Efficacy and SARS CoV-2 viral decay in nasopharynx, saliva and plasma in high-risk vaccinated patients treated with monoclonal antibodies (mAb).

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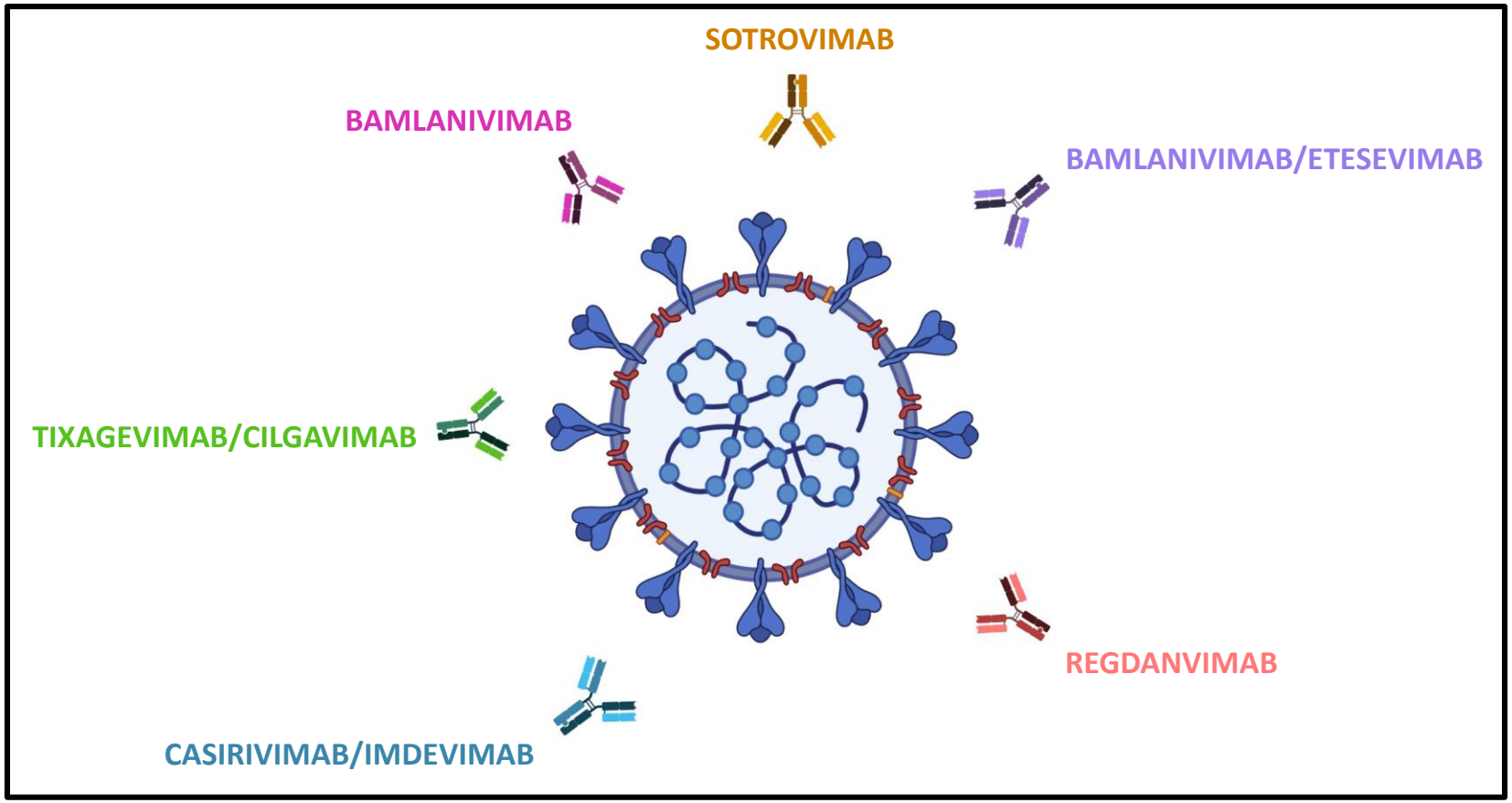
- **SARS CoV-2 Monoclonal antibodies (mAbs)** target the SARS-CoV-2 spike protein, which the virus utilizes to enter host cells, thus **blocking viral attachment and entry into human cells.**



Corti D. et al, Cell. 2021 Jun 10;184(12):3086-3108.

- **RCT have shown that mAbs were associated with clinical benefits** in treating COVID-19 caused by variants predominant during the earlier stages of the pandemic.

- Real-life data demonstrated that **Casirivimab/Imdevimab and Sotrovimab were similarly associated** with a reduced risk of hospitalization or death in mild-moderate patients with Delta variant.

