COVID-19 dopo oltre 3 anni, come è cambiato: Strategie attuali di profilassi e trattamento

Chiara Dentone

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DISCLOSURES

Advisor/speaker (past 5 years)

Angelini, Gilead, Menarini, Novartis, MSD

COVID-19 dopo oltre 3 anni, come è cambiato:

Strategie attuali di profilassi

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Clinical case (February 2022)

-- 75y old man with a **granulomatosis with polyangiitis** with renal involvement on **maintenance therapy with rituximab 500 mg every 6 months and prednisone 5 mg q24h** (last administration of rituximab in December 2021)

-- A recent finding of atrial fibrillation, and a mitral prolapse.

- **Vaccinated with 3 doses of mRNA vaccine (the last in November 2021)**

- **January 2022:** mild COVID-19 with fever, asthenia and wheezing cough at the onset
not early treatment, not pre-exposure prophylaxis

SARS-CoV-2 RT-PCR nasopharyngeal swab remains positive 15 and 30 days later

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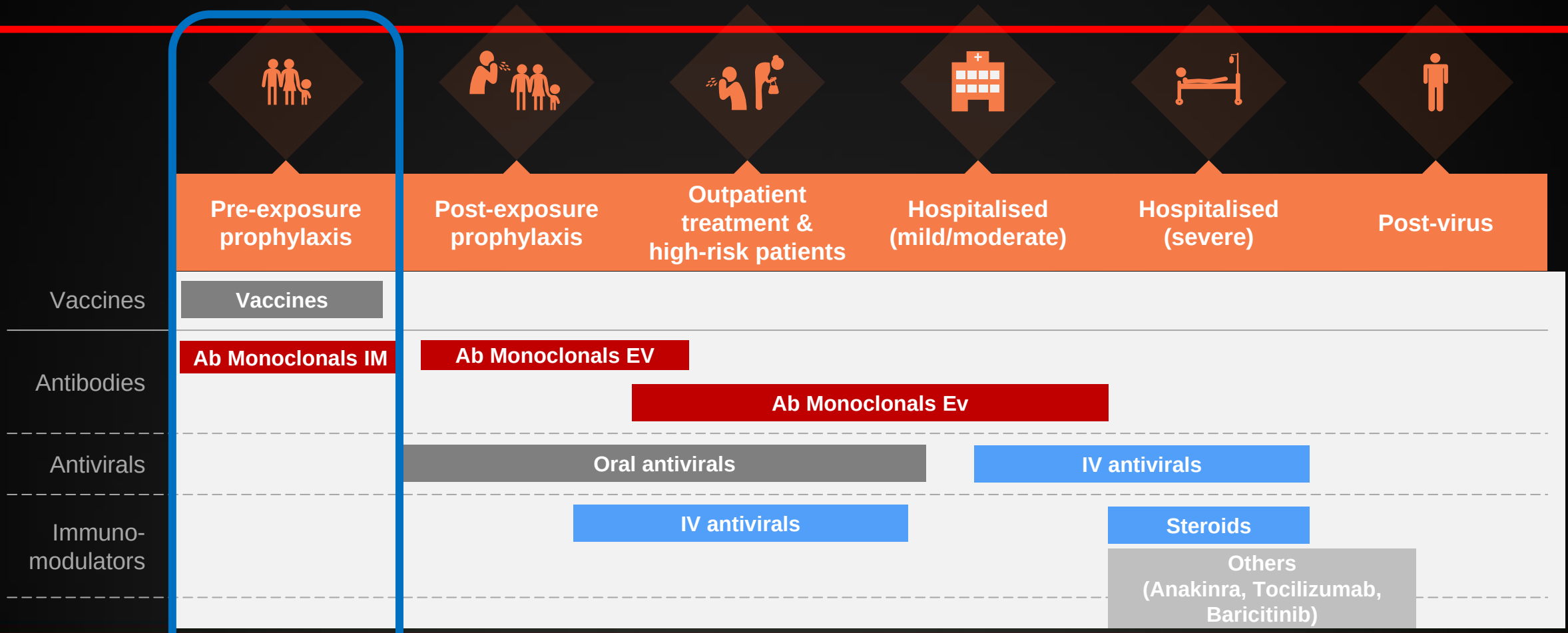
Potential role in the treatment of COVID-19 (based on available data)



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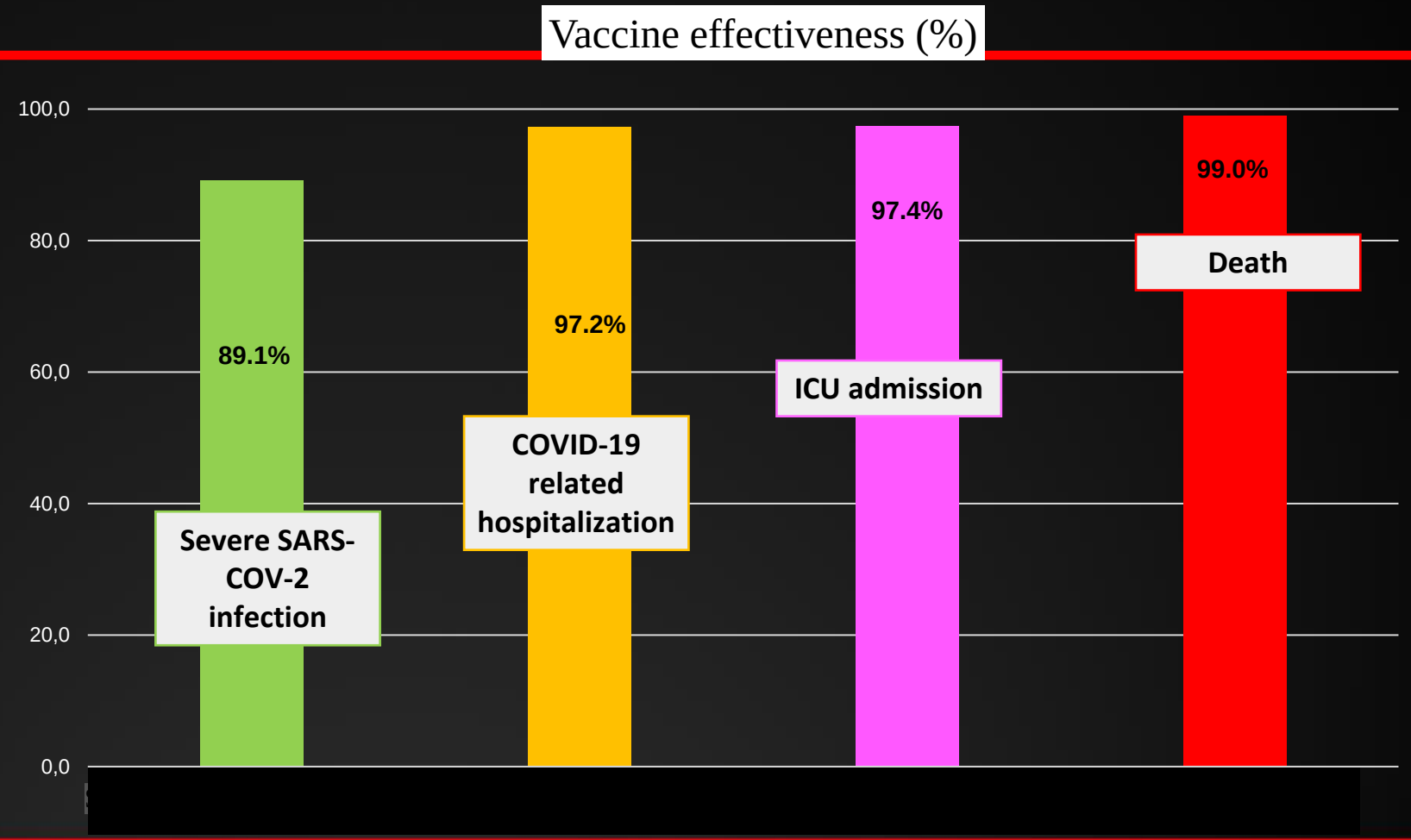
Song. Int J Antimicrob Agents 2020; Xu. Mil Med Res 2020; Pascarella. J Intern Med 2020

Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis

Meta-analysis including **51 studies** reporting COVID -19 vaccine effectiveness (Aug 2020-Oct 2021) against concerned outcomes in real-world settings.



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Zheng C et al; Int J Infect Dis 2022;114: 252-260

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Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression

Feikin DR et al,. *The Lancet* 2022

Interpretation COVID-19 vaccine efficacy or effectiveness against severe disease remained high, although it did decrease somewhat by 6 months after full vaccination. By contrast, vaccine efficacy or effectiveness against infection and symptomatic disease decreased approximately 20–30 percentage points by 6 months. The decrease in vaccine efficacy or effectiveness is likely caused by, at least in part, waning immunity, although an effect of bias cannot be ruled out. Evaluating vaccine efficacy or effectiveness beyond 6 months will be crucial for updating COVID-19 vaccine policy.

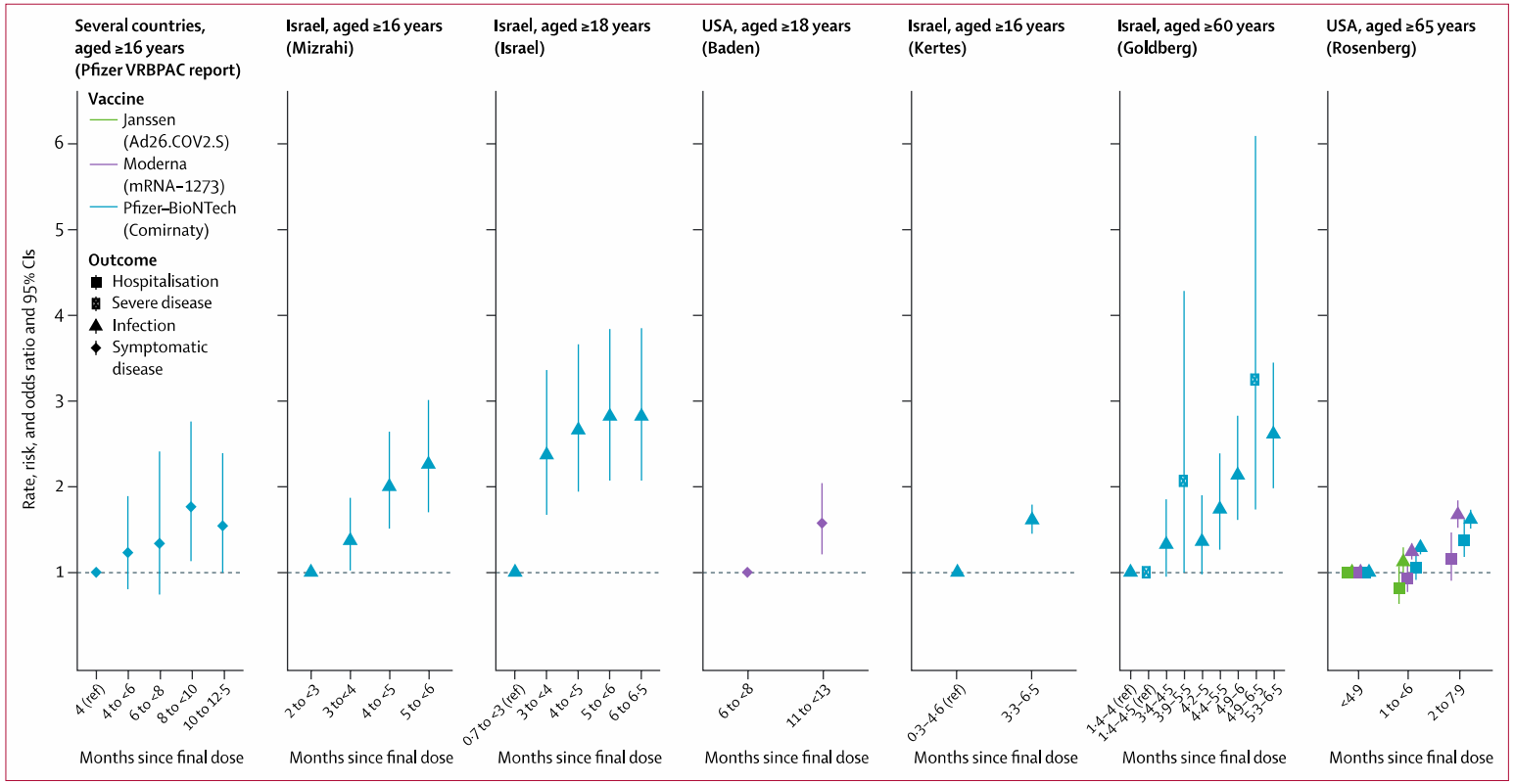


Figure 3: Rate, risk, and odds ratios of COVID-19 breakthrough cases caused by the delta variant by time of vaccination

