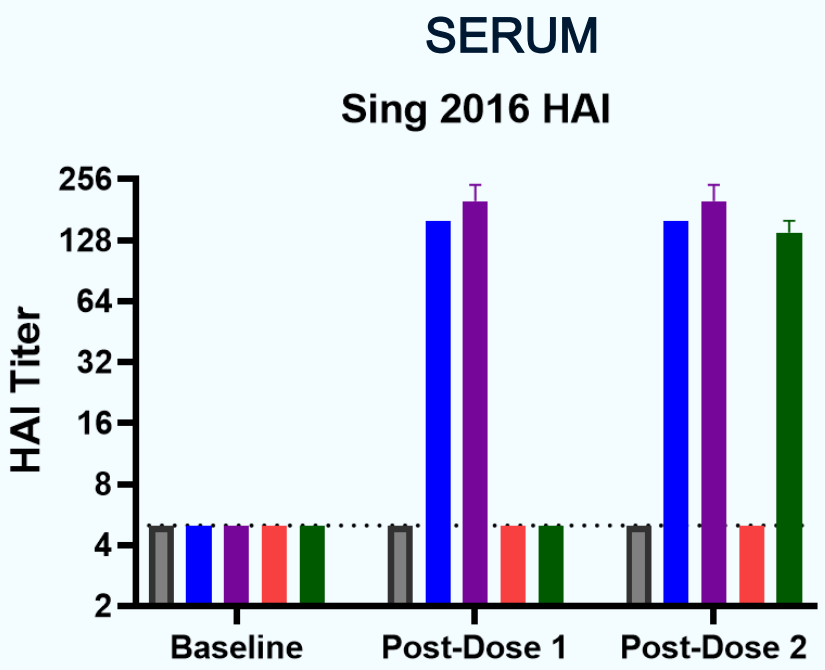
BALF after two doses

n=4/group

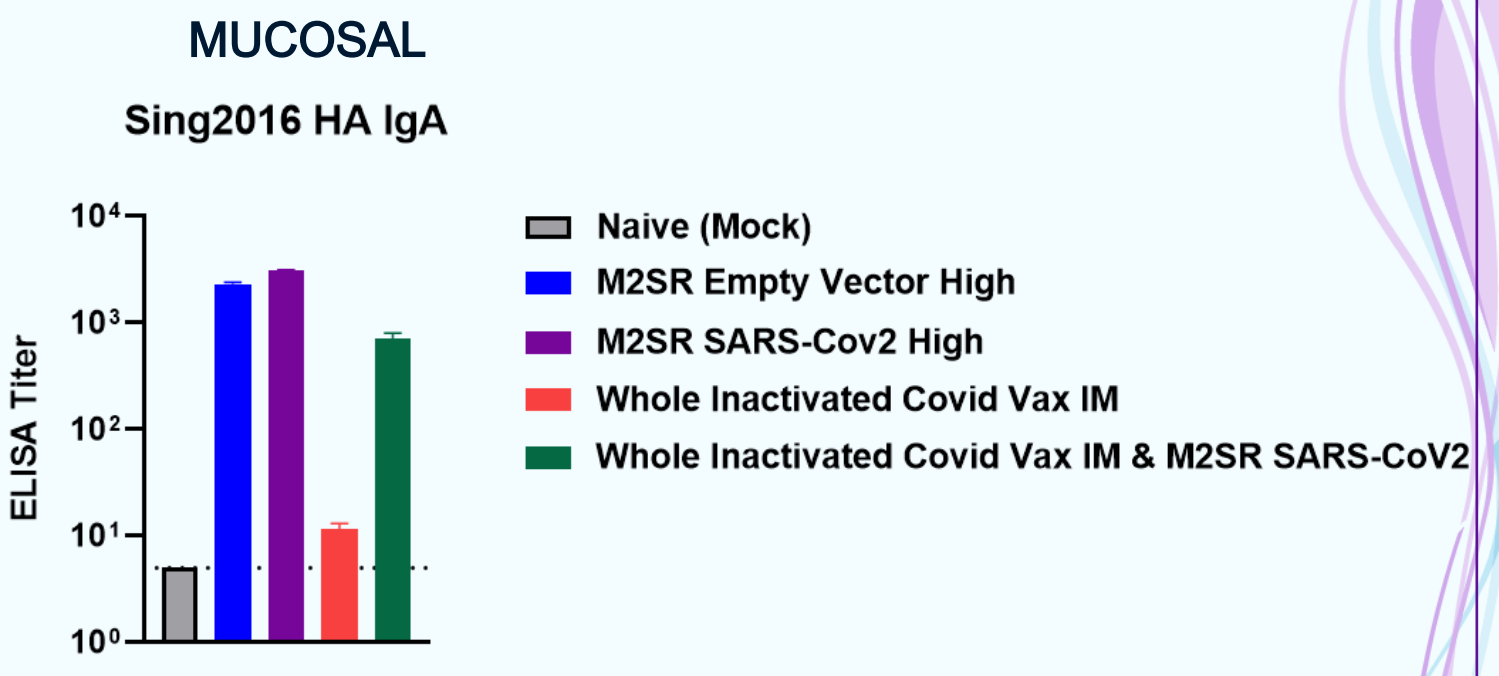


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M2SR SARS-CoV2 Influenza Serum and Mucosal Antibody Responses Similar to Empty Vector



