Clinical Immunology of Vaccination

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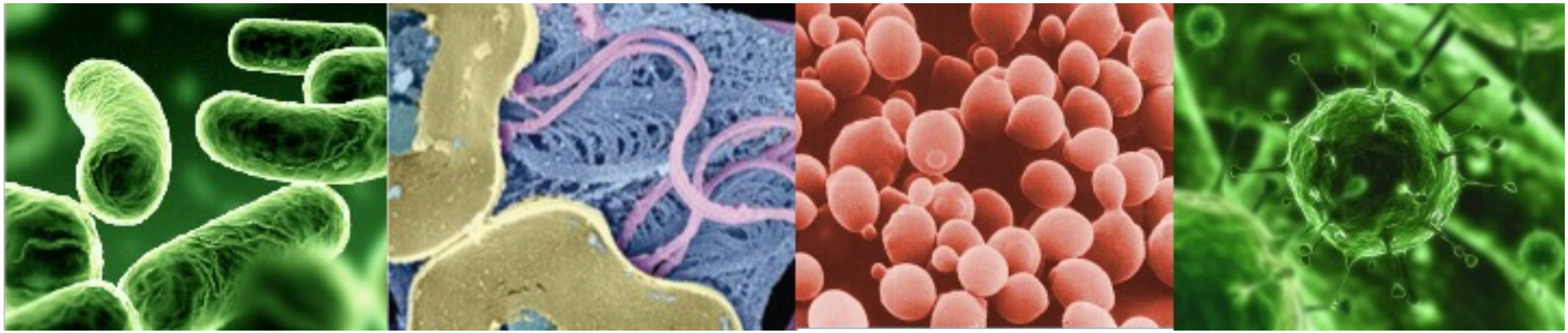


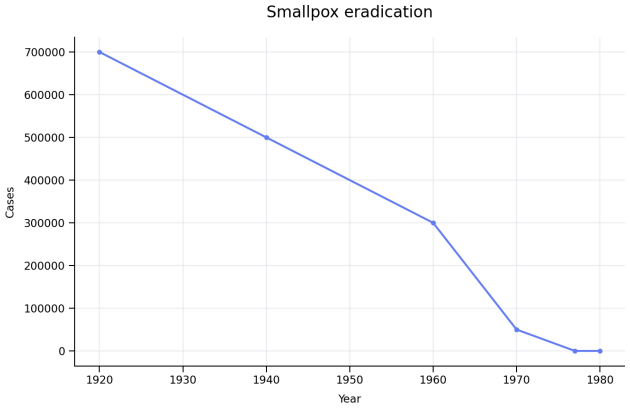
Clinical Immunology Course (FOCIS 2026)

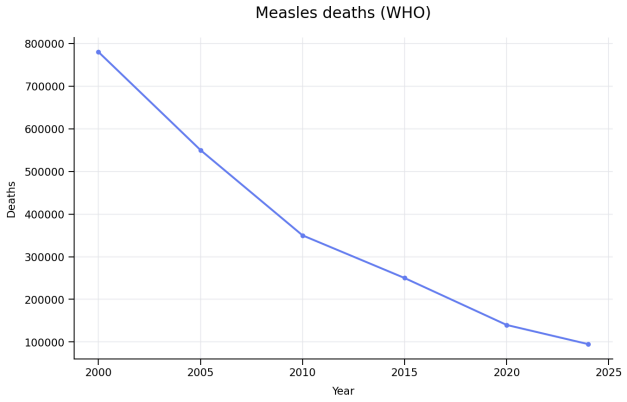
Vaccines are the most cost-effective interventions to prevent infectious diseases

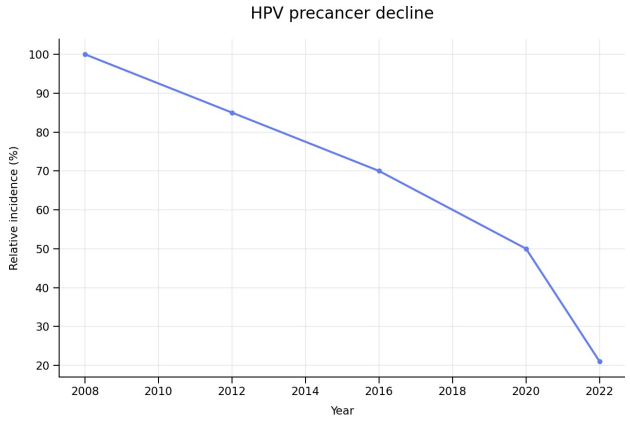
https://www.unicef.org/immunization/polio

https://www.cdc.gov/measles/hcp/vaccine-considerations/index.html

https://www.nfcr.org/blog/hpv-vaccine-gets-expanded-approval-from-fda/







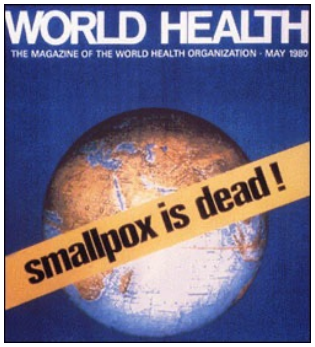
Rapid reduction of disease incidence after vaccine introduction

- Smallpox eradicated globally (1980)
- HPV vaccination reduces cervical cancer risk
- Strong economic return: $16–44 per $1 invested

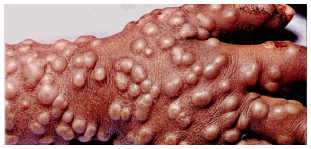
WHO vaccine safety | CDC vaccine safety monitoring | EMA pharmacovigilance

Infectious diseases controlled by vaccines

Smallpox



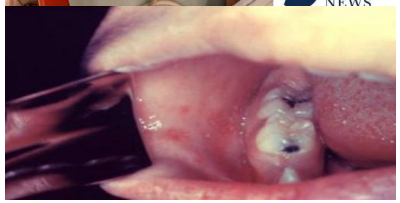
https://es.wikipedia.org/wiki/Viruela



https://www.cdc.gov/smallpox/index.html

3 deaths /10 cases

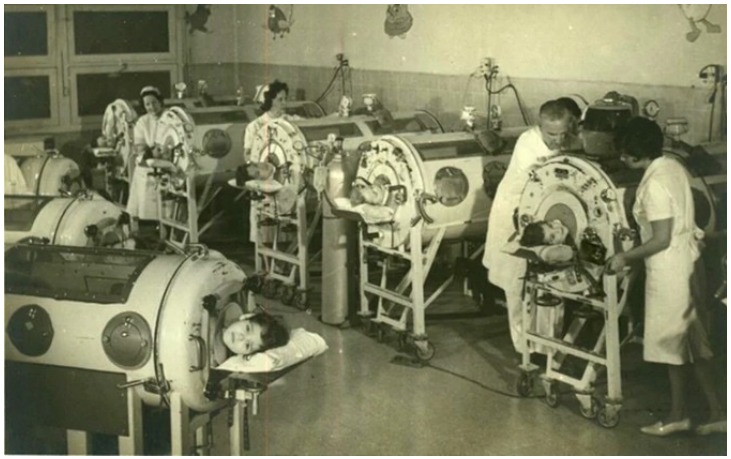
Measles



2 millones deaths annually

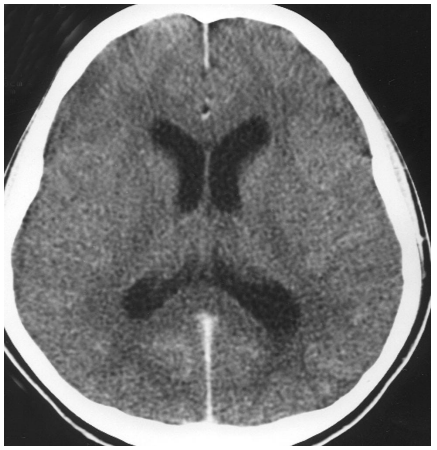
Polio

https://www.unl.edu.ar/



1/200 cases results in paralysis
5 -10 deaths per 100 cases

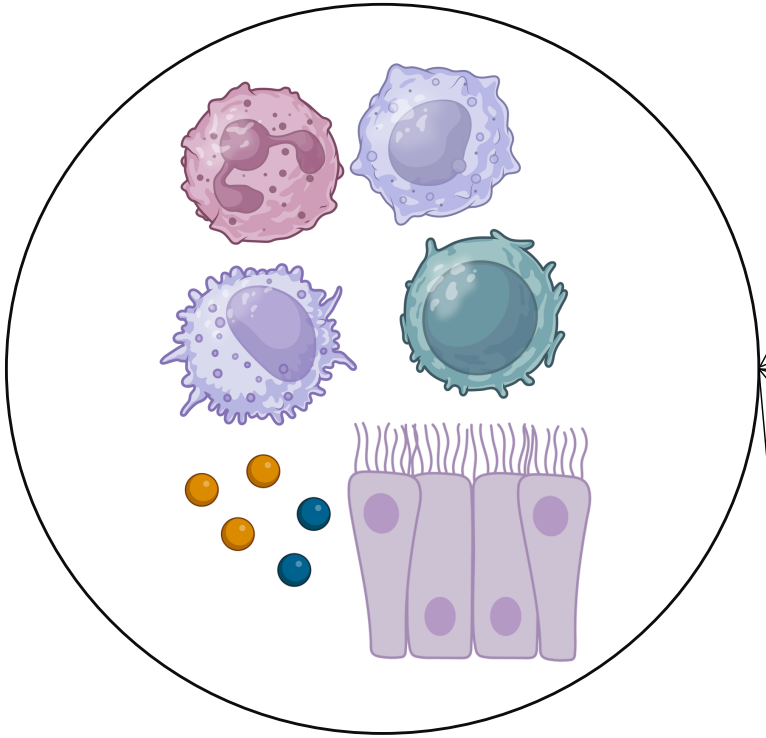
Meningitis



https://emedicine.medscape.com/article/232915-overview

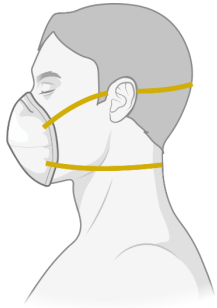
over 70% lethality in children

Conditions involved in the balance between pro- and anti-inflammatory mediators during infection



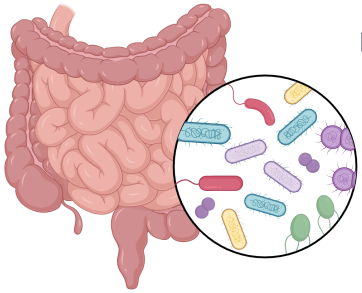
Age

Immunocompromised conditions

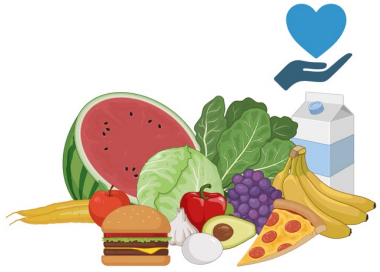


Gender

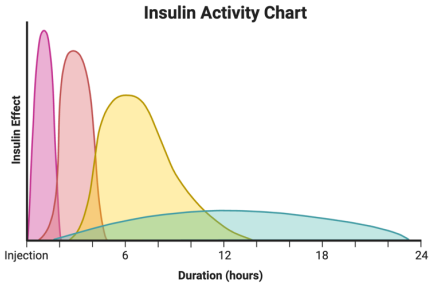
Microbiota



Nutrient Status

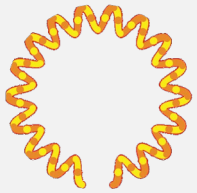
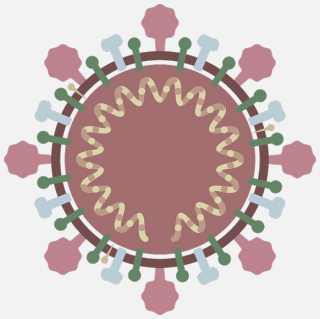
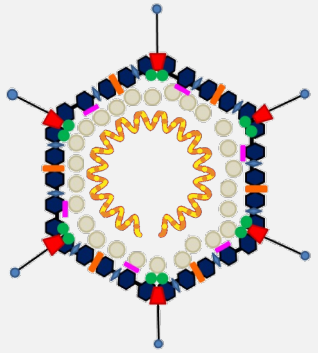


Hormonal status



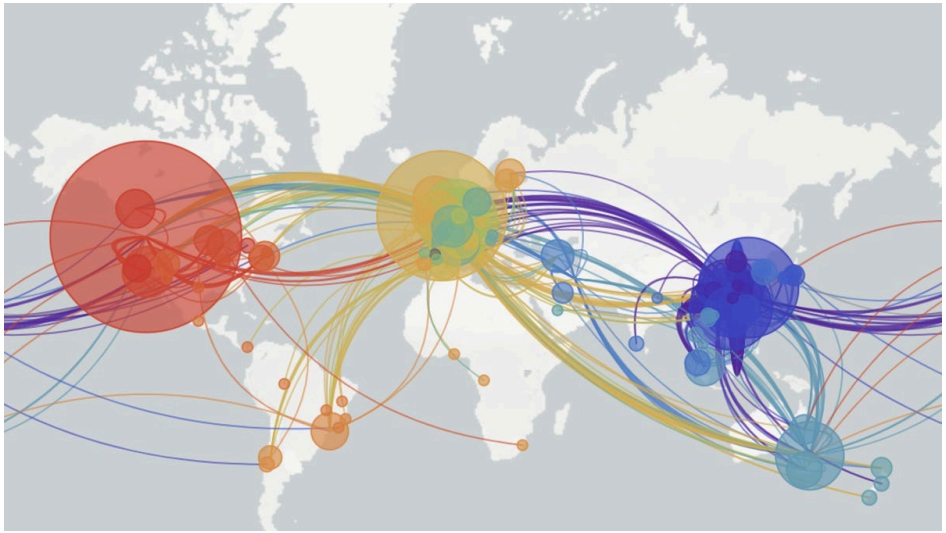
Slide prepared by Allison Salazar and Sofía Campos, SBlab

The kind of immune response induced by vaccines depends on multiple factors: vaccine

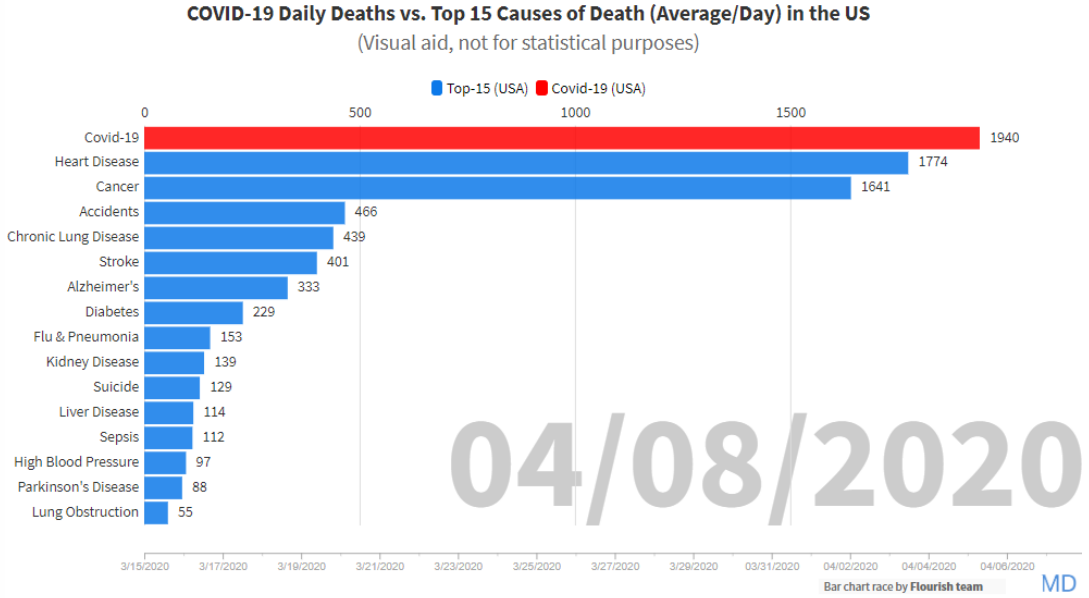
	DNA/RNA	Live attenuated	Inactivated	Subunit	Viral vector
					
