Il punto sui vaccini anti-SARS-CoV-2

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Conflict of Interest Disclosure

I received speaker's honorarium from the following companies:

- Gilead
- VIIV
- MERCK
- MSD
- Sanofi
- Glaxo
- Novartis
- Roche

Challenges facing the Covid-19 vaccine field

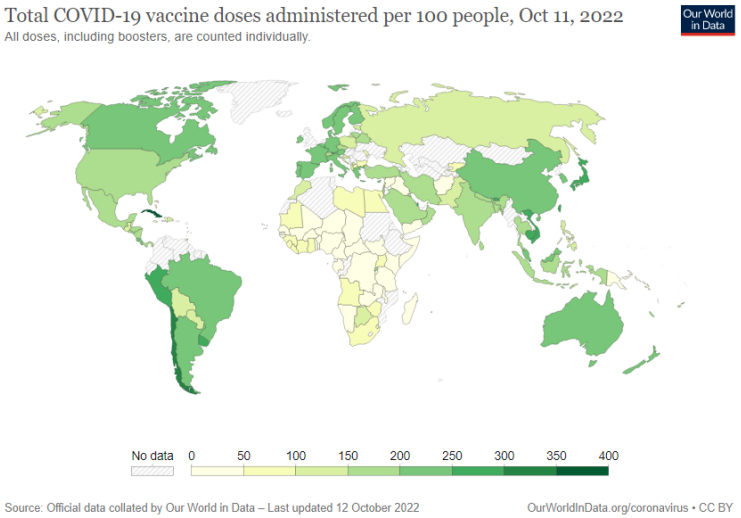
- It has been estimated that global Covid-19 vaccination saved approximately 20 million lives during the first year of the vaccine rollout

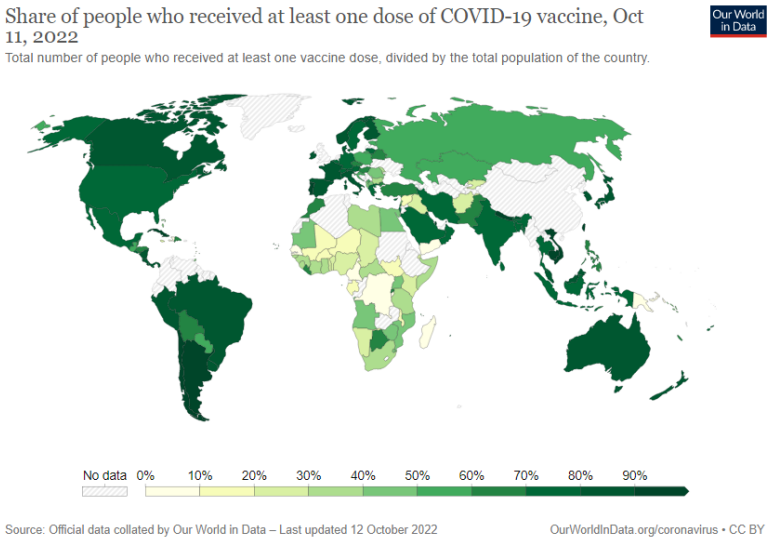
- Inequitable vaccine distribution
- Vaccine hesitancy
- Waning immunity
- The emergence of highly transmissible viral variants that partially escape antibodies.

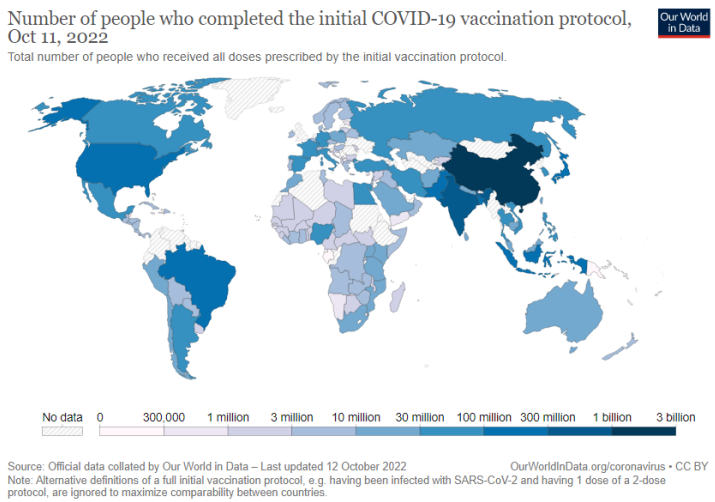
World vaccination coverage

- 68.2% of the world population has received at least one dose of a COVID-19 vaccine
- 12.8 billion doses have been administered globally
- 3.65 million doses are now administered each day
- Only 22.9% of people in low-income countries have received at least one dose