- Conversely, real-world evidence about Sotrovimab during the Omicron was contrasting: this mAb resulted effective in preventing clinical progression in some observational studies, while it did not reduce mortality in others.

Huang DT, JAMA Network Open 2022;5(7):e2220957.
Gupta et al, N Eng J of Med, 2021; 385(21):1941-1950.
Gupta et al, JAMA. 2022;327(13):1236–1246.
Piccicacco et al, J Antimicrob Chemother. 2022 Sep 30;77(10):2693-2700.
Amani B, Rev Med Virol 2022; 32(6):e2402.

- Furthermore, **Sotrovimab could have a partial reduction in neutralisation activity in vitro against Omicron subvariants**, even if these data are difficult to interpret; it could maintain preserved effector functions such as antibody-dependent cell cytotoxicity and antibody-dependent cell phagocytosis.

- Given the not well-known efficacy against the circulating viral variants, **mAbs are currently recommended** in patients diagnosed with a mild-moderate infection at **high risk of clinical progression and contraindications to antivirals**.

- Given the well-established efficacy of COVID-19 vaccination in protecting from severe disease, **the additional clinical and virological value of mAb in high risk vaccinated people needs further investigation**.

Iketani S et al, Nature 2022; 604(7906):553-556
Hoffmann M et al, Cell 2022;185(3):447-456
Bruel T et al, Cell Rep Med 2022; 3(12):100850
https://www.covid19treatmentguidelines.nih.gov
Yang ZR et al, Lancet Microbe, 2023; 4(4):e236-e246..

Aim of the study

- To investigate the **efficacy** of mAbs (Bamlanivimab, Bamlanivimab/Etesevimab, Casirivimab/Imdevimab, Sotrovimab) in a cohort of patients diagnosed with a mild-moderate SARS CoV-2 infection, at high risk of clinical progression

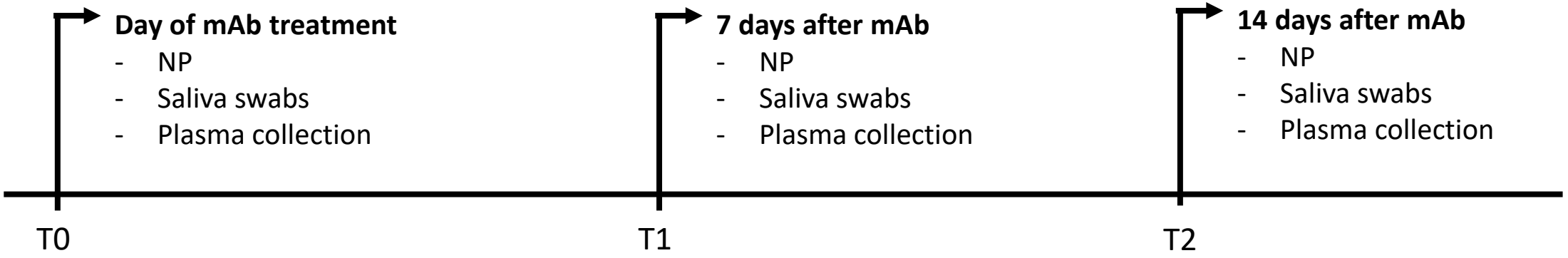
- To study **SARS CoV-2 viral load** in three different compartments (nasopharynx (NP), saliva and plasma) according to vaccination

- **ENDPOINTS:**
  - PRIMARY:
    - **comparison of efficacy** (composite outcome defined as proportion of patients with clinical recovery vs hospitalization after treatment vs death) between unvaccinated (unvax) and vaccinated patients (vax);
  - SECONDARY:
    - **virological clearance at day 7 after treatment** (T1, antigenic or molecular NP swab) and median time from symptoms' onset to first antigenic or molecular negative NP swab according to vaccination
    - **Comparison of NP, saliva and plasma viral load** between unvaccinated (unvax) and vaccinated patients (vax).

Study and Methods

STUDY POPULATION: Patients diagnosed with SARS-CoV-2 infection (inpatients and outpatients), at high risk of clinical progression for severe COVID-19 disease, treated with mAbs between 03/2021 and 05/2022.
Risk factors for progression were: age >65 years, chronic diseases or immunodeficiencies.
Patients were treated ≤ 10 days from symptoms onset.

