Il COVID 4 anni dopo

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DISCLOSURES

Advisor/speaker (past 5 years)

Angelini, Gilead,
Novartis, MSD, Astrazeneca

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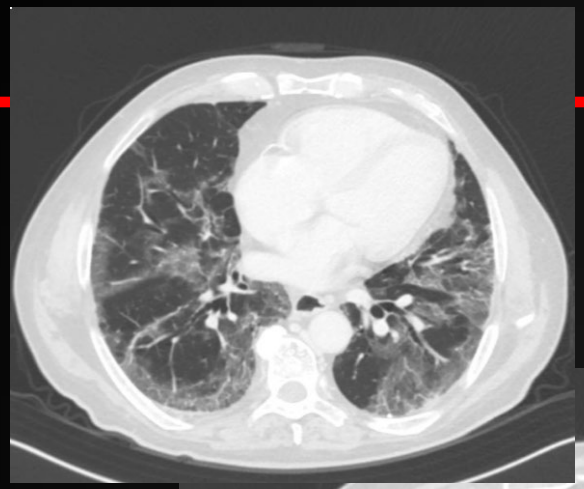
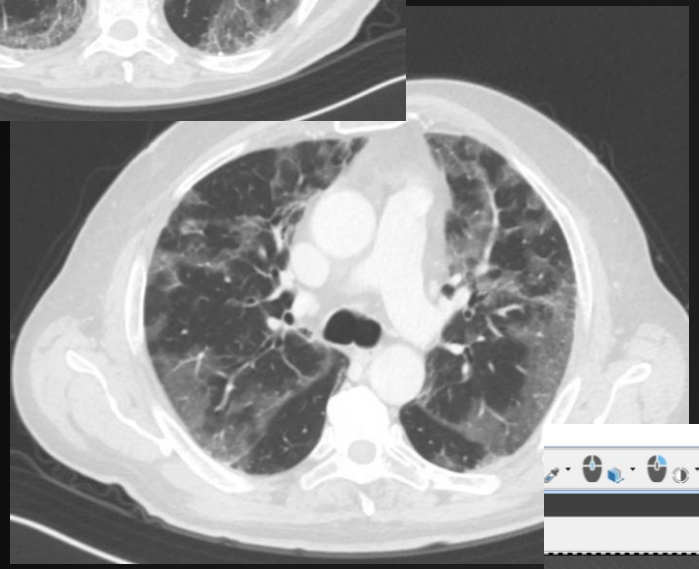
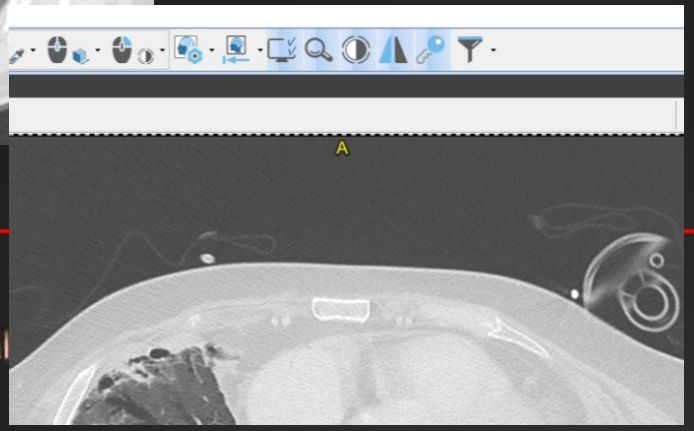
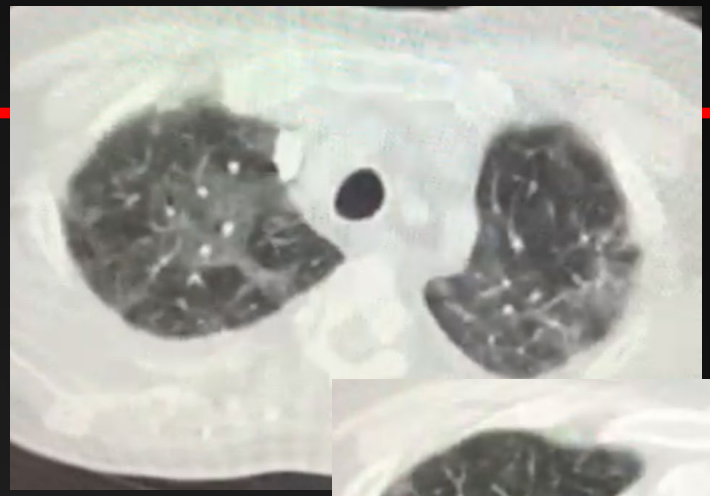
Aprile 2020: 70 aa, Diabete insulino dip, iperteso, pregresso STEMI, non vaccinato

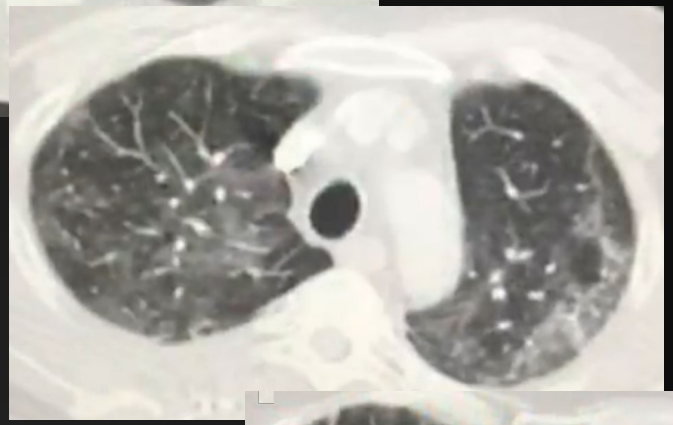
Novembre 2023: 63 aa, LNH mantellare, auto-HSCT 2020, in mantenimento con Rituximab, vaccinato 4 dosi

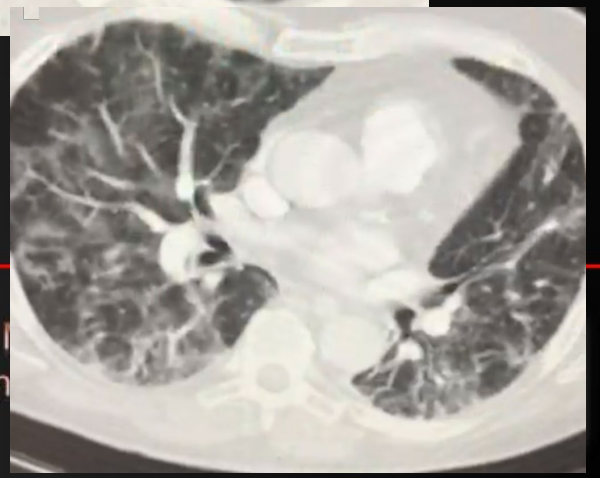












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Clinica
Ospedale Polidinico San

Severity of symptoms might depend on the interaction between the SARS-CoV-2 and the immune system of patient