How it works	This uses DNA or RNA to teach the immune system to target key viral proteins.	This is a weakened version of the actual virus.	An inactivated vaccine uses the whole virus after it has beenkilled with heat or chemicals.	This vaccine uses a piece of a virus' surface to focus your immune system on a single target.	This approach takes a harmless virus and uses it to deliver viral genes to build immunity.
Advantages	Easy an quick to desing.	Stimulates a robust immune response without causing serious disease.	Safe because the virus is already dead and is easy to make.	Focuses the immune response on the most important part of the virus for protection and cannot cause infection.	Live viruses tend to elicit stronger immune responses than dead viruses or subunit vaccines.
Disadvantages	Never been done before. There are no licensed DNA or RNA vaccines in use.	May not be safe for those with compromised immune systems.	Effective as a live virus. Some previous inactivated vaccines have made the disease worse.	May not stimulate a strong response, other chemicals may need to be added to boost long-term immunity.	Important to pick a viral vector that is truly safe. An immune response to the viral vector could make the vaccine less efective.
Existing examples	COVID-19	Measles, Mumps and Rubella Chickenpox	Polio Influenza Rabies	Pertussis Hepatitis B Human papilomavirus	Ebola COVID-19 Veterinary medicine

Emergence of SARS-CoV-2 and the COVID-19 pandemic

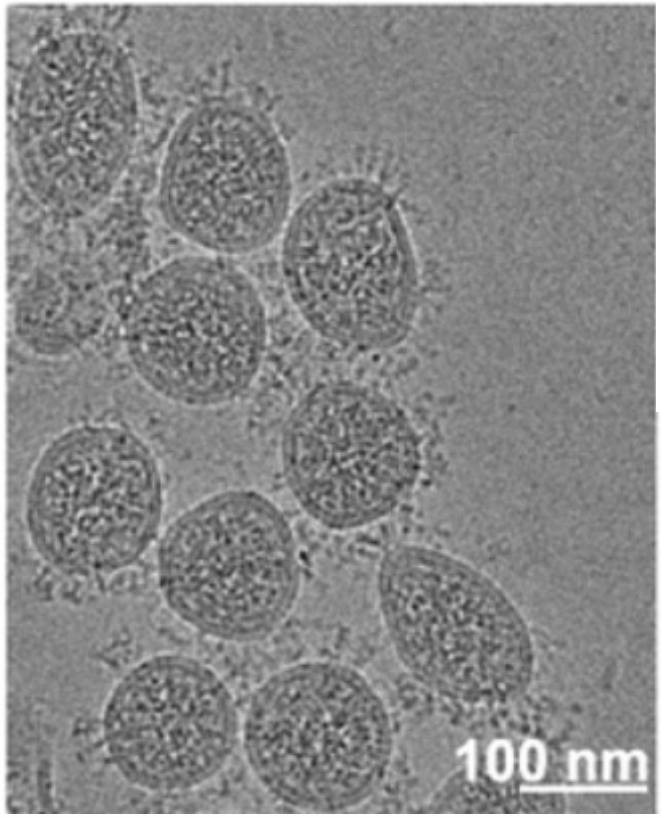
December 2019



US Today



Emergence of SARS-CoV-2 and the COVID-19 pandemic: vaccine design



Science REPORTS

Cite as: Q. Gao *et al.*, *Science* 10.1126/science.abc1932 (2020).

Development of an inactivated vaccine candidate for SARS-CoV-2

Qiang Gao[1]*, Linlin Bao[2]*, Haiyan Mao[3]*, Lin Wang[1]*, Kangwei Xu[4]*, Minnan Yang[5]*, Yajing Li[1], Ling Zhu[5], Nan Wang[5], Zhe Lv[5], Hong Gao[2], Xiaoqin Ge[1], Biao Kan[6], Yaling Hu[1], Jiangning Liu[2], Fang Cai[1], Deyu Jiang[1], Yanhui Yin[1], Chengfeng Qin[7], Jing Li[1], Xuejie Gong[1], Xiuyu Lou[3], Wen Shi[3], Dongdong Wu[1], Hengming Zhang[1], Lang Zhu[1], Wei Deng[2], Yurong Li[1], Jinxing Lu[6]†, Changgui Li[4]†, Xiangxi Wang[5]†, Weidong Yin[1]†, Yanjun Zhang[3]†, Chuan Qin[2]†

Q. Gao et al., Science 10.1126/science.abc1932 (2020)

Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial

Yanjun Zhang, Gang Zeng*, Hongxing Pan*, Changgui Li*, Yaling Hu, Kai Chu, Weixiao Han, Zhen Chen, Rong Tang, Weidong Yin, Xin Chen, Yuansheng Hu, Xiaoyong Liu, Congbing Jiang, Jingxin Li, Minnan Yang, Yan Song, Xiangxi Wang, Qiang Gao†, Fengcai Zhu†*

www.thelancet.com/infection **Published online November 17, 2020**
https://doi.org/10.1016/S1473-3099(20)30843-4

Launch of Phase 3 Trial (Nov 27th, 2020)

Overview of Coronovac03CL

Stage 1

Participants
Healthcare Workers
>18 years old

Intervention
Inoculation with CoronaVac or placebo (3:1)

Vaccination Schedule
0-14 days

Stage 2

Participants
General Population
>18 years old

Intervention
Inoculation with CoronaVac, two schedules (1:1)

Vaccination Schedules
0-14 days, 0-28 days

clinicaltrials.gov #NCT04651790

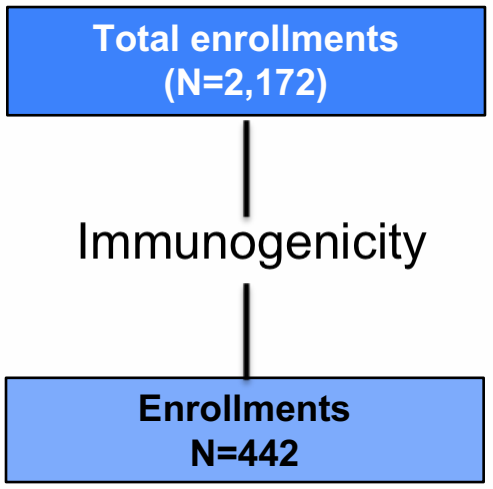
Brief description

The study evaluated the efficacy, safety, and immunogenicity of two vaccination schedules of an inactivated vaccine against SARS-CoV-2 infection in adults.

Two doses of the vaccine will be administered in a **0-14 and a 0-28-day schedule.**

Follow-up of safety and efficacy was assessed for 12 months after the first dose.

Immunogenicity was studied in a subgroup of participants.

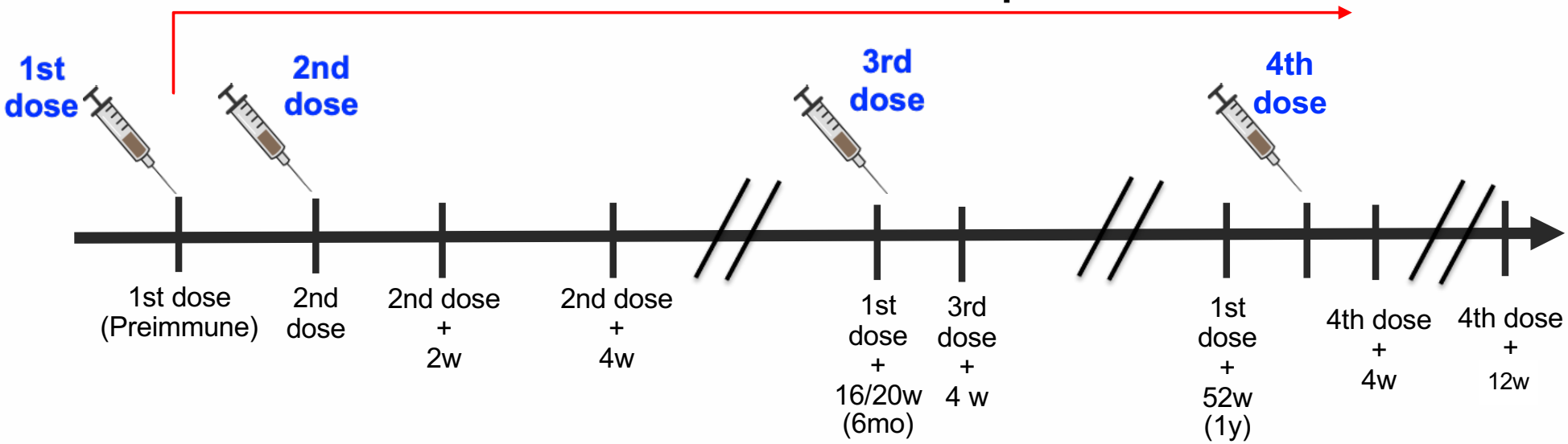


Bueno S *et al*., 2021. *Clin Infect Dis* (doi:10.1093/cid/ciab823)
Abarca et al, Vaccines (Basel). 2022 Jul 6;10(7):1082. (doi: 10.3390/vaccines10071082).

Immunogenicity Assays: Schedules 0-14 / 0-28

CoronaVac Fase 3 Chile

Evaluation of the Inmune Response



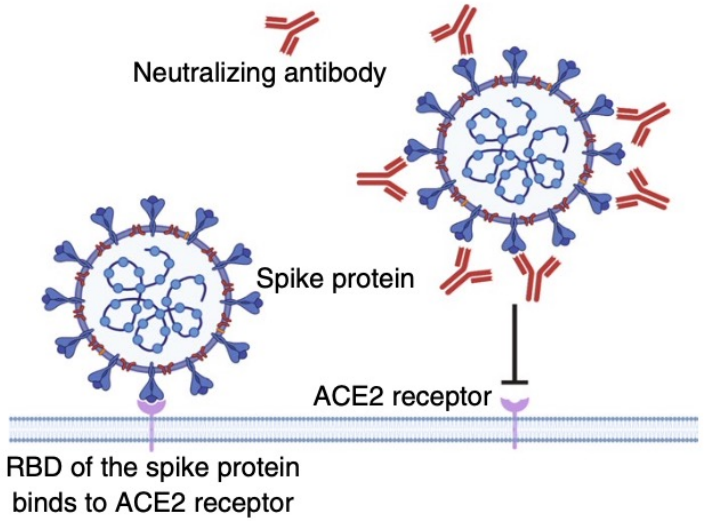
Serum
4-6 ml serum
Humoral Immune Response

PBMCs
15-90 MM cells
Cellular Immune Response

Bueno S *et al*., 2021. *Clin Infect Dis* (doi:10.1093/cid/ciab823)c

Evaluation of Neutralizing Antibodies

PedCoronaVac Fase 3 Chile

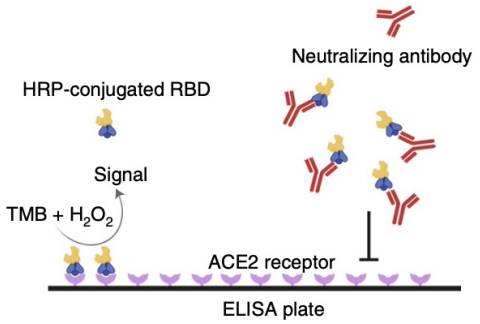


Neutralizing antibodies
S1-RBD
Ancestral Strain
Variants of Concern

cVNT

Dr. Eugenio Ramírez
Dra. Judith Mora
Dr. Rodrigo Fasce
Dr. Jorge Fernández

Instituto de Salud Pública
Ministerio de Salud
Gobierno de Chile



sVNT

Genscript

International Units

PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE

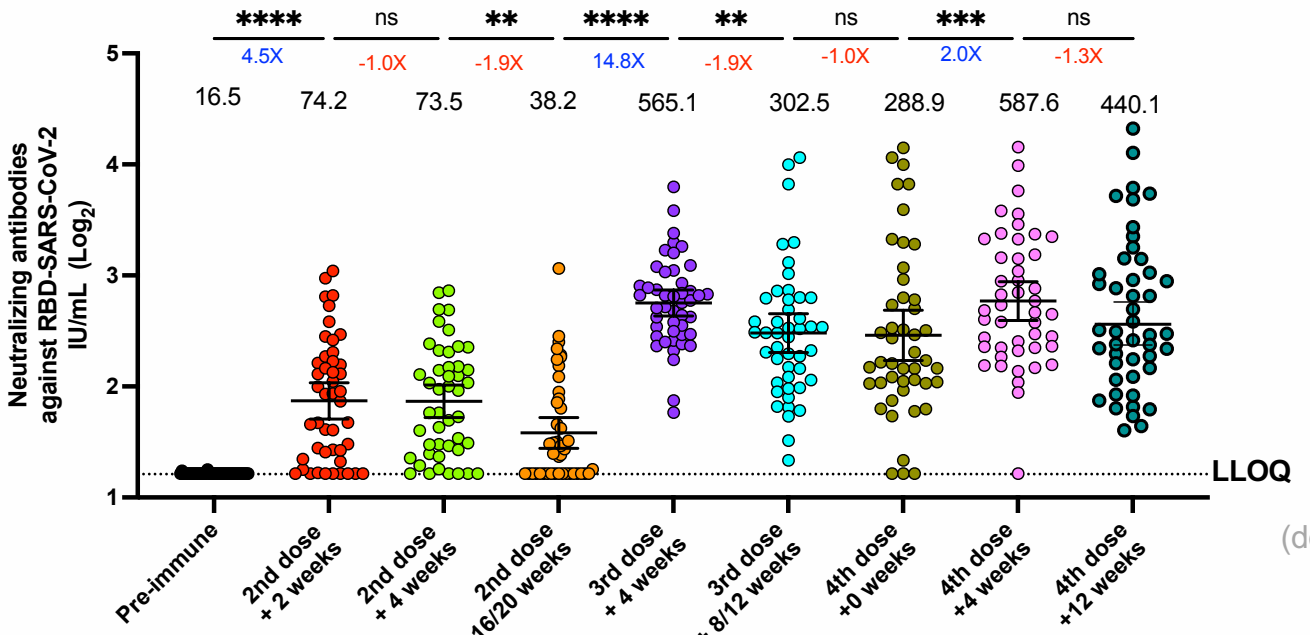
Bueno et al, Clin Infect Dis 2021
Duarte et al. Front Immunol, 2021
Melo-González et al, Front Immunol 2021
Schultz et al, mBio, 2022
Galvez et al, eLife, 2022
Soto et al., mBio, 2022
Mendez et al., EBioMedicine 2023