STUDY DESIGN: Prospective cohort study

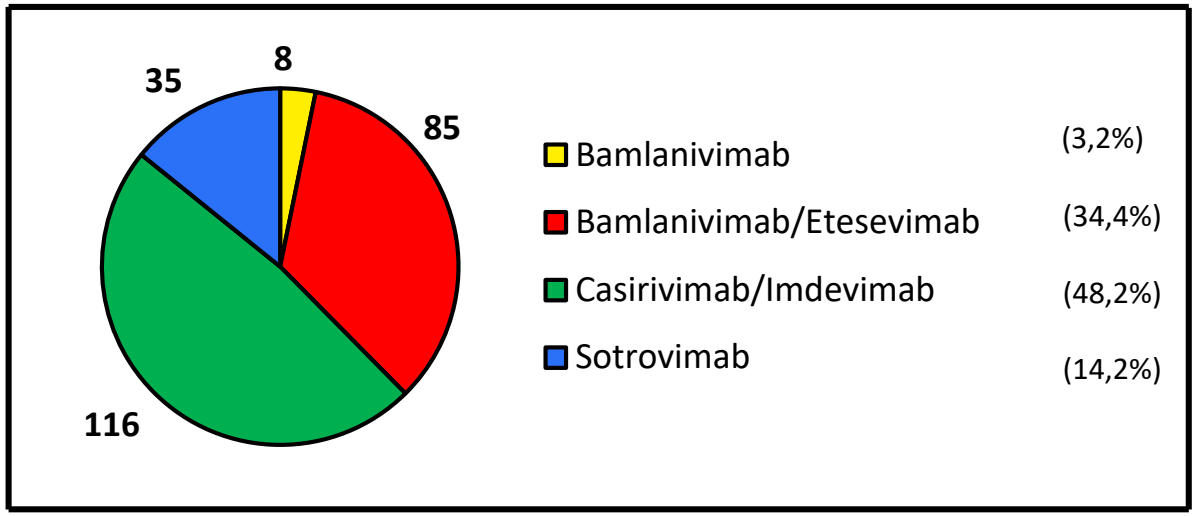


- SARS CoV-2 viral load was measured on NP, saliva and plasma by quantitative RT-PCR (SARS CoV-2 RNA was extracted by the QiAmp RNA viral kit and viral load was measured on specimens by quantitative RT-PCR targeting the viral N gene).
- In a subgroup of patients viral variant was available (Sanger sequencing of the S gene was performed for variants characterization).

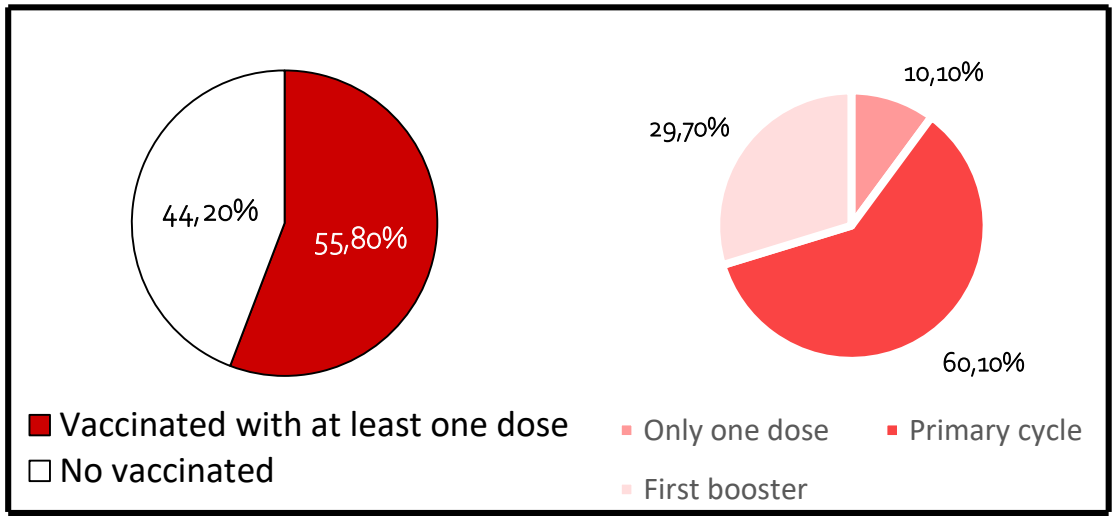
STATISTICAL ANALYSIS: Mann-Whitney, Chi-square and Wilcoxon test were used for statistics.

Results

- **247** patients treated with mAb



- **138/247 (55.8%)** patients had received at least one dose of any kind of COVID-19 vaccine.