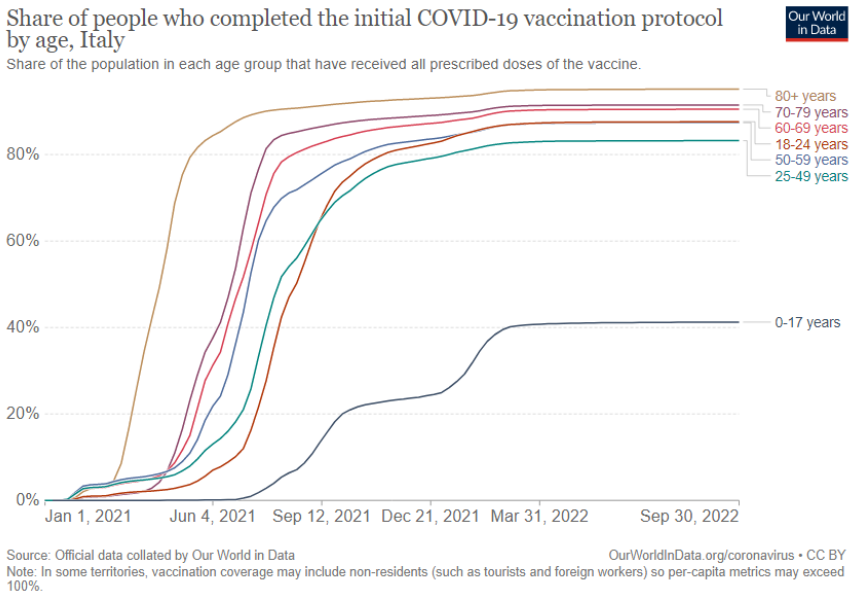
World vaccination coverage

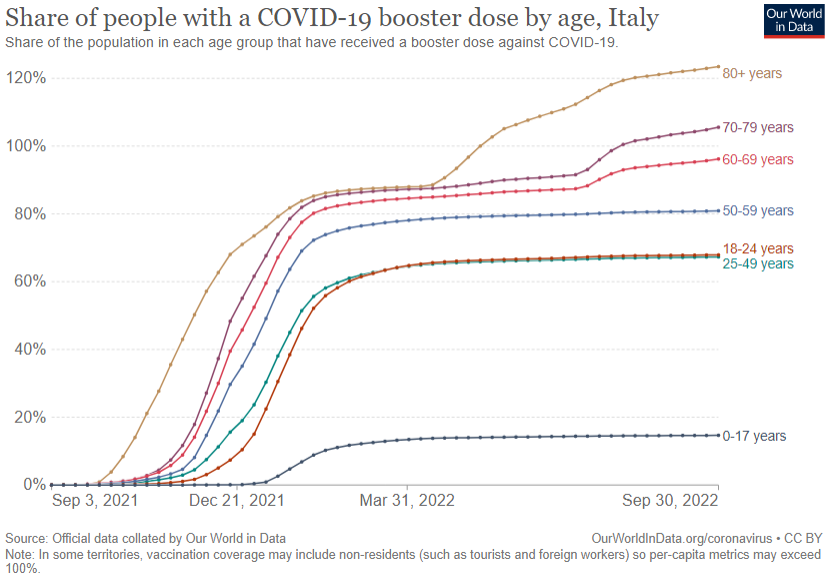


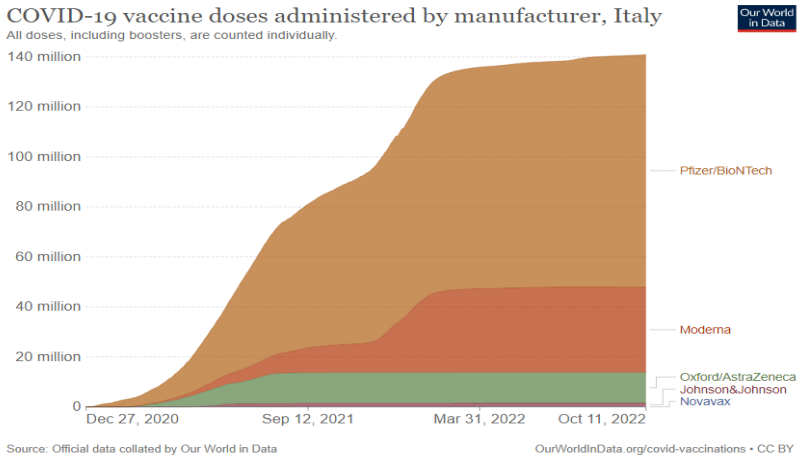




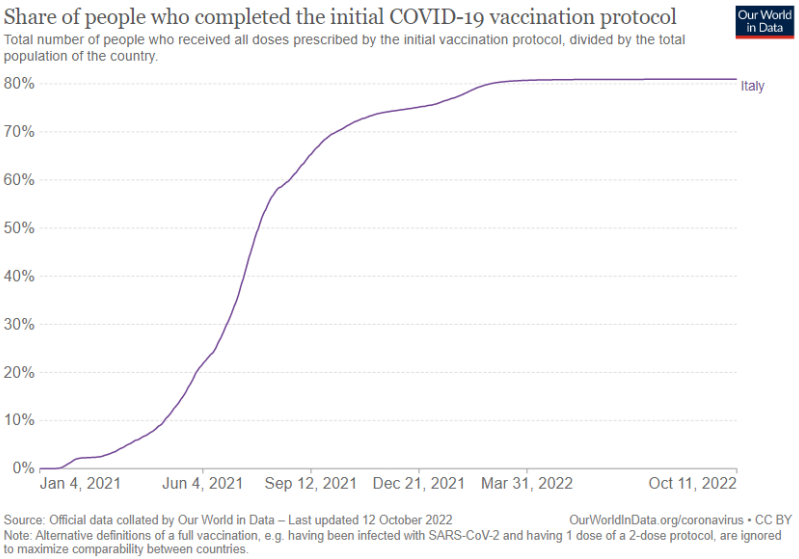
Italian vaccination coverage

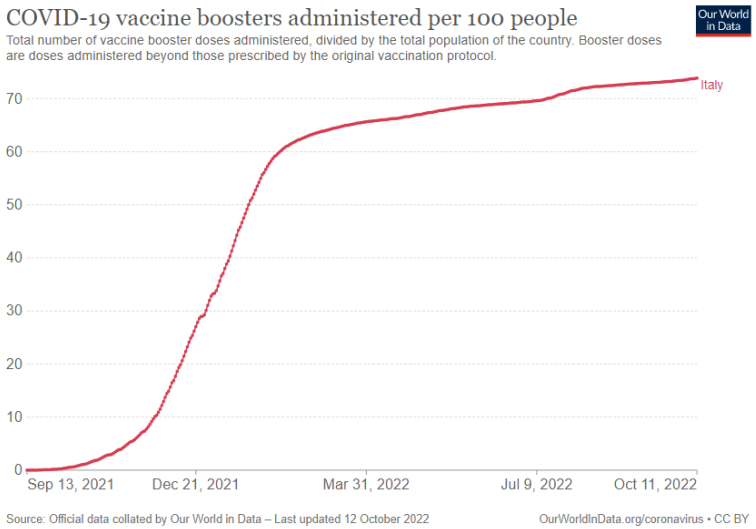






Italian vaccination coverage





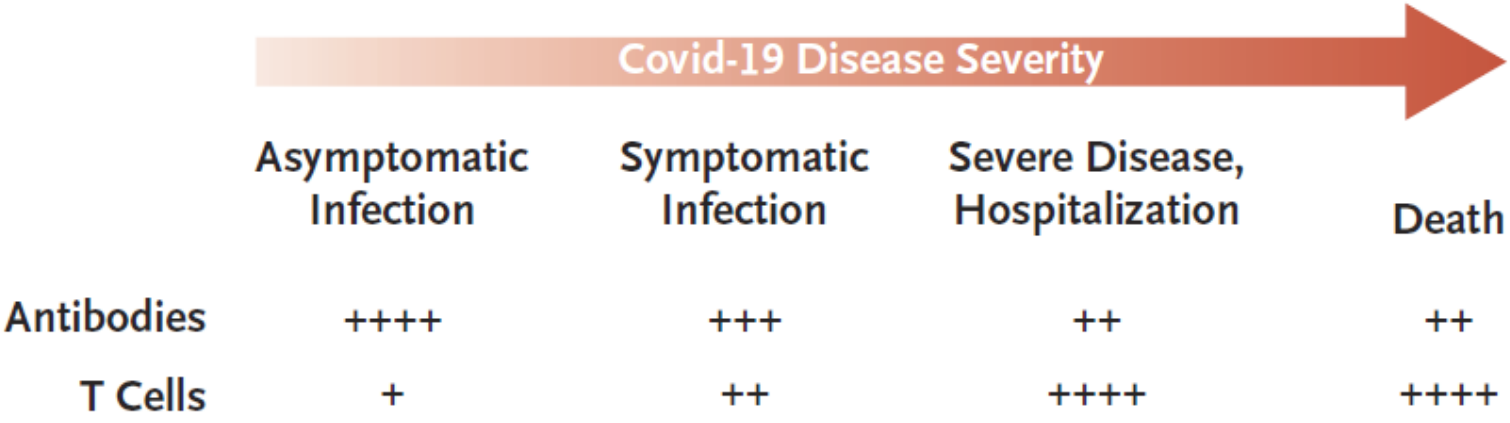
IV dose

3.621.125

18.94% della platea

6.11% della popolazione

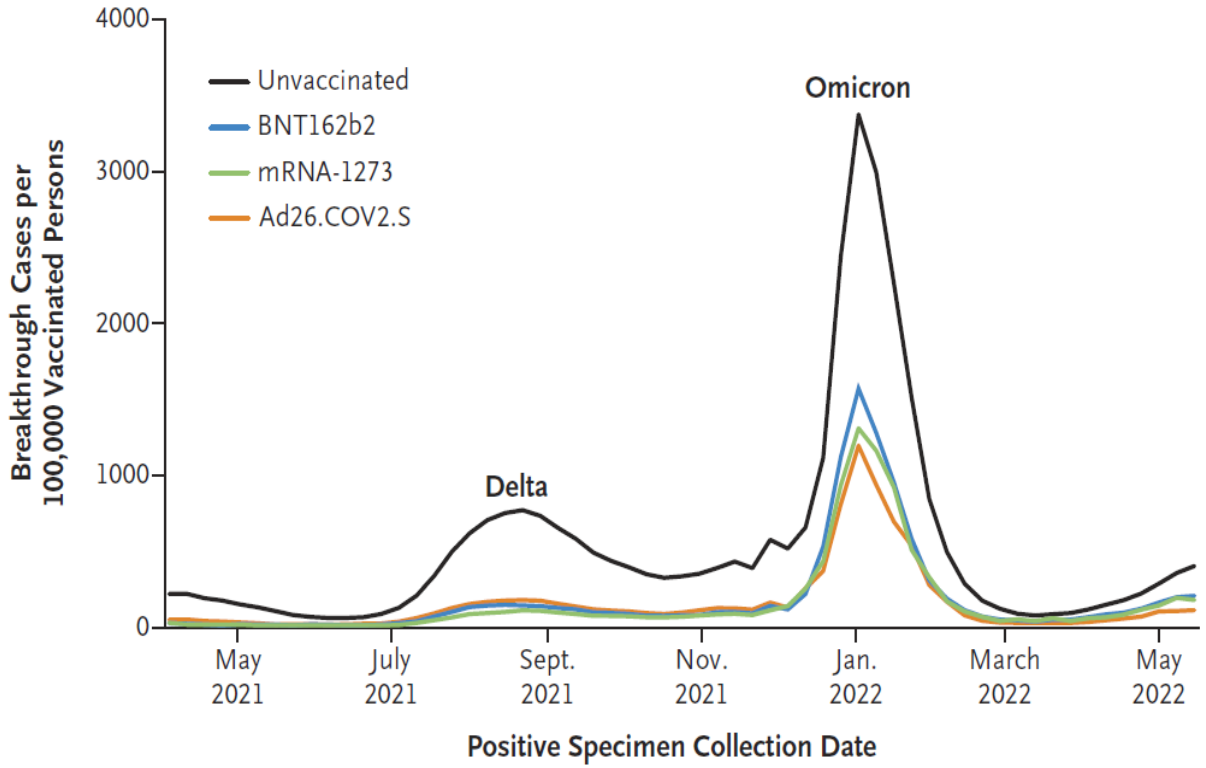
Immune Responses for Protection against SARS-CoV-2



Protective Efficacy of Covid-19 Vaccines against the Ancestral Viral Strain in the US and against the Omicron Variant in South Africa

Vaccine (Dose)	Efficacy against Symptomatic Disease	Efficacy against Hospitalization	Efficacy against ICU Admission
	United States, Ancestral Strain*	South Africa, Omicron Variant†	
	percent	*percent*	
Pfizer BNT162b2 (two shots)	95	70	70
Moderna mRNA-1273 (two shots)	94	ND	ND
Janssen Ad26.COV2.S (two shots)	94	72	82
Janssen Ad26.COV2.S (one shot)	72	ND	ND

Protective Efficacy of Covid-19 Vaccines in the United States



	Breakthrough Cases per 100,000 Vaccinated Persons	
	Peak	May 21, 2022
Unvaccinated	3381	395
BNT162b2	1566	198
mRNA-1273	1305	174
Ad26.COV2.S	1190	106

IDSA hivma
The Journal of Infectious Diseases

The relationship between anti-spike SARS-CoV-2 antibody levels and risk of breakthrough COVID-19 among fully vaccinated adults

	Models	Exposure variables	aHR (95% CI)	*p*-value
Pre-omicron era	Model 1	Elecsys total spike	0.66 (0.46, 0.93)	0.017
	Model 2	VPLEX spike IgG	0.65 (0.44, 0.97)	0.035
	Model 3	VPLEX RBD IgG	0.63 (0.41, 0.98)	0.041
Omicron era	Model 1	Elecsys total spike	0.83 (0.68, 0.99)	0.045
	Model 2	VPLEX spike IgG	0.80 (0.65, 0.98)	0.037
	Model 3	VPLEX RBD IgG	0.79 (0.65, 0.96)	0.020

Multivariate analysis of association between antibody levels and risk of COVID-19 infection

Michael Asamoah-Boaheng,et al.

Vaccini autorizzati in Italia

- **Vaccini a m-RNA nella formulazione bivalente**:
  - Original/Omicron/BA.4-5 di Comirnaty - il 12 settembre 2022 è stato autorizzati dall'EMA e il 14 settembre dall'AIFA
  - Original/Omicron BA.1 di Spikevax e Comirnaty - il 1° settembre 2022 sono stati autorizzati dall'EMA e il 5 settembre dall'AIFA
- Vaccino **Nuvaxovid (Novavax)** - il 20 dicembre 2021 è stato autorizzato dall'EMA e il 22 dicembre dall'AIFA.
- Vaccino **Janssen (Johnson & Johnson)** - l'11 marzo 2021 è stato autorizzato dall'EMA e il 12 marzo dall'AIFA
- Vaccino **Vaxzevria di AstraZeneca** - il 29 gennaio 2021 è stato autorizzato dall'EMA e il 30 gennaio dall'AIFA.
- Vaccino **Spikevax** (**Moderna)** - il 6 gennaio 2021 è stato autorizzato dall'EMA e il 7 gennaio dall'AIFA
- Vaccino **Comirnaty di Pfizer-BioNtech** - è il primo vaccino ad essere stato autorizzato in Unione Europea: il 21 dicembre 2020 dall'EMA e il 22 dicembre da AIFA

Vaccine effectiveness

after two doses of either Pfizer or Moderna against the omicron variant

Vaccine Type	2-4 weeks after 2nd dose	25 weeks after 2nd dose
Pfizer-BioNTech	~65.5%	~8.8%
Moderna	~75.1%	~14.9%

after two primary doses of Pfizer vaccine followed by a booster dose of Pfizer against the omicron variant