HOST MAKES THE DIFFERENCE

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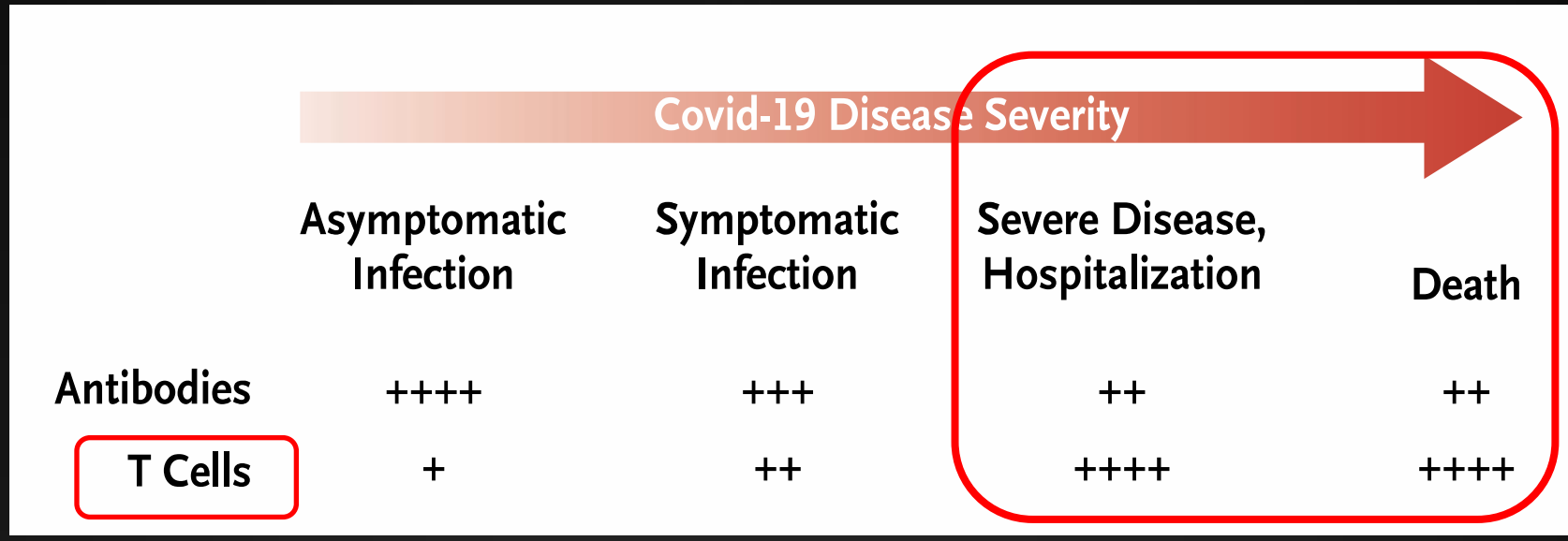
Immune Responses for Protection against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).



Cellular immunity to SARS-CoV-2 includes virus-specific B cells and T cells, which provide long-term immunologic memory and rapidly expand on reexposure to antigen.

Combination of humoral and cellular immune responses controls viral replication after infection and prevents progression to severe disease, hospitalization, and death

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Barouch DH NEJM, 2022

Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study

Evans RA et al. The Lancet Regional Health - Europe 2023

Retrospective cohort design UK
immunocompromised vs general population
(01/01/2022-31/12/ 2022)
COVID-19-related hospitalisations,
ICU admissions and deaths

IC accounted for 3.9% of the study population,

- **22% (4585/ 20,910) of COVID-19 hospitalisations**
- **28% (125/440) of COVID-19 ICU admissions**
- **24% (1145/4810) of COVID-19 deaths**

"Broadly-defined immunocompromised"

"Stringently-defined immunocompromised"

- Moderate/severe primary immunodeficiency
- Active treatment with immunosuppressive or immunomodulatory therapy
- treatment with high-dose corticosteroids
- Solid organ transplant ≤2 years
- Haematopoietic stem cell transplant ≤2 years
- solid tumour [s] or haematologic malignancies on treatment ≤6 months
- LLC, LNH, MM, LMA ≤2 years
- AIDS

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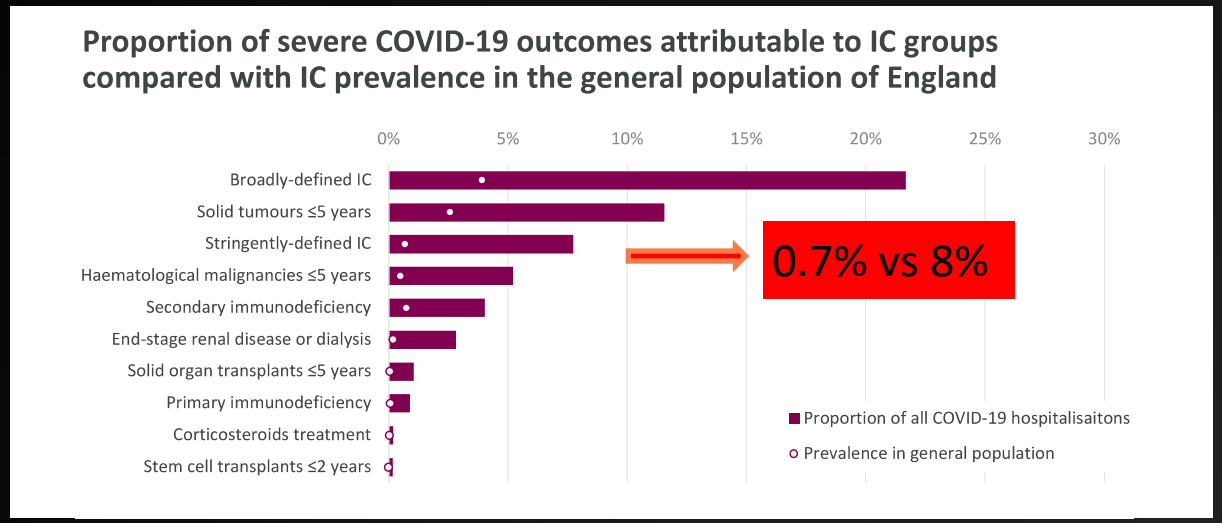
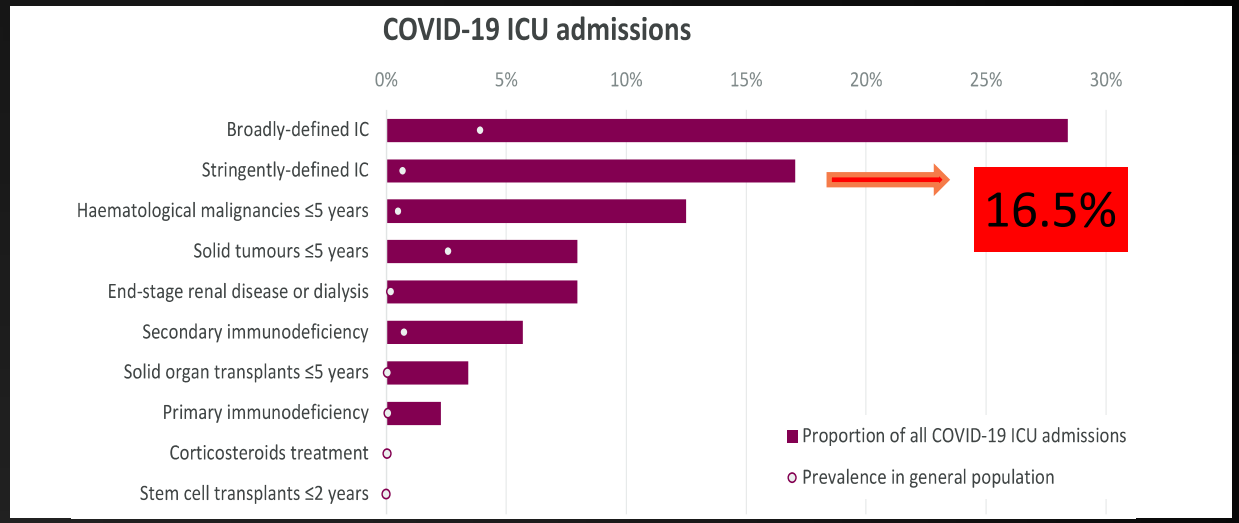
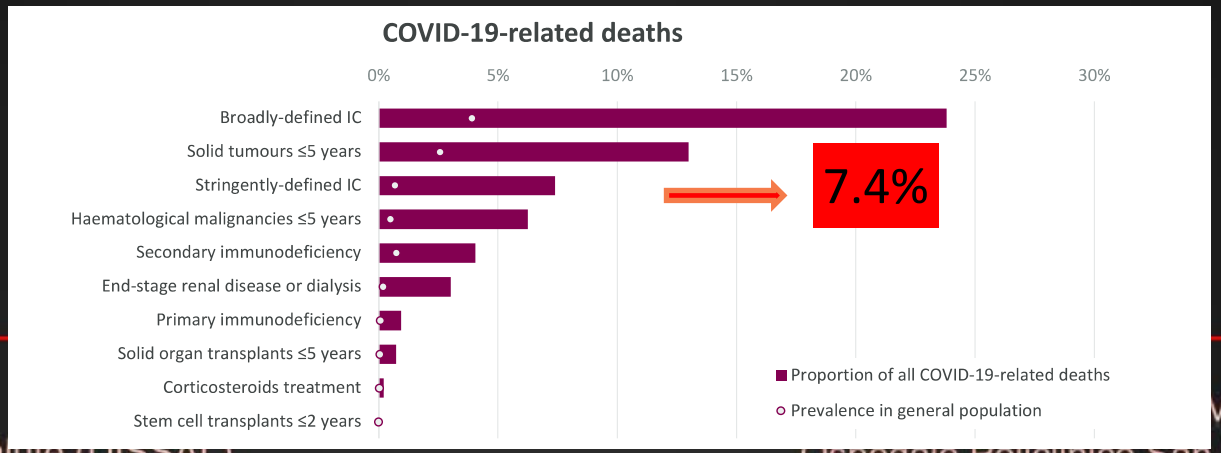
Hospitalisation for Severe COVID-19



ICU admission



COVID-19 deaths



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Evans RA et al. The Lancet Regional Health - Europe 2023

Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study

Vaccinated with ≥3 doses (~84% IC and 51% of the general population):
all IC groups remained at increased risk of severe COVID-19 outcomes,
with adjusted incidence rate ratios (aIRR) for hospitalisation ranging from 1.3 to 13.1.