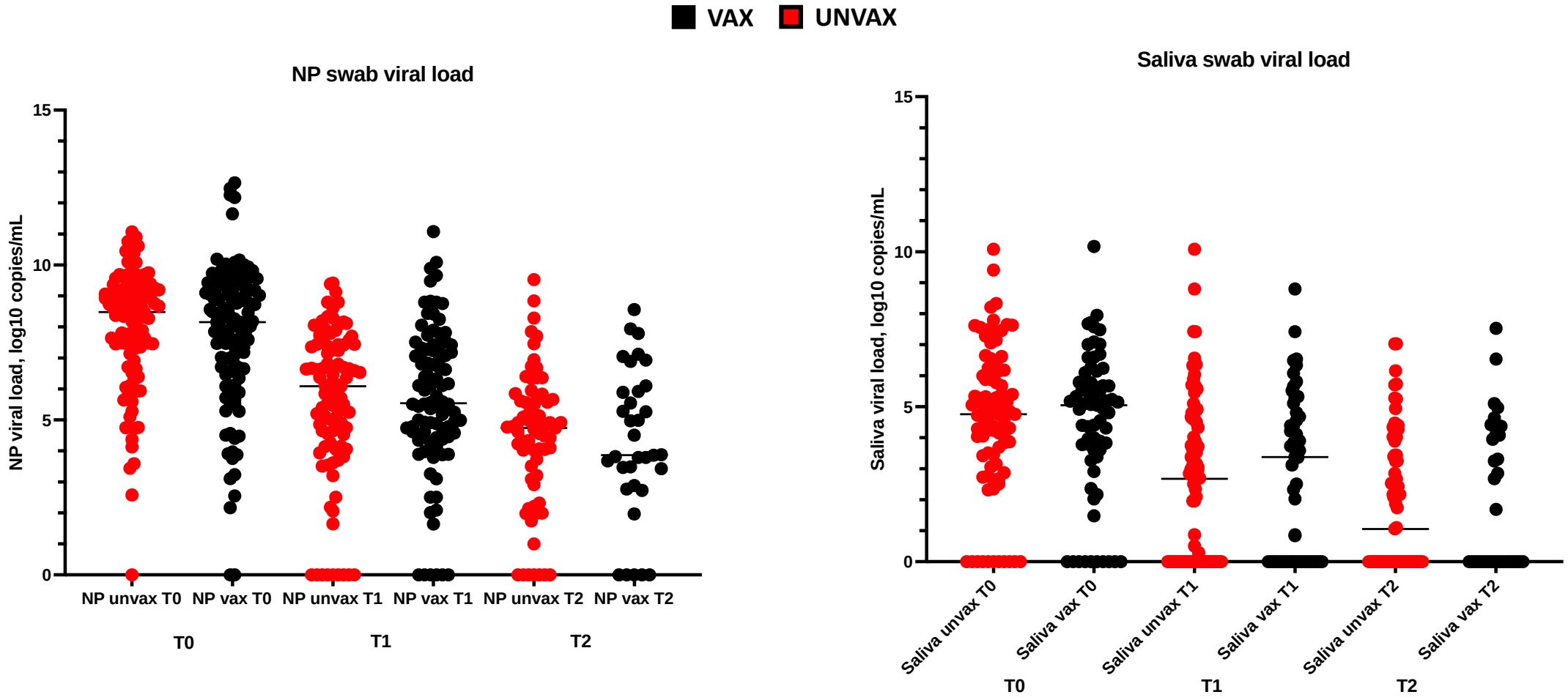
- Median days from the last vaccine dose to mAb treatment: **132** (IQR 65-178)

- **53,2%** of patients received mAb more than 120 days from the last vaccine dose.

Demographic and clinical characteristics of patients with mild/moderate COVID-19, according to vaccination

Characteristics	Study population N 247	Unvaccinated patients N 109 (44.2%)	Vaccinated patients N 138 (55.8%)	p values
Age [years], median (IQR)	66 (51-77)	59 (48-72)	69 (57-79)	<0.001
Female sex, n (%)	102 (41.3%)	47 (43.1%)	55 (39.9%)	0.605
Risk factor, n (%):				
Chronic diseases	141 (57.1%)	58 (53.2%)	83 (60.1%)	
Immunodeficiency/Cancer	45 (18.2%)	18 (16.5%)	27 (19.6%)	0.017
BMI > 30	32 (13%)	23 (21.1%)	9 (6.5%)	
Only age > 65 years	25 (10.1%)	9 (8.3%)	16 (11.6%)	
Unknown	4 (1.6%)	1 (0.9%)	3 (2.2%)	
Setting, n (%):				
Outpatient service	180 (72.9%)	77 (90.6%)	59 (72.8%)	0.002
Hospitalization because diseases other than COVID-19	18 (7.3%)	2 (2.4%)	12 (14.8%)	
Hospitalization for COVID-19	49 (19.8%)	6 (7.1%)	10 (12.3%)	
Days from symptom onset to antiviral treatment, median (IQR)	4 (2-6)	4 (3-6)	3 (2-5)	0.006
Viral variant, n (%):	N 154	N 90	N 64	
Alfa	56 (36.5%)	53 (58.6%)	3 (4.7%)	
Beta	1 (0.6%)	1 (1.1%)	0	
C.36.6	2 (1.3%)	2 (2.2%)	0	<0.001
Delta	81 (52.6%)	28 (31.1%)	53 (82.8%)	
Omicron	13 (8.4%)	5 (5.6%)	8 (12.5%)	
L18F	1 (0.6%)	1 (1.1%)	0	