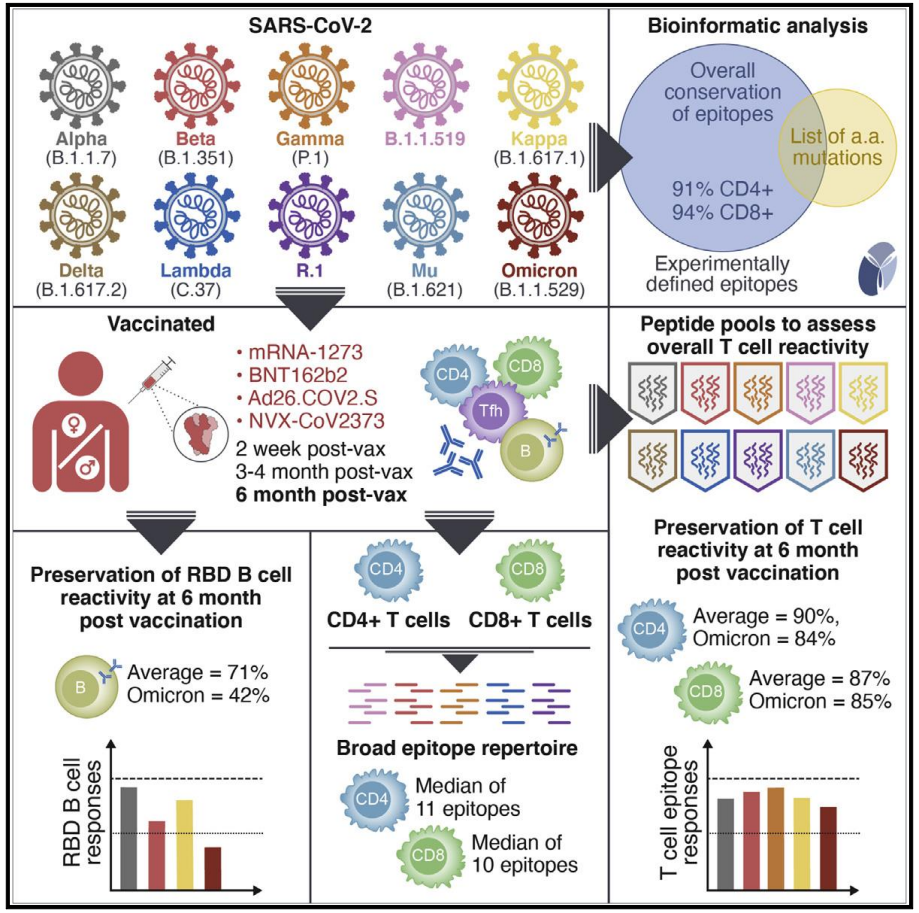
Cell

Article

SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron

Tarke et al., 2022, Cell *185*, 847–859

Graphical abstract



Highlights

- T cells of vaccinees recognize SARS-CoV-2 variants, including Omicron
- RBD memory B cells' recognition of Omicron is reduced
- A median of 11 CD4 and 10 CD8 spike epitopes are recognized in vaccinees
- Average preservation > 80% for Omicron at the epitope level

In brief

Human memory T cells induced by SARS-CoV-2 vaccines maintain the ability to recognize viral variants, including the Omicron variant.

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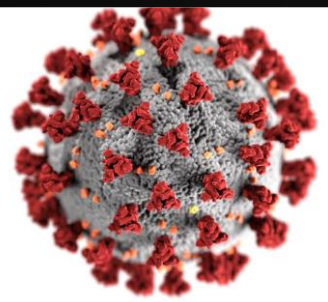
Evidence to Recommendation Framework:

An Additional Dose of mRNA COVID-19 Vaccine Following a Primary Series in Immunocompromised People

Dr. Kathleen Dooling, MD, MPH
Advisory Committee on Immunization Practices
August 13, 2021



cdc.gov/coronavirus

Immunocompromised people:

- ✓ **Active or recent treatment for solid tumor and hematological malignancies**
- ✓ Receipt of solid organ or recent hematopoietic stem cell transplants
- ✓ **Severe primary immunodeficiency**
- ✓ Advanced or untreated HIV infection
- ✓ **Active treatment with high dose corticosteroids, alkylating agents, antimetabolites TNF blockers and other immunosuppressive or immunomodulatory**
- ✓ Chronic medical conditions such as asplenia and chronic renal disease may be associated with varying degrees of immune deficit

Immunocompromised People and Vaccine Breakthrough Infection

- More likely to have breakthrough infection
  - 40-44% of hospitalized breakthrough cases are immunocompromised people in US study[1-2]
- Lower vaccine effectiveness
  - 59--72% VE among immunocompromised people vs. 90--94% among non-immunocompromised people after 2nd dose[1, 3-5]

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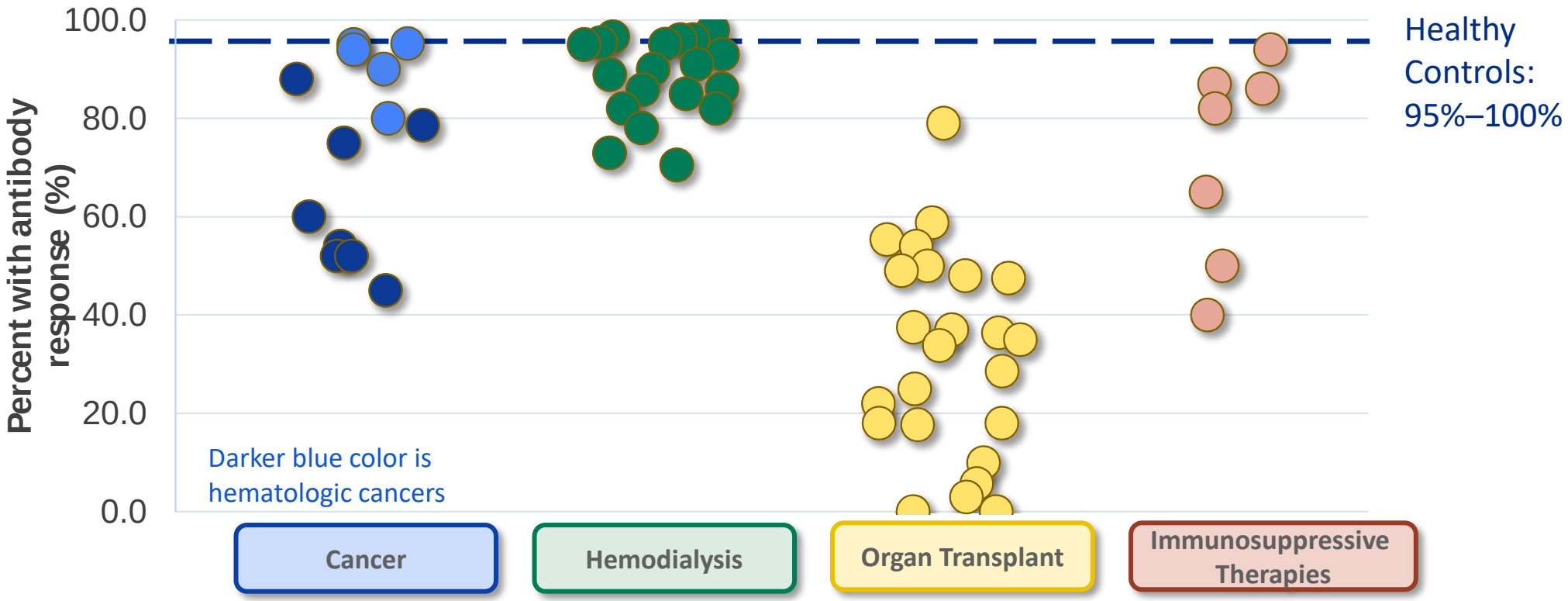
Hensley et al. CID 2021
Baang et al. JID 2021
Choi et al. NEJM 2020

Percent of subjects with antibody response after two mRNA COVID-19 vaccine doses by immunocompromising condition and study (n=63)



Studies that compared response after 1st and 2nd dose demonstrated less robust response after dose 1

Antibody measurement and threshold levels vary by study protocol

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CDC.gov/vaccines 2021

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Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis

WHAT IS ALREADY KNOWN ON THIS TOPIC

Immunocompromised patients show lower seroconversion rates than immunocompetent people after vaccination, such as with the influenza vaccine

Less is known about the response to covid-19 vaccines, particularly mRNA based vaccines

Lee A R et al.
BMJ 2022

WHAT THIS STUDY ADDS

Seroconversion rates after covid-19 vaccination were found to be reduced among all immunocompromised groups, except people with HIV, but significantly increased after the second dose; in organ transplant recipients seroconversion remained severely reduced even after a second dose

Among the immunocompromised groups studied, antibody titres were lower than in immunocompetent controls

These findings suggest that a third dose of covid-19 vaccine would be efficacious in immunocompromised patients

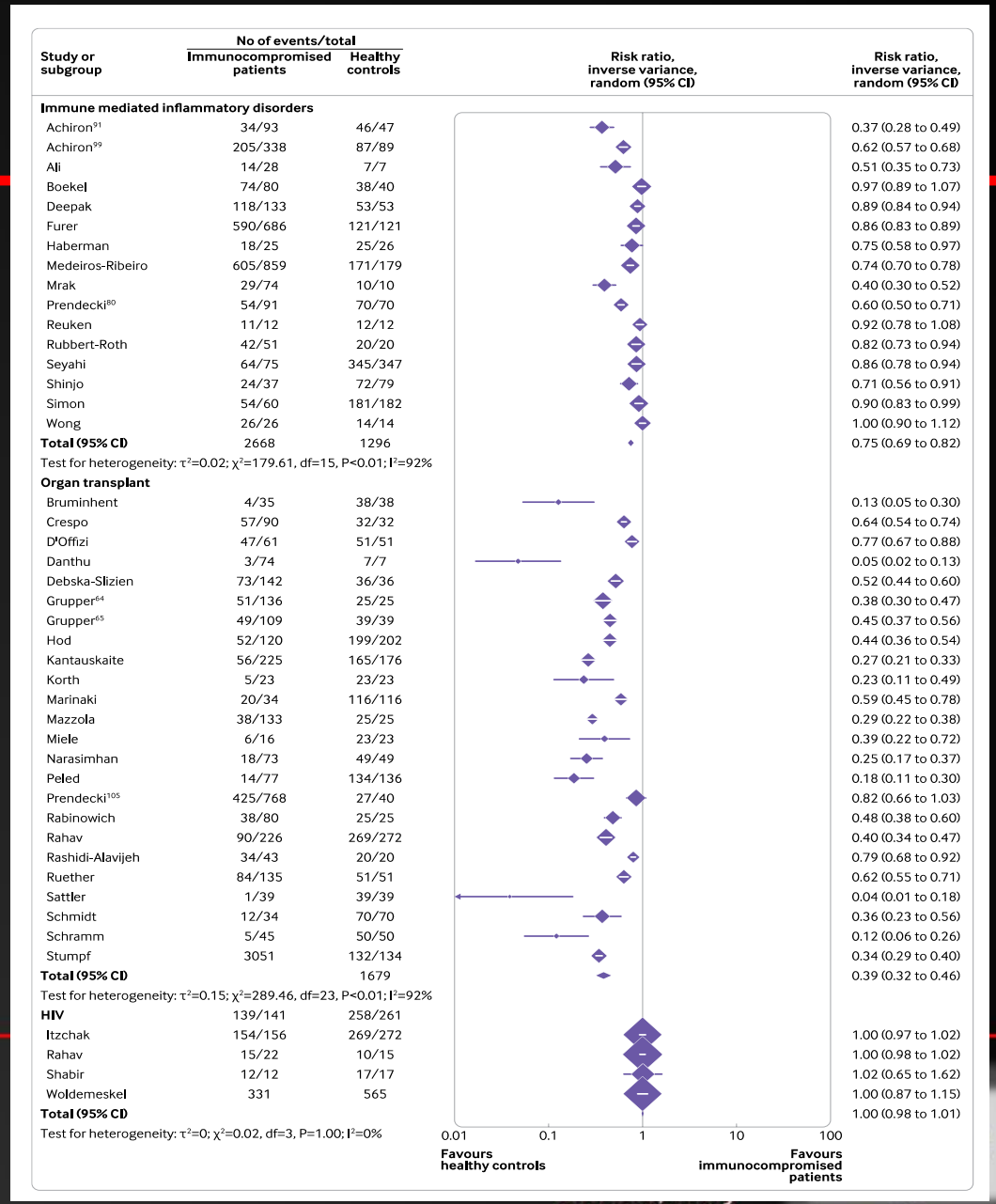

Fig 4 | Risk ratios for seroconversion among immunocompromised patients with immune mediated inflammatory disorders, organ transplant recipients, and people with HIV compared with immunocompetent controls after a second dose of covid-19 vaccine

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Clinical case (February 2022)

-- 75y old man with a **granulomatosis with polyangiitis** with renal involvement on **maintenance therapy with rituximab 500 mg every 6 months and prednisone 5 mg q24h** (last administration of rituximab in December 2021)

-- A recent finding of atrial fibrillation, and a mitral prolapse.