NATURE BIOTECHNOLOGY | VOL 38 | SEPTEMBER 2020 | 1073–1078 | www.nature.com/naturebiotechnology

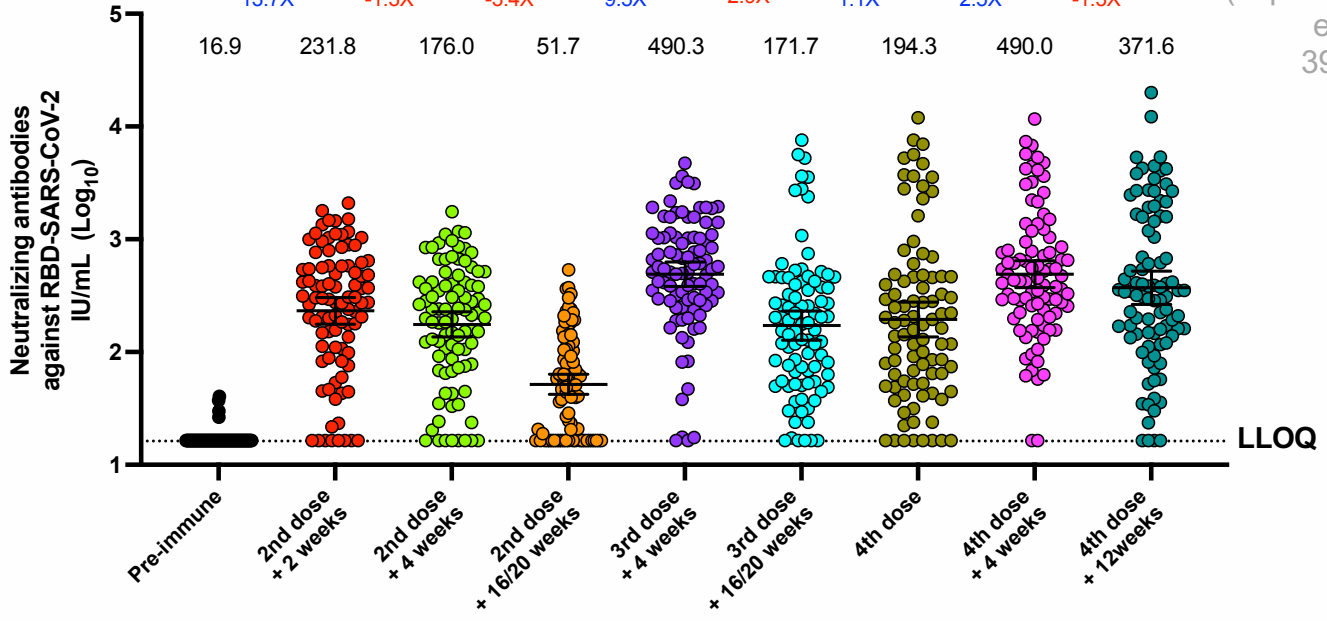
Neutralizing antibodies increase after the administration of boosters doses of CoronaVac (sVNT)

CoronaVac Fase 3 Chile

0-14
N=46



0-28
N=91



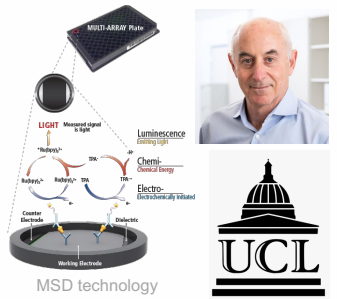
Bueno S *et al*
Clin Infect Dis 2021
(doi:10.1093/cid/ciab823)

Schultz et al
mBIo, 2022
(doi: 10.1128/mbio.01423-22)

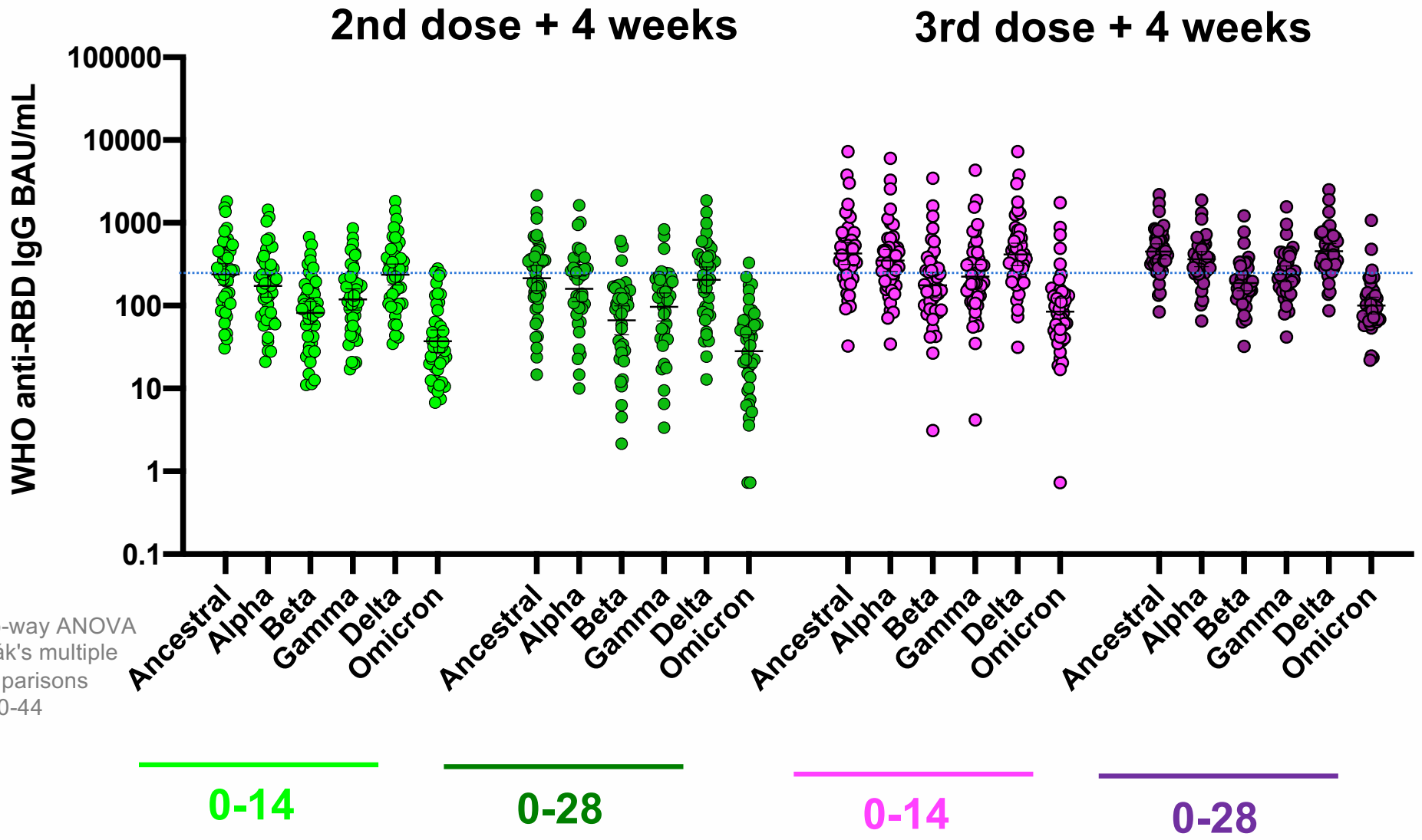
Méndez, Peñaloza et al
EBioMedicine 2023
(https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(23)00128-7/fulltext)

Neutralizing antibodies that bind S1-RBD from VOC are increased after a CoronaVac booster

Collaboration with David Goldblatt



MSD technology

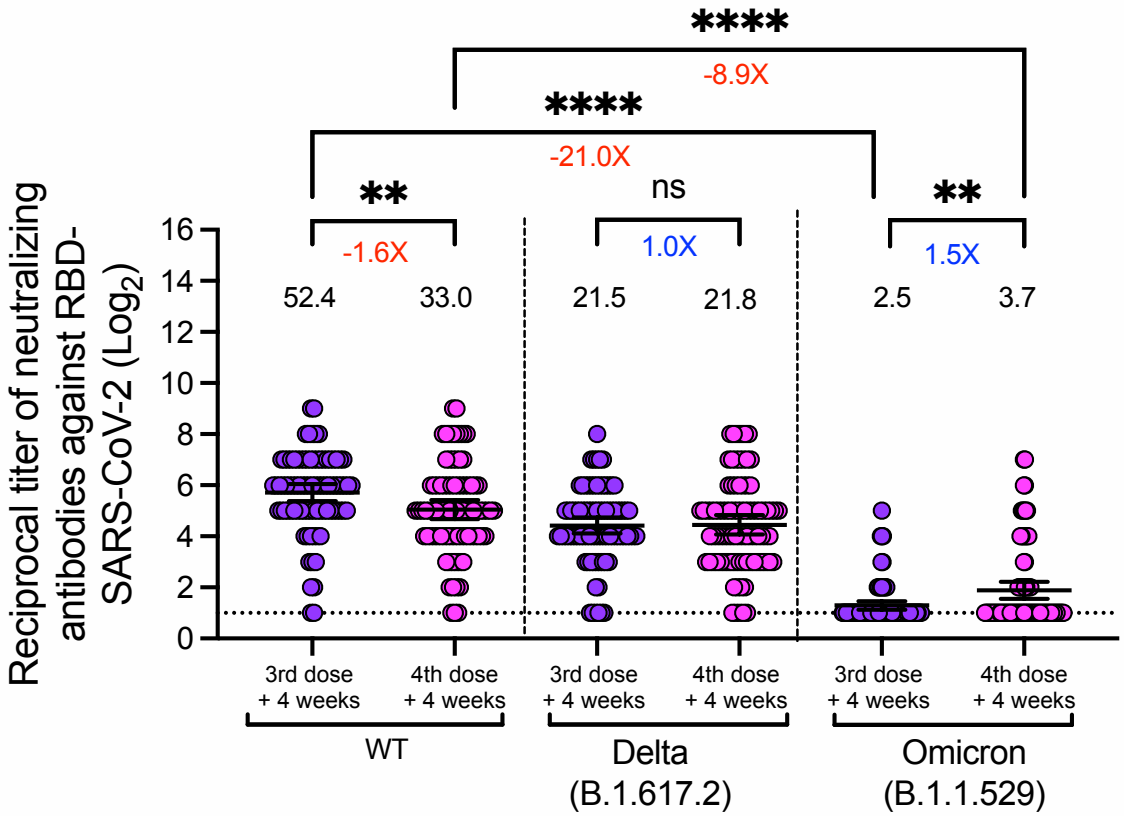


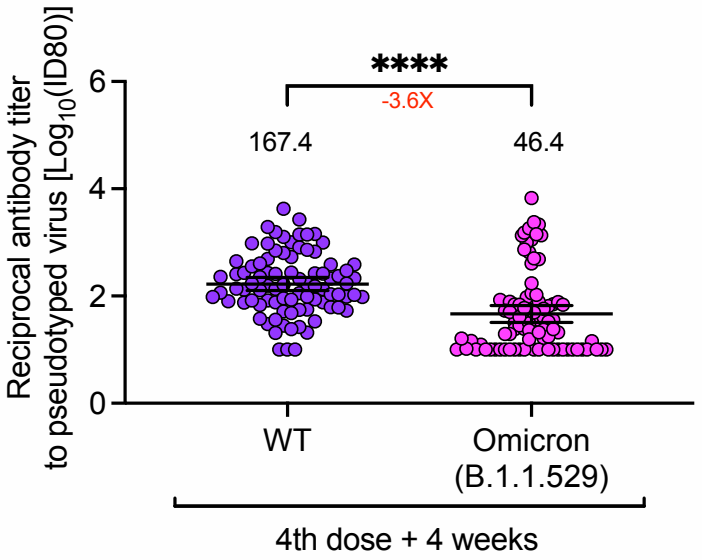
Two-way ANOVA
Šídák's multiple comparisons
n=40-44

0-14 0-28 0-14 0-28

Galvez et al, eLife 2022, https://elifesciences.org/articles/81477

Neutralizing antibodies induced by a first or a second booster of CoronaVac show reduced neutralization against Omicron variant (sVNT and pVNT)





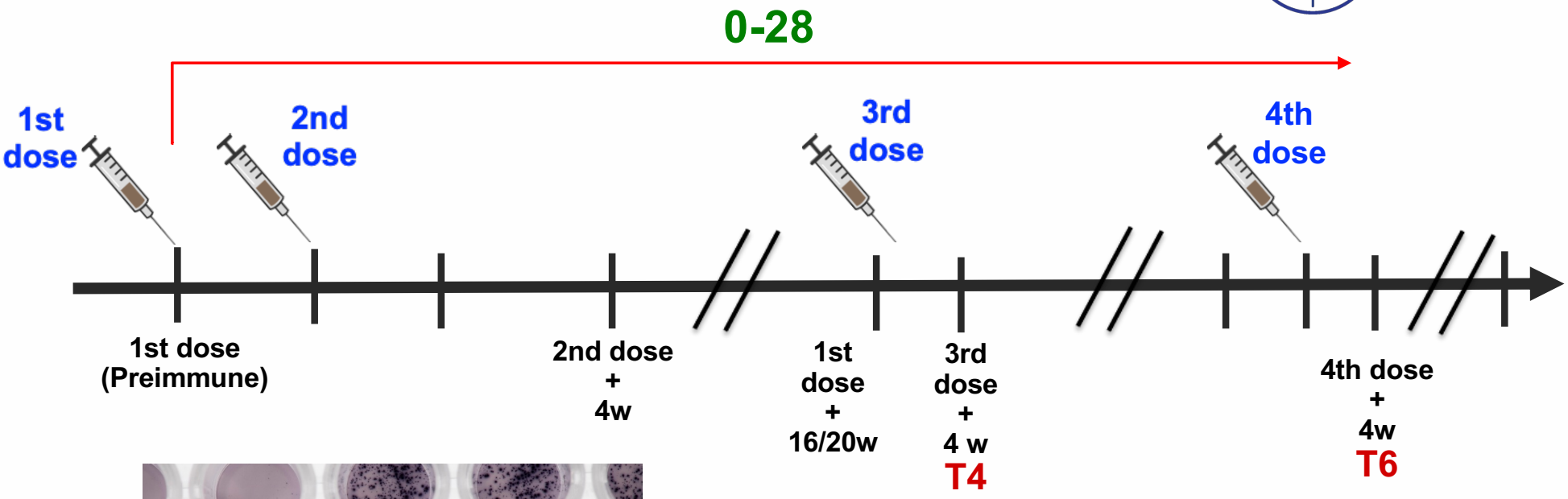
0-28 Schedule
n= 87 Two-way ANOVA + Tukey's multiple comparisons test
n= 87 Paired t-test
Geo Mean with 95% CI