Vaccine Type	2-4 weeks after 2nd dose	25 weeks after 2nd dose	Pfizer Booster (2-4 weeks after booster dose)	Pfizer Booster (10 weeks after booster dose)
Pfizer	~65.5%	~8.8%	~67%	~45%

after two primary doses of Pfizer vaccine followed by a booster dose of Moderna against the omicron variant

Vaccine Type	2-4 weeks after 2nd dose	25 weeks after 2nd dose	Moderna Booster (2-4 weeks after booster dose)	Moderna Booster (5-9 weeks after booster dose)
Pfizer	~65.5%	~8.8%	~74%	~64%

Vaccine effectiveness

after two primary doses of Moderna vaccine followed by a booster dose of Moderna against the omicron variant

Vaccine Type	2-4 weeks after 2nd dose	25 weeks after 2nd dose	Moderna Booster (2-4 weeks after booster dose)
Moderna	~75.1%	~14.9%	~66%

after two primary doses of Moderna vaccine followed by a booster dose of Pfizer against the omicron variant

Vaccine Type	2-4 weeks after 2nd dose	25 weeks after 2nd dose	Pfizer Booster (2-4 weeks after booster dose)
Moderna	~75.1%	~14.9%	~65%

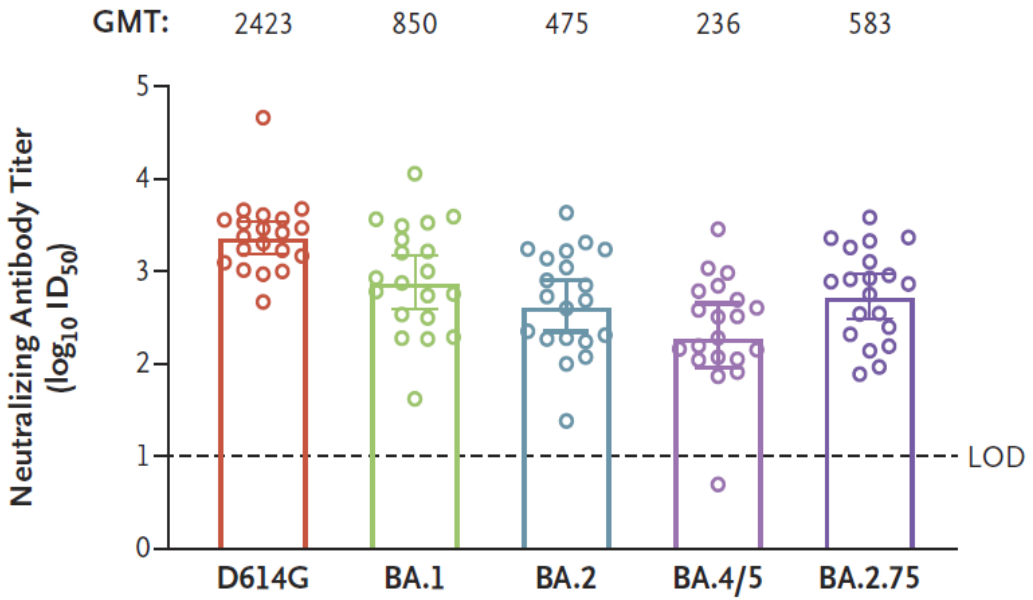
after two primary doses of AstraZeneca vaccine followed by a booster dose of Pfizer against the omicron variant

Vaccine Type	20 weeks after 2nd dose	Pfizer Booster (2-4 weeks after booster dose)	Pfizer Booster (10 weeks after booster dose
AstraZeneca	~0%	~62%	~40%

after two primary doses of AstraZeneca vaccine followed by a booster dose of Moderna against the omicron variant

Vaccine Type	20 weeks after 2nd dose	Moderna Booster (2-4 weeks after booster dose)	Moderna Booster (5-9 weeks after booster dose)
AstraZeneca	~0%	~70%	~61%

Neutralization of SARS-CoV-2 Omicron BA.2.75 after mRNA-1273 Vaccination



Factor reduction in GMT as compared with D614G	—	2.9×	5.1×	10.3×	4.2×
Factor reduction in GMT as compared with BA.1	0.4×	—	1.8×	3.6×	1.5×

Emi Takashita et al.

COVID-19 Update: Bivalent Pfizer and Moderna COVID-19 Vaccines for Booster Immunization

- The FDA has amended its EUAs for the mRNA COVID-19 vaccines manufactured by Pfizer/BioNTech and Moderna to permit use of bivalent formulations of the products as a single booster dose in persons ≥12 years old (Pfizer) or ≥18 years old (Moderna) whose most recent COVID-19 vaccine dose was a monovalent product given ≥2 months previously as a booster or for completion of a primary series.
- The bivalent formulations are not authorized for primary immunization.
- Monovalent Pfizer and Moderna COVID-19 vaccines are no longer authorized for use as booster doses in persons ≥12 years old.
- The bivalent vaccine formulations contain equal amounts of two mRNA strands. One strand, which codes for the spike protein of the original (Wuhan-Hu-1) strain of SARS-CoV-2, is identical to that used in the monovalent vaccines. The other strand codes for the spike protein common to the BA.4 and BA.5
- No randomized trials of the new bivalent vaccine formulations are available.
- Their authorization was based on clinical data with the monovalent products and on the results of randomized immunogenicity studies that compared bivalent formulations of the vaccines containing mRNA from the original and BA.1 Omicron strains of SARS-CoV-2 (not authorized in the US) with their respective monovalent formulations

COVID-19 Update: Bivalent Pfizer and Moderna COVID-19 Vaccines for Booster Immunization

- The immunogenicity studies included 610 adults ≥55 years old (Pfizer) and 594 adults ≥18 years old (Moderna) who had no history of SARS-CoV-2 infection and had previously received two primary-series doses and one booster dose of the applicable monovalent vaccine.
- Subjects received either a second booster dose of the same monovalent vaccine or a booster dose of the corresponding original/BA.1 bivalent vaccine.
- In both studies, at ~1 month after the second booster dose, the geometric mean neutralizing antibody titer level and the seroresponse rate against the BA.1 variant were higher with the bivalent vaccine than with the monovalent vaccine
- It is presumed that the newly authorized bivalent formulations of the Pfizer and Moderna vaccines will induce a similar immunogenic response against the BA.4 and BA.5 variants of SARS-CoV-2.
- ADVERSE EFFECTS – In the immunogenicity studies, adverse effects of the original/BA.1 bivalent Pfizer and Moderna vaccines were similar to those with the corresponding monovalent products
- **DOSAGE AND ADMINISTRATION –** CDC guidelines recommend that adolescents and adults who have completed a primary immunization series with any COVID-19 vaccine receive a booster dose of either the bivalent Pfizer vaccine (≥12 years old) or the bivalent Moderna vaccine (≥18 years old) ≥2 months after their most recent monovalent vaccine dose

Table 1. Immunogenicity Study Results

Vaccine Composition	GMT[1]	Seroresponse Rate[2]
Pfizer/BioNTech Study (n=610)[3]		
Bivalent[4]	711.0[5]	71.6%[6]
Monovalent	455.8	57.0%
Moderna Study (n=594)[7]		
Bivalent[4]	2479.9[5]	74.9%[6]
Monovalent	1421.2	53.9%

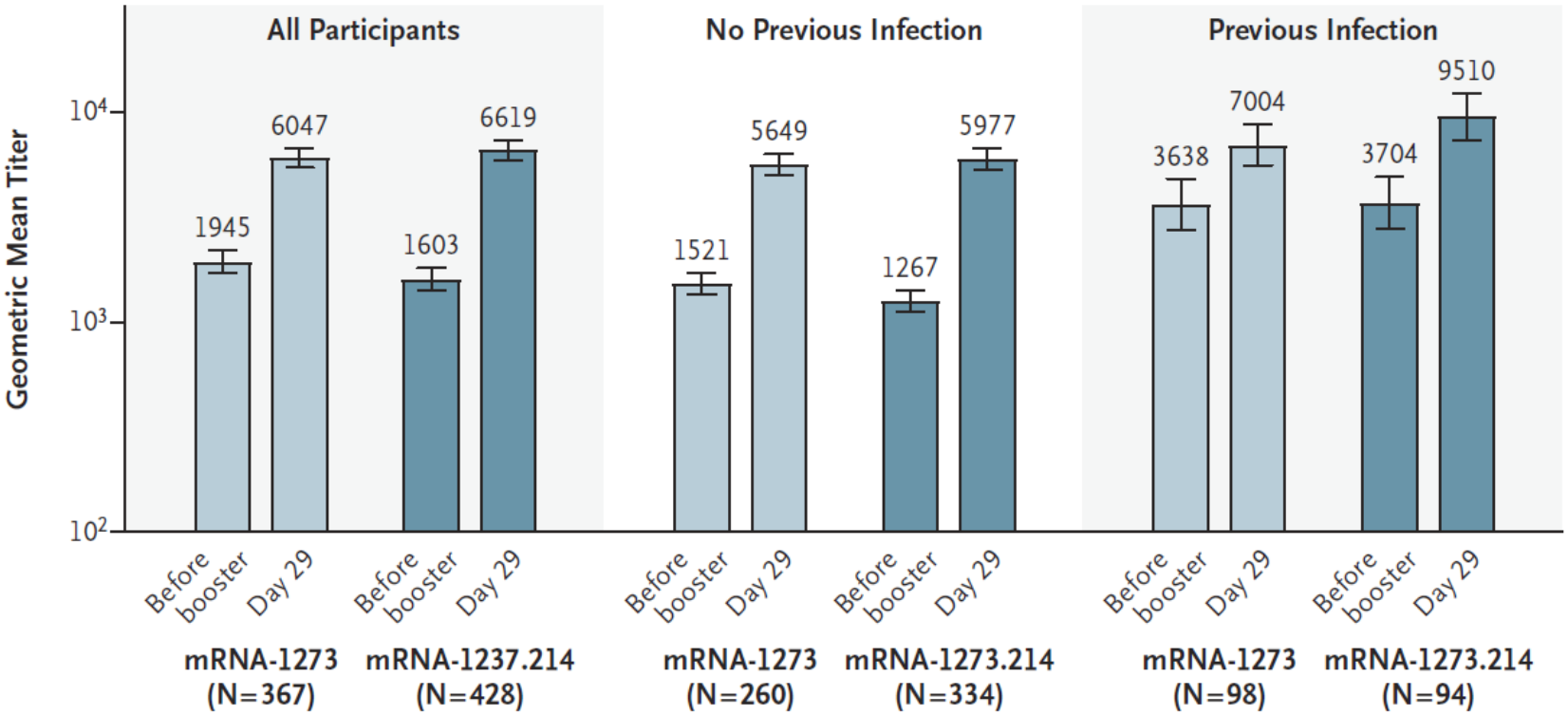
A Bivalent Omicron-Containing Booster Vaccine against Covid-19

Spyros Chalkias, M.D., Charles Harper, M.D., Keith Vrbicky, M.D., Stephen R. Walsh, M.D., Brandon Essink, M.D., Adam Brosz, M.D., Nichole McGhee, B.S., Joanne E. Tomassini, Ph.D., Xing Chen, Sc.D., Ying Chang, M.S., Andrea Sutherland, M.D., M.P.H., David C. Montefiori, Ph.D., Bethany Girard, Ph.D., Darin K. Edwards, Ph.D., Jing Feng, M.S., Honghong Zhou, Ph.D., Lindsey R. Baden, M.D., Jacqueline M. Miller, M.D., and Rituparna Das, M.D., Ph.D.