- **Vaccinated with 3 doses of mRNA vaccine (the last in November 2021)**

SARS-CoV-2 serology resulted non-reactive:

IgG anti Receptor-Binding Domain (RBD) < 1 U/mL <12 neg)

IgG anti Spike 1 (S1) < 1 U/mL (<21 ne), IgG anti Spike 2 (S2) < 1 U/mL (< 9 neg)

IgG anti Nucleocapsid < 1 U/mL (< 23 neg)

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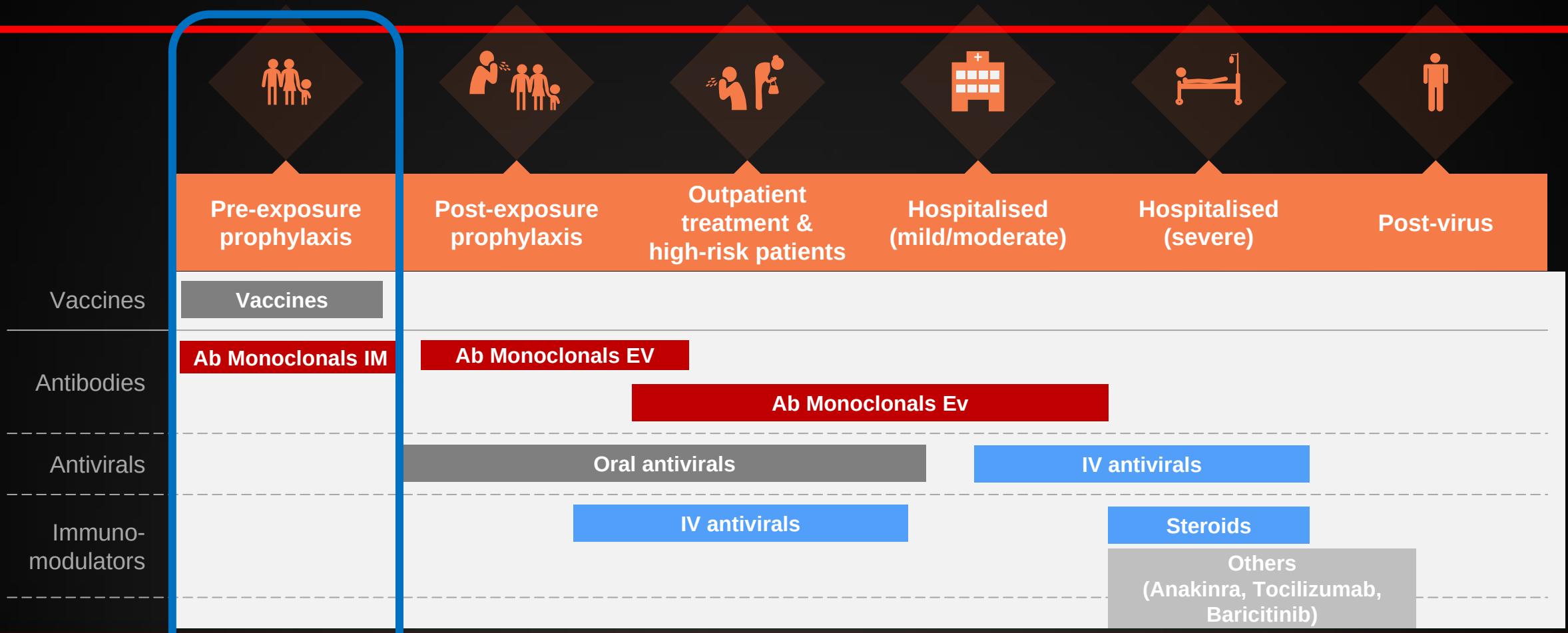

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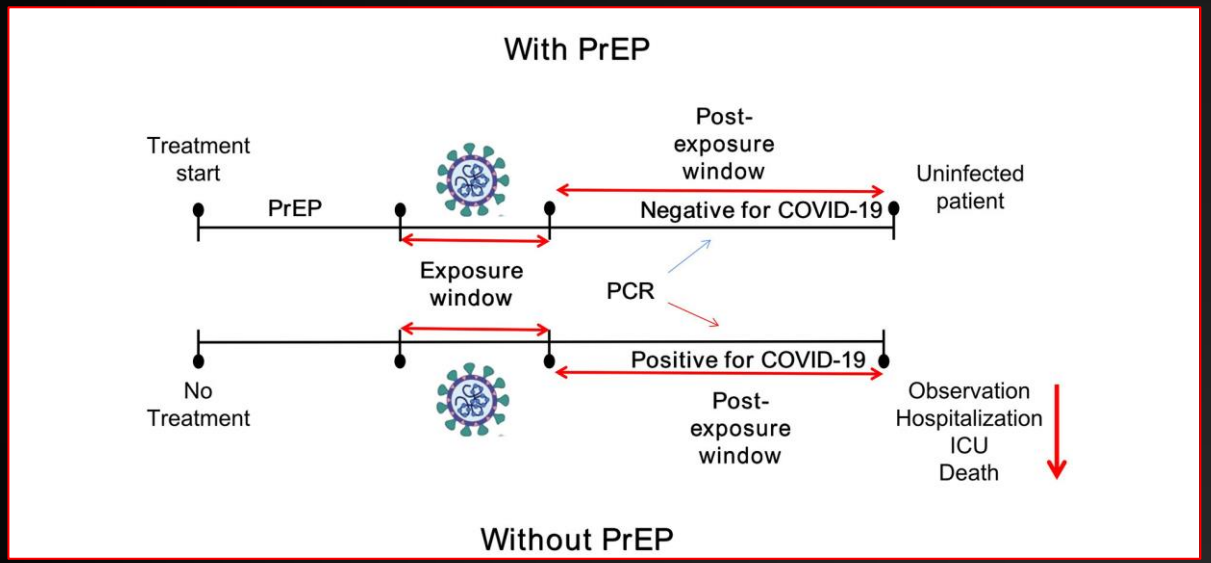
Song. Int J Antimicrob Agents 2020; Xu. Mil Med Res 2020; Pascarella. J Intern Med 2020

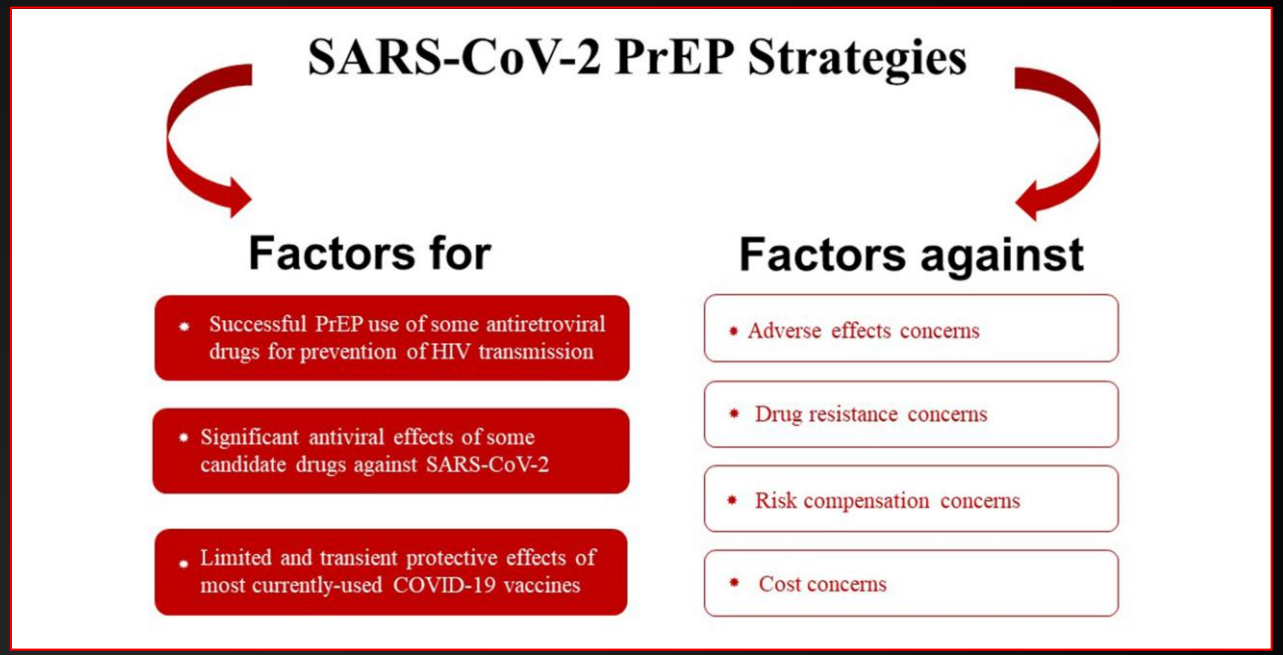
SARS-CoV-2 pre-exposure prophylaxis: A potential COVID-19 preventive strategy for high-risk populations, including healthcare workers, immunodeficient individuals, and poor vaccine responders

frontiers | Frontiers in Public Health

TYPE Review
PUBLISHED 08 August 2022
DOI 10.3389/fpubh.2022.945448

Ouyang J, et al





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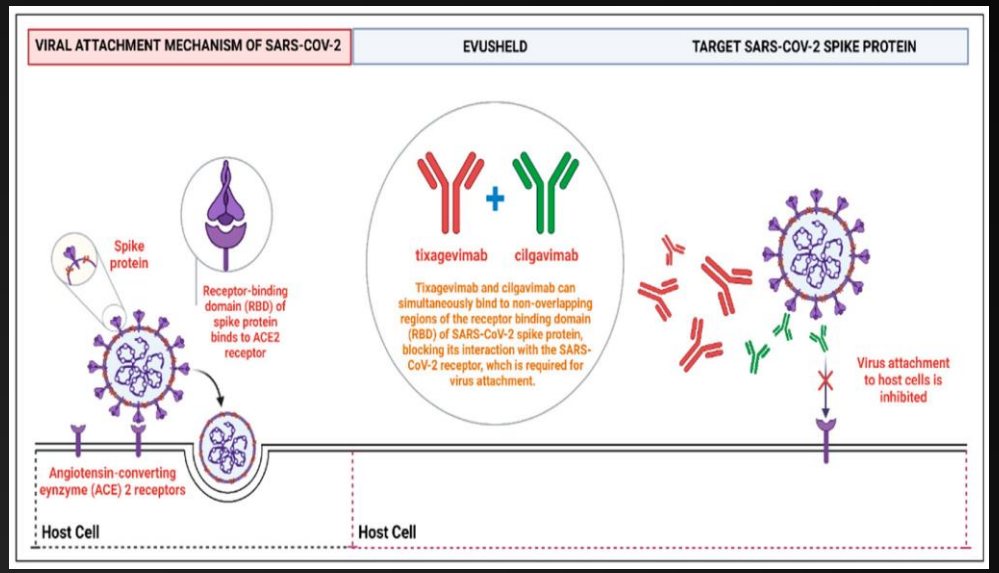
Monoclonal Antibodies

- **BAM**lanivimab
- **ETE**sevimab
- **CAS**irivimab
- **IMD**evimab
- **SOT**rovimab
- **CIL**gavimab
- **TIX**agevimab
- **REG**danvimab
- **BEB**telovimab



- **Combination of two monoclonal antibodies**
- **SARS-cov-2 spike protein directed attachment inhibitors**
- **Extended half-life**
- **Intramuscolar injection**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19

M.J. Levin, A. Ustianowski, S. De Wit, O. Launay, M. Avila, A. Templeton, Y. Yuan, S. Seegobin, A. Ellery, D.J. Levinson, P. Ambery, R.H. Arends, R. Beavon, K. Dey, P. Garbes, E.J. Kelly, G.C.K.W. Koh, K.A. Near, K.W. Padilla, K. Psachoulia, A. Sharbaugh, K. Streicher, M.N. Pangalos, and M.T. Esser, for the PROVENT Study Group*

PROVENT study

Aim: To assess the safety and efficacy of a single dose of Tixagevimab/Cilgavimab in comparison to placebo for Pre-EP of COVID-19

Participants who had an increased risk of an inadequate response to Covid-19 vaccination, an increased risk of exposure to SARS-CoV-2, or both were randomly assigned in a 2:1 ratio

Primary endpoint: SARS-Cov-2 RT-PCR positive symptomatic illness within 183 days post-single dose

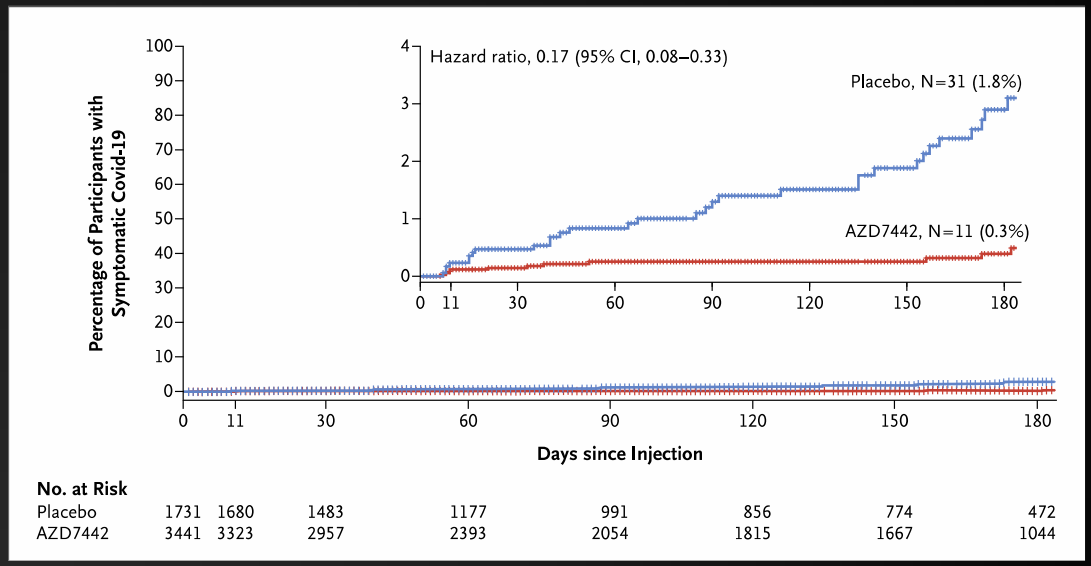
Table 3. Primary End Point and Key Supportive Efficacy Analyses in the Full Preexposure Analysis Set.*

First Case of SARS-CoV-2 RT-PCR–Positive Symptomatic Illness	Primary Analysis				Median 6-Mo Follow-up†		
	AZD7442 (N=3441)	Placebo (N=1731)	Relative Risk Reduction % (95% CI)	P Value	AZD7442 (N=3441)	Placebo (N=1731)	Relative Risk Reduction % (95% CI)
	no. of participants (%)				*no. of participants (%)*		
Primary end point: first case of illness, with data censored at unblinding or receipt of Covid-19 vaccine	8 (0.2)	17 (1.0)	76.7 (46.0–90.0)	<0.001	11 (0.3)	31 (1.8)	82.8 (65.8–91.4)
Key supportive analyses							
First case of illness, regardless of unblinding or receipt of Covid-19 vaccine	10 (0.3)	22 (1.3)	77.3 (52.0–89.3)	<0.001	20 (0.6)	44 (2.5)	77.4 (61.7–86.7)
First case of illness, including all deaths, with data censored at unblinding or receipt of Covid-19 vaccine	12 (0.3)	19 (1.1)	68.8 (35.6–84.9)	0.002	18 (0.5)	36 (2.1)	75.8 (57.3–86.2)

* The full preexposure analysis set consisted of all the participants who had undergone randomization, received at least one injection of AZD7442 or placebo, and did not have RT-PCR–confirmed SARS-CoV-2 infection at baseline. Estimates were based on a Poisson regression with robust variance. The model included trial group (AZD7442 or placebo) and age at informed consent (≥60 years or <60 years), with the log of the follow-up time as an offset. Unadjusted relative risk reductions (95% CI) for the primary end point were the same as the adjusted relative risk reductions for both the primary analysis and the median 6-month follow-up. An estimated relative risk reduction greater than 0 favored AZD7442, with a P value of less than 0.05 indicating statistical significance.