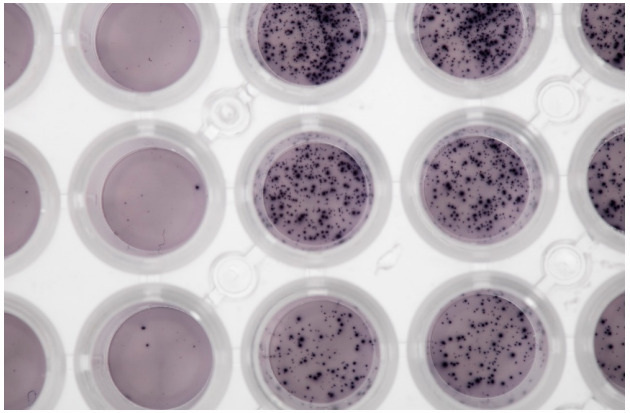
Méndez, Peñaloza et al. *EBioMedicine 2023* (doi: 10.1016/j.ebiom.2023.104563)

Collaboration Ricardo Soto-Rifo, Lab VirCelMol, ICBM

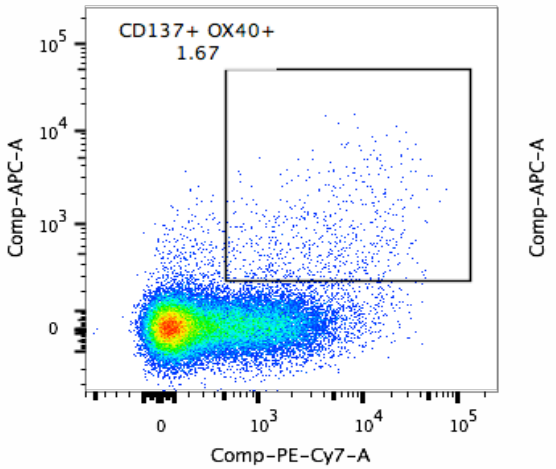
Evaluation of T cell Responses using MP peptides

CoronaVac Fase 3 Chile





ELISPOT (IFN-g/IL-4)



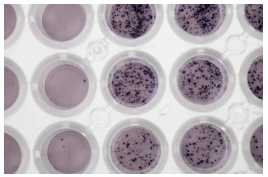
Flow Cytometry

CD4+, CD137+, OX40+

CD8+, CD137+, CD69+

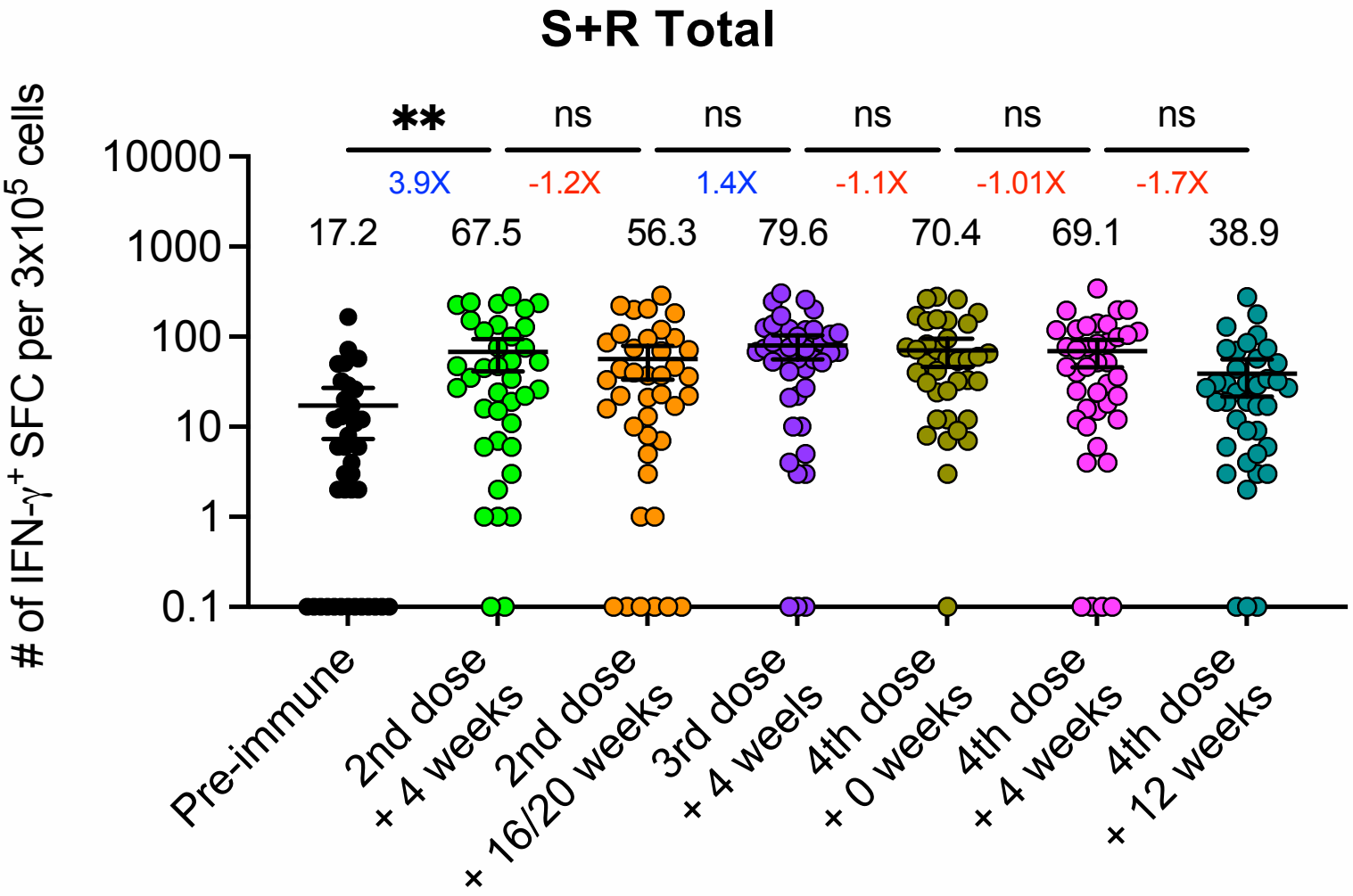
La Jolla Institute FOR IMMUNOLOGY

IFN-γ-producing T cells remain elevated after CoronaVac vaccination



ELISPOT (IFN-g/IL-4)

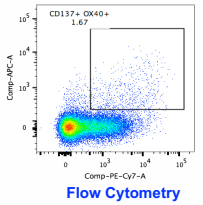
CoronaVac Fase 3 Chile



n=40 subjects
0-28 schedule
Friedman test

Bueno S *et al*., 2021. *Clin Infect Dis 2021*(doi:10.1093/cid/ciab823)
Schultz et al, *mBIo* 2022 (doi: 10.1128/mbio.01423-22)
Méndez, Peñaloza et al. *EBioMedicine 2023* (doi: 10.1016/j.ebiom.2023.104563)

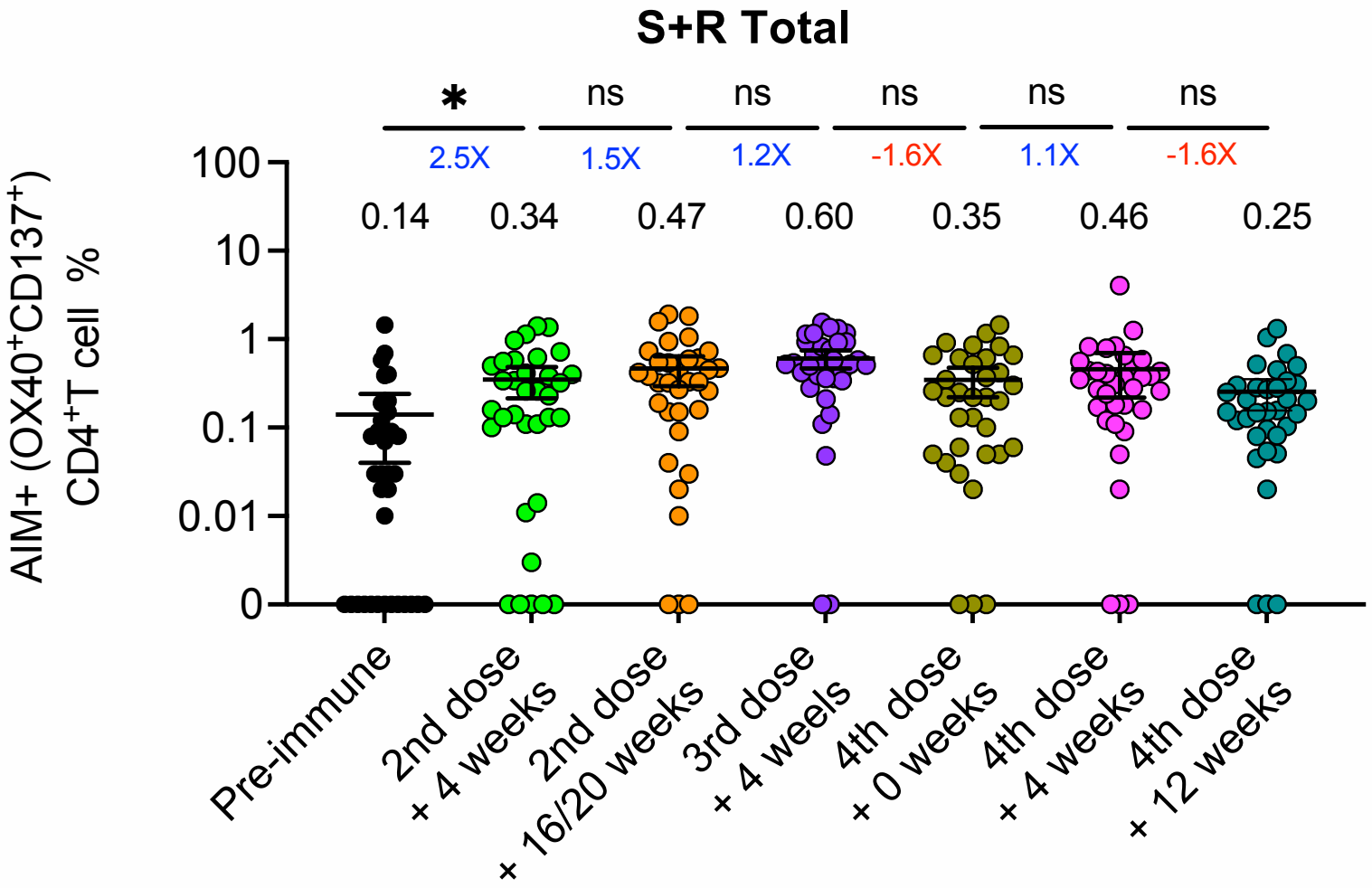
AIM CD4⁺ T cells remain elevated after CoronaVac vaccination



CD4+, CD137+, OX40+

CD8+, CD137+, CD69+

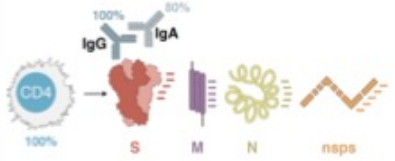
CoronaVac Fase 3 Chile



n=34 subjects
0-28 schedule
Friedman test

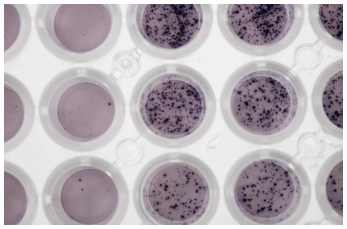
Bueno S *et al*., 2021. *Clin Infect Dis 2021*(doi:10.1093/cid/ciab823)
Schultz et al, *mBIo* 2022 (doi: 10.1128/mbio.01423-22)
Méndez, Peñaloza et al. *EBioMedicine 2023* (doi: 10.1016/j.ebiom.2023.104563)

CoronaVac induces IFN-γ producing T cells that recognize the SARS-CoV-2 Omicron variant

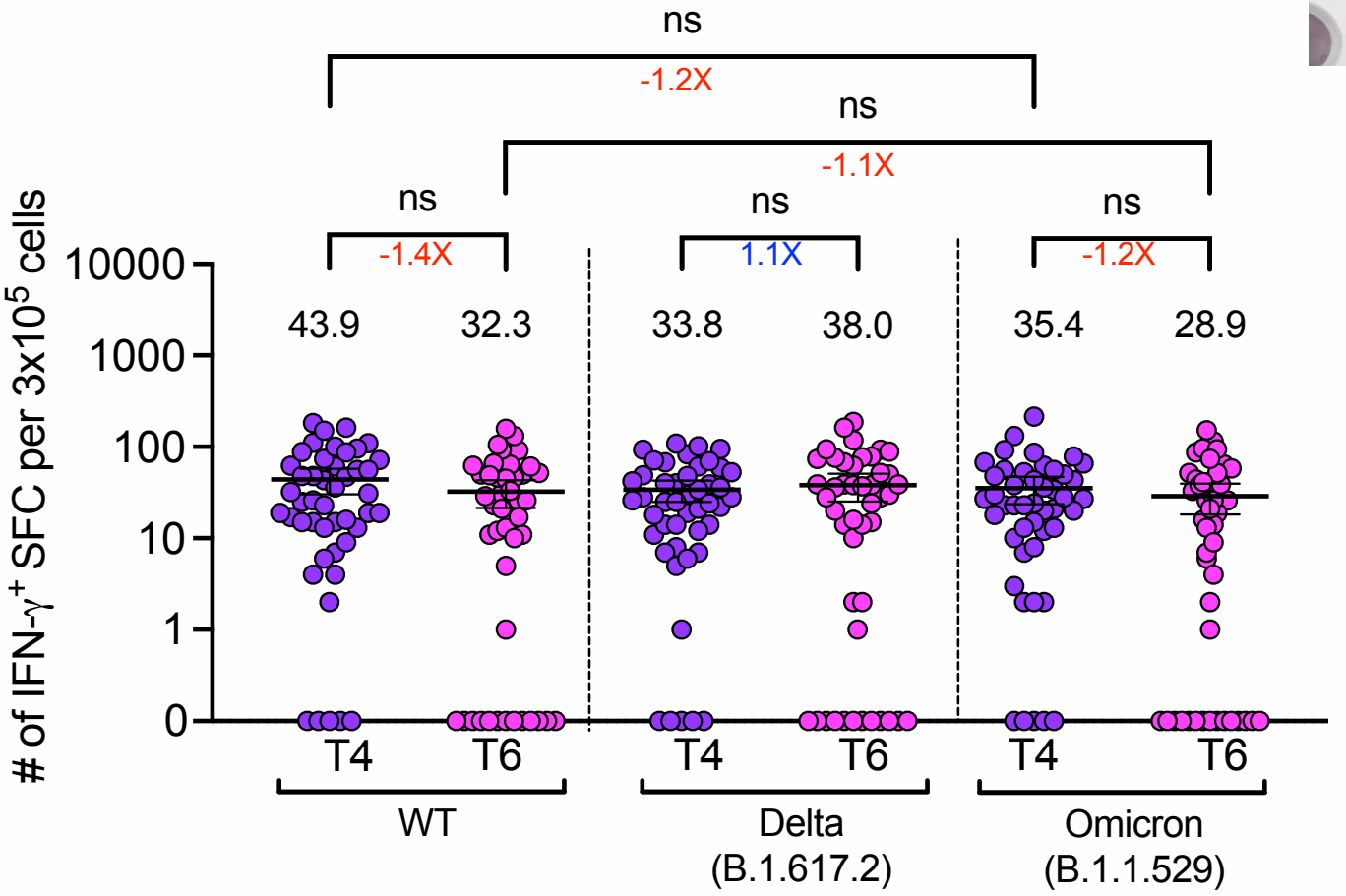


Cell *181*, 1489–1501, June 25, 2020

T4: 3rd dose + 4 weeks
T6: 4th dose + 4 weeks



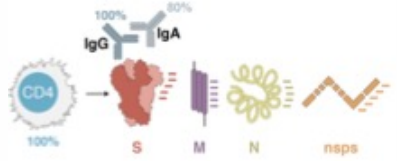
ELISPOT (IFN-g/IL-4)