At highest risk for COVID-19 hospitalisation:

- **solid organ transplant (aIRR 13.1, 95% confidence interval [95% CI] 11.2–15.3),**
- **Moderate/severe primary immunodeficiency (aIRR 9.7, 95% CI 6.3–14.9),**
- **stem cell transplant (aIRR 11.0, 95% CI 6.8–17.6)**
- **recent treatment for haematological malignancy (aIRR 10.6, 95% CI 9.5–11.9).**

Results were similar for COVID-19 ICU admissions and deaths.

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Evans RA et al. The Lancet Regional Health - Europe 2023

Early Treatment

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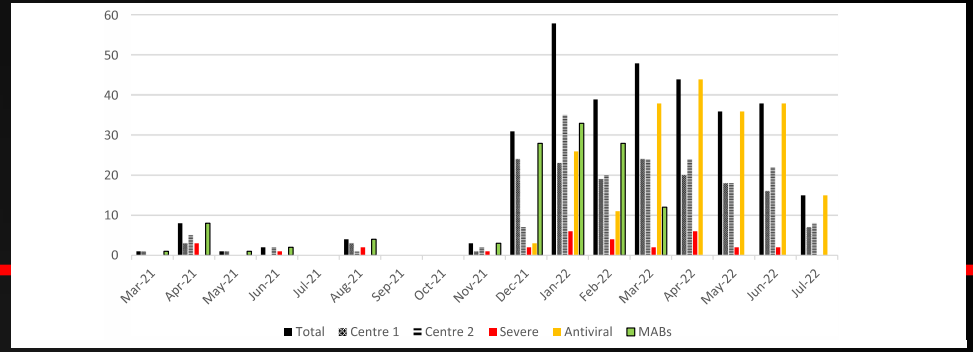
Outcome of early treatment of SARS-CoV-2 infection in patients with haematological disorders

Mikulska M, Testi D, Russo C et al. B J Haem 2023



Studio retrospettivo: HM 328 paziente da marzo 21-luglio2022

120 mABs, 208 antivirals, **mediana 2 gg dai sintomi**

End point composito: treatment failure (COVID-19 grave o decesso COVID-19 relato)

Rate of failure Omicron **7.8%** e 36.8 % pre Omicron, ma >> vs pop generale **1.2-1.4%**

AML/MDS (oltre età e < vaccino) associato a treatment failure e mortalità

NHL/CLL associato a shedding prolungato

TABLE 5 Multivariable analysis of predictors of COVID-19-associated mortality and overall 90-day mortality (all variables included in multivariate models are shown).

	Adjusted cause specific HR	95% CI	*p*
COVID-19 associated mortality			
Age, years	1.068	1.011–1.129	0.012
AML/MDS versus other diseases	3.564	1.055–12.039	0.041
Early treatment with antivirals versus MABs	0.434	0.124–1.518	0.191
Omicron period versus pre-Omicron	0.121	0.034–0.437	0.001
Overall 90-day mortality			
Age, years	1.056	1.015–1.099	0.007
AML/MDS versus other diseases	5.172	1.991–13.437	0.001
Omicron period versus pre-Omicron	0.237	0.076–0.742	0.013

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Vi sono pazienti che devono ricevere early combination therapy?

C’è un beneficio clinico e/o virologico?

SPAIN Calderon- Parra J, et al. 2024
Single-centre, prospective, cohort study (2022)
304 immunocompromised: 43 (14.1%) received sotrovimab plus antiviral, 261 (85.9%) monotherapy

COVID-19 progression at 90 days, defined as hospital admission or death due to COVID-19 C 0 vs M **4.6%** (p=.154)

C’è un beneficio clinico?

anti-S IgG <750 BAU/mL,
COVID-19 progression M 23.9% vs. C 0%, P=0.001),
COVID-related admission M 15.2% vs. C 0%, P=0.014)

Anti-S IgG titre <750 BAU/mL and anti-CD20 associated with higher risk of progression (OR 13.70, 95% CI 2.77-67.68; and OR 3.05, 95% CI 1.20-10.94,

Vi sono pazienti che devono ricevere early combination therapy?

C’è un beneficio clinico e/o virologico?

GERMANY Orth H, et al. 2024
Retrospective multicentre study (2022-2023)
144 IC, 96 antiviral + mAbs, 29 with 2 antiviral , 19 with 2 antiviral + mAbs.

C’è un beneficio virologico?

Highest risk for **prolonged viral shedding**:
- **HM (28.5%) (OR 3.5; 95% CI 1.2–9.9; *p* = 0.02)**

- Pts on **immunosuppressive medication following allogenic stem cell transplantation (OR 4.5; 95% CI 0.8–21.4; *p* = 0.04)**

Immunocompromised Patients with Protracted COVID-19: a Review of "Long Persisters"

Veronica Dioverti[1] · Sonsoles Salto-Alejandre[1,2] · Ghady Haidar[3]

Current Transplantation Reports (2022) 9:209–218

Proposed diagnostic criteria for protracted COVID- 19 in immunocompromised hosts (long persisters)

Criteria	
Virologic	Persistently positive SARS-CoV-2 PCR ≥ 21 days
Clinical	Persistent/relapsing symptoms (fever, dyspnea, hypoxemia) after extensive negative infectious work up
Imaging	Persistent/relapsing changes on chest-X ray or CT scan after extensive negative infectious work up
Host	Underlying immunocompromise: HCT, CAR T-cell recipient CLL, DLBCL, other lymphoma, or B-cell malignancy SOT Anti-CD19/20 therapy or other B/T cell targeted therapies Primary and acquired immunodeficiencies

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D.Abramo A et al. immunoCOVID team, Front Med 2024

Observational retrospective study in 88 B-cell depleted immunocompromised patients from 2 centers hospitalized with a **prolonged (> 21 days) or relapsed SARS-CoV-2 infection**

Monoterapia : RDV 10 o Mabs o CP 9

Combination:
RDV+mAb + CP: 45
RDV+ NMV/r: 11
RDV+NMV+mAb: 13

Reduced Lenght of hospitalization C vs M
21 vs. 30 days for LOS, *p* = 0.047

Time to negative SARS-CoV-2 NPS in the C vs M
23 vs. 40 days, *p* = 0.002

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

Clinical Infectious Diseases

MAJOR ARTICLE

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)

Day +14 75%

Day +30 73%

w/ Mabs higher response rate

p = 0.032

p=0.046

CLINICAL RESPONSE (alive, well and PCR negative)

Last FU 82%

higher n.vaccine doses

p=0.013

SAFETY (adverse events at last FU)

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

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Terapia di combinazione in prolonged shedding or persistent infection

Successful use of combination therapy including antiviral + Mabs or CP

Copin R, *et al.* Cell 2021
***Baum A, et al.* Science 2020**
Magyari F, *et al*. Ann Hematol 2022
Hashemian SMR, *et al*. Microbes, Inf and Chem 2022
Dioverti et al, OFID 2022
Bavaro DF et al Viruses 2023

Successful use of combination therapy including wo antivirals: RDV + NMV/r (+/- Mabs)

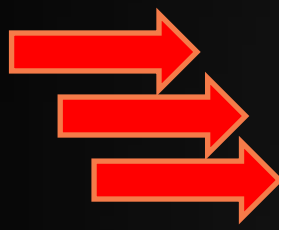
Pasquini et al. 2023
Mikulska et al. 2023
Meijer et al. 2024
Brosh-Nissimov et al. 2024
Lanzafame et al 2023
Dentone et al. 2023

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)

Successful Combination Treatment for Persistent Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Table 1. Local Protocol for the Treatment of Prolonged COVID-19 in Patients With Severe Immunosuppression at the Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