† This analysis was not prespecified in the trial protocol, so P values were not calculated.

Time to First SARS-CoV-2 RT-PCR–Positive Symptomatic Illness.



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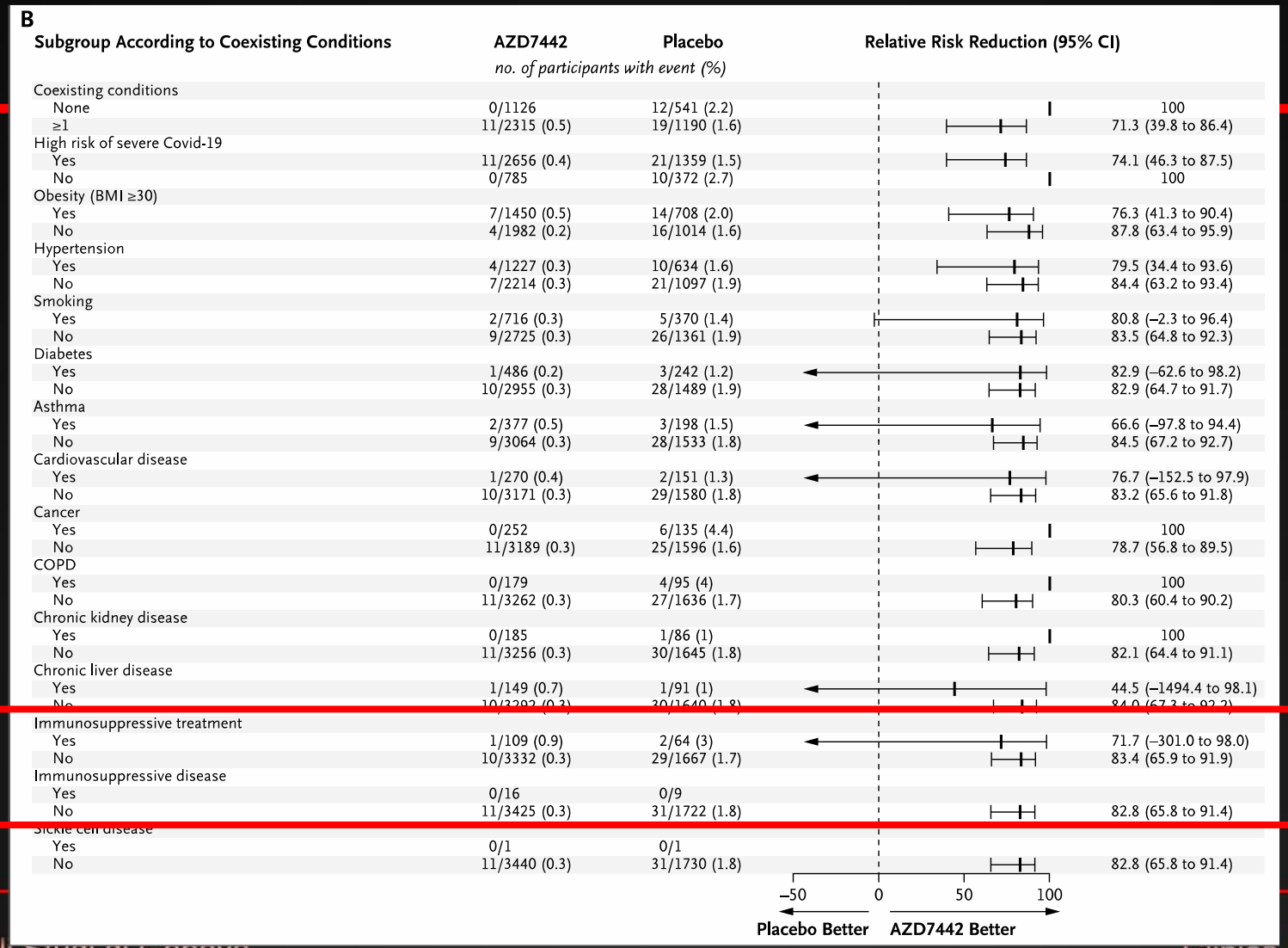
Provent Study: Efficacy across subgroups



B

Subgroup According to Coexisting Conditions	AZD7442	Placebo	Relative Risk Reduction (95% CI)
	no. of participants with event (%)		
Coexisting conditions			
None	0/1126	12/541 (2.2)	100
≥1	11/2315 (0.5)	19/1190 (1.6)	71.3 (39.8 to 86.4)
High risk of severe Covid-19			
Yes	11/2656 (0.4)	21/1359 (1.5)	74.1 (46.3 to 87.5)
No	0/785	10/372 (2.7)	100
Obesity (BMI ≥30)			
Yes	7/1450 (0.5)	14/708 (2.0)	76.3 (41.3 to 90.4)
No	4/1982 (0.2)	16/1014 (1.6)	87.8 (63.4 to 95.9)
Hypertension			
Yes	4/1227 (0.3)	10/634 (1.6)	79.5 (34.4 to 93.6)
No	7/2214 (0.3)	21/1097 (1.9)	84.4 (63.2 to 93.4)
Smoking			
Yes	2/716 (0.3)	5/370 (1.4)	80.8 (–2.3 to 96.4)
No	9/2725 (0.3)	26/1361 (1.9)	83.5 (64.8 to 92.3)
Diabetes			
Yes	1/486 (0.2)	3/242 (1.2)	82.9 (–62.6 to 98.2)
No	10/2955 (0.3)	28/1489 (1.9)	82.9 (64.7 to 91.7)
Asthma			
Yes	2/377 (0.5)	3/198 (1.5)	66.6 (–97.8 to 94.4)
No	9/3064 (0.3)	28/1533 (1.8)	84.5 (67.2 to 92.7)
Cardiovascular disease			
Yes	1/270 (0.4)	2/151 (1.3)	76.7 (–152.5 to 97.9)
No	10/3171 (0.3)	29/1580 (1.8)	83.2 (65.6 to 91.8)
Cancer			
Yes	0/252	6/135 (4.4)	100
No	11/3189 (0.3)	25/1596 (1.6)	78.7 (56.8 to 89.5)
COPD			
Yes	0/179	4/95 (4)	100
No	11/3262 (0.3)	27/1636 (1.7)	80.3 (60.4 to 90.2)
Chronic kidney disease			
Yes	0/185	1/86 (1)	100
No	11/3256 (0.3)	30/1645 (1.8)	82.1 (64.4 to 91.1)
Chronic liver disease			
Yes	1/149 (0.7)	1/91 (1)	44.5 (–1494.4 to 98.1)
No	10/3282 (0.3)	30/1640 (1.8)	84.0 (67.3 to 92.2)
Immunosuppressive treatment			
Yes	1/109 (0.9)	2/64 (3)	71.7 (–301.0 to 98.0)
No	10/3332 (0.3)	29/1667 (1.7)	83.4 (65.9 to 91.9)
Immunosuppressive disease			
Yes	0/16	0/9	
No	11/3425 (0.3)	31/1722 (1.8)	82.8 (65.8 to 91.4)
Sickle cell disease			
Yes	0/1	0/1	
No	11/3440 (0.3)	31/1730 (1.8)	82.8 (65.8 to 91.4)

–50 0 50 100

Placebo Better AZD7442 Better

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From The Medical Letter on Drugs and Therapeutics

January 25, 2022

Tixagevimab and Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis of COVID-19

Box. Some Moderately or Severely Immunocompromising Conditions[5]

- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection
- Receipt of CAR T-cell therapy or hematopoietic cell transplant within the previous 2 years
- Active treatment for a solid tumor or hematologic malignancy
- Use of immunosuppressive therapy after a solid-organ transplant
- Active treatment with other immunosuppressive or immuno-modulatory drugs, such as high-dose corticosteroids (≥20 mg/d of prednisone or equivalent) and tumor necrosis factor (TNF) inhibitors.

Indicazione autorizzata e rimborsata SSN: *Evusheld (tixagevimab + cilgavimab) è indicato per la profilassi pre-esposizione dell'infezione da SARS-CoV-2 in soggetti adulti ed adolescenti di età pari o superiore a 12 anni e con peso corporeo di almeno 40kg, con un controllo sierologico completamente negativo (anticorpi IgG anti-Spike negativi) e che presentano almeno uno dei seguenti fattori di rischio :*

- *Pazienti che abbiano assunto nell'ultimo anno terapie che comportano deplezione dei linfociti B (ad es. rituximab, ocrelizumab, ofatumumab, alemtuzumab)*
- *Pazienti in trattamento con inibitori della tirosin-chinasi Bruton*
- *Pazienti trattati con CarT*
- *Pazienti trapiantati di cellule ematopoietiche che hanno una malattia di rigetto o che stanno assumendo farmaci immunosoppressori*
- *Pazienti con malattia onco-ematologica in fase attiva*
- *Pazienti trapiantati di polmone*
- *Pazienti trapiantati di organo solido (diverso dal trapianto di polmone) entro 1 anno dal trapianto*
- *Pazienti trapiantati di organi solidi con recente trattamento per rigetto acuto con agenti che riducono le cellule T o B*
- *Pazienti con immunodeficienze combinate gravi*
- *Pazienti con infezione da HIV non in trattamento e una conta dei linfociti T CD4 <50 cellule/mm3*
- *Pazienti con altra compromissione del sistema immunitario che ha determinato mancata sieroconversione*

AIFA AGENZIA ITALIANA DEL FARMACO

Pre-exposure prophylaxis with tixagevimab and cilgavimab (Evusheld) for COVID-19 among 1112 severely immunocompromised patients

Nguyen Y, et al. CMI 2022

Observational multicentre cohort study of immunocompromised patients receiving tixagevimab/cilgavimab as preexposure prophylaxis between December 28, 2021 and March 31, 2022.

Tixagevimab/cilgavimab was administered to 1112 immunocompromised patients.
After a median (range) follow-up of 63 days, **COVID-19 was confirmed in 49/1112 (4.4%) > 5 days after treatment.**

Characteristics of the 49 patients with confirmed COVID-19 infection at least 5 days after tixagevimab/cilgavimab preexposure prophylaxis

	Overall ($n = 49$)	Mild COVID-19 ($n = 43$)	Moderate-to-severe COVID-19 ($n = 6$)
Age, y	58.9 (20.7)	55.7 (20.2)	78.0 (12.9)
Underlying cause of immunosuppression			
Heart transplant	4 (8.2)	4 (9.3)	0 (0.0)
Lung transplant	3 (6.1)	3 (7.0)	0 (0.0)
Kidney transplant	17 (34.7)	13 (30.2)	4 (66.7)
Haematologic malignancies	12 (24.5)	11 (25.6)	1 (16.7)
Treatment with rituximab	10 (20.4)	9 (20.9)	1 (16.7)
Treatment with azathioprine	1 (2.0)	1 (2.3)	0 (0.0)
Primary immune deficiency	2 (4.1)	2 (4.7)	0 (0.0)
Days between treatment and infection	26 (17)	27 (18)	20 (11)

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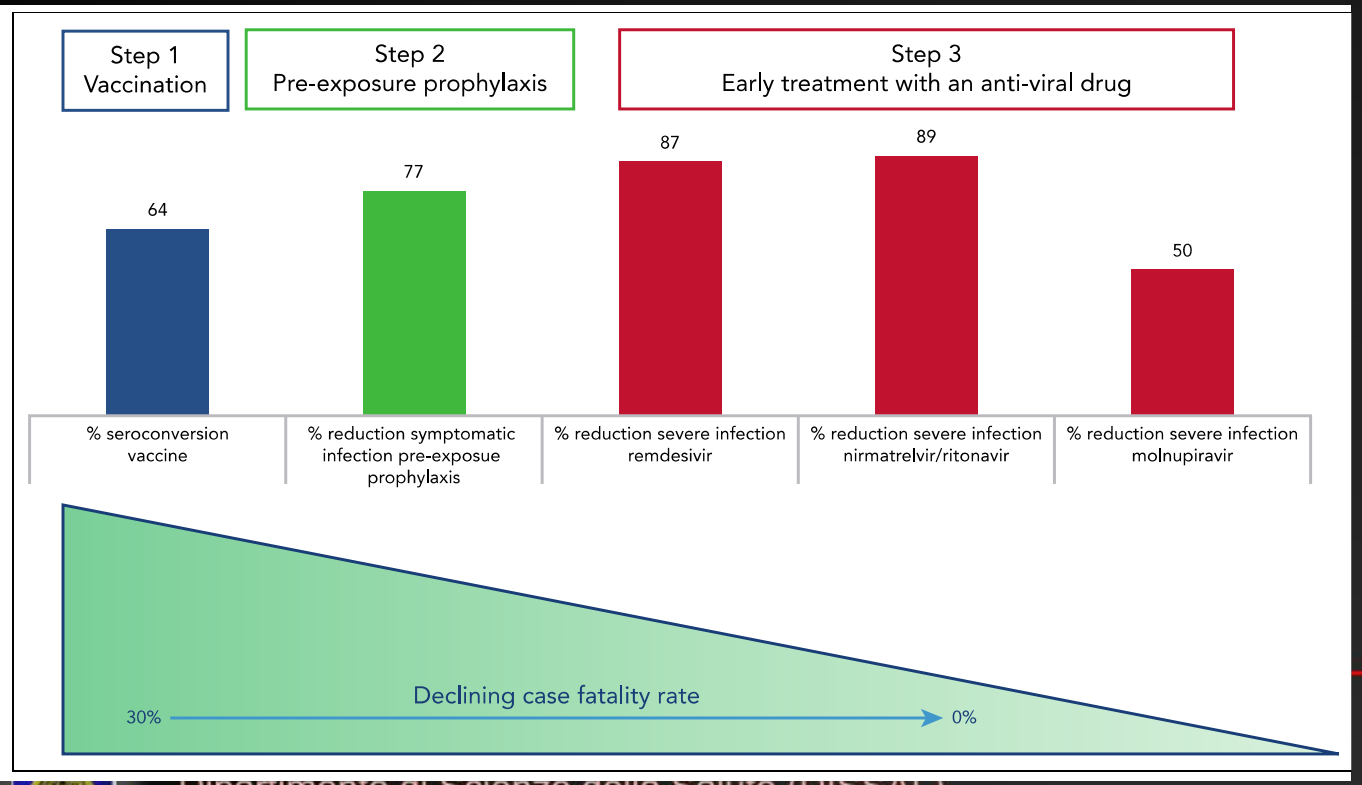
COVID-19 prophylaxis: half-full or half-empty glass?