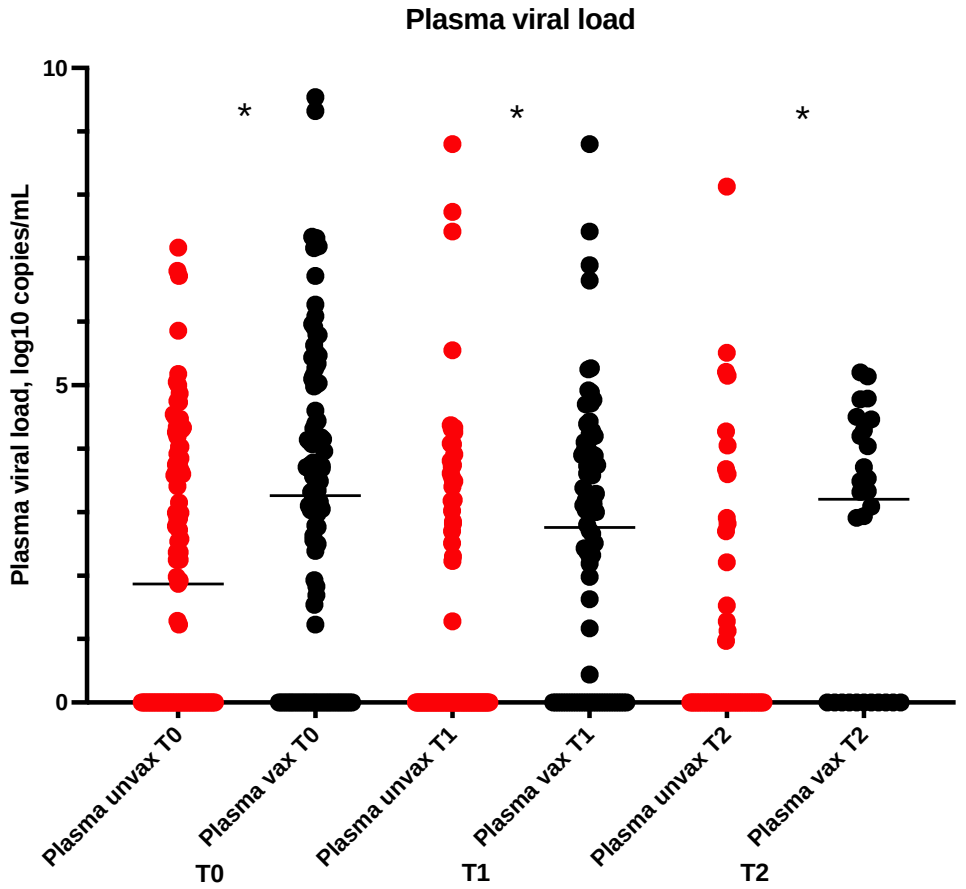
Viral load on NP and saliva at the different time points according to vaccination



→ Median NP and saliva viral load were similar at T0 between vaccinated and unvaccinated patients and presented a similar decay at T1-T2

Viral load on plasma at the different time points according to vaccination

VAX UNVAX



Legend: * p<0.05 for comparison between unvax and vax.

→ Vaccinated patients displayed higher median plasma viremia at T0, compared to unvaccinated individuals, that was maintained at T1-T2

Proportion of patients with positive SARS CoV-2 NP, saliva and plasma viral load in unvaccinated and vaccinated patients