Treatment criteria
1. Underlying immunosuppression (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-who-are-immunocompromised.html)
2. Documented NPH SARS-CoV-2 PCR positivity during period 6 wk with high viral load (Ct value <25)
3. Documented inadequate response to antiviral monotherapy (assessed 10 d after end of treatment)
4. Clinical symptoms of COVID-19 alternatively planned for severe immunosuppressive treatment for underlying disease
5. No contraindications for planned treatment



Successful Combination Treatment for Persistent Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Table 1. Local Protocol for the Treatment of Prolonged COVID-19 in Patients With Severe Immunosuppression at the Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden

Treatment
10 days of treatment with remdesivir + nirmatrelvir/ritonavir (in case of remaining low Ct value [<25] on day 9, therapy might be extended to 14 d)
Nirmatrelvir: 150 mg 2 x 2, together with ritonavir: 100 mg 1 x 2, for 10 d. Nirmatrelvir/ritonavir dose should be adjusted in case of impaired renal function: GFR 30–60 mL/min: Nirmatrelvir: 150 mg 1 x 2, with ritonavir: 100 mg 1 x 2; GFR <30 mL/min: contraindicated
Remdesivir: 200 mg on day 1, then 100 mg once daily for a total of 10 d

Blennow O, et al CID 2023

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Sia strategie di combinazione, sia durata di trattamento

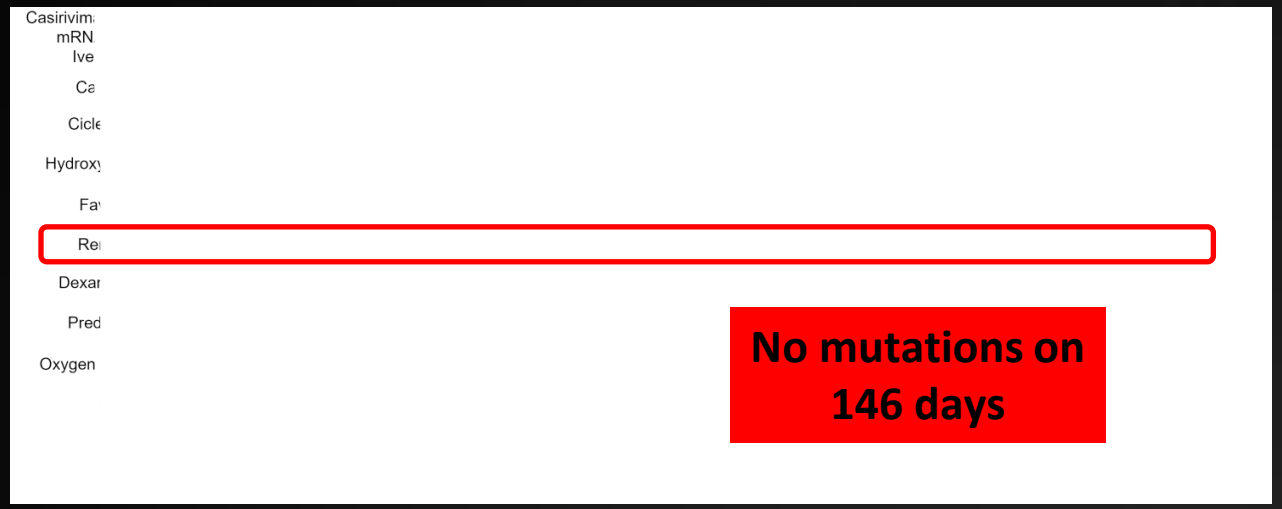
‘Extended course’ of Remdesivir and/or Nirmatrelvir/r

Martinez MA, et al. OFID 2022
Brown Li An K, et al JACI 2022
Blagdon S et al Research Square 2022
Ford ES, et al CID 2023
Blennow O, et al CIVD 2023
Trottier CA, et al. CID 2023

Focosi D, …Nicastri E et al. Antiviral combination therapies for persistent COVID-19 in immunocompromised patients. IJID 2023

Remdesivir: Rare emergence mutations

ACTT1 trial



No mutations on 146 days

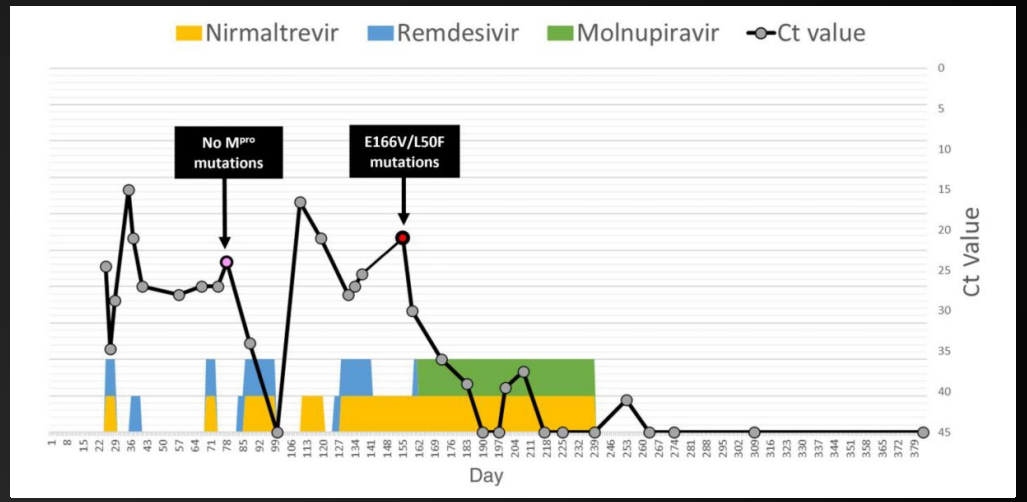
Japanese pt with follicular lymphoma (obinotuzumab) treated with 7 cycles of RDV (14 or 28 days), for 146 days of RDV

Nagai H et al Jap In f Dis 2022

NMV/r: fisrt case of resistance

JOURNAL ARTICLE

Nirmatrelvir Resistance—de Novo E166V/L50V Mutations in an Immunocompromised Patient Treated With Prolonged Nirmatrelvir/Ritonavir Monotherapy Leading to Clinical and Virological Treatment Failure—a Case Report



Zuckerman NS, CID Feb 2024

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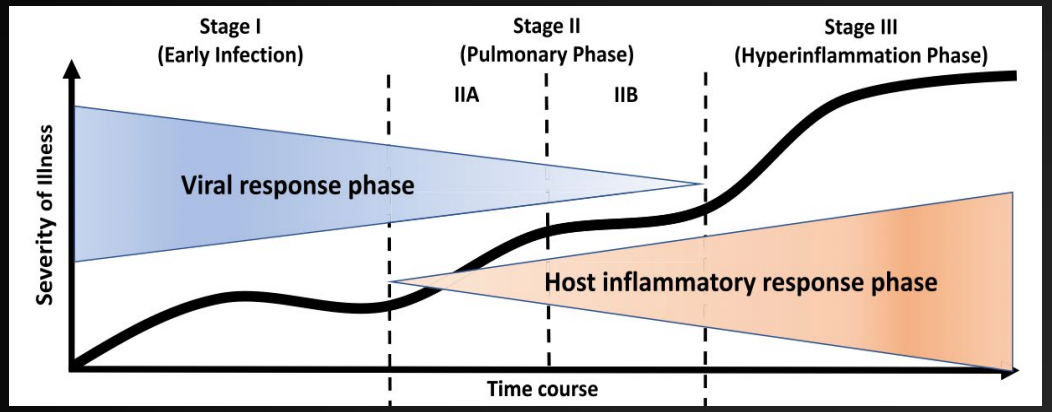
Maggio 2020 …