0-28 Schedule
N= 46
Mean with 95% CI
Two-way ANOVA + Dunn's test

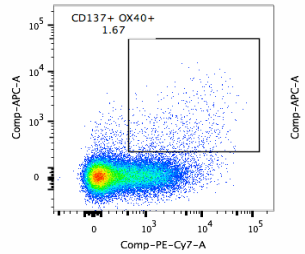
Méndez, Peñaloza et al. *EBioMedicine 2023* (doi: 10.1016/j.ebiom.2023.104563)

CoronaVac induces activated T cells that recognize the SARS-CoV-2 Omicron variant (Flow cytometry)



Cell *181*, 1489–1501, June 25, 2020

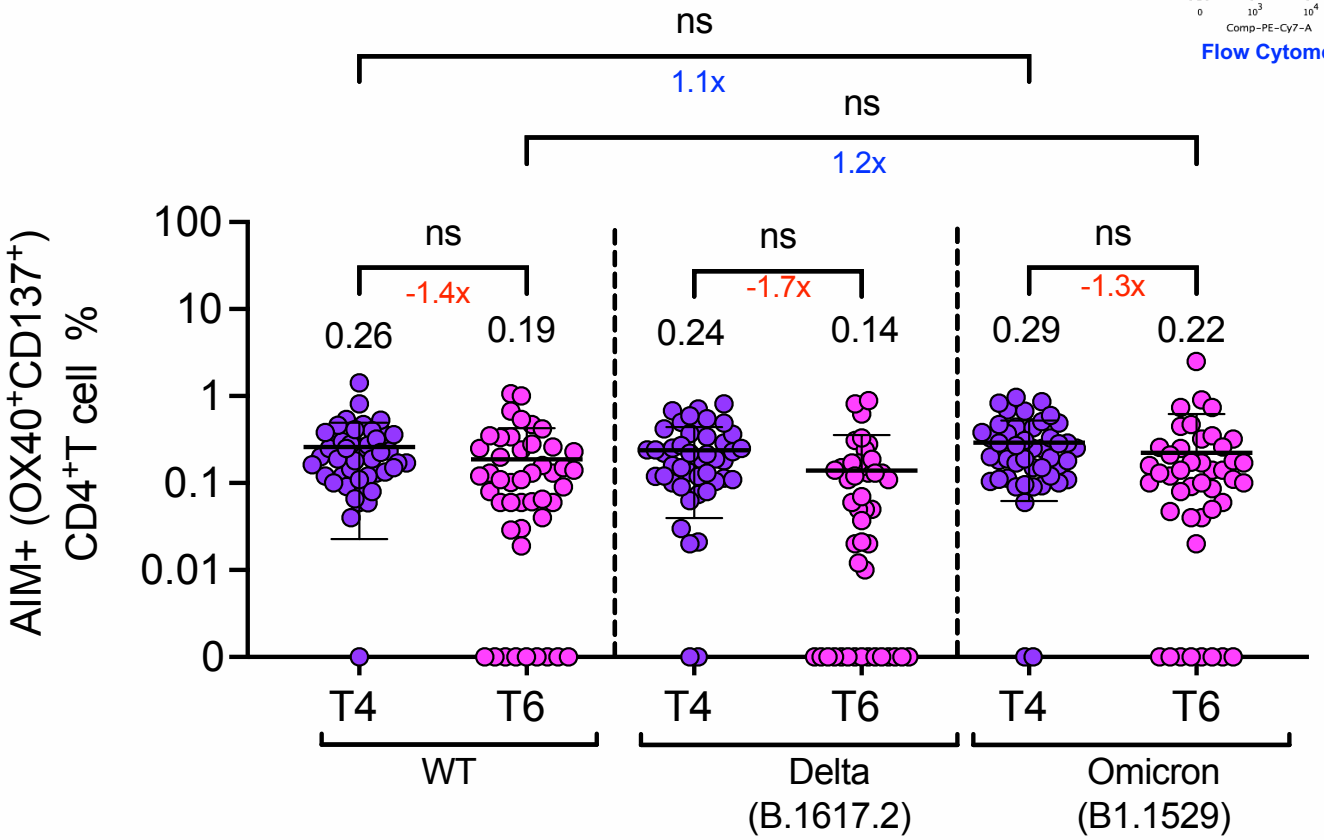
T4: 3rd dose + 4 weeks
T6: 4th dose + 4 weeks



Flow Cytometry

CD4+, CD137+, OX40+

CD8+, CD137+, CD69+



0-28 Schedule
N= 46
Mean with 95% CI
Two-way ANOVA + Dunn's test

Méndez, Peñaloza et al. *EBioMedicine 2023* (doi: 10.1016/j.ebiom.2023.104563)

Conclusions

Immunization with an inactivated vaccine increases the levels of neutralizing antibodies after two and three doses.

Immunization schedule influences the magnitude of the antibody response after two doses.

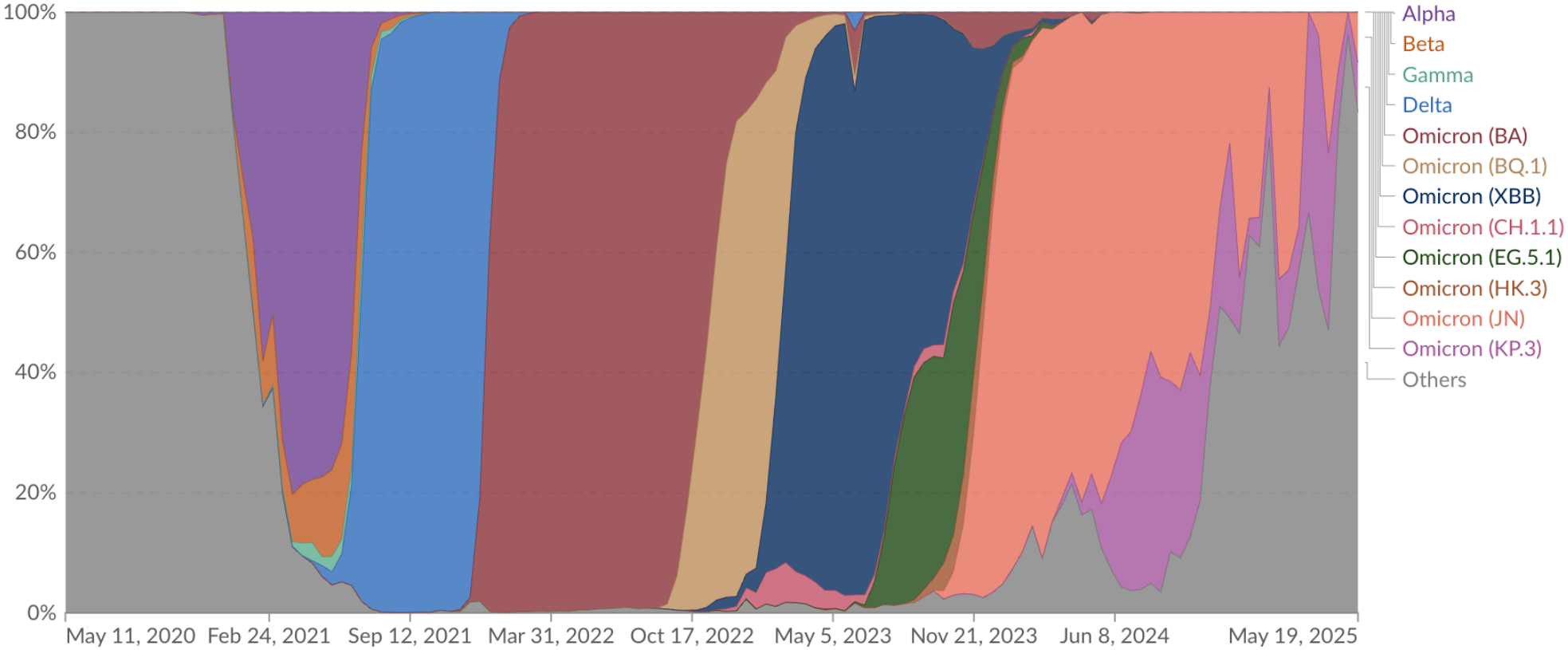
Antibodies induced by ancestral inactivated vaccine show reduce binding to variant SARS-CoV-2 strains.

Immunization with variant vaccines change the level of IFN-g-producing and AIM^+ $CD4^+$ or $CD8^+$ T cells after immunization.

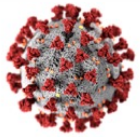
$CD4^+$ and $CD8^+$ T cells recognizes the SARS-CoV-2 variants of concern .

Inactivated vaccines induces neutralizing antibodies and specific T cells after three doses, and are increased after further boosters

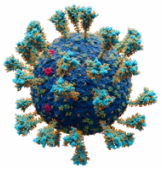
Appearance of Variants of Concern (VOC) imposed new challenges to the SARS-CoV-2 vaccine development



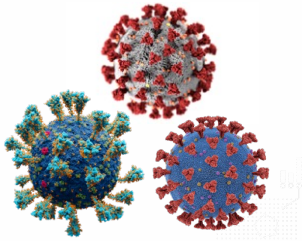
SARS-CoV-2 variants in analyzed sequences, France (The word in data)
Data source: GISAID, via CoVariants.org (2025)



CoronaVac
Strain CZ02
(ancestral)
600SU/dose



Omicron Vaccine
Omicron strain
1200SU/dose



Trivalent Vaccine
Ancestral strain
Omicron and Delta variants
1200SU of each strain/dose

Next step: A Phase 2 clinical trial to evaluate the immunogenicity of a 5th boost of inactivated variant COVI-19 vaccine

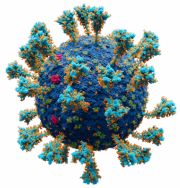
Estudio científico-clínico
CoronaVarCL

We tested the effect of booster doses of vaccines based on inactivated SARS-CoV-2 variants

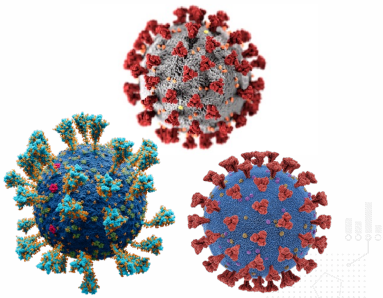
https://www.vacunavariantescovid.cl

CoronaVarCL

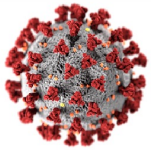
Vaccines to be tested



Omicron Vaccine
Omicron strain
1200SU/dose
Alum hydroxide

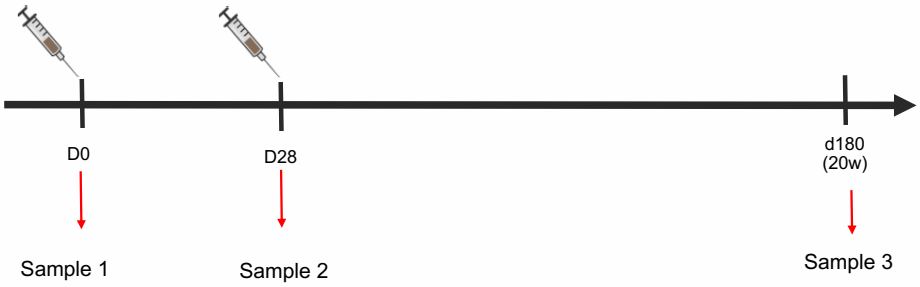


Trivalent Vaccine
Ancestral strain
Omicron and Delta variants
1200SU of each strain/dose
Alum hydroxide

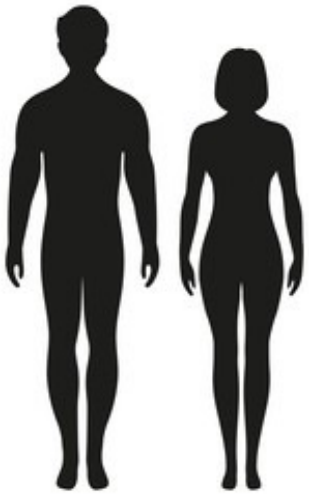


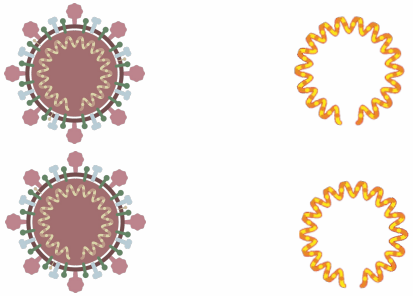
CoronaVac
Strain CZ02
(ancestral)
600SU/dose
Alum hydroxide