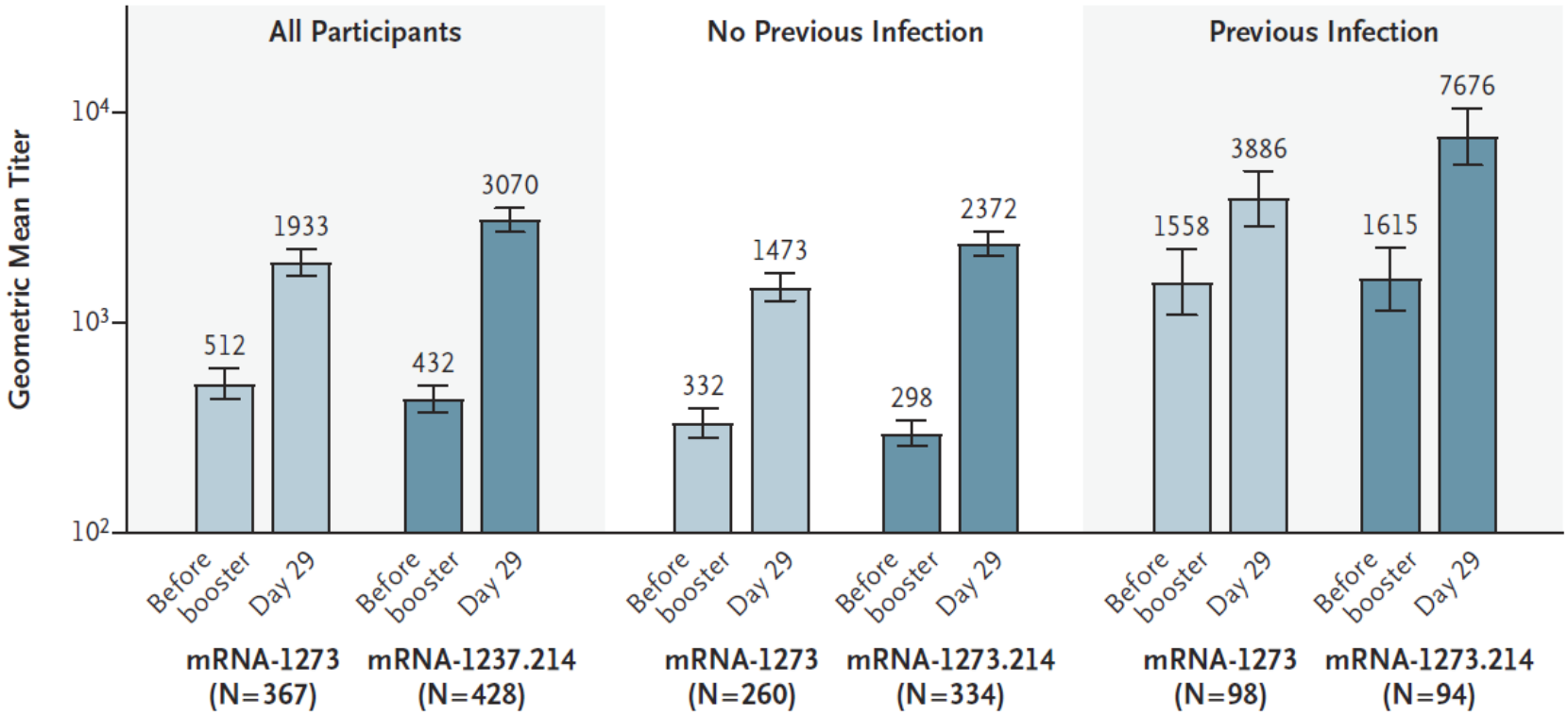
The NEW ENGLAND JOURNAL of MEDICINE

- Phase 2–3 study
- Comparison of the 50-µg bivalent vaccine mRNA 1273.214 (25 µg each of ancestral Wuhan-Hu-1 and omicron BA.1 spike mRNAs) with the previously authorized 50-µg mRNA-1273 booster
- mRNA-1273.214 or mRNA-1273 as a second booster in adults who had previously received a two-dose (100-µg) primary series and first booster (50-µg) dose of mRNA-1273 (≥3 months earlier)

Neutralizing Antibody Titers against Ancestral SARS-CoV-2 (D614G)

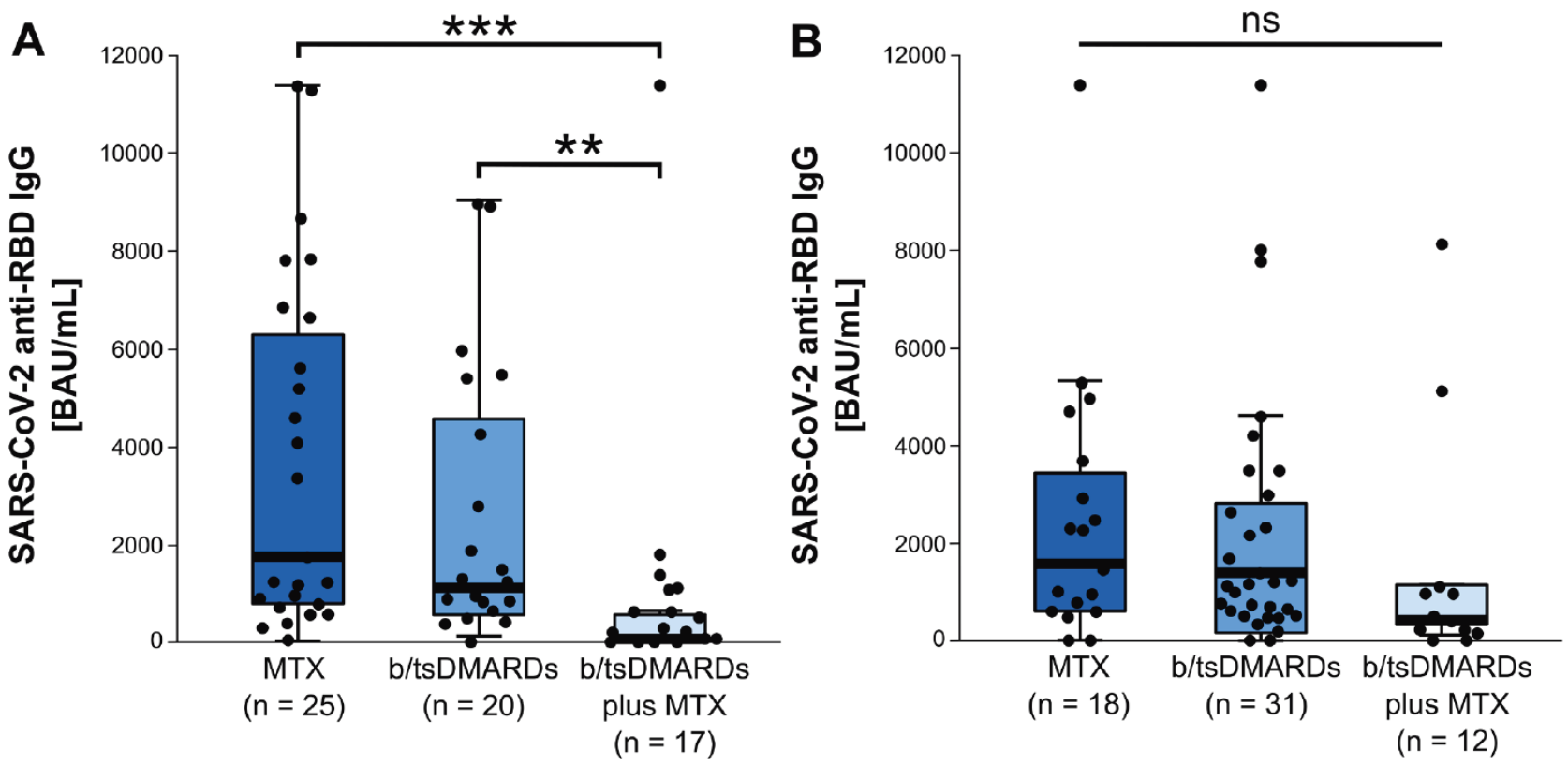


Neutralizing Antibody Titers against Omicron Variant



Reduced humoral response to a third dose of SARS-CoV-2 mRNA vaccines by concomitant methotrexate therapy in elderly patients with rheumatoid arthritis

RMD Open
Rheumatic & Musculoskeletal Diseases



Elderly patients with RA (> 65)