Scarfò L and Cuneo A. Blood 2023

Sequence of interventions to prevent and successfully treat COVID-19 infection in patients with B-cell malignancies



Comment on Davis et al

251 pts B cells malignancies (80% no response to Vax)
27 (11%) experienced a breakthrough infection with 22 (9%) at least 30 days after tixagevimab–cilgavimab administration.

Only 4 (15%) patients required hospitalization, and no COVID-19-related death was reported.

We have won some battles against COVID-19 but not (yet) the war, as SARS-CoV-2 variants are rapidly changing over time

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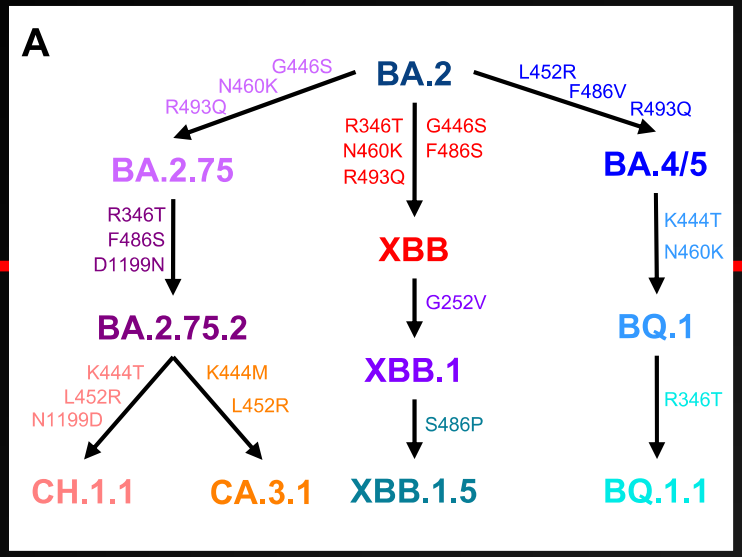
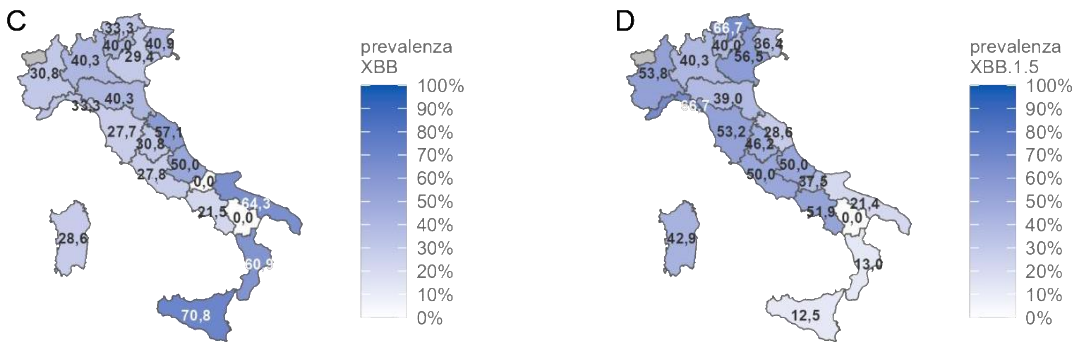


Rapporto n. 31 del 28 aprile 2023



prevalenza nazionale
ᵛXBB: 36,1%

prevalenza nazionale
§XBB.1.5: 45,3%

Rapporto n. 31 del 28 aprile 2023

Indagine rapida di prevalenza delle varianti (Flash Survey)
Aprile 2023:

- **XBB.1.5** risultava essere predominante, con una prevalenza **45,3%**,

- In diminuzione la proporzione di sequenziamenti BQ.1 e BA.2.75, con una prevalenza nazionale stimata pari rispettivamente al 9,7% e al 6,3%.

XBB.1.5
ricombinante di BA.2,
dei sotto-lignaggi BJ.1 e BM.1.1.1
con mutazione addizionale S:F486P

Marzo – Aprile 2023: La piattaforma per la sorveglianza genomica delle varianti di SARS-CoV-2 (I-Co-Gen): più di 199.000 sequenze provenienti da 71 strutture dislocate sull'intero territorio nazionale.

- **- XBB risulta predominante (76,4%), con 62 differenti sotto-lignaggi identificati; di questi, XBB.1.5 si conferma maggioritario (30,9%).**

- **- XBB.1.9.1, risulta il secondo lignaggio più frequente tra le XBB, con una frequenza pari al 14,5% nelle ultime sei settimane di osservazione.**

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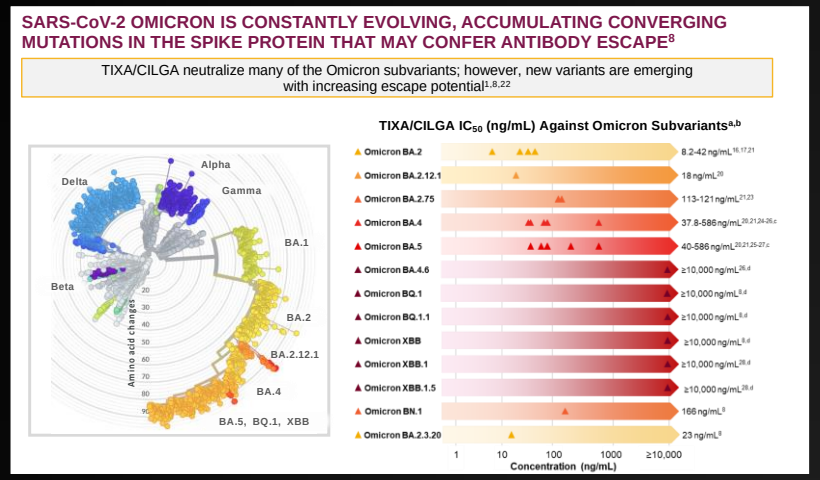
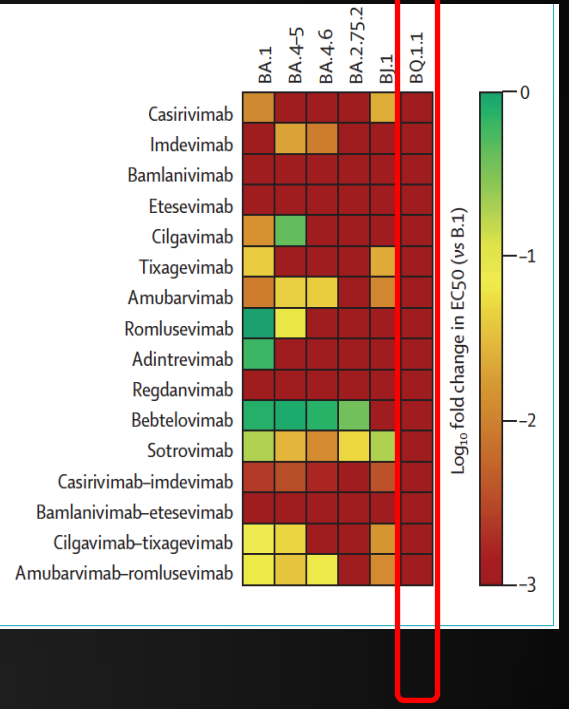
January 2023: mAbs and their decline vs BQ.1.1



		B.1	BA.1	BA.4-5	BA.4.6	BA.2.75.2	BJ.1	BQ.1.1
Single mAbs	Casirivimab	21	1890	>50000	>50000	>50000	880	>50000
	Imdevimab	19	>50000	994	2109	>50000	>50000	>50000
	Bamlanivimab	16	>50000	>50000	>50000	>50000	>50000	>50000
	Etesevimab	53	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab	37	2658	88	24200	>50000	>50000	>50000
	Tixagevimab	7	173	10090	27740	>50000	304	>50000
	Amubarvimab	53	5641	1234	1290	>50000	4762	>50000
	Romlusevimab	852	866	8279	>50000	>50000	>50000	>50000
	Adintrevimab	14	23	>50000	>50000	>50000	>50000	>50000
	Regdanvimab	7	>50000	>50000	>50000	6336	>50000	>50000
	Bebtelovimab	5	7	6	7	14	>50000	>50000
	Sotrovimab	157	833	5554	13000	3239	825	>50000
Cocktails of mAbs	Casirivimab–imdevimab	9	3642	2611	5395	>50000	2456	>50000
	Bamlanivimab–etesevimab	18	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab–tixagevimab	7	97	155	7131	>50000	482	>50000
	Amubarvimab–romlusevimab	64	657	1819	1015	>50000	5359	>50000

EC50 (ng/ml)



Arora P, Kempf A, Nehlmeier I. et al. The Lancet 2023

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NIH | COVID-19 Treatment Guidelines

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Anti-SARS-CoV-2 Monoclonal Antibodies

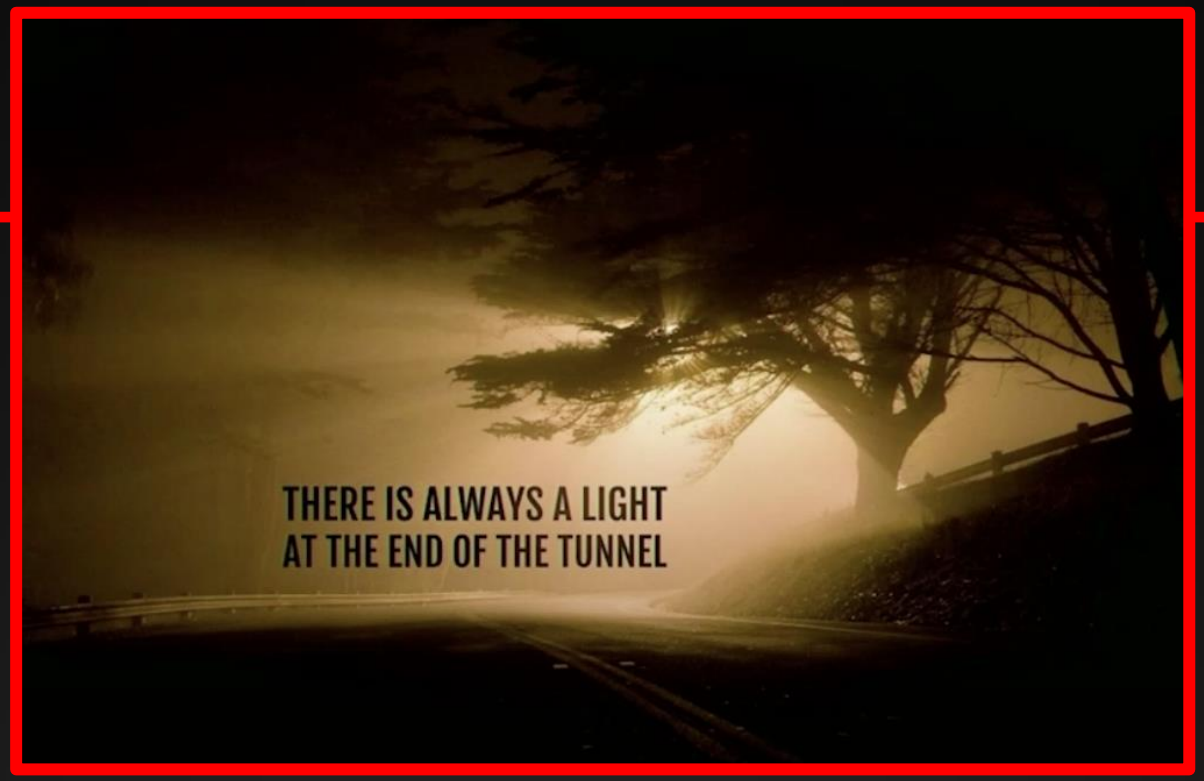
Drug Info | Clinical Data

Last Updated: March 6, 2023

Monoclonal antibodies (mAbs) that target the SARS-CoV-2 spike protein have been shown to have clinical benefits in treating SARS-CoV-2 infection. However, laboratory studies have found that the activity of anti-SARS-CoV-2 mAbs against specific variants and subvariants can vary dramatically. Because of this, these products are not expected to be effective treatments or preventives for COVID-19 in areas where the circulating variants and subvariants are resistant to mAbs.

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of anti-SARS-CoV-2 mAbs for the treatment or prevention of COVID-19 (AIII) because the dominant Omicron subvariants in the United States are not expected to be susceptible to these products.
- For the Panel's recommendations on treating nonhospitalized patients with COVID-19, see Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Nonhospitalized Children With COVID-19.



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First participant dosed in SUPERNOVA Phase I/III trial evaluating AZD5156, a next-generation long-acting antibody combination, for prevention of COVID-19

Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA) (SUPERNOVA)

AZD5156 is an investigational, long-acting antibody combination of cilgavimab, a component of EVUSHELD (tixagevimab and cilgavimab, formerly AZD7442), and a new long-acting monoclonal antibody (mAb), AZD3152.