SARS CoV-2 positive viral load	Unvaccinated patients	Vaccinated patients	p values
NP swab, T0:	N 98 97 (99%)	N 114 112 (98.2%)	1.000
Saliva swab, T0: **positive viral load**	N 85 74 (87.1%)	N 67 57 (85.1%)	0.725
Plasma viral load, T0: **positive viral load**	N 98 52 (53.1%)	N 109 75 (68.8%)	**0.020**
NP swab, T1: **positive viral load**	N 92 83 (90.2%)	N 89 83 (93.3%)	0.458
Saliva swab, T1: **positive viral load**	N 78 46 (59%)	N 49 30 (61.2%)	0.801
Plasma, T1: **positive viral load**	N 91 28 (30.8%)	N 84 53 (63.1%)	**<0.001**
NP swab, T2: **positive viral load**	N 69 63 (91.3%)	N 34 29 (85.3%)	0.353
Saliva swab, T2: **positive viral load**	N67 34 (50.7%)	N 33 16 (48.5%)	0.832
Plasma, T2: **positive viral load**	N 59 16 (27.1%)	N 28 17 (60.7%)	**0.003**

→ Vaccinated patients displayed a higher proportion of positive plasma viral load at T0, compared to unvaccinated individuals, that was maintained at T1-T2

Clinical efficacy and virological clearance according to vaccination

Characteristics	Study population N 247	Unvaccinated patients N 109 (44.2%)	Vaccinated patients N 138 (55.8%)	p values
Outcome, n (%):				
Recovery	205 (83%)	78 (71.6%)	127 (93.4%)	
Hospitalization	19 (7.7%)	18 (16.5%)	1 (0.7%)	<0.001
Death	9 (3.6%)	4 (3.7%)	5 (3.7%)	
Lost to follow up	12 (4.9%)	9 (8.3%)	3 (2.2%)	
Adverse events, n (%):	21 (8.5%)	18 (16.5%)	3 (2.2%)	<0.001
Virological clearance at T7, n (%):				
No	153 (61.9%)	71 (65.1%)	82 (59.4%)	0.557
Yes	86 (34.8%)	34 (31.2%)	52 (37.7%)	
Unknown	8 (3.2%)	4 (3.7%)	4 (2.9%)	
Days from symptom onset to virological clearance, median (IQR)	16 (12-21)	18 (13-24)	15 (11-21)	0.011

Results

Probability of favorable outcome in vaccinated patients receiving mAbs by fitting a logistic regression analysis

Parameters	OR	95%CI	p	AOR	95%CI	p
Vaccination:						
Yes	Ref			**Ref**		
No	0.168	0.065-0.431	<0.001	**0.274**	**0.986-0.781**	**0.015**
Age, each year more	0.983	0.957-1.010	0.206			
Comorbidities:						
Age >65 yrs	Ref			Ref		
Chronic diseases	0.365	0.046-2.907	0.341	0.728	0.078-6.832	0.781
Immunodeficiencies	0.411	0.045-3.765	0.431	0.696	0.064-7.575	0.766
BMI >30	0.263	0.028-2.443	0.240	0.547	0.048-6.171	0.625
Days from symptom onset to mAb therapy, each day more	0.793	0.682-0.921	0.002	**0.819**	**0.694-0.968**	**0.019**
Setting:						
Hospitalization because diseases other than COVID-19	Ref			Ref		
Outpatient service	3.732	1.171-11.898	0.026	2.878	0.713-11.620	0.138
Hospitalization for COVID-19	4.318	0.987-18.896	0.232	2.554	0.452-14.421	0.288
Log_{10} NP viral load T0, each cp/mL more	0.932	0.764-1.137	0.485			
Log_{10} saliva viral load T0, each cp/mL more	1.015	0.849-1.213	0.870			
Log_{10} plasma viral load T0, each cp/mL more	1.147	0.949-1.386	0.155			
Plasma viral load at T0:						
Positive	Ref			Ref		
Negative	0.626	0.276-1.418	0.261	0.869	0.357-2.117	0.757

Limitations of the study

- Lack of **control group** of unvaccinated and vaccinated patients not receiving mAbs
- Few data about viral variant; **small sample size** for sensitivity analyses on fully vaccinated patients, immunocompromised patients, Omicron variant, Sotrovimab
- Lack of **TIXAGEVIMAB/CILGAVIMAB treatment**
- Lack of **neutralizing Ab titers before mAbs treatment**

- **Treatment with mAbs was confirmed safe and effective** in protecting towards diseases progression (few deaths observed), also in unvaccinated patients receiving mAb.

- Despite featuring higher risk factors and higher plasma SARS-COV-2 viremia, **vaccinated patients receiving mABs were significantly more protected** toward severe outcomes as compared to unvaccinated patients.

- These results emphasize the **importance of prompt and early mAb treatment in high-risk patients** with comorbidities even when vaccinated and need to be confirmed in future studies on current viral variants and mAbs including a control group.