Diversi Stadi di malattia e Terapie

Maggio 2024 …

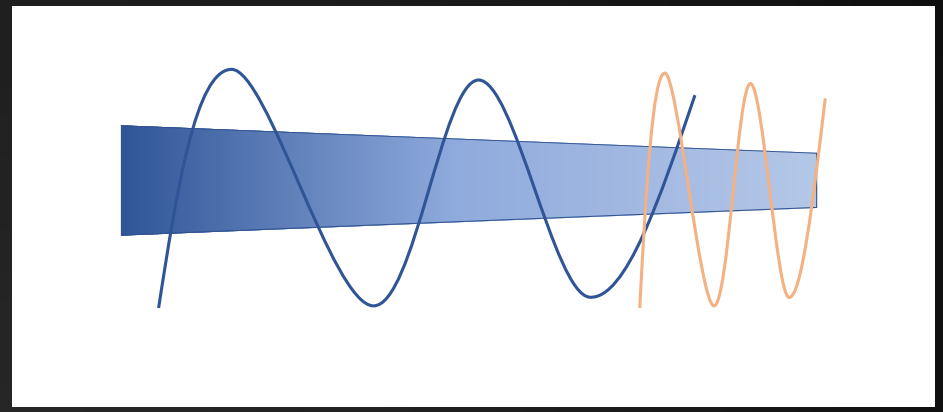
Fase virale → **Fase infiammatoria**



Siddiqi HK et al. The Journal of Heart and Lung Transplantation 2020

"Broadly-defined immunocompromised"*

Fase virale → **Fase virale** → **Fase virale** → **Fase infiammatoria**



Cesaro S et al. ECIL 9. Leukemia 2022

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*Lymphopenia, recent anti-CD20 therapy, CART therapy, hypogammaglobulinaemia and haematopoietic stem cell transplantation

The fast evolution of treatment during the COVID-19 pandemic……

2021

SITA & SIP 2021

2022

ESCMID
Nov 2021
Aug 2022

2023

WHO clinical guidelines Vers 13 Updated Jan 2023

IDSA guidelines. Vers 11 Updated Jun 2023

NIH COVID-19 Treatment guidelines Updated Oct 2023

No RCT for combination therapy

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Remdesivir effectiveness and safety profile have been assessed across a broad range of patient populations and disease severity

Non-hospitalized population

Reduces hospitalisation or all-cause of death vs placebo

Pts high risk of severe disease:
RCT: PINETREE

Hospitalized population

Shortens time to recovery vs placebo

Overall population:
- RCT: ACTT-1

Reduces disease progression vs placebo

Overall population:
- **RCT: ACTT-1**
- **Solidarity**

Reduces mortality vs placebo or Soc

Low flow oxygen:
- **RCT: ACTT-1**

Metanalyses
Supplemental oxygen
- **RCT Solidarity**
- **RWE**

No oxygen
- **RWE**

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The REDPINE Study: Efficcy and Safety of Remdesivir in People With Moderately and Severely Reduced Kidney Function Hospitalised for COVID-19 Pneumonia

Jose Ramon Santos,[1,*] Jason D. Goldman,[2] Katherine R. Tuttle,[3] J. Pedro Teixeira,[4] Yiannis Koullias,[5] Joe Llewellyn,[5] Yang Zhao,[5] Hailin Huang,[5] Robert H. Hyland,[5] Anu Osinusi,[5] Rita Humeniuk,[5] Henry Hulter,[6] Robert L. Gottlieb,[7] Dahlene N. Fusco,[8] Rita Birne,[9] Fernando F. Stancampiano,[10] Claudia R. Libertin,[10] Mark J. McPhail,[11] Meghan Sise[12]

[1]Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [2]Swedish Medical Center, Seattle, WA, USA; [3]Providence Inland Northwest Health, Spokane, WA, USA; [4]University of New Mexico Hospital, Albuquerque, NM, USA; [5]Gilead Sciences, Inc., Foster City, CA, USA; [6]University of California San Francisco, San Francisco, CA, USA; [7]Baylor University Medical Center and Baylor Scott & White Research Institute, Dallas, TX, USA; [8]Tulane University, New Orleans, LA, USA; [9]Centro Hospitalar de Lisboa Ocidental EPE, Lisbon, Portugal; [10]Mayo Clinic College of Medicine and Science, Jacksonville, FL, USA; [11]King's College Hospital, London, UK; [12]Massachusetts General Hospital, Boston, MA, USA.

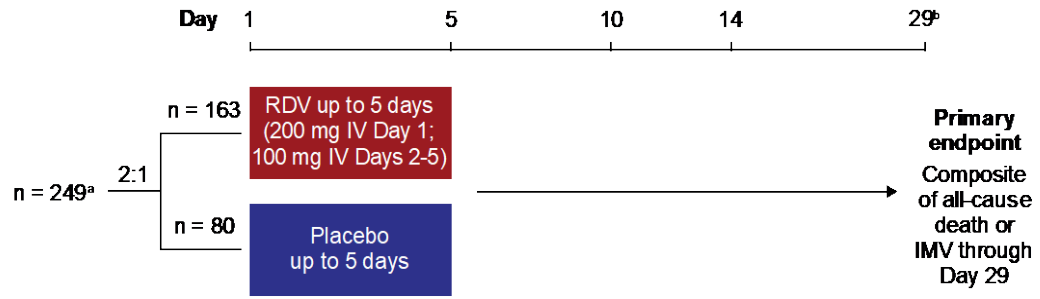
Poster 2635 33° ECCMID 2023

Studio GS-US-540-5912

- REDPINE was a Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre study conducted internationally at 55 centres across 5 countries (Brazil, Portugal, Spain, the United Kingdom, and the United States; EudraCT Registration Number: 2020-005416-22; ClinicalTrials.gov Identifier: NCT04745351)
- Eligible participants had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, were hospitalised with severe COVID-19, were aged ≥12 years, weighed ≥40 kg, had oxygen saturation ≤94% on room air or required oxygen supplementation, and had eGFR <30 mL/min/1.73 m^2 due to either CKD or AKI

RDV= 163 Placebo= 80

Figure 1. Study Design



Studio interrotto per problemi di fattibilità e sottodimensionato per end-point di efficacia primari

Conclusions:

- ✓ **ESRD or dialisis: No significant difference in all-cause death or IMV by Day 29 between the RDV and placebo groups;**
- ✓ **No dose adjustment is recommended in patients who have an eGFR <30 mL/min/1.73 m2, regardless of the need for dialysis**

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Genoa, Italy

Remdesivir Reduced Mortality in Immunocompromised Patients Hospitalized for Coronavirus Disease 2019 Across Variant Waves: Findings From Routine Clinical Practice

Essy Mozaffari,[1] Aastha Chandak,[2] Robert L. Gottlieb,[3,4,5,6] Chidinma Chima-Melton,[7] Stephanie H. Read,[8] Heng Jiang,[9] Mel Chiang,[1] EunYoung Lee,[1] Rikisha Gupta,[1] Mark Berry,[1] and Andre C. Kalil[10]

Clinical Infectious Diseases

MAJOR ARTICLE

August 2023

Retrospective Cohort

COVID19

Comparison of survival outcomes among immunocompromised patients hospitalized for COVID-19 and treated with remdesivir vs. not treated with remdesivir, across different variant waves of the pandemic

Remdesivir cohort: initiation of remdesivir upon hospital admission

n = 14,169

Non-remdesivir cohort: did not receive remdesivir during the hospitalization

n = 14,169

Immunocompromised adults hospitalized with a primary diagnosis of COVID-19

14-day all-cause in-hospital mortality

14

30% lower risk

p = <.0001

28-day all-cause in-hospital mortality

28

25% lower risk

p = <.0001

Dec 2020-Apr 2022

Immunocompromised patients are at high risk of COVID-19 mortality. Remdesivir treatment is associated with a significant reduction in 14- and 28-day mortality among immunocompromised patients hospitalized for COVID-19.

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ORIGINAL ARTICLE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Jennifer Hammond, Ph.D., Heidi Leister-Tebbe, B.S.N., Annie Gardner, M.P.H., M.S.P.T., Paula Abreu, Ph.D., Weihang Bao, Ph.D., Wayne Wisemandle, M.A., MaryLynn Baniecki, Ph.D., Victoria M. Hendrick, B.Sc., Bharat Damle, Ph.D., Abraham Simón-Campos, M.D., Rienk Pypstra, M.D., and James M. Rusnak, M.D., Ph.D., for the EPIC-HR Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

Feb 2022

Lower risk of mortality, disease progression and need for oxygen therapy; shorter time to achieving low viral burden during Omicron BA.2

A phase 2–3 double-blind,randomized, controlled trial symptomatic, unvaccinated, nonhospitalized adults at high risk for progression
to severe COVID-19 were assigned in a 1:1 ratio.
COVID-19–related hospitalization or death from any cause through day 28, viral load, and safety were evaluated.