AZD5156 retains in vitro neutralization activity against all SARS-CoV-2 variants known to date, including BQ.1 and BQ.1.1

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	3256 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	D7000C00001 is a Phase I/III study that will be conducted in approx. 3256 participants to evaluate the safety and neutralizing activity of AZD3152 compared with AZD7442 for pre exposure prophylaxis of COVID-19, and separately evaluate the safety and PK of AZD5156, a combination of AZD3152& AZD1061. The study will consist of 2 cohorts: a Sentinel and Main Cohort. The Sentinel Cohort will enroll 56 healthy adults, 18-55 years old, who will be randomized to receive AZD5156 (40 participants) or placebo (16 participants). Dosing in the Sentinel Cohort will be staggered, with participants allocated sequentially to 4 subcohorts (1a, 1b, 2a, 2b). An ESDR will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort. Participants in the Main Cohort will be randomized 1:1 to receive AZD3152 (+placebo to preserve the blind) or AZD7442 administered IM in the thigh on Day 1. Participants will receive a 2nd dose of their original randomized study intervention 6 months after Visit 1.
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Prevention
Official Title:	A Phase I/III Randomized, Double Blind Study to Evaluate the Safety and Neutralizing Activity of AZD5156/AZD3152 for Pre Exposure Prophylaxis of COVID 19 in Participants With Conditions Causing Immune Impairment
Actual Study Start Date :	December 16, 2022
Estimated Primary Completion Date :	November 30, 2023
Estimated Study Completion Date :	January 21, 2025

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COVID-19 dopo oltre 3 anni, come è cambiato:

Strategie attuali di trattamento

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Clinical case (February 2022)

-- 75y old man with a **granulomatosis with polyangiitis** with renal involvement on **maintenance therapy with rituximab 500 mg every 6 months and prednisone 5 mg q24h** (last administration of rituximab in December 2021)

-- A recent finding of atrial fibrillation, and a mitral prolapse.

- **Vaccinated with 3 doses of mRNA vaccine (the last in November 2021)**

- **January 2022:** mild COVID-19 with fever, asthenia and wheezing cough at the onset not early treatment, not pre-exposure prophylaxis

SARS-CoV-2 RT-PCR nasopharyngeal swab remains positive 15 and 30 days later

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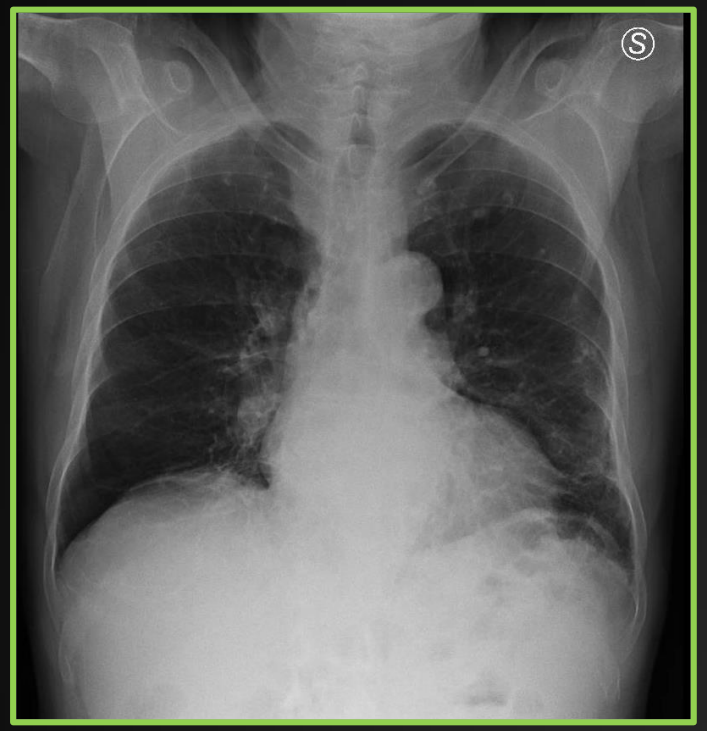
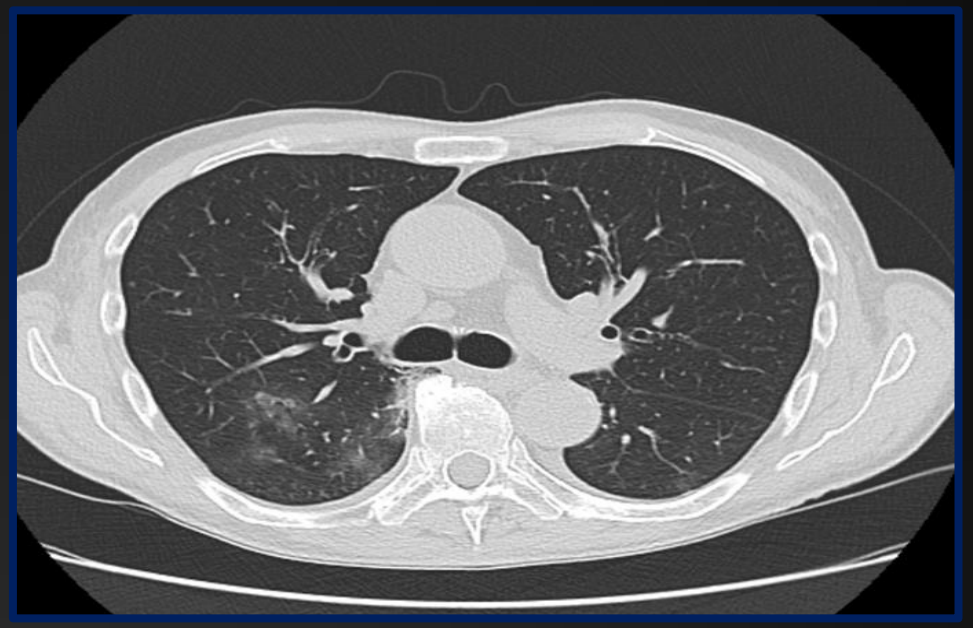
Beginning of February 2022: recurrent fever up to 38 °C

At ED **SARS-CoV-2 RT-PCR NP swab positive**

Chest Rx: no lesions



Chest CT: few peripheral small nodules and ground glass opacities postero-basal and para-scissural



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Clinical case

Blood Tests at the ED at Day 0 (Feb 2022)

White Blood Cells	6500/microL (range 4500-9800)
Creatinine	1 mg/dl (0.6-1.1)
Liver function	AST/ALT 51/60 (nv < 40 UI/ml)
D-dimer	428 mcg/L (0-500)
C-reactive protein	85 mg/dl (0-3)
Interleukin-6	8.8 ng/L (nv < 3.4)
Ferritin	338 mcg/L (range 30-400)

- Arterial blood gas analysis: pH 7.39, $pa0_2$ 80 mmHg, $pC0_2$ 46 mmHg, $Pa0_2/Fi0_2$ 228, $S0_2$ 97% (on air resting)

A blood sample was analyzed for SARS-CoV-2 RNAemia and resulted positive

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Immunocompromised patients…..

Immunocompromised patients :
have an **increased mortality** linked to SARS-CoV-2 infection compared to the general population, with **high hospitalization and mortality rates** of 39% and 34% respectively

In this population the **negative prognosis** seems more related **to the virologic phase** than to the inflammatory phase, and the virologic phase **could be prolonged with the presence of SARS-CoV-2 in the blood for months** after the beginning of the infection

The **progression over time of SARS-CoV-2 infection** in the immunocompromised host can be different than in the general population, and **antivirals could maintain a therapeutic role** even beyond the first 5-10 days from the beginning of symptoms

Passamonti F, et al. Lancet Haematol. 2020;7(10):e737-e745. Vijenthira A, et al. Blood. 2020;136(25):2881-2892. Ljungman P, et al. Leukemia. 2021;35(10):2885-2894. Spanjaart AM, et al. Leukemia. 2021;35(12):3585-3588. Ljungman P, et al. Bone Marrow Transplant. 2020;55(11):2071-2076. Sepulcri C, Dentone C, Mikulska M, et al. Open Forum Infect Dis. 2021;8(11):ofab217. Cesaro S, Ljungman P, Mikulska M, et al. Leukemia. April 29, 2022:1-14.

What could be the best treatment for our patient?

75y old man with a **granulomatosis with polyangiitis** with renal involvement on **maintenance therapy with rituximab 500 mg every 6 months and prednisone 5 mg q24h** (last administration of rituximab in December 2021)

**Pts with B-cell depletion,
had an impaired antibody response
linked to ineffective viral clearance**

In February 2022 in our region, the prevalence of Omicron, BA.1 variant, was more than 80%.

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…. Dual combination therapy?

Antiviral monotherapy might be insufficient treatment option in the absence of humoral immunity
Buckland MS, *et al.* Nat Commun 2020

Some case reports and case series have reported successful use of combination therapy including antiviral and convalescent plasma or MAbs or two antivirals
Magyari F, *et al.* Ann Hematol 2022
Hashemian SMR, *et al.* Microbes, Inf and Chem 2022

RECOVERY was the first randomized, controlled, open-label trial to demonstrate the efficacy of the monoclonal antibodies combination of casirivimab/imdevimab and remdesivir (Lancet 2022)

The combination mAb and antiviral prevent the escape mutans virus and help to reduce viral burden
Copin R, *et al.* Cell 2021
***Baum A, et al.* Science 2020**

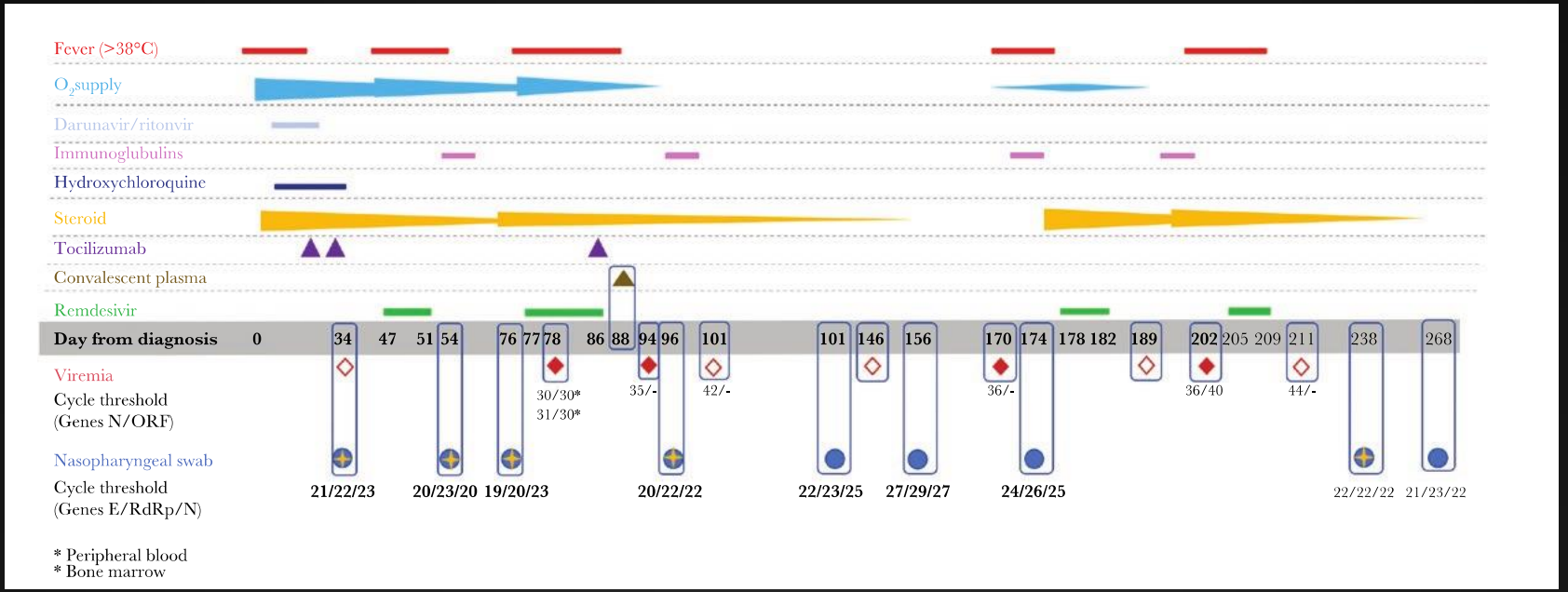
The Longest Persistence of Viable SARS-CoV-2 With Recurrence of Viremia and Relapsing Symptomatic COVID-19 in an Immunocompromised Patient—A Case Study

Chiara Sepulcri,[1,a] Chiara Dentone,[2,a] Malgorzata Mikulska,[1,2] Bianca Bruzzone,[3] Alessia Lai,[4] Daniela Fenoglio,[5,6] Federica Bozzano,[2] Annalisa Bergna,[4] Alessia Parodi,[6] Tiziana Altosole,[5] Emanuele Delfino,[2] Giulia Bartalucci,[7] Andrea Orsi,[3,8] Antonio Di Biagio,[1,2] Gianguglielmo Zehender,[9] Filippo Ballerini,[10] Stefano Bonora,[11] Alessandro Sette,[15,16] Raffaele De Palma,[6,12] Guido Silvestri,[13,14] Andrea De Maria,[1,2] and Matteo Bassetti[1,2]

Open Forum Infectious Diseases

MAJOR ARTICLE

2021



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….Why not triple combination therapy?

Combination of antiviral agents has been successfully used in numerous chronic infections due RNA viruses

Combining
antiviral agents with anti-Spike monoclonal antibodies
Could be a potential advantage
of higher efficacy due to a combination of two different antiviral mechanisms,

since inhibition of viral proliferation might be insufficient
for viral clearance in the absence of humoral immunity.

Buckland MS, et al. Nature Communications **2020**
Tepasse PR, et al. e. Br J Haematol **2020,**
Magyari F, et al. Ann Hematol **2022**

Outpatient- Health clinic
At Infectious Diseases Dpt

In February 2022 in our region, the prevalence of Omicron, BA.1 variant, was more than 80%.