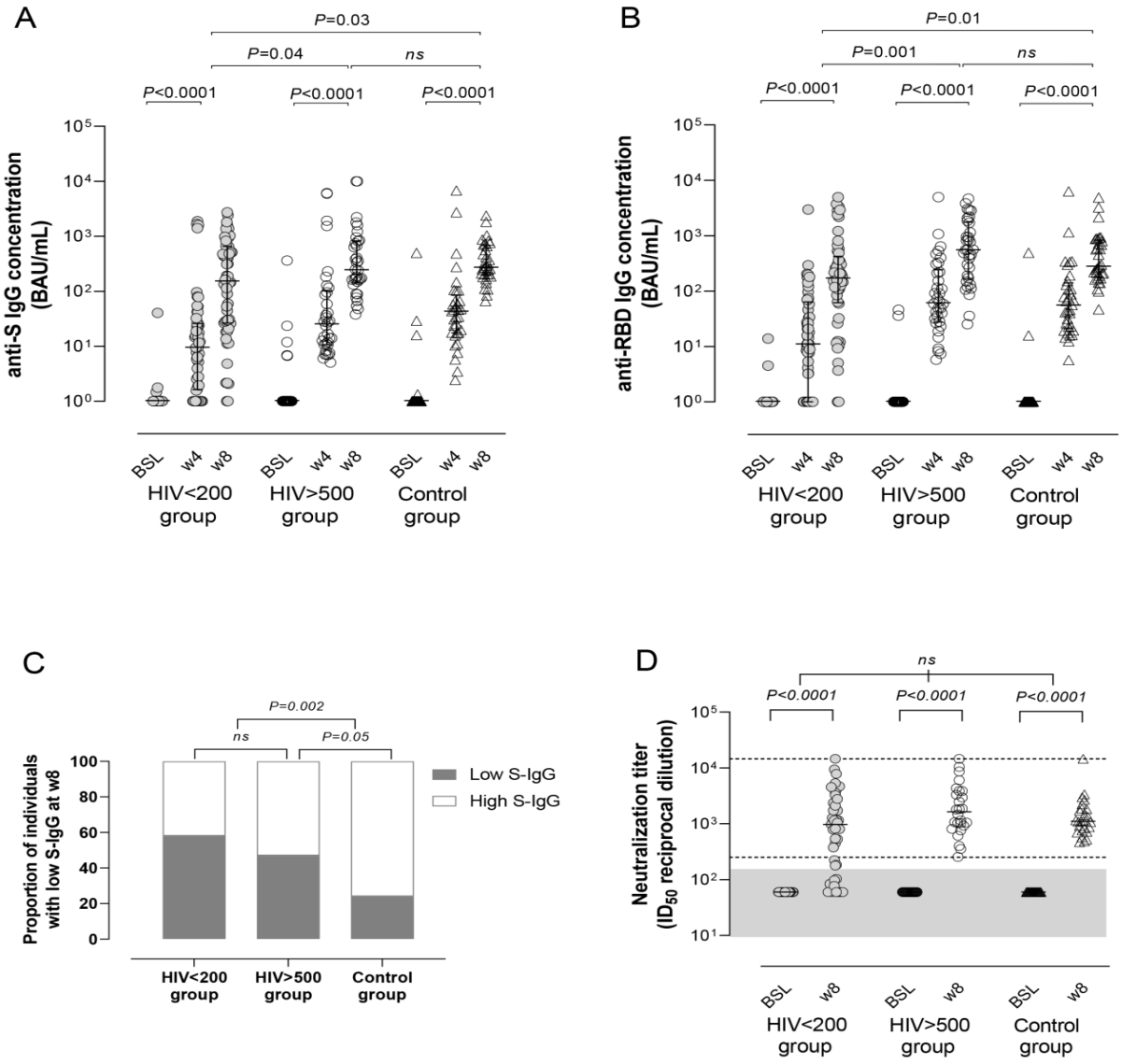
Younger RA patient (< 64.5)

David Stahl, et al.

Limited humoral and specific T-cell responses after SARS-CoV-2 vaccination in PLWH with poor immune reconstitution

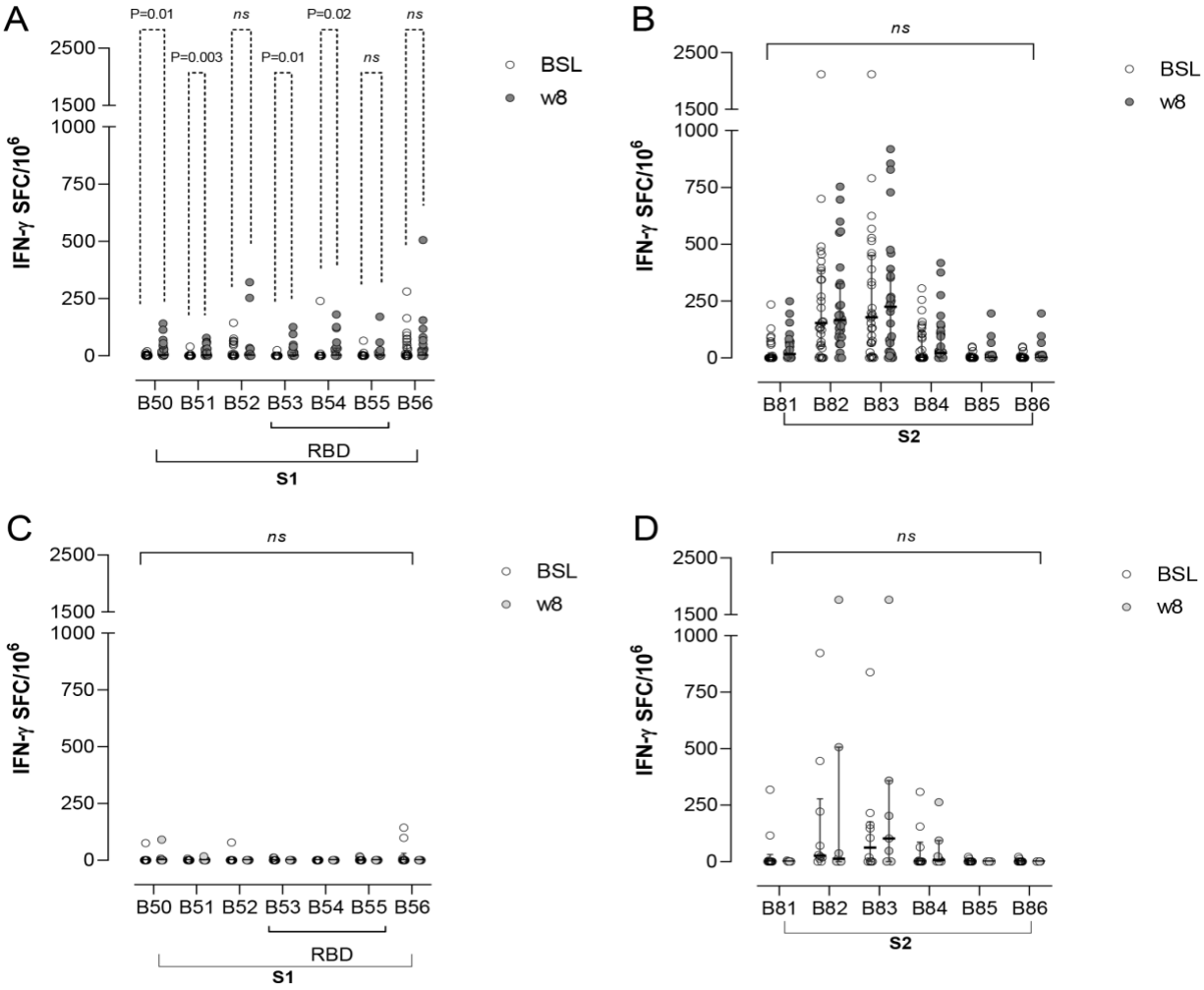
The Journal of Infectious Diseases

Vaccine-induced humoral immune responses



Susana Benet, et al.

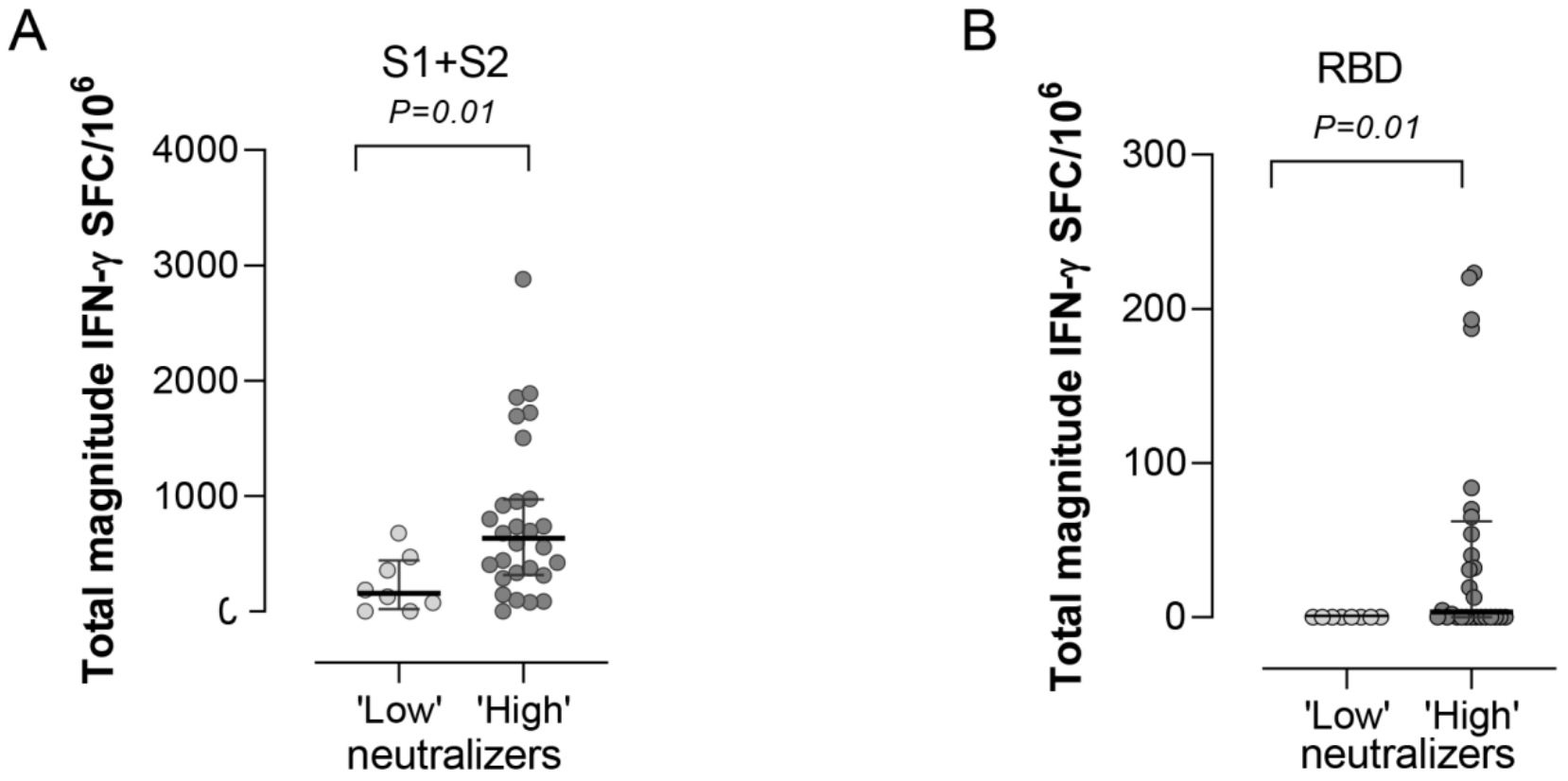
Vaccine-induced T-cell immune responses against the S1 and S2 subunits 23 from the SARS-CoV-2 Spike protein in ‘High and Low neutralizers’ from HIV<200 group