Reduction in hospitalization and death at 28 days by 89% in unvaccinated patients

2020

2024

1st COVID-19 case HSM

Severe COVID-19 treatment

Vaccine

Early treatment

Prophylaxis

Combination treatment

Immunomodulants

Remdesivir

mAbs

Nirmatrelvir/r

Molnupiravir

In-hospital mortality

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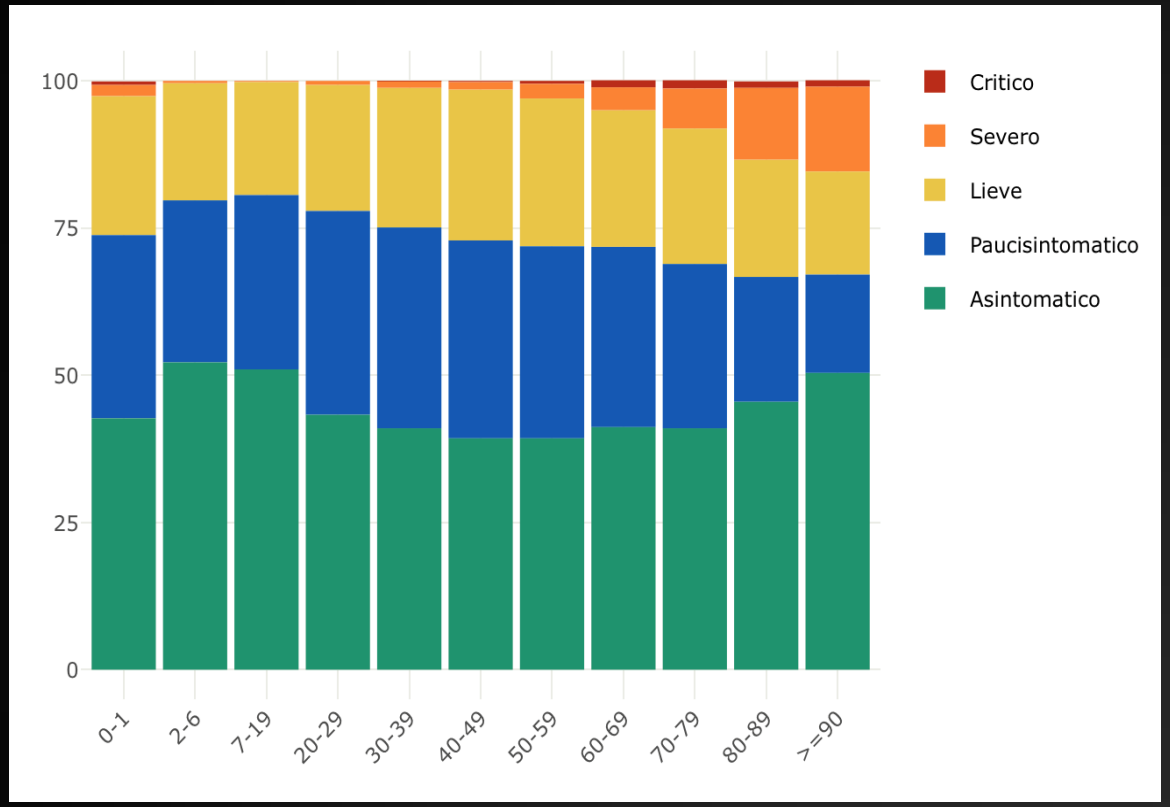
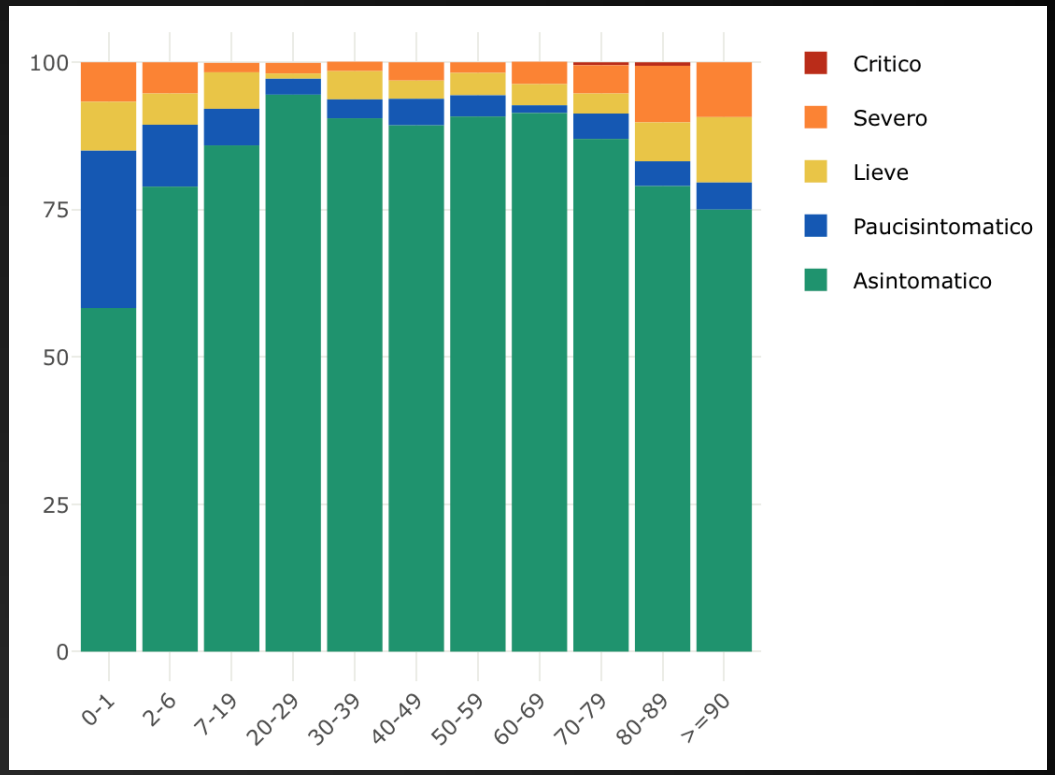
Courtesy off dott C. Sepulcri

Lo scenario è cambiato….

Settembre 2021



Aprile 2024



…. per le vaccinazioni, per l'utilizzo di terapie precoci…

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Ospedale San Martino
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Identificare e trattare precocemente pts con COVID-19 lieve/moderato sul territorio e in Ospedale

Creare network tra Ospedale e territorio e intraospedaliero.

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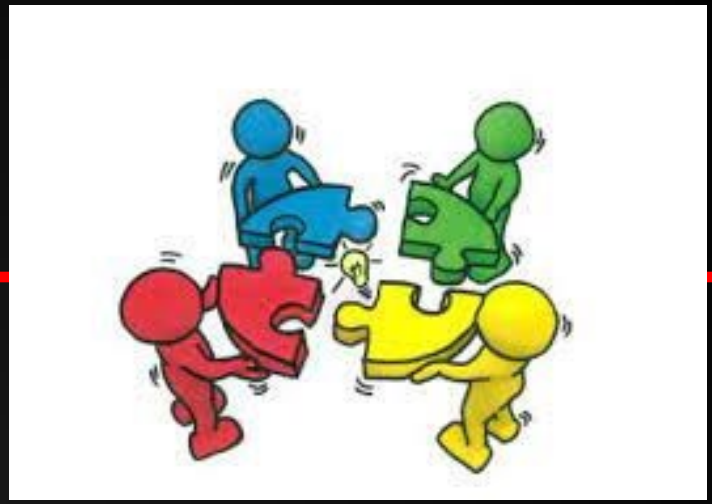
The outcome of our best practice…. HSM



1st January 2022 – 30 th September 2023	
Oral antiviral treatment	N= 630 patients
Early treatment Remdesivir 3 days	N= 850 patients
	N= 400 in out-patient clinic

- Infettivologi, pneumologi, internisti, medici PS e area critica possono prescrivere remdesivir e nirmatrelvir/ritonavir
- Medici di famiglia: nirmatrelvir/r + fast track (telefono > DH) con DH o reparto malattie infettive per remdesivir early treatment

A model of:

-- early access to antiviral therapy

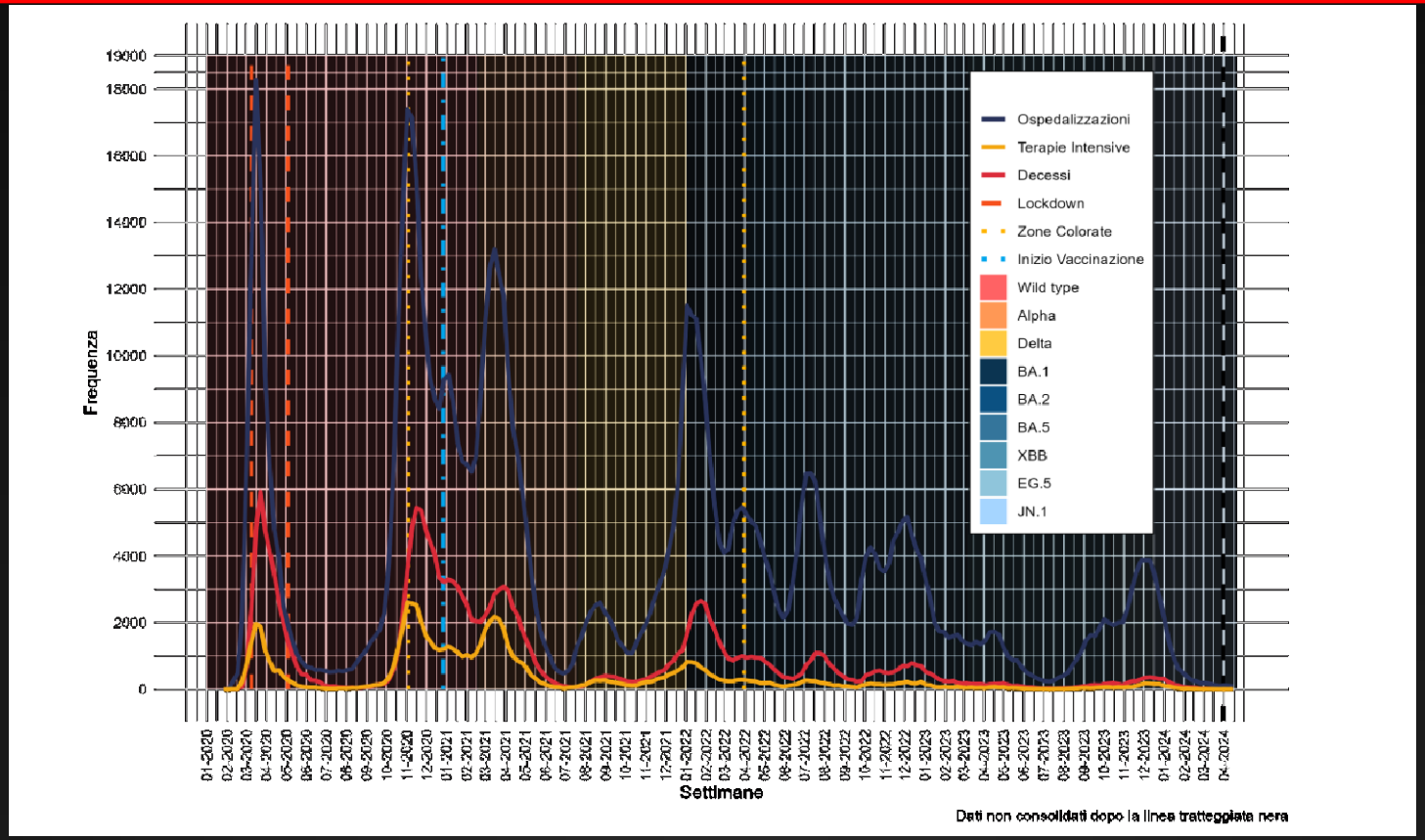
-- easy way to prescription

A path to avoid the overcrowding in Emergency Dpt

Lo scenario è cambiato….

ISS Aprile 2024

2020 → 2024



…. E per le differenti varianti di SARS-COV-2 …

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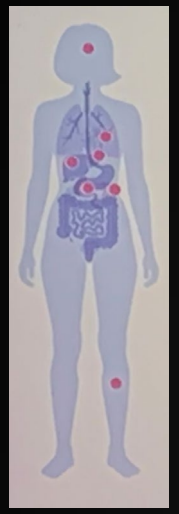
The clinical picture of COVID-19 has evolved as variants have emerged



Wild Type Dec 2019

- ✓ High death rates
- ✓ Extrapulmonary manifestations

Hammer MM Acad Radiol 2023
Mao R, Lancet Gastroent Hepatol 2020
Guo T, JAMA Cardiol 2020
Mao L, JAMA Neurol 2020

Delta from Dec 2020

- ❖ Higher rate of hospitalisation in young adults vs previous era
- ❖ Higher rates of trombosis than previous era

Gottlieb R , ECIM 2023
Manzur- Paneda K, J Vasc Surg 2022

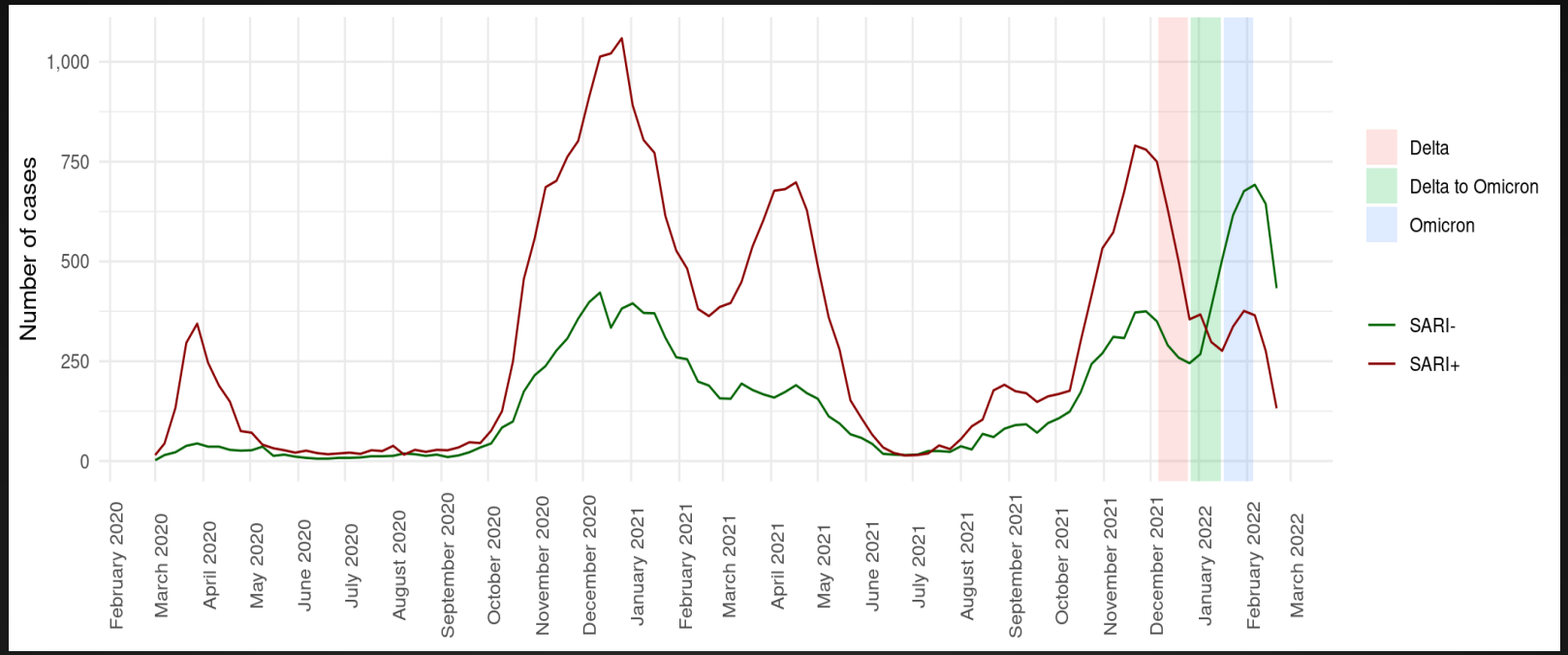
Omicron from Nov 2021

- **Highly transmissible**
- Immune escape from early vaccines and nAbs
- **Fewer COVID-19 pneumonia cases than Alpha and Delta era** (significantly higher vaccination rate in Omicron era than previous wave group, $p < 0.001$)
- Extrapulmonary manifestations in 16.4% pts (vax 58%)

ECDC 2023
Willell BJ, Nat microbiol 2022
Ito N, Respir Investig 2022
Niu J, Healthcare (Basel) 2023

Characteristics and outcomes of COVID-19 patients during B.1.1.529 (Omicron) dominance compared to B.1.617.2 (Delta) in 89 German hospitals