The off-label protocol has been approved by the dedicated Hospital Board for Evaluation of Off-label Studies

An off-label combination therapy of monoclonal antibodies and antivirals was started:

- **single infusion of IV sotrovimab 500 mg**,
- **10-day course of IV remdesivir (200 mg of loading dose, 100 mg of maintenance dose)**
- **plus five days of nirmatrelvir/ritonavir 300mg/100mg q12h.**

No adjunctive anti-inflammatory treatment (i.e. IL-6 or IL-1 receptor inhibitors) or steroids treatment were added absence of SARS-CoV-2 - related inflammatory pattern.
--No adverse effects were observed.

.....

- **On Day 5 SARS-CoV-2 RNAemia and NP swab resulted still positive**
- **On Day 10 SARS-CoV-2 RNAemia and NP swab resulted negative with stable peripheral saturation values on room air and he was discharged from our outpatient clinic.**

This possible strategy could change
the way of how we treat COVID-19 in the immunocompromised patient
and to prevent the prolonged shedding linked to the emergence of variants

Baldi F, Dentone C, Mikulska M, et al. *Front. Med.* 9:1062450. 2023

Clinical Infectious Diseases

MAJOR ARTICLE

Triple Combination Therapy With 2 Antivirals and Monoclonal Antibodies for Persistent or Relapsed Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Immunocompromised Patients

Mikulska M, Sepulcri S, et al CID 2023

Retrospective Cohort

COVID19

Severely immunocompromised patients are at risk for prolonged or relapsed COVID-19 leading to increased morbidity and mortality.
Aim: evaluate outcome after triple combination therapy: two antivirals + Mabs, if available

22 patients with prolonged/relapsed COVID-19:
19 (86%) had hematological malignancy, mainly NHL (n=15)
9 (41%) were HSCT recipients
15 (68%) received anti-CD20
2 were renal transplant recipients

Triple combination therapy (2 antivirals + Mabs), n=18
Mabs unavailable, n=4

Antivirals:
Remdesivir + nirmatrelvir/r, n=20/22
Remdesivir + molnupiravir, n=2/22

VIROLOGICAL RESPONSE
(negative PCR)

CLINICAL RESPONSE
(alive, well and PCR negative)

SAFETY
(adverse events at last FU)

Day +14
75%

Day +30
73%

w/ Mabs
higher response rate

p = 0.032

p=0.046

Last FU
82%

higher
n.vaccine doses
p=0.013

n=2

1 myocardial Infarction
1 bradycardia

Median follow-up 63 days

Combination therapy including two antivirals (mainly remdesivir and nirmatrelvir/ritonavir) + Mabs was associated with high rate of virological and clinical response in immunocompromised patients with prolonged/relapsed COVID-19.

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The number of doses of SARS-CoV-2 vaccine was associated with higher overall success rate

e Infettive
no IRCCS
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COVID-19 dopo oltre 3 anni, come è cambiato:

Strategie attuali di trattamento

The question now is not only
what combination,
but how long…..

Extended course of Remdesivir and Nirmatrelvir/r

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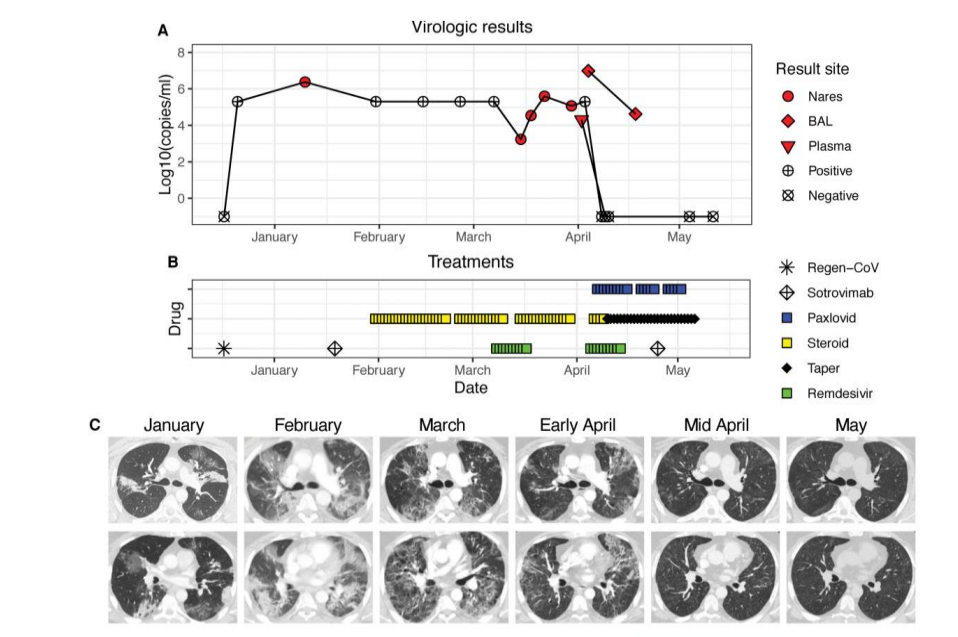
Successful Treatment of Prolonged, Severe Coronavirus Disease 2019 (COVID-19) Lower Respiratory Tract Disease in a B-cell Acute Lymphoblastic Leukemia (ALL) Patient With an Extended Course of Remdesivir and Nirmatrelvir/Ritonavir

Clinical Infectious Diseases
BRIEF REPORT

Ford ES, et al, CID 2022



The treatment includes:
3 mAb infusions
2 courses of 10 days Remdesivir
20 days of NM/r
Steroids
[VOC BA.1.1]

By day 20 of NM/r he was off of 02
Chest CT one week after end NM/r substantial improvement

At 4 months after end NM/r he is stable w/o recrudescent of infections

Prolonged infection is associated with within-host viral evolution and represents a source of global variants

Prolonged and potent combination of antiviral therapy in IC pts need to be evaluated for clinical and virological cure

Corey L, et al. NEJM 2021
Ghandi S, et al. Nat Commun 2022
Nussenblatt V,et al. JID 2022

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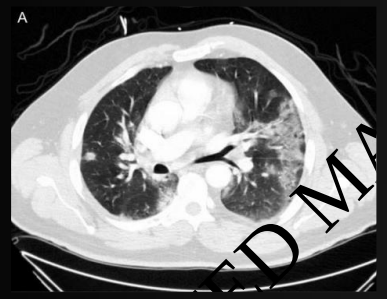
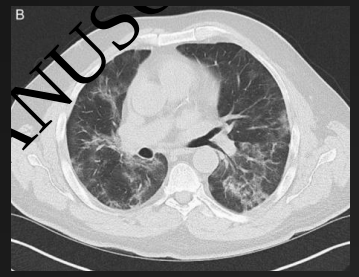
Dual antiviral Therapy for persistent COVID-19 and associated OP in an immunocompromised host

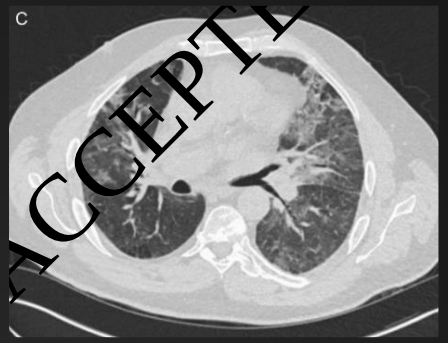
Trottier CA, et al CID 2022

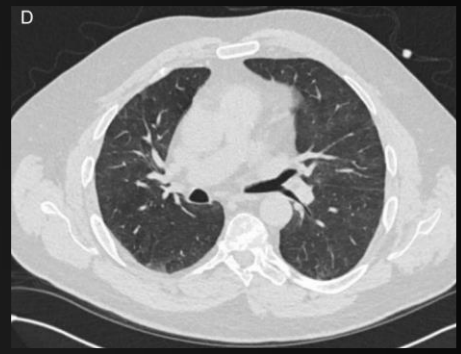
Pt vaccinated (3 doses Feb 2022) with chronic lymphocytic leukemia wtih symptomatic SARS-COV-2 infection and organizing pneumonia (over a 4 months period) >> treated with extended course of combination antiviral therapy

1. NM/r 5 days → 2. Steroids and Remdesivir 10 D → 3. Steroids and Bemtelovimab → **4. Steroids, Remdesivir 20D, NM/r 20D** → **FU visit 2 months after therapy NP swab neg**









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~~New perspectives…..~~

Old perspectives!!!!

Sospensione di utilizzo del medicinale Lagevrio® (molnupiravir)

L'AIFA rende noto che nella seduta della Commissione Tecnico Scientifica del 10 marzo 2023 è stato deciso di sospendere l'utilizzo del medicinale antivirale Lagevrio® (molnupiravir) a seguito del parere negativo formulato dal CHMP di EMA, in data 24/02/2023, per la mancata dimostrazione di un beneficio clinico in termini di riduzione della mortalità e dei ricoveri ospedalieri (documento EMA disponibile nei "Link correlati").

Non sono stati rilevati particolari problemi di sicurezza collegati al trattamento.

Il molnupiravir era stato inizialmente reso disponibile, per il trattamento del COVID-19 lieve-moderato, tramite autorizzazione alla distribuzione in emergenza ai sensi del'Art.5.2 del DL 219/2006 (Decreto Ministeriale del 26 novembre 2021 e successive proroghe).

Il provvedimento di sospensione di utilizzo sarà effettivo a seguito della pubblicazione in Gazzetta Ufficiale.

Pubblicato il: 10 marzo 2023

Triple antiviral treatment for COVID-19 in an immunocompromised patient

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkad159

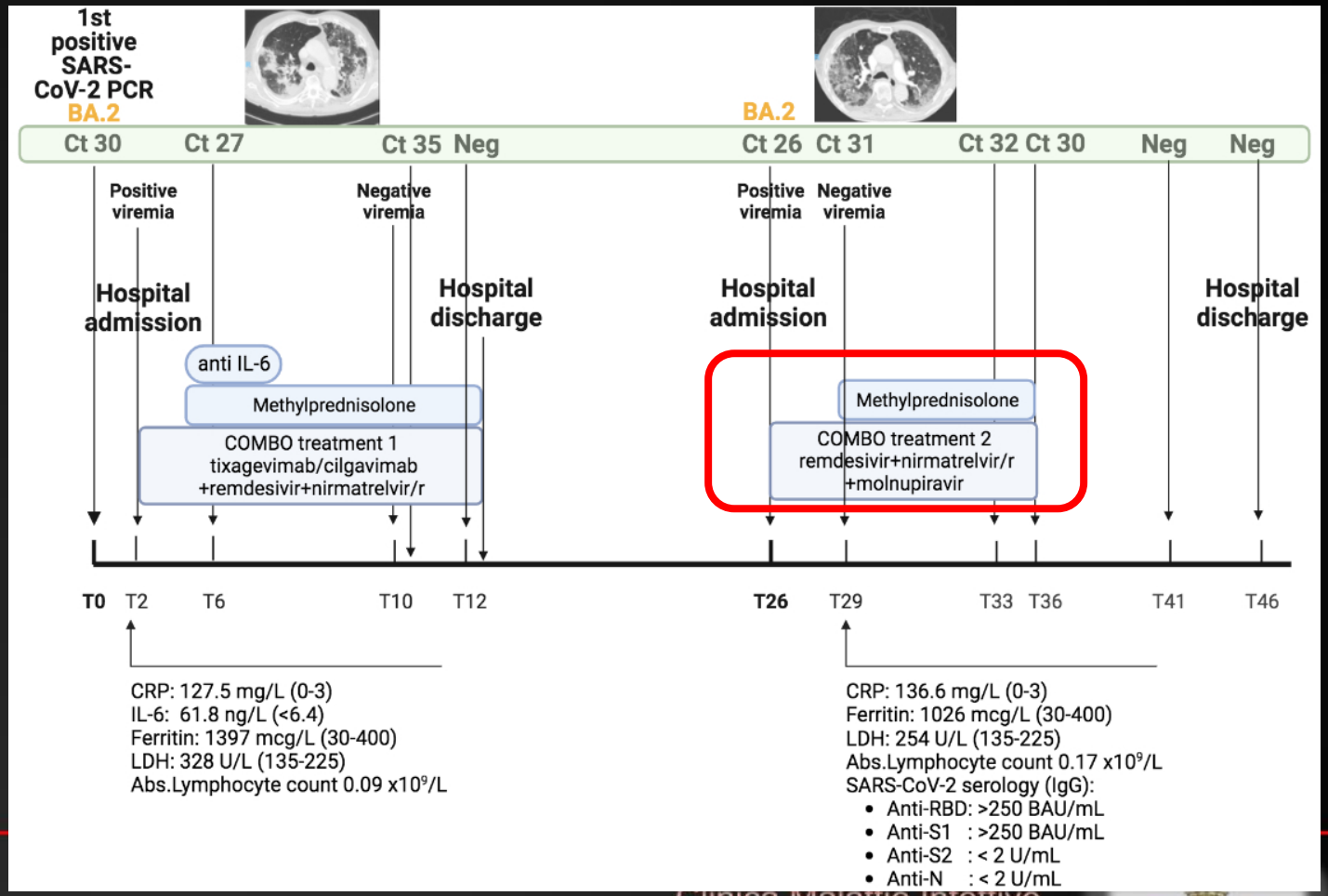
Chiara Dentone [1], Malgorzata Mikulska[1,2], Chiara Sepulcri [2*], Elisa Balletto[1,2], Vanessa De Pace[3], Sabrina Beltramini[4] and Matteo Bassetti[1,2]

January 2023 Clinical Case:
patient 80 yo, CLL, follicular NHL R-benda, severe relapse COVID-19

In the 2 nd combo treatment:
10 days for remdesivir, nirmatrelvir/ritonavir and molnupiravir

Repeat nasopharyngeal swabs resulted negative on Days 15 and 19.