Serum Pools, n=20/group



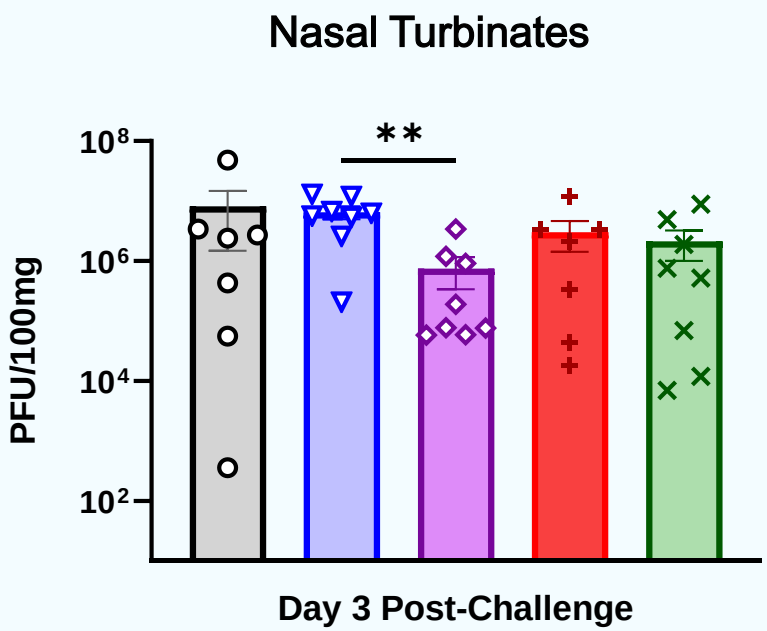
BALF after two doses, n=4/group

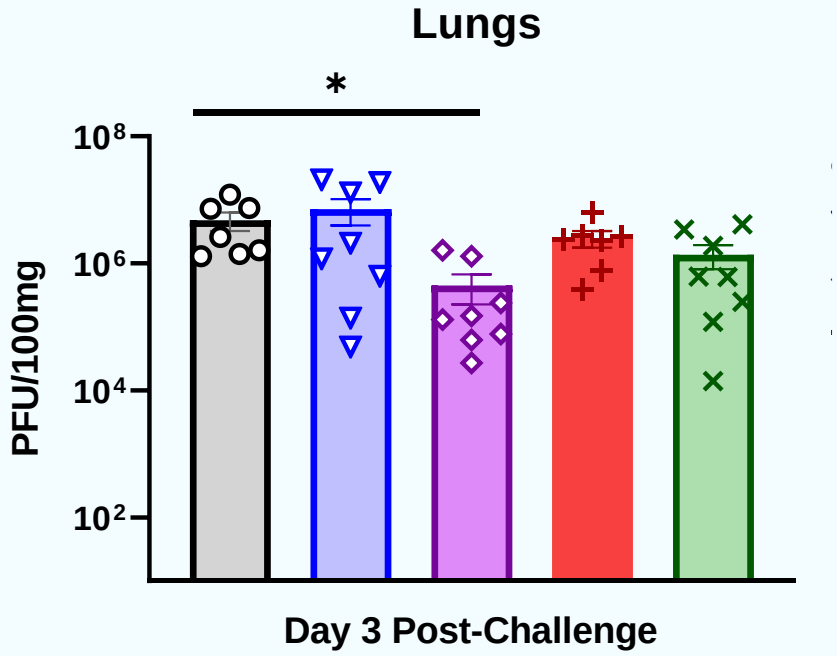
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M2SR SARS-CoV-2 Controls Wuhan Challenge Virus Replication in Respiratory Tract