COVID-19 cases since beginning of 2020 stratified by encoded SARI



The coloured bars represent three phases with respect to the dominating SARS-CoV-2 variants. SARI = Severe Acute Respiratory Infection; SARI- = COVID-19 without SARI; SARI+ = COVID-19 with SARI

Leiner et al. BMC Infect Dis 2022

Characteristics of hospitalized patients with SARS-CoV-2 infection during successive waves of the COVID-19 pandemic in a reference hospital in Spain

200 consecutively admitted hospital patients from each wave prospectively enrolled

Patients in the fifth wave were considerably younger than before, and **the mortality rate fell from 22.5 to 2.0%.**

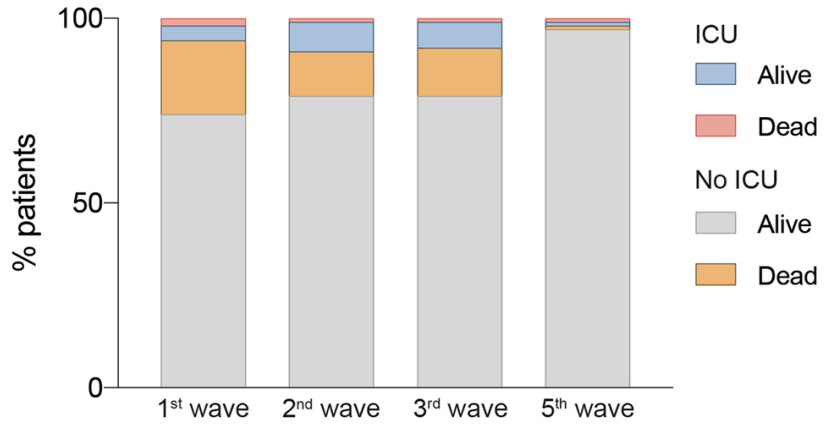


Figure 1. Percentage of patients admitted to the Intensive Care Unit (ICU) or not, in each of the waves studied.

Admissions to the ICUdecreased from 10 to 2%.

Patients in the fifth wave had fewer comorbidities.
The age of the patients who died was higher than those who survived.

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Iftimie S, et al. Sci Rep, 2022

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Genoa, Italy

Real life experience through different COVID-19 waves in an Italian Hospital: the challenge of facing a continuous evolving enemy

Silvia Dettori [1], Giorgia Brucci [1], Federica Portunato [2], Chiara Dentone [2], Marta Ponzano [3], Laura Magnasco [2], Michele Mirabella [2], Federica Magne [2], Emanuele Delfino [2], Elisa Balletto [2], Antonio Vena [2, 1], Daniele Roberto Giacobbe [2, 1], Malgorzata Mikulska [2, 1], Antonio Di Biagio [2, 1], Bianca Bruzzone [4], Alessio Signori [3], Paolo Pelosi [5, 6], Matteo Bassetti [2, 1]

1 Department of Health Sciences (DISSAL), University of Genoa, Italy - Genoa (Italy), 2 Infectious Di... n Martino, Genoa, Italy - Genoa (Italy), 5 Anesthesia and Intensive Care, IRCCS Ospedale Policlinico San Martino, Genoa, Italy - Genoa (Italy), 6 Department of Surgica...

EW0408
Copenhagen, Denmark
15–18 April 2023
33rd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Objective: To describe characteristics and outcome predictors of patients admitted in an Infectious Disease Unit (University Hospital, Genoa, Italy) during the four pandemics waves.

1040 pts, retrospective data were collected (Feb 2020 – Jan 2022) considering timeframe of different waves

Patients with at least one comorbidity were 786 (76%)
Immunodeficiency conditions were present in 142(14%)

During different COVID-19 waves, **length of hospital stay, positive airway pressure ventilation, severe respiratory failure and ICU admission significantly decreased.**

Table 1 Characteristics of patient population through the four COVID-19 waves

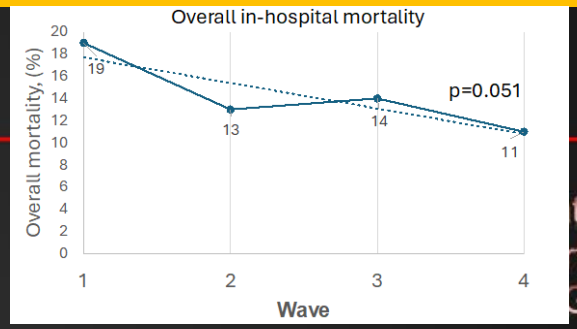
	Overall N=1040	Wave 1 N=250(24%)	Wave 2 N=238(23%)	Wave 3 N=346(33%)	Wave 4 N=206(20%)	p-value
Age, mean(SD)	65.58(14.45)	65.85(14.53)	65.43(13.99)	66.16(13.85)	64.47(15.82)	0.594
Male sex, N(%)	648(62%)	162(65%)	153(64%)	204(59%)	129(63%)	0.437
Comorbidity, N(%)	786(76%)	180(72%)	169(71%)	286(83%)	151(73%)	**0.002**
Immunodeficiency and/or oncologic condition, N(%)	141(14%)	38(15%)	35(15%)	45(13%)	23(11%)	0.585
Vaccination, N(%) [N=1038]	102(10%)	0(0%)	0(0%)	25(7%)	77(38%)	**<0.001**
Days from symptoms to hospitalization, mean(SD) [1012]	6.84(5.32)	7.06(6.53)	6.63(6.14)	6.99 (4.31)	6.56(4.07)	0.231
PaO2/FiO2 at admission<200, mean(SD) [N= 876]	206(24%)	66(32%)	68(30%)	42(16%)	30(17%)	**<0.001**
ICU admission, N(%)	153(15%)	59(24%)	32(13%)	33(10%)	29(14%)	**<0.001**
Steroids, N(%)	881(85%)	172(69%)	220(92%)	305(88%)	184(89%)	**<0.001**
Remdesivir, N(%)	501(48%)	8(3%)	128(54%)	227(66%)	138(67%)	**<0.001**
Monoclonal Antibodies, N(%)	127(12%)	0(0%)	0(0%)	23(7%)	104(50%)	**<0.001**
Anti-inflammatory therapies, N(%)	187(18%)	110(44%)	0(0%)	21(6%)	56(27%)	**<0.001**
Days to nasal swab negativity, mean(SD) [N=824]	17.50(16.97)	17.94(11.88)	16.06(10.02)	19.10(25.58)	16.02(7.60)	0.228
Lenght of hospitalization days, mean(SD)[N=907]	14.62(14.45)	20.47(15.14)	15.40(14.23)	12.42(14.36)	10.73(11.76)	**<0.001**
Oxygen Support						
CPAP and/or HFNC, N(%)	370(36%)	139(56%)	82(34%)	85(25%)	64(31%)	**<0.001**
VM, N(%)	780(75%)	209(84%)	189(79%)	250(72%)	132(64%)	**<0.001**
RES, N(%)	439(42%)	131(52%)	96(40%)	135(39%)	77(37%)	**0.002**
Positive SARS-CoV-2 serology, N(%) [N=845]	348(41%)	74(47%)	88(44%)	79(27%)	107(56%)	**<0.001**

In multivariable analysis:
- ✓ age (HR 2.80, 95%CI 2.28-3.43 for 10-year increase)
- ✓ comorbidities (HR 2.25, 95%CI 1.06-4.76)
- ✓ immunodepression (HR 1.73, 95%CI 1.13-2.65)

significantly associated with worst outcome in all waves

- ✓ positive SARS-CoV-2 serology was associated with a better outcome (HR 0.63, 95%CI 0.42-1.03)

In hospital mortality rate gradually decreased over time from 17% to 11%.



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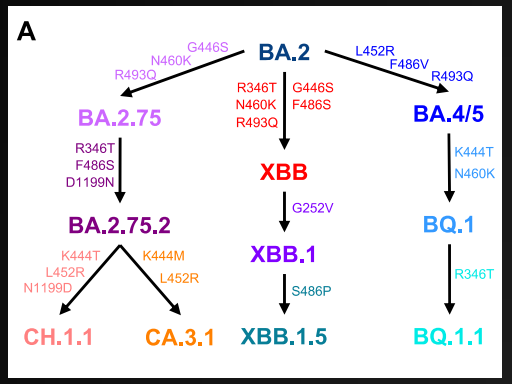