Retrospective study comparing outcome, safety and virological clearance at day 7 in patients with mild-moderate COVID-19 disease treated with MNP, NMV/r and short course of RDV

T. Beringheli, F. Bai, V. Vitaletti, F. Molà, A. Copes, N. Gemignani, S. Pettenuzzo, D. Barbanotti, G. Mulè, R. Castoldi, B. Varisco, R. Nardo, L. Lundgren, L. Albertini, M. Augello, L. Biasioli, C. Falcinella, D. Tomasoni, T. Bini, G. Marchetti, A. d'Arminio Monforte

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- Currently, therapeutic strategies for COVID-19 include **antiviral therapies** with different mechanisms of action (Nirmatrelvir/Ritonavir and Remdesivir) and **intravenous monoclonal antibodies** directed against the Receptor Binding Domain (RBD) of the Spike Protein.

- **Monoclonal antibodies** currently have limited use as they have **demonstrated a reduced efficacy in vitro** against circulating viral variants.

- Therefore, guidelines about COVID-19 treatments recommend antivirals as the **first choice in outpatients and hospitalized individuals**.

Malin JJ et al, Clin Microbiol Rev 2020; 34; Corti D et al. Cell 2021; 184: 4593-5.; AIFA, Agenzia Italiana del Farmaco Elenchi farmaci di classe A e H. 2020-15-07; https://www.aifa.gov.it/liste-farmaci-a-h 2020.

Aim of the study

- In the **EPIC-HR trial** NMV-r was able to **reduce viral load in nasopharynx at day 5** compared to placebo, but similar virological data in real-life settings and data on direct comparisons of the different treatments also regarding virological efficacy are still scarce

- We thus compared the **efficacy, safety and virological clearance 7 days after the start of treatment** with NMV-r, MNP and RDV in SARS-CoV-2-infected patients at high risk of clinical progression

Hammond J., et al. N Engl J Med 2022; 386:1397-1408

- **STUDY DESIGN**: **Retrospective study** enrolling patients with documented COVID-19 disease who received one antiviral treatment (*Nirmatrelvir/Ritonavir, NMV-r; Molnupiravir, MPN; Remdesivir, RDV*) at the COVID-19 antiviral therapy outpatient service or during hospitalization for other reasons than COVID-19 at the San Paolo Hospital in Milan, Italy, from January 2022 to October 2022.

- **Inclusion criteria** were:
  - mild-moderate disease
  - no need for supplemental oxygen therapy or hospitalization for COVID-19
  - one or more comorbidities indicated by the "Agenzia Italiana del Farmaco" (AIFA) as risk factor of developing severe COVID-19 disease
  - symptoms onset within 5-7 days
  - risk factors for clinical progression

- **STUDY OUTCOMES:**
  - **clinical recovery at day 7** (T7, defined as complete resolution of symptoms of COVID-19 for at least 72 hours or hospitalisation or death due to any reason);
  - **virological clearance at T7**, defined by a negative PCR or antigenic swab.
  - We also collected **median time to virological clearance** (days from symptom onset to the first negative PCR or antigenic nasopharyngeal swab).
  - The **occurrence of adverse events** was collected at T7.

- **STATISTICAL ANALYSIS:** Kruskal-Wallis nonparametric test, Chi-squared test and multivariable logistic regression analyses were used for statistical analyses.

Demographic and clinical characteristics of patients with mild/moderate COVID-19, according to anti-SARS-CoV-2 antiviral treatment

Characteristics	Study population N 376	NMV-r N 150 (39.9%)	MNP N 92 (24.5%)	RDV N 134 (35.6%)	p value
Age [years], median (IQR)	75 (63-84)	70 (56-80)	79 (67-84)	78 (68-86)	<0.001
Female sex, n (%)	167 (44.4%)	78 (52%)	33 (35.9%)	56 (41.8%)	0.037
COVID-19 vaccination, n (%):					0.015
No	29 (7.7%)	14 (9.3%)	6 (6.5%)	9 (6.7%)	
Yes	327 (87%)	121 (80.7%)	84 (91.3%)	121 (91%)	
Unknown	20 (5.3%)	15 (10%)	2 (2.2%)	3 (2.2%)	
Yes, only 1 dose	4 (1.3%)	0	3 (3.6%)	1 (0.8%)	0.227
Yes, complete first schedule	35 (10.7%)	14 (11.6%)	10 (11.9%)	11 (9.1%)	
Yes, first booster	247 (75.5%)	92 (76%)	64 (76.2%)	91 (75.2%)	
Yes, second booster	40 (12.2%)	14 (11.6%)	7 (8.3%)	18 (14.9%)	
Unknown	1 (0.3%)	1 (0.8%)	0	0	
Risk factor, n (%):					
Age >65 years	234 (62.2%)	68 (45.3%)	66 (71.7%)	100 (74.6%)	<0.001
BMI >30	28 (7.4%)	11 (7.3%)	7 (7.6%)	10 (7.5%)	0.997
Cardio-vascular disease	139 (37%)	34 (22.7%)	47 (51.1%)	58 (43.3%)	<0.001
COPD or other respiratory disease	76 (20.2%)	33 (22%)	17 (18.5%)	26 (19.4%)	0.770
Neurological disease	35 (9.3%)	13 (8.7%)	4 (4.3%)	18 (13.4%)	0.065
Diabetes mellitus	63 (16.8%)	16 (10.7%)	16 (17.4%)	31 (23.1%)	0.019
Chronic kidney failure	21 (5.6%)	3 (2%)	7 (7.6%)	11 (8.2%)	0.047
Cancer	30 (8%)	9 (6%)	7 (7.6%)	14 (10.4%)	0.381
Immunodeficiency	49 (13%)	30 (20%)	8 (8.7%)	11 (8.2%)	0.005
Setting, n (%):					
Outpatient service	284 (75.5%)	130 (86.7%)	89 (96.7%)	65 (48.5%)	<0.001
Hospitalization	92 (24.5%)	20 (13.3%)	3 (3.3%)	69 (51.5%)	