"High neutralizers"

"Low neutralizers"

Comparison of vaccine-induced T-cell responses at w8 between 'High and Low neutralizers' from HIV<200 group



CANCER EPIDEMIOLOGY

IJC INTERNATIONAL JOURNAL of CANCER

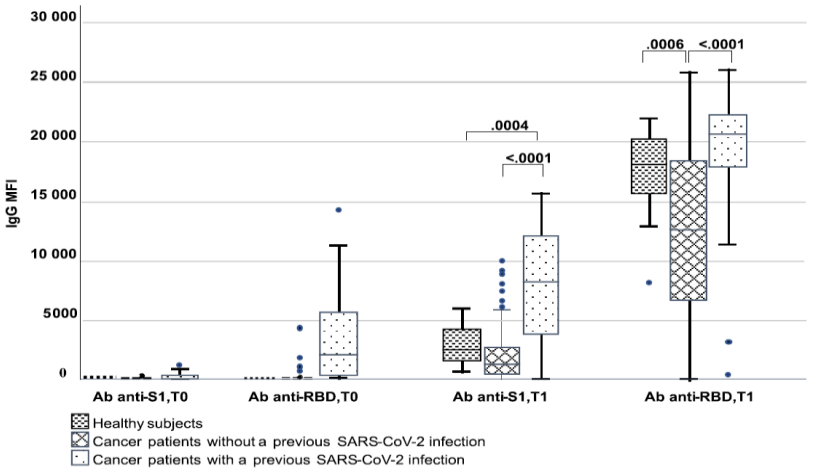
Immunogenicity of two doses of BNT162b2 and mRNA-1273 vaccines for solid cancer patients on treatment with or without a previous SARS-CoV-2 infection

Nicla La Verde[1] | Agostino Riva[2,3] | Maria Silvia Cona[1] | Arianna Gabrieli[3] | Monica Cattaneo[1] | Cinzia Fasola[1] | Giuseppe Lipari[3] | Claudia De Stradis[3] | Valentina Favorito[1] | Benedetta Lombardi Stocchetti[1] | Davide Chizzoniti[1] | Alice Covizzi[2] | Eliana Rulli[4] | Francesca Galli[4] | Lorenzo Ruggieri[1] | Anna Gambaro[1] | Sabrina Ferrario[1] | Davide Dalu[1] | Maciej S. Tarkowski[3]

Oncology

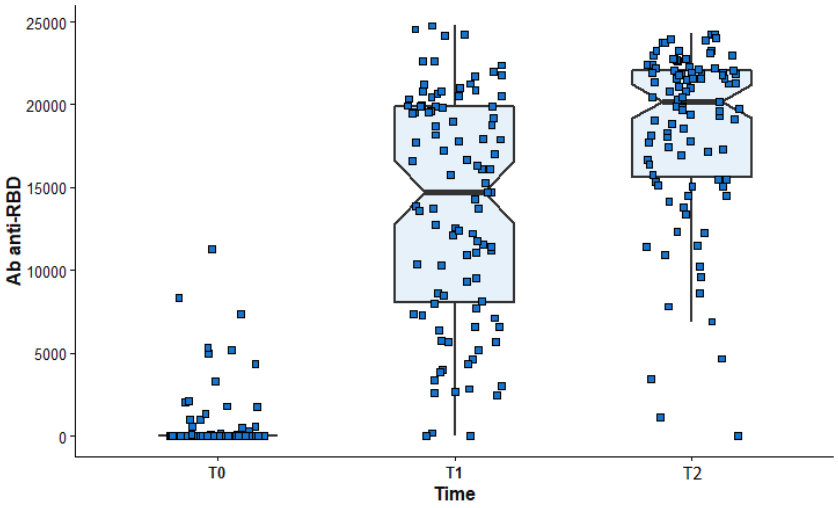
- 195 consecutive cancer patients and 20 healthy controls were enrolled.
- 31 cancer patients had a previous exposure to SARS-CoV-2.
- Cancer patients previously exposed to the virus had significantly higher median levels of anti-S1 and anti-RBD IgG, compared to healthy controls and to cancer patients without a previous infection
- Vaccine type, comorbidities negatively affected the antibody response.
- Vaccine immunogenicity in cancer patients with a previous exposure to SARS-CoV-2 seems comparable to that of healthy subjects.
- Clinical variables of immune frailty negatively affect humoral immune response to vaccination

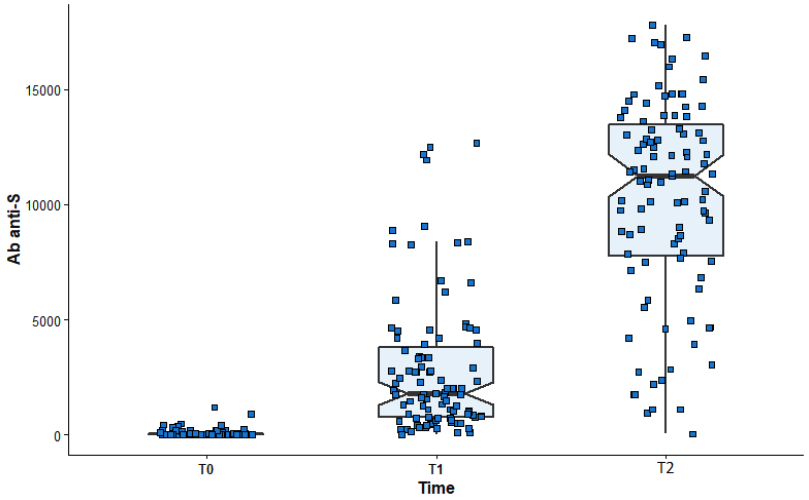
	SOGGETTI SANI	PAZIENTI ONCOLOGICI	
		no pre esp SARS-CoV-2	pre esp SARS-CoV-2
Anticorpi anti-S1 (MFI)			
Media (DS)	3003.1 (1533.0)	1957.7 (2018.3)	7374.6 (4370.0)
Mediana	2590.0	1322.0	8279.8
(Q1-Q3)	(1731.8-4253.0)	(473.0-2733.0)	(4288.0-11936.0)
Min - Max	663.0 - 5961.0	5.0 - 10038.5	95.0 - 15649.0
Responder	19 (95.0)	110 (66.7)	28 (93.3)



Oncology

Immunogenicity of three doses of BNT162b2 and mRNA-1273 vaccines for solid cancer patients





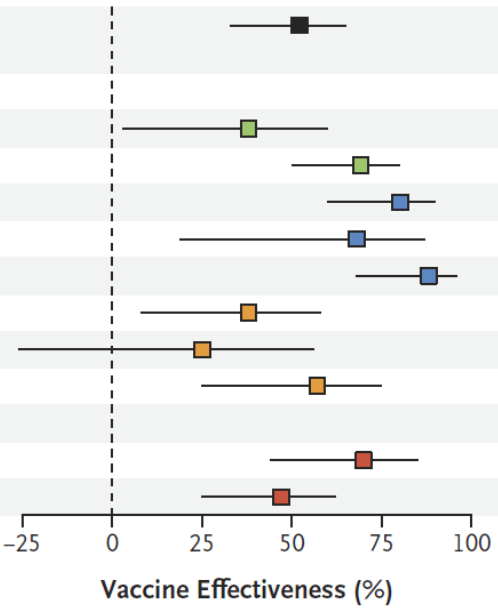
Ab anti-S e anti-RBD al T2	n (%)
Responder: Ab ≥700 MFI	98 (99.0%)
Non responder: Ab <700 MFI	1 (1.0%)

Factors associated with IgG anti-RBD and anti-S1 SARS-CoV-2 vaccine response in cancer patients

	Anti-S1 antibody response (N = 194)		Anti-RBD antibody response (N = 194)	
Parameter	Exp (estimate [95% CI])	*P*-value	Exp (estimate [95% CI])	*P*-value
Intercept	2793.55		13 947.35	
BNT162b2 vaccine (vs mRNA-1273)	0.39 [0.26-0.60]	**<.0001**	0.57 [0.39-0.84]	**.0045**
One comorbidity (vs none)	1.01 [0.65-1.58]	.9517	1.03 [0.70-1.53]	.8786
More than one comorbidity (vs none)	0.57 [0.34-0.94]	**.0274**	0.53 [0.34-0.82]	**.0048**
Previous SARS-CoV-2 infection	5.41 [3.15-9.28]	**<.0001**	2.08 [1.30-3.34]	**.0026**
Steroids	0.67 [0.37-1.20]	.1799		
G-CSF	0.38 [0.18-0.83]	**.0151**		

Maternal Vaccination and Risk of Hospitalization for Covid-19 among Infants

Subgroup	Case Infants	Control Infants	Effectiveness of Maternal Vaccination
	no. of vaccinated mothers/total no. (%)		*% (95% CI)*
Overall effectiveness of maternal vaccination	87/537 (16)	147/512 (29)	52 (33 to 65)
Timing of vaccination			
During first 20 wk of pregnancy	46/496 (9)	62/427 (15)	38 (3 to 60)
After 20 wk of pregnancy	31/481 (6)	79/444 (18)	69 (50 to 80)
Delta-predominant period	14/181 (8)	61/216 (28)	80 (60 to 90)
Vaccinated during first 20 wk of pregnancy	8/175 (5)	22/177 (12)	68 (19 to 87)
Vaccinated after 20 wk of pregnancy	5/172 (3)	37/192 (19)	88 (68 to 96)
Omicron-predominant period	73/356 (21)	86/296 (29)	38 (8 to 58)
Vaccinated during first 20 wk of pregnancy	38/321 (12)	40/250 (16)	25 (–26 to 56)
Vaccinated after 20 wk of pregnancy	26/309 (8)	42/252 (17)	57 (25 to 75)
Type of hospital admission			
ICU	11/113 (10)	147/512 (29)	70 (42 to 85)
Non-ICU	76/424 (18)	147/512 (29)	47 (25 to 62)