Immunization schedule



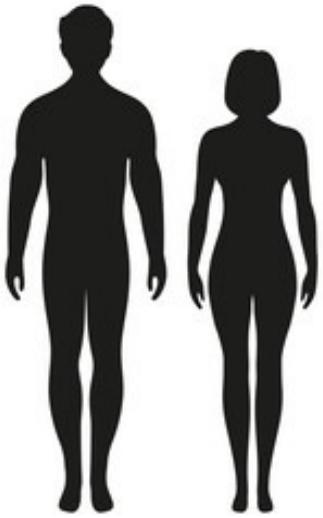
Population included

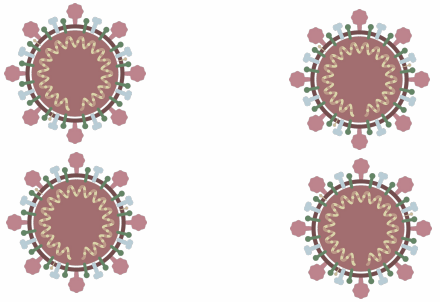




1st+2nd dose **3rd+4th dose**

Heterologous group

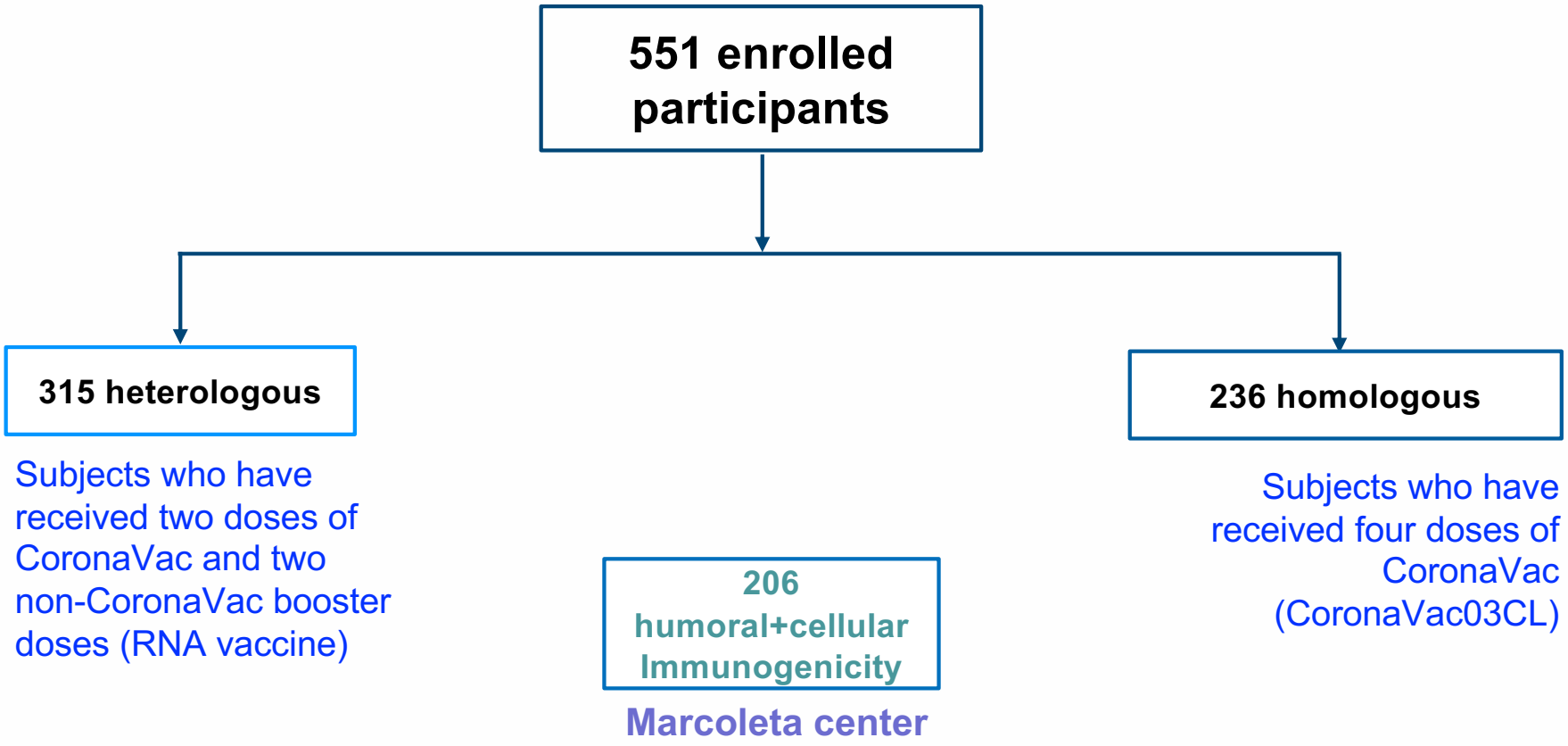




1st+2nd dose **3rd+4th dose**

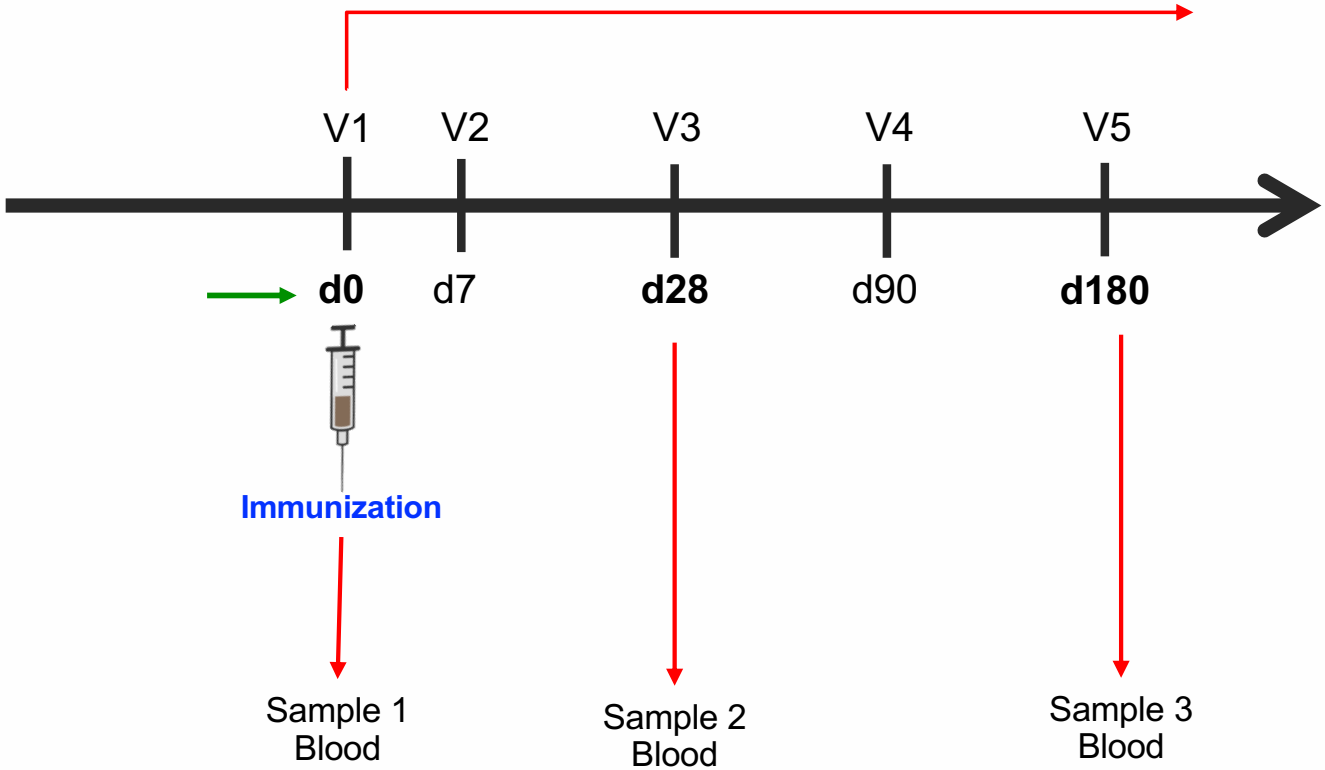
Homologous group

Actual enrolled participants



Immunogenicity Blood Sampling for CoronaVarCL

Evaluation of the Inmune Response



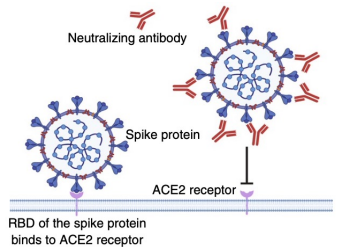
PBMCs
10-30 MM cells
Cellular Immune Response

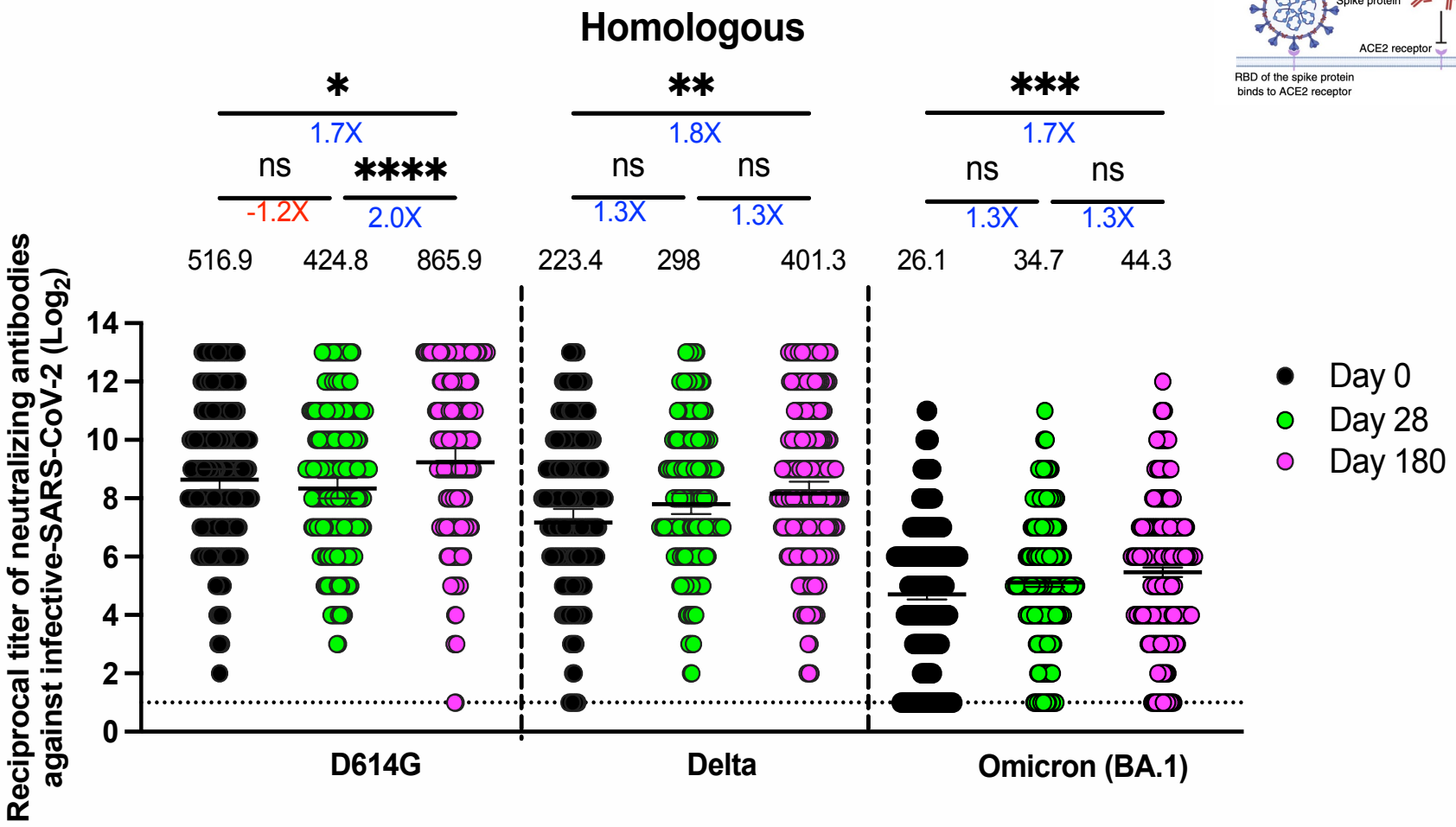
10 ml serum
Humoral Immune Response

RESULTS

cVNT assay: a booster dose of variant vaccine induce increased of neutralizing antibodies at 4 and 12 weeks after immunization **in the homologous group**.

Estudio científico-clínico CoronaVarCL





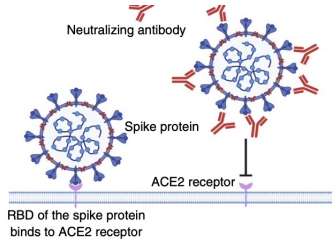
N: 219 subjects (homologous group)

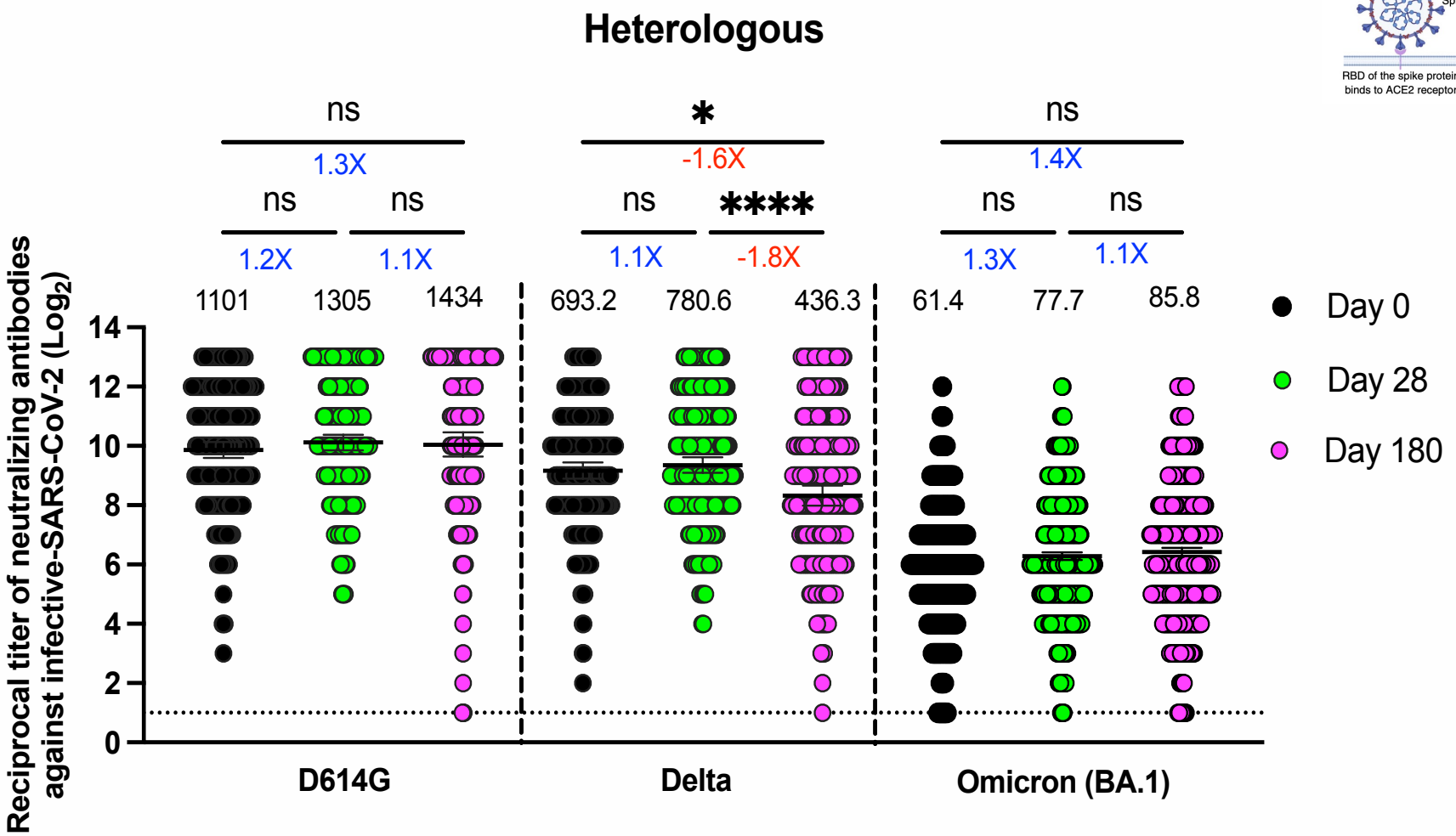
Méndez et al., BMC Medicine, 2025

*Data was analyzed with ANOVA with the Geisser-Greenhouse correction test followed by a post-hoc Sidak multiple test. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

RESULTS

cVNT assay: a booster dose of variant vaccine induce increased of neutralizing antibodies against Delta at 12 weeks after immunization **in the heterologous group**.