Demographic and clinical characteristics of patients with mild/moderate COVID-19, according to anti-SARS-CoV-2 antiviral treatment

Characteristics	Study population N 376	NMV-r N 150 (39.9%)	MNP N 92 (24.5%)	RDV N 134 (35.6%)	p value
Days from symptom onset to antiviral treatment, median (IQR)	3 (1-4)	2 (1-3)	3 (2-4)	2 (1-4)	0.161
Outcome, n (%):	N 322	N 117	N 79	N 126	0.185
Recovery	309 (96%)	115 (98.3%)	77 (97.5%)	117 (92.9%)	
Hospitalization	1 (0.3%)	0	0	1 (0.8%)	
Death	12 (3.4%)	2 (1.7%)	2 (2.5%)	8 (6.3%)	
Adverse events, n (%):	N 322	N 117	N 79		
No	311 (82.7%)	108 (72%)	78 (84.8%)	125 (93.3%)	<0.001
Yes	11 (2.9%)	9 (6%)	1 (1.1%)	1 (0.7%)	
Days from symptom onset to virological clearance, median (IQR)	13 (10-17)	10 (8-15)	14 (11-18)	13 (10-19)	0.002
Virological clearance at day 7 from treatment start, n (%):	N 250	N 85	N 59	N 109	<0.001
No	139 (37%)	32 (37.6%)	44 (74.6%)	66 (60.6%)	
Yes	111 (29.5%)	53 (62.4%)	15 (25.4%)	43 (39.4%)	

Factors associated with virological clearance at T7 (negative antigenic or RNA nasopharyngeal swab at day 7 after beginning of antiviral treatment) by fitting a logistic regression analysis

Parameters	OR	95% CI	p values	AOR	95% CI	p values
Age, Each year more	0.978	0.963-0.994	0.007	0.984	0.967-1.001	0.069
Gender: Female Male	 1 0.812	 0.493-1.336	 0.412			
Vaccination: >120 days ≤120 days	 1 0.735	 0.424-1.275	 0.273			
Immunodeficiency: Yes No	 1 0.752	 0.365-1.550	 0.440	 1.295	 0.574-2.924	 0.534
Days from symptoms onset to treatment, Each day more	 0.992	 0.968-1.018	 0.543			
Antiviral treatment: Nirmatrelvir/Ritonavir Remdesivir Molnupiravir	 1 0.393 0.206	 0.220-0.705 0.099-0.428	 <0.001 0.002 <0.001	 1 0.445 0.222	 0.240-0.826 0.105-0.472	 <0.001 0.010 <0.001

Limitations of the study

- The **retrospective** nature of the study
- The **lack of a control group** of patients not receiving any antiviral treatment
- **Unmeasured confounders** for the association between antiviral treatment and virological clearance
- The **lack of daily nasopharyngeal swabs** to assess the actual time to viral response
- The **limited sample size** and losses to follow-up.

- However, this is one of the first studies directly comparing three different antiviral treatments for high-risk outpatients in a real-life setting.

- Antivirals succeeded in obtaining a **clinical cure in more than 90% of patients** without differences among the three drugs

- A higher proportion of adverse events was reported with NMV-r compared to MNP and RDV, but **no severe adverse events and no discontinuation was observed**.

- **NMV-r seemed to have a better and faster virological response**, that is crucial to shorten time of isolation and contagiousness, mainly in patients who need diagnostic procedures or the continuation of life-saving therapies.

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