The patient was discharged home with minimal oxygen requirement (1 L/min). No adverse effects were observed.



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Antiviral drugs for treatment of SARS-CoV-2 infection

-- **molnupiravir** a nucleoside analog targeting RNA-dependent viral RNA polymerase. (AIFA…)

-- **remdesivir**, an inhibitor of the viral RNA-dependent RNA polymerase;
-- **nirmatrelvir**, a 3C-like protease inhibitor administered with **ritonavir booster**;

-- **ensitrelvir**, a SARS-CoV-2 3CL Protease Inhibitor

Efficacy and Safety of Ensitrelvir in Patients With Mild-to-Moderate Coronavirus Disease 2019: The Phase 2b Part of a Randomized, Placebo-Controlled, Phase 2/3 Study

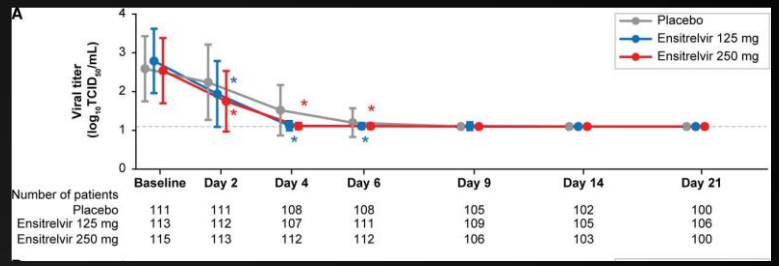
Mukae H, CID 2023

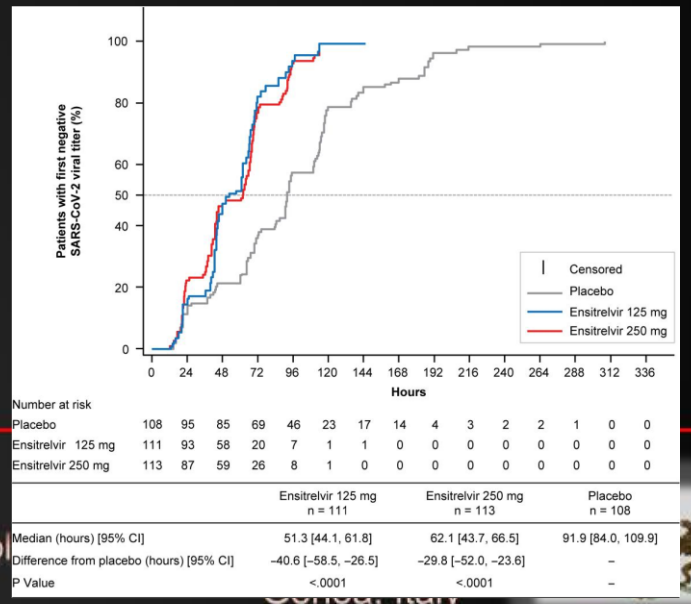
Background. This phase 2b part of a randomized phase 2/3 study assessed the efficacy and safety of ensitrelvir for mild-to-moderate coronavirus disease 2019 (COVID-19) during the Omicron epidemic.

Methods. Patients were randomized (1:1:1) to orally receive ensitrelvir fumaric acid 125 mg (375 mg on day 1) or 250 mg (750 mg on day 1) or placebo once daily for 5 days. The co-primary endpoints were the change from baseline in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) titer on day 4 and time-weighted average change from baseline up to 120 hours in the total score of predefined 12 COVID-19 symptoms. Safety was assessed through adverse events.

Results. A total of 341 patients (ensitrelvir 125-mg group: 114; ensitrelvir 250-mg group: 116; and placebo group: 111; male: 53.5–64.9%; mean age: 35.3–37.3 years) were included in the efficacy analyses. The change from baseline in SARS-CoV-2 titer on day 4 was significantly greater with both ensitrelvir doses than with placebo (differences from placebo: −0.41 $\log_{10}$ 50% tissue-culture infectious dose/mL; $P < .0001$ for both). The total score of the 12 COVID-19 symptoms did not show a significant difference between the ensitrelvir groups and placebo group. The time-weighted average change from baseline up to 120 hours was significantly greater with ensitrelvir versus placebo in several subtotal scores, including acute symptoms and respiratory symptoms. Most adverse events were mild in severity.

Conclusions. Ensitrelvir treatment demonstrated a favorable antiviral efficacy and potential clinical benefit with an acceptable safety profile.





The primary virologic outcome was change from baseline (day 1, before drug administration) in the SARS-CoV-2 viral titer on day 4 of treatment. The primary clinical outcome was time- weighted average change from baseline up to 120 hours in the total score of 12 COVID-19 symptoms

In conclusion, 5-day, once-daily, oral ensitrelvir treatment demonstrated rapid and favorable antiviral efficacy with an acceptable safety profile in patients with mild-to-moderate COVID-19, a majority of whom had been vaccinated.

The NEW ENGLAND JOURNAL of MEDICINE

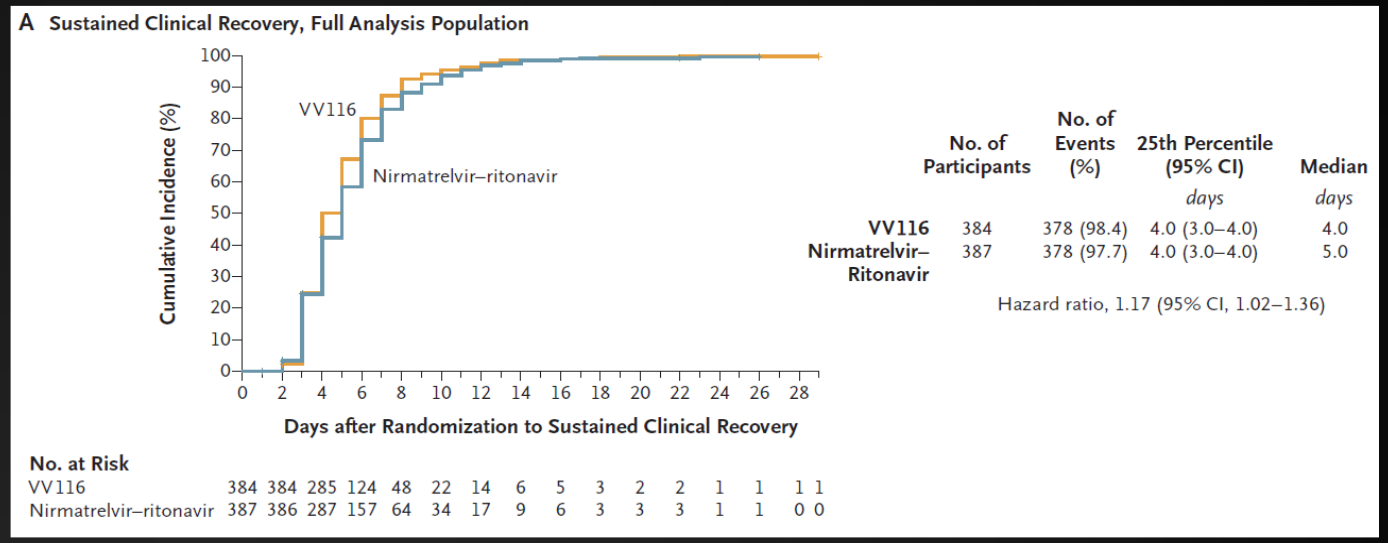
ORIGINAL ARTICLE

VV116 versus Nirmatrelvir–Ritonavir for Oral Treatment of Covid-19

Cao Z, et al. NEJM 2022

VV116 is an oral analogues of remdesivir.
Study: phase 3, noninferiority, observer-blinded, randomized trial

Primary endpoint:
Time from randomization to **sustained clinical recovery** (alleviation of all COVID-19 symptoms according a predefined scale) through day 28.



	No. of Participants	No. of Events (%)	25th Percentile (95% CI)	Median
			days	*days*
VV116	384	378 (98.4)	4.0 (3.0–4.0)	4.0
Nirmatrelvir–Ritonavir	387	378 (97.7)	4.0 (3.0–4.0)	5.0

Hazard ratio, 1.17 (95% CI, 1.02–1.36)

The hazard ratio for the time from randomization to sustained clinical recovery indicated that the noninferiority of VV116 to nirmatrelvir–ritonavir was established.

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ORIGINAL ARTICLE

Early Treatment with Pegylated Interferon Lambda for Covid-19

BACKGROUND

The efficacy of a single dose of pegylated interferon lambda in preventing clinical events among outpatients with acute symptomatic coronavirus disease 2019 (Covid-19) is unclear.

METHODS

We conducted a randomized, controlled, adaptive platform trial involving predominantly vaccinated adults with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brazil and Canada. Outpatients who presented with an acute clinical condition consistent with Covid-19 within 7 days after the onset of symptoms received either pegylated interferon lambda (single subcutaneous injection, 180 μg) or placebo (single injection or oral). The primary composite outcome was hospitalization (or transfer to a tertiary hospital) or an emergency department visit (observation for >6 hours) due to Covid-19 within 28 days after randomization.

RESULTS

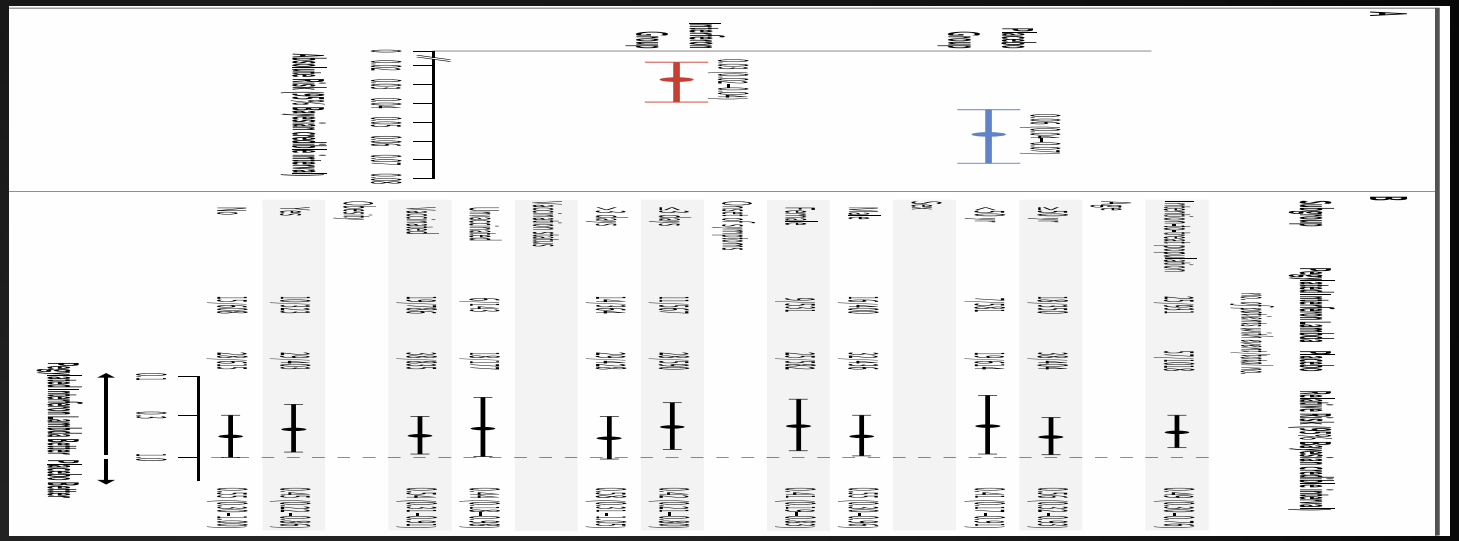
A total of 933 patients were assigned to receive pegylated interferon lambda (2 were subsequently excluded owing to protocol deviations) and 1018 were assigned to receive placebo. Overall, 83% of the patients had been vaccinated, and during the trial, multiple SARS-CoV-2 variants had emerged. A total of 25 of 931 patients (2.7%) in the interferon group had a primary-outcome event, as compared with 57 of 1018 (5.6%) in the placebo group, a difference of 51% (relative risk, 0.49; 95% Bayesian credible interval, 0.30 to 0.76; posterior probability of superiority to placebo, >99.9%). Results were generally consistent in analyses of secondary outcomes, including time to hospitalization for Covid-19 (hazard ratio, 0.57; 95% Bayesian credible interval, 0.33 to 0.95) and Covid-19–related hospitalization or death (hazard ratio, 0.59; 95% Bayesian credible interval, 0.35 to 0.97). The effects were consistent across dominant variants and independent of vaccination status. Among patients with a high viral load at baseline, those who received pegylated interferon lambda had lower viral loads by day 7 than those who received placebo. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

Among predominantly vaccinated outpatients with Covid-19, the incidence of hospitalization or an emergency department visit (observation for >6 hours) was significantly lower among those who received a single dose of pegylated interferon lambda than among those who received placebo. (Funded by FastGrants and others; TOGETHER ClinicalTrials.gov number, NCT04727424.)

The primary composite outcome:

COVID-19 related hospitalization (or transfer from an emergency department to a tertiary hospital) owing to the progression of COVID-19 within 28 days after randomization.



Secondary outcomes: clearance of SARS-CoV-2, the time from randomization to hospitalization for any cause or due to progression of Covid-19, the time from randomization to death from Covid-19, the number of days in the hospital and days with mechanical ventilation, adverse events, and adverse reactions to interferon or placebo

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Reis G, Moreira Silva E, Medeiros Silva SC et al, NEJM Feb 2023

COVID-19 dopo oltre 3 anni, come è cambiato: Strategie attuali di profilassi e trattamento

1. L'infezione da SARS-CoV-2 determina differenti quadri clinici

2. La gravità dei sintomi dipende dall'interazione tra virus e risposta immunitaria del paziente

3. Considerare sempre non solo virus e varianti, ma anche i fattori di rischio dell'ospite per una terapia ragionata (quale, quando e per quanto tempo)

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Grazie per l'attenzione

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