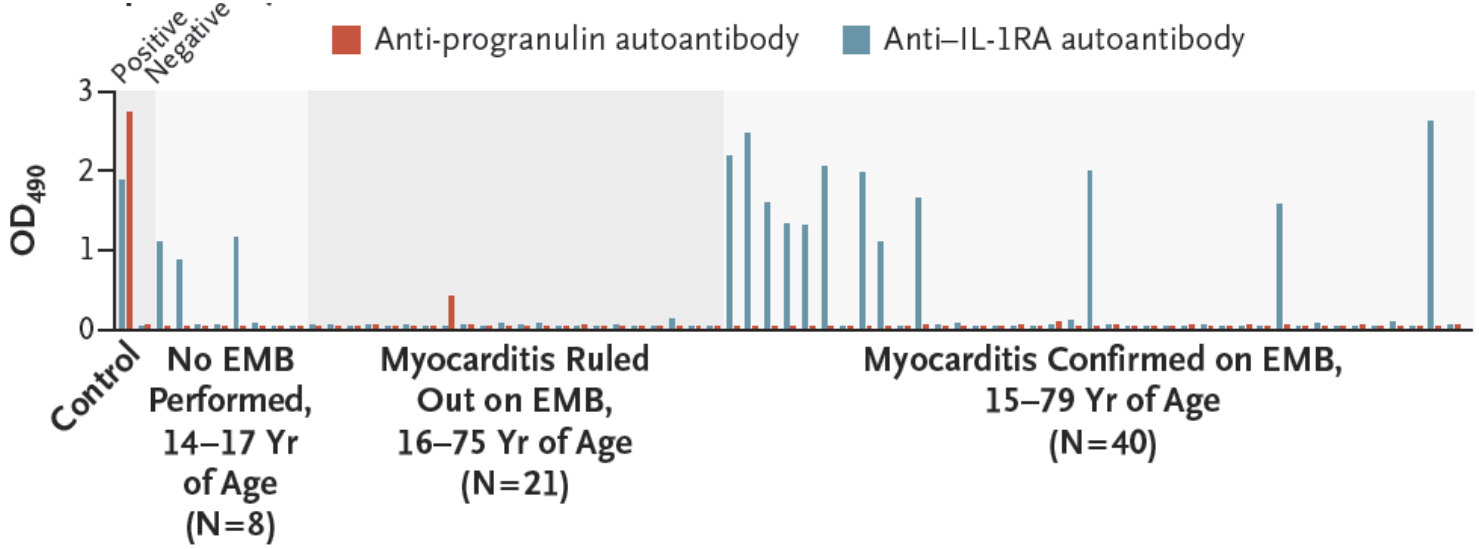
Effectiveness of Maternal Two-Dose mRNA Vaccination against Hospitalization for Covid-19 among Infants, Stratified According to Vaccination Timing, Variant, and Type of Admission

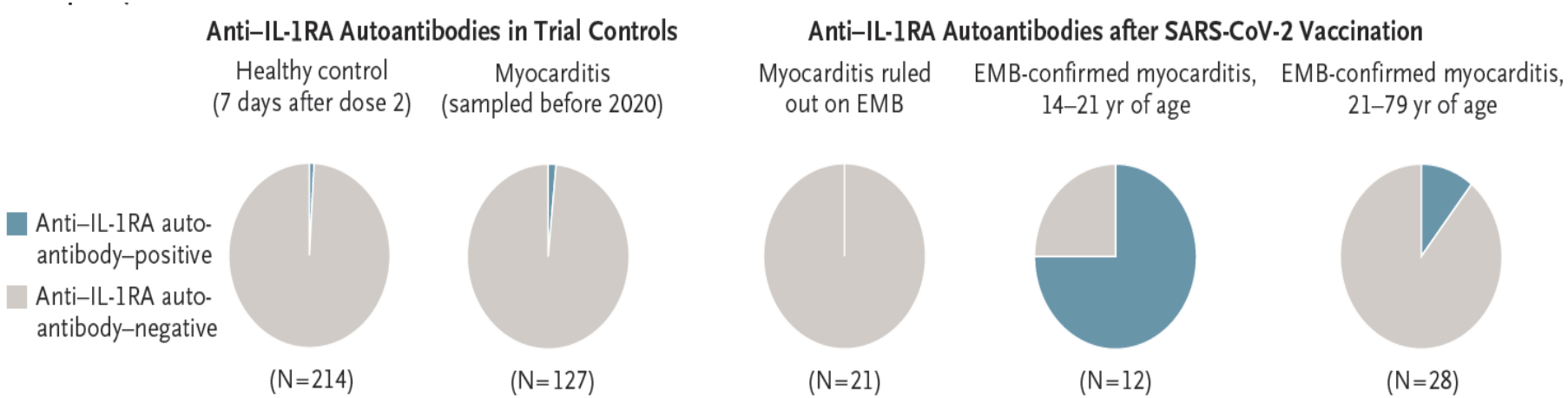
N.B. Halasa, et al.

IL-1RA Antibodies in Myocarditis after SARS-CoV-2 Vaccination

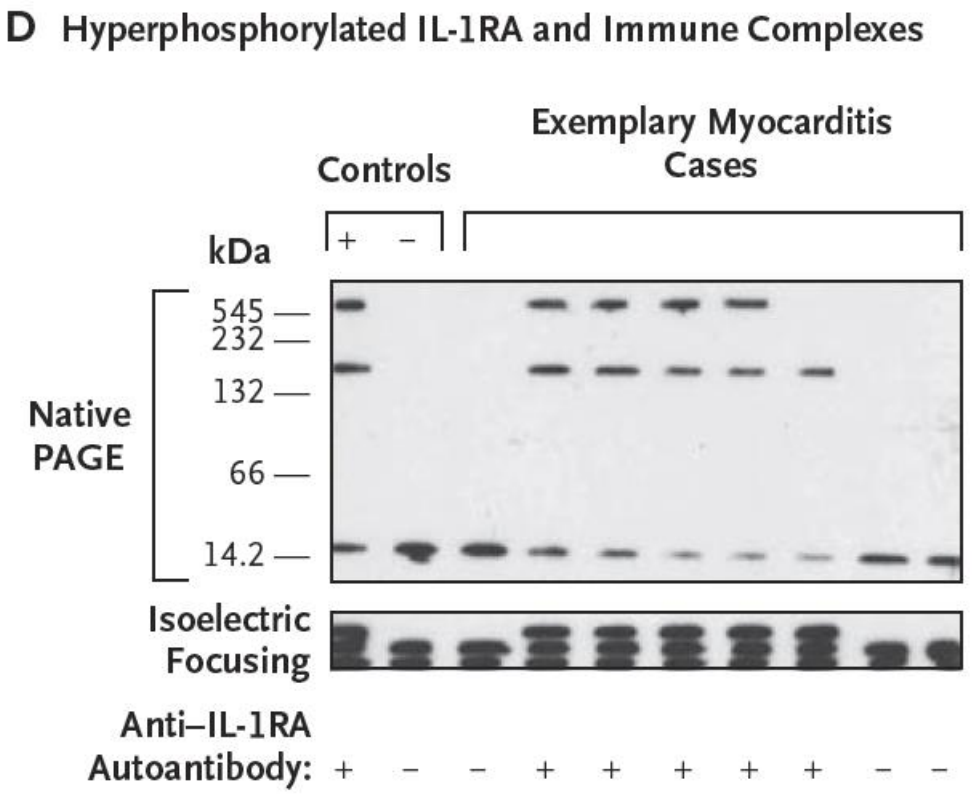
- Neutralizing antibodies against IL-1RA and a hyperphosphorylated IL-1RA isoform were observed in young male patients with biopsy-confirmed myocarditis after the receipt of SARS-CoV-2 mRNA vaccine
- These antibodies
  - impaired IL-1RA bioactivity *in vitro*
  - were associated with low circulating levels of IL-1RA
  - were found in patients with biomarker evidence of cardiac damage and inflammation

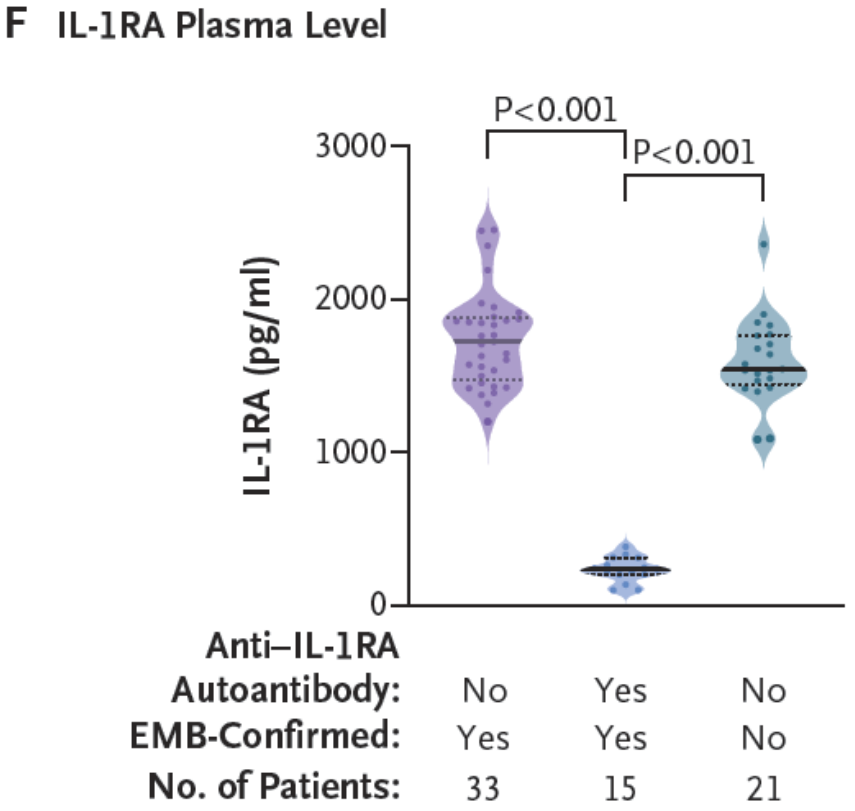
Frequency of Anti–IL-1RA Autoantibodies





Autoantibodies Targeting IL-1RA in Myocarditis after SARS-CoV-2 Vaccination





Second-dose mRNA COVID-19 vaccine safety in patients with immediate reactions after the first dose: A case series