- Mock
- M2SR empty
- M2SR SARS-Cov2
- Whole Inactivated Covid Vax IM
- Whole Inactivated Covid Vax IM & M2SR SARS-CoV2





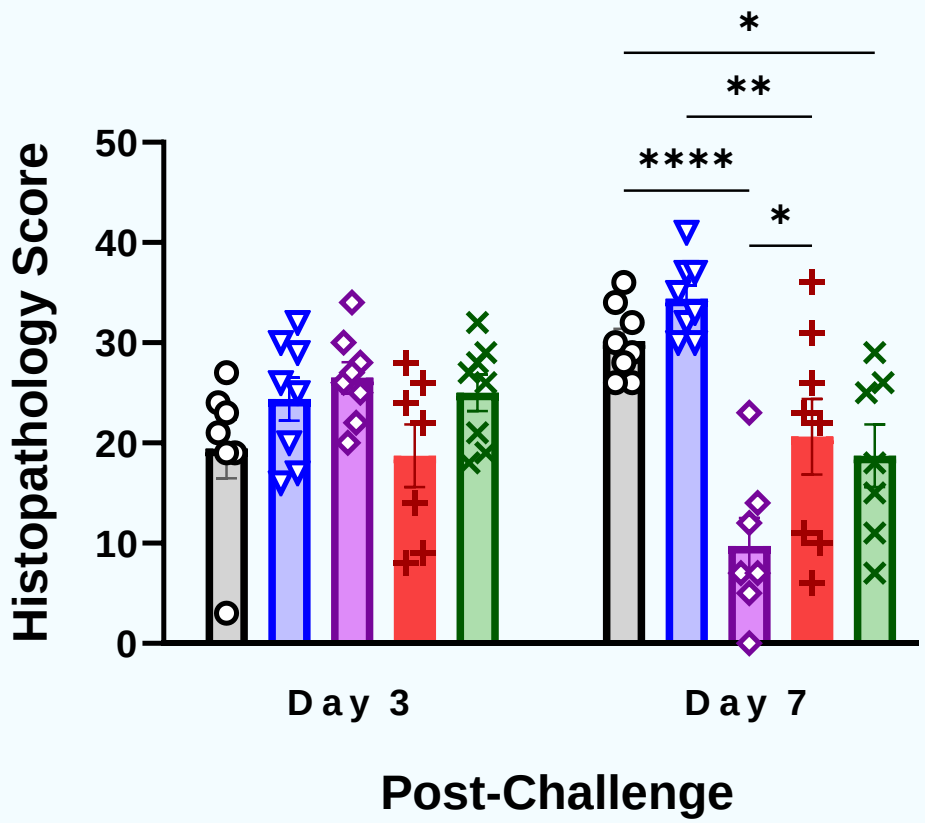
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*$P<0.05$

n=8/group



M2SR SARS-CoV-2 Demonstrates Significant Reduction in Lung Inflammation Post-Challenge



- Mock
- M2SR SARS-Cov2
- M2SR empty vector
- Whole Inactivated Covid Vax IM
- Whole Inactivated Covid Vax IM & M2SR SARS-CoV2

*P<0.05. ****P<0.0001, **P=0.0014

n=8/group



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Summary

- Intranasal M2SR elicits multi-faceted immune responses in adults 18-49 year olds
- Protective immune responses are also induced in older adults, 65-85 year olds
- M2SR induces mucosal sIgA responses not seen with HD IIV vaccine alone
- M2SR additionally induces T cell responses compared with HD IIV in a significantly greater proportion of study subjects
- M2SR platform can be used as dual vaccines for other respiratory pathogens (COVID, RSV)

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Acknowledgements

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