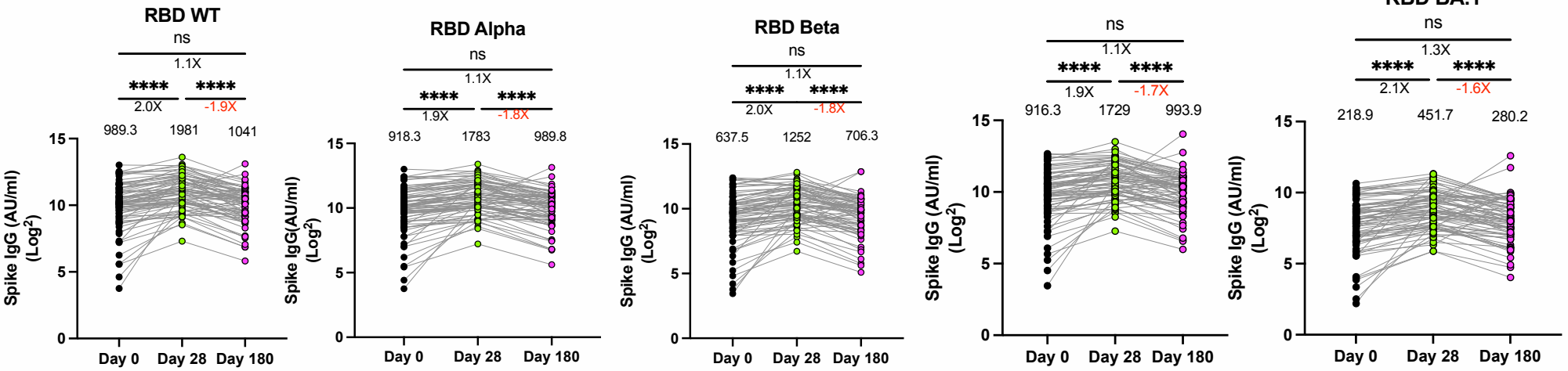
N: 286 subjects (homologous group)

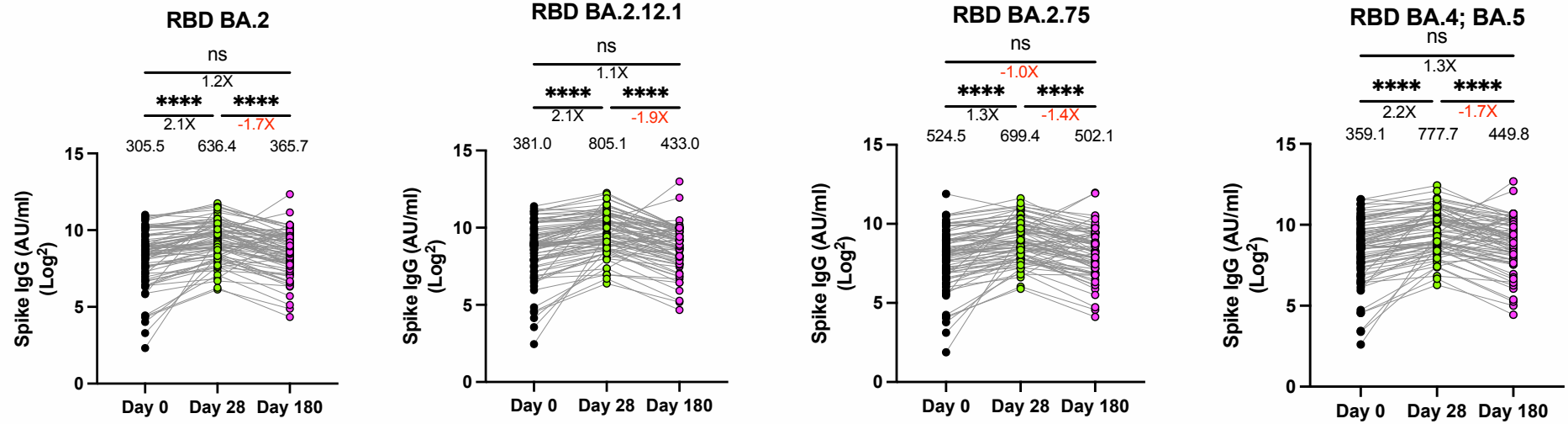
Méndez et al., BMC Medicine, 2025

*Data was analyzed with ANOVA with the Geisser-Greenhouse correction test followed by a post-hoc Sidak multiple test. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

RESULTS

MSD assay: a booster dose of variants vaccine induce increased of neutralizing antibodies at 4 weeks and decrease at 12 weeks after immunization **<u>in the homologous group</u>**. n=76 subjects, T test



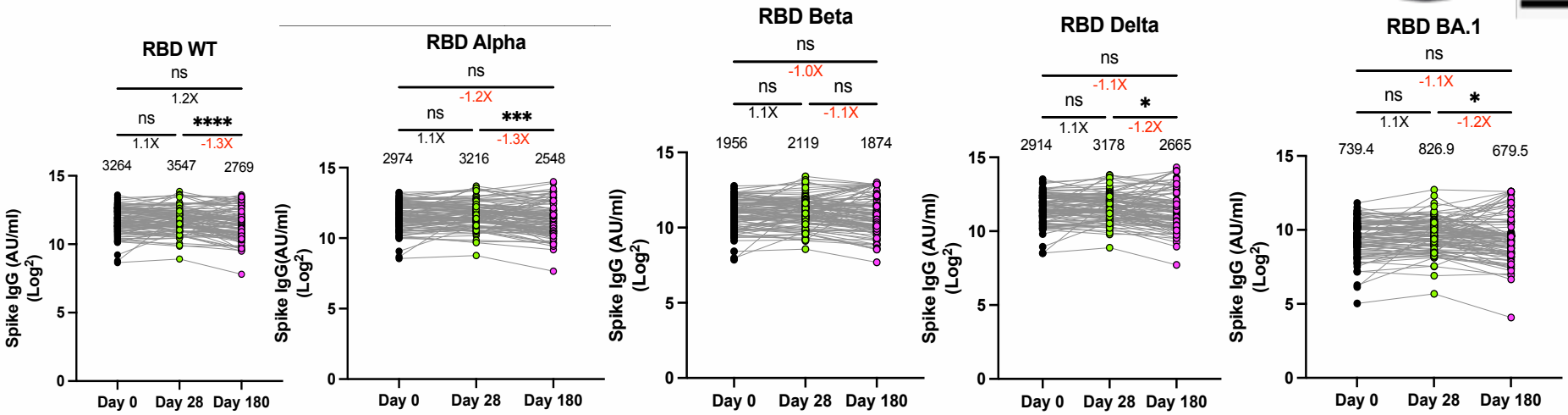


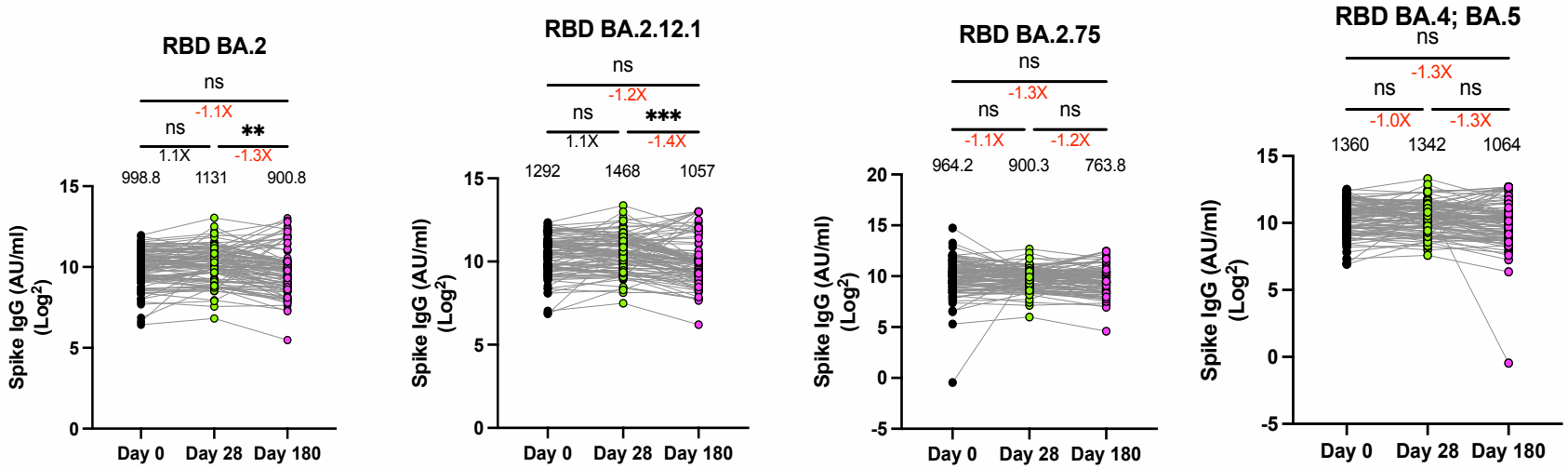
Méndez et al., BMC Medicine, 2025

RESULTS

MSD assay: a booster dose of variants vaccine do not change the levels of total antibodies at 4 weeks after immunization **in the heterologous group**. A decrease is observed at 12 weeks.

n=99 subjects, T test

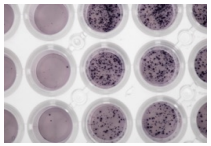




Méndez et al., BMC Medicine, 2025

RESULTS

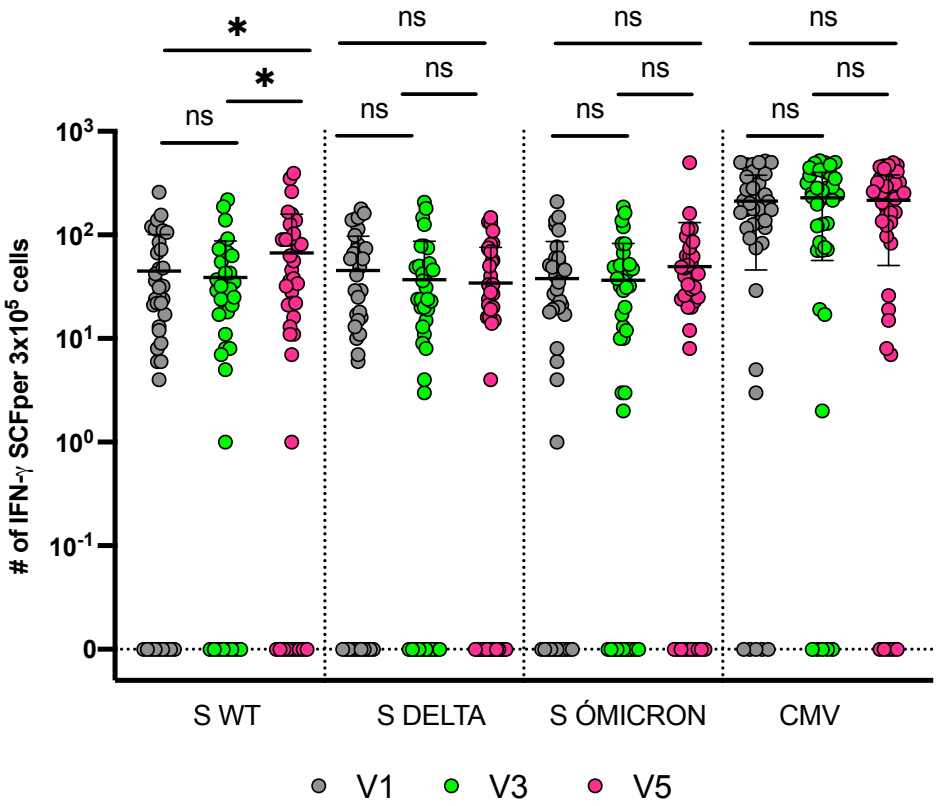
ELISPOT: IFN-γ response increases in PBMCs from subjects that received an inactivated vaccine against the SARS-CoV-2 variant at 12 weeks in the homologous group.



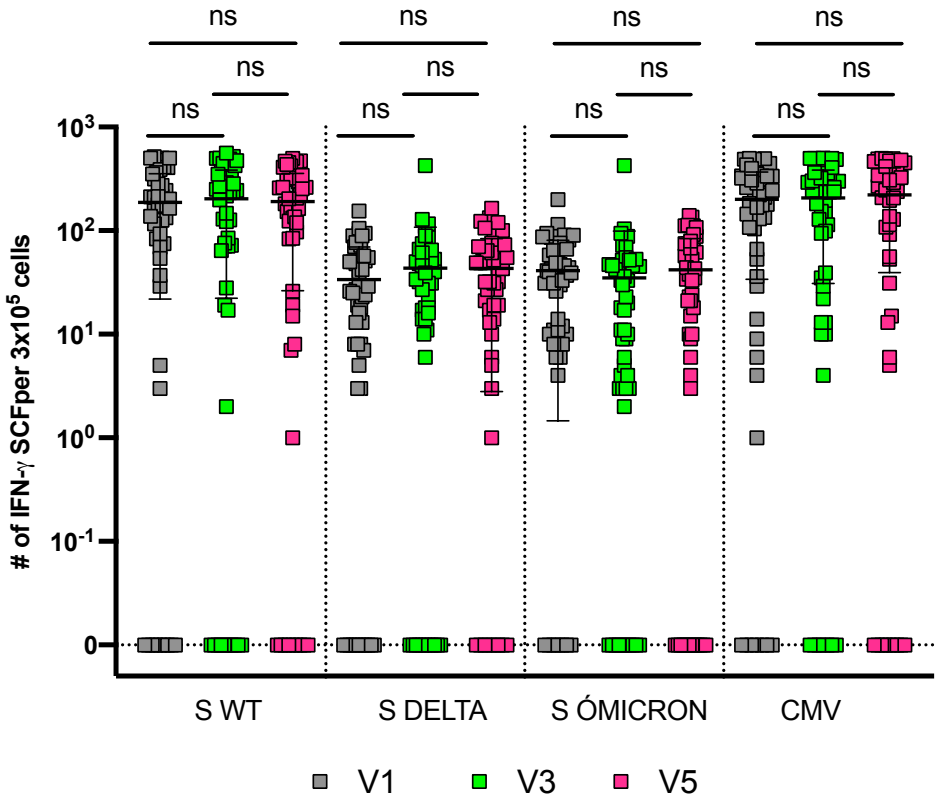
ELISPOT (IFN-γ)

La Jolla Institute FOR IMMUNOLOGY

Homologous



Heterologous



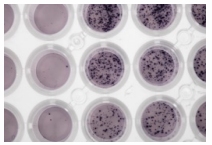
N=40 homologous, 49 heterologous

ANOVA with Fisher's Least Significant Difference (LSD) post-hoc test

Méndez et al., BMC Medicine, 2025

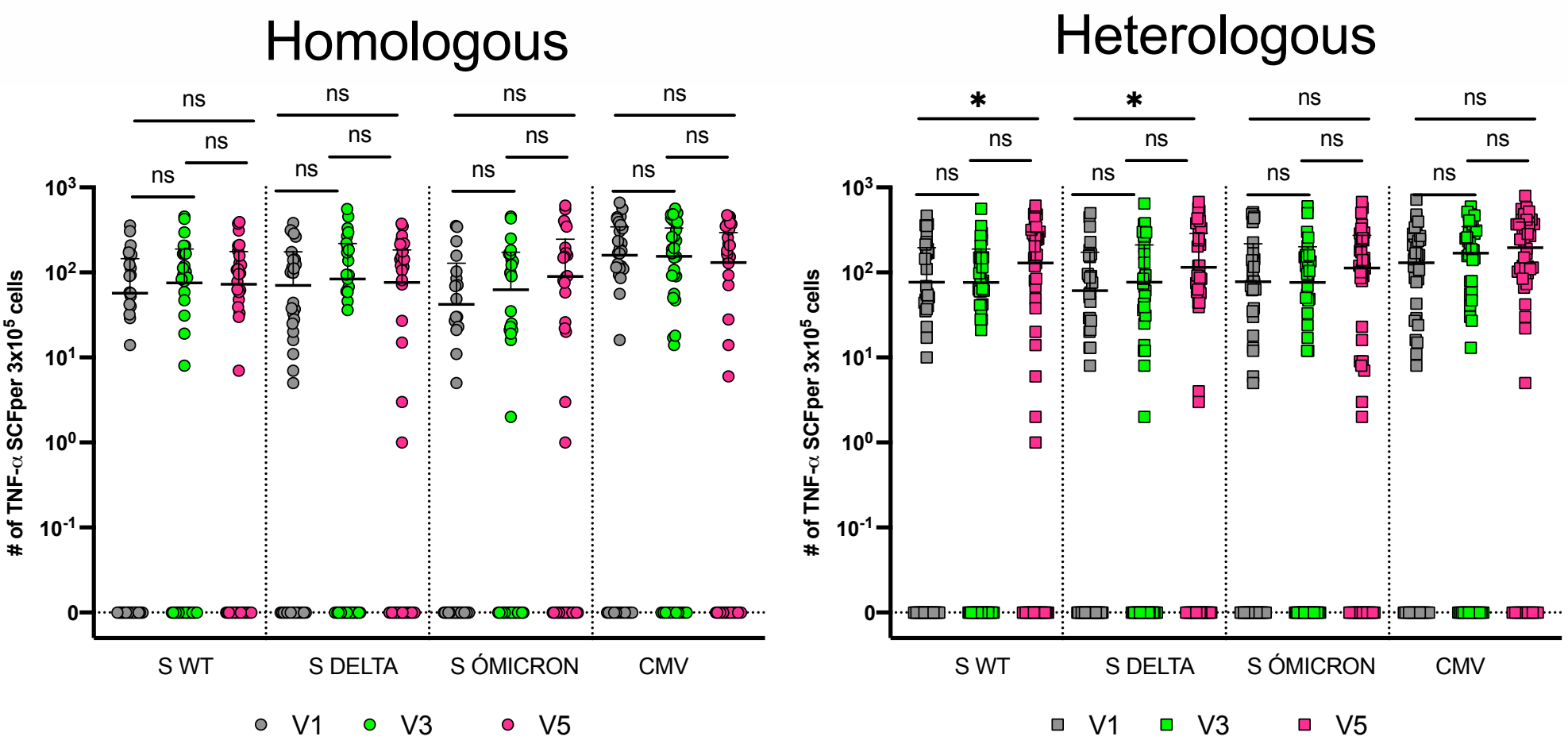
RESULTS

ELISPOT: TNF-α response increases in PBMCs from subjects that received an inactivated vaccine against the SARS-CoV-2 variant at 12 weeks in the **heterologous group**.



ELISPOT (TNF-α)

La Jolla Institute FOR IMMUNOLOGY

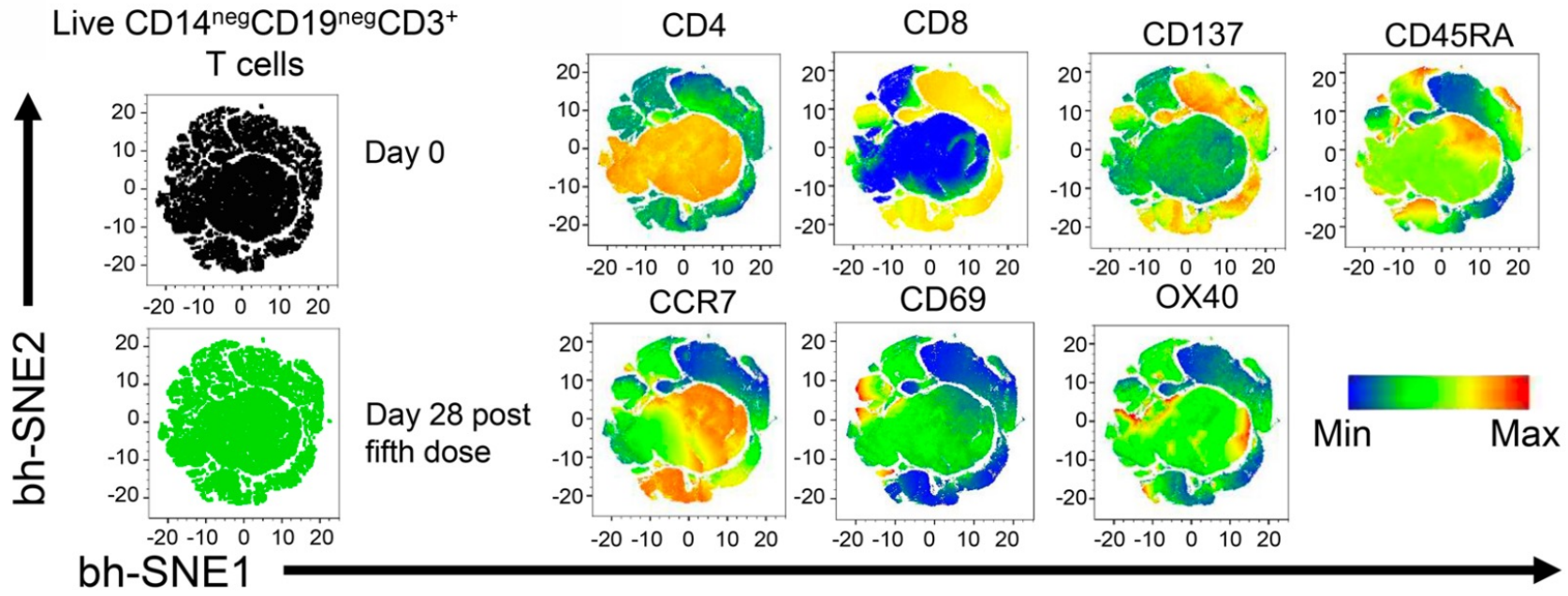


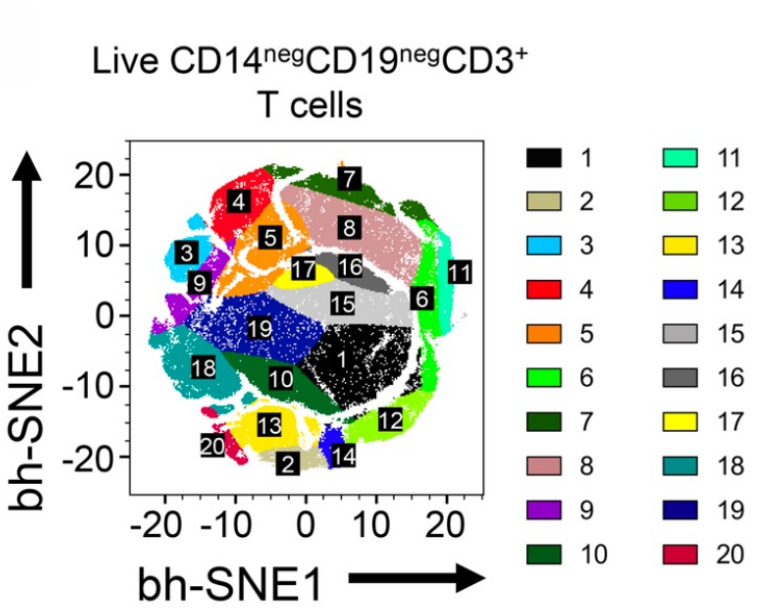
N=40 homologous, 49 heterologous

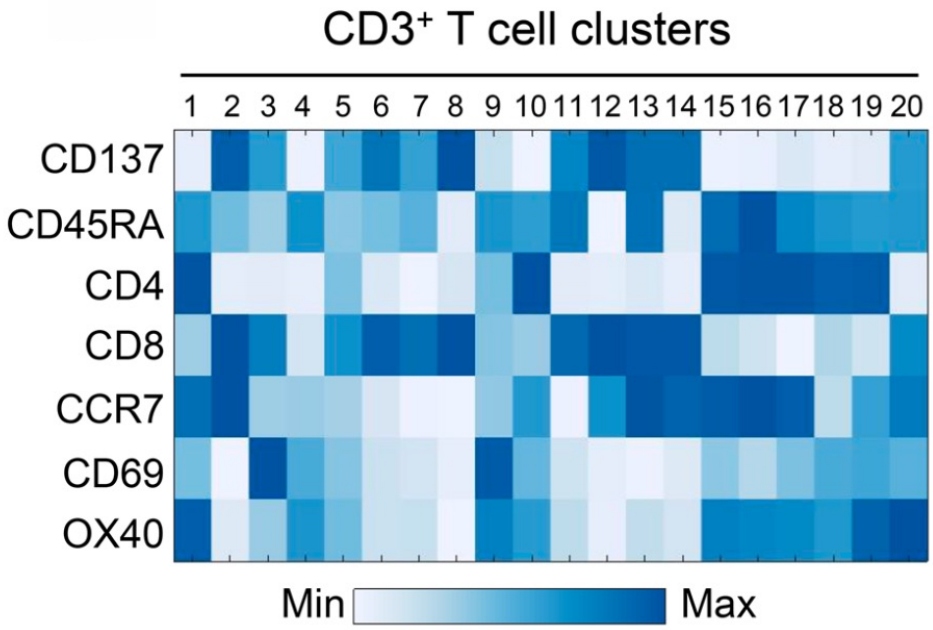
ANOVA with Fisher's Least Significant Difference (LSD) post-hoc test

Méndez et al., BMC Medicine, 2025

Unsupervised Multiparametric Flow Cytometry Analyses

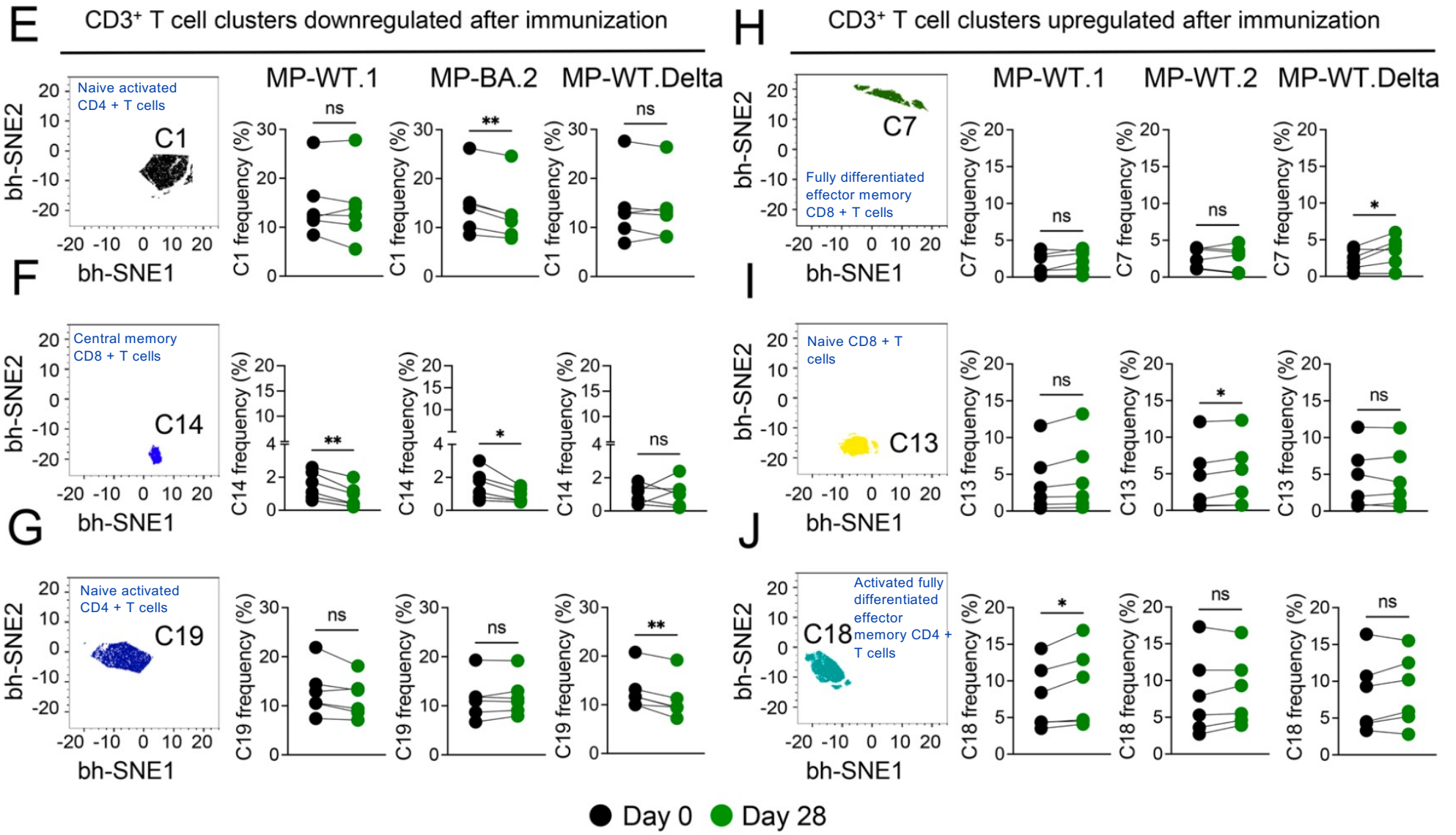






Roman et al., Eur J Immumol 2025

Multiparametric Flow cytometry: Specific changes in the frequency of CD3⁺ T cells clusters are observed in subjects in the **homologous group** that received an inactivated vaccine against SARS-CoV-2 (Wuhan).



Roman et al., Eur J Immumol 2025

Conclusions

Immunization with variant vaccines increases the levels of neutralizing and total antibodies for three variants at 12 weeks in the homologous group.

Immunization with variants vaccines increases the levels of neutralizing antibodies for Delta and Omicron at 12 weeks in the heterologous group.

Increase IFN-γ (homologous) and TNF-α (heterologous) producing cells are observed upon stimulation with pool of peptides derived from Spike proteins from variants of concern at 12 weeks of immunization.

Immunization with variant vaccines do not change the level of AIM^+ $CD4^+$ or $CD8^+$ T cells at 4 or 12 weeks after immunization.

Multiparametric flow cytometry analyses revealed changes in specific subpopulations of CD3+ T cells after a fifth dose of SASR-CoV-2 vaccine.

A booster with inactivated variants vaccines against SARS-CoV-2 induces changes in the immune response in adults that received either homologous or heterologous vaccination schedules

Acknowledgements CoronoVac

CoronaVac Fase 3 Chile

SINOVAC

Millennium Institute IMMUNOLOGY & IMMUNOTHERAPY

Immunogenicity Team

Gobierno de Chile

CPC Confederacion de la Produccion y del Comercio

La Jolla Institute for Immunology

PATH

Clinical Team

Immunogenicity Team + Sinovac

ISP Instituto de Salud Pública

Eugenio Ramírez
Jorge Fernández
Rodrigo Fasce
Judith Mora

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Facultad de Medicina Universidad de Chile

ICBM Instituto de Ciencias Biomédicas