Cases, no.	Female, no. (%)	Age (y) mean (SD)	History of asthma, no. (%)	History of autoimmunity, no. (%)*	Pfizer vaccine, no. (%)	Moderna vaccine, no. (%)	Anaphylaxis, no. (%)†	Epinephrine given, no. (%)
47	46 (98)	48.7 (15.5)	14 (30)	9 (19)	43 (91)	4 (9)	15 (32)	18 (38)

First-dose characteristics of 47 patients who had suspected allergic reactions after an mRNA COVID-19 vaccine

No. of cases	Same brand, no. (%)*	Interval between doses (wk), mean (SD)	Premedication, no. (%)†	1-Step administration, no. (%)‡	Immediate symptoms, no. (%)§	Tolerance, (%)‖
47	42 (89)	15.2 (5.6)	38 (81)	45 (96)	21 (45)	46 (98)

Second-dose characteristics of 47 patients who had suspected allergic reactions after a first dose of mRNA COVID-19 vaccine

- Suspected allergic reactions to COVID-19 mRNA vaccines occur in up to 2% of individuals.
- These case series provides evidence that second COVID-19 mRNA vaccine doses can be given with a good safety profile in patients with suspected allergic reactions to the first dose.
- It is hoped that our safety data on second COVID-19 vaccine doses will lead to less vaccine hesitancy, increased numbers of second doses administered

Aled Iaboni,et al.

Maturation of SARS-CoV-2 Spike-specific memory B cells drives resilience to viral escape

bioRχiv

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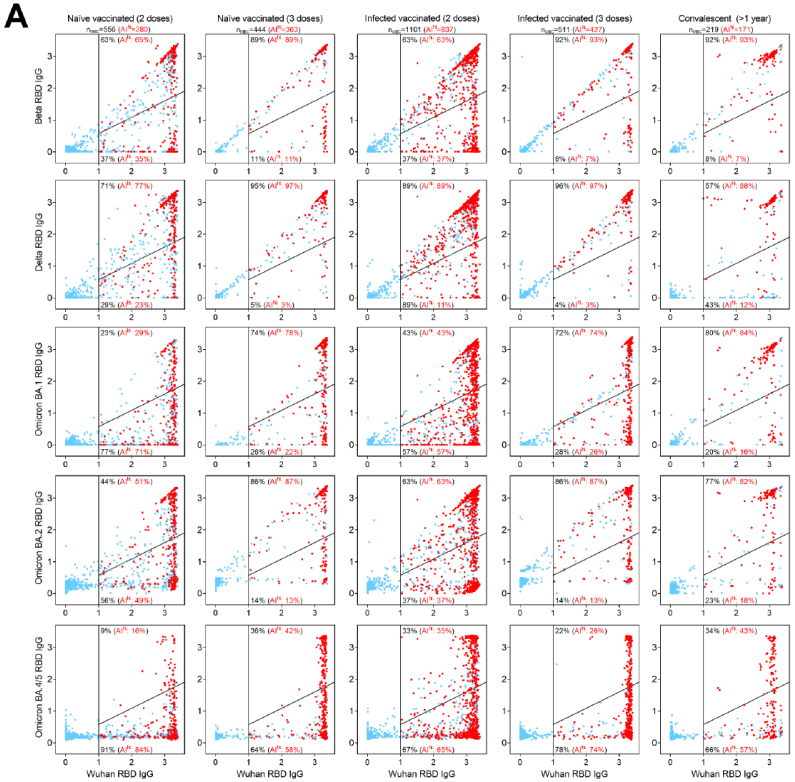
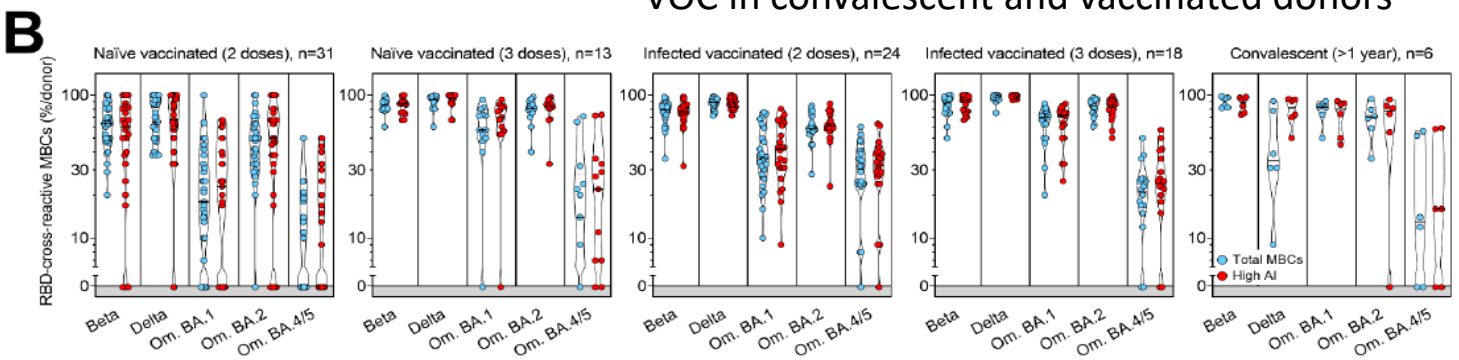
- MBCs generate rapid antibody responses upon secondary encounter with a pathogen
- Kinetics, avidity and cross-reactivity of serum antibodies and MBCs in 155 SARS-CoV-2 infected and vaccinated individuals over a 16-month timeframe
- SARS-CoV-2-specific MBCs and serum antibodies reached steady-state titers with comparable kinetics in infected and vaccinated individuals
- Whereas MBCs of infected 47 individuals targeted both pre- and postfusion Spike, most vaccine-elicited MBCs were specific for prefusion S, consistent with the use of prefusion-stabilized S in mRNA vaccines
- Furthermore, a large fraction of MBCs recognizing postfusion S cross-reacted with human 50 betacoronaviruses
- The avidity of MBC-derived and serum antibodies increased over time resulting in enhanced resilience to viral escape by SARS-CoV-2 variants, including Omicron BA.1 and BA.2 sub-lineages, albeit only partially for BA.4 and BA.5 sublineages
- Overall, the maturation of high-affinity and broadly-reactive MBCs provides the basis for effective recall responses to future SARS-CoV-2 variants.

Resilience to viral escape of VOC by high-avidity MBCs primed by SARS-CoV-2 infection and/or vaccination



Cumulative MBC cross-reactivity between RBD from Wuhan SARS-CoV-2 and Beta, Delta, Omicron BA.1, BA.2 and BA.4/5 VOC

Individual fractions of total and high-avidity SARS-CoV-2 RBD-cross-reactive MBCs that maintain binding with the RBDs of different VOC in convalescent and vaccinated donors



scientific reports

A novel vaccine based on SARS-CoV-2 CD4+ and CD8+ T cell conserved epitopes from variants Alpha to Omicron

- Multiepitope vaccines based on 100% conserved epitopes of multiple proteins of all SARS-CoV-2 variants, rather than a single highly mutating antigen, could offer more long-lasting protection.
- A multiepitope multivariant vaccine was designed using immunoinformatics and in silico approaches.
- It is composed of highly promiscuous and strong HLA binding CD4+ and CD8+ T cell epitopes of the S, M, N, E, ORF1ab, ORF 6 and ORF8 proteins.
- Based on the analysis of one genome per WHO clade, the epitopes were 100% conserved among the Wuhan-Hu1, Alpha, Beta, Gamma, Delta, Omicron, Mμ, Zeta, Lambda and R1 variants.
- An extended epitope-conservancy analysis performed using GISAID metadata of 3,630,666 SARS-CoV-2 genomes of these variants and the additional genomes of the Epsilon, Lota, Theta, Eta, Kappa and GH490 R clades, confirmed the high conservancy of the epitopes.
- All but one of the CD4 peptides showed a level of conservation greater than 97% among all genomes.
- All but one of the CD8 epitopes showed a level of conservation greater than 96% among all genomes, with the vast majority greater than 99%.
- A multiepitope and multivariant recombinant vaccine was designed and it was stable, mildly hydrophobic and non-toxic.
- The vaccine has good molecular docking with TLR4 and promoted, without adjuvant, strong B and Th1 memory immune responses and secretion of high levels of IL-2, IFN-γ, lower levels of IL-12, TGF-β and IL-10, and no IL-6.

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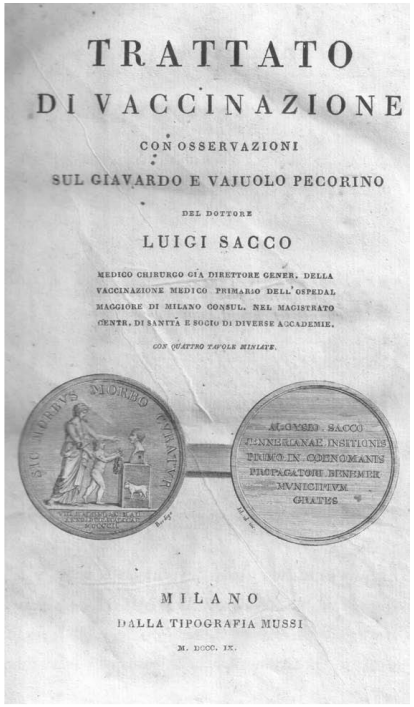
TRATTATO
DI VACCINAZIONE
CON OSSERVAZIONI
SUL GIAVARDO E VAJUOLO PECORINO
DEL DOTTORE
LUIGI SACCO
MEDICO CHIRURGO GIÀ DIRETTORE GENER. DELLA VACCINAZIONE MEDICO PRIMARIO DELL' OSPEDAL MAGGIORE DI MILANO CONSUL. NEL MAGISTRATO CENTR. DI SANITÀ E SOCIO DI DIVERSE ACCADEMIE.
CON QUATTRO TAVOLE MINIATE.
MILANO
DALLA TIPOGRAFIA MUSSI
M. DCCC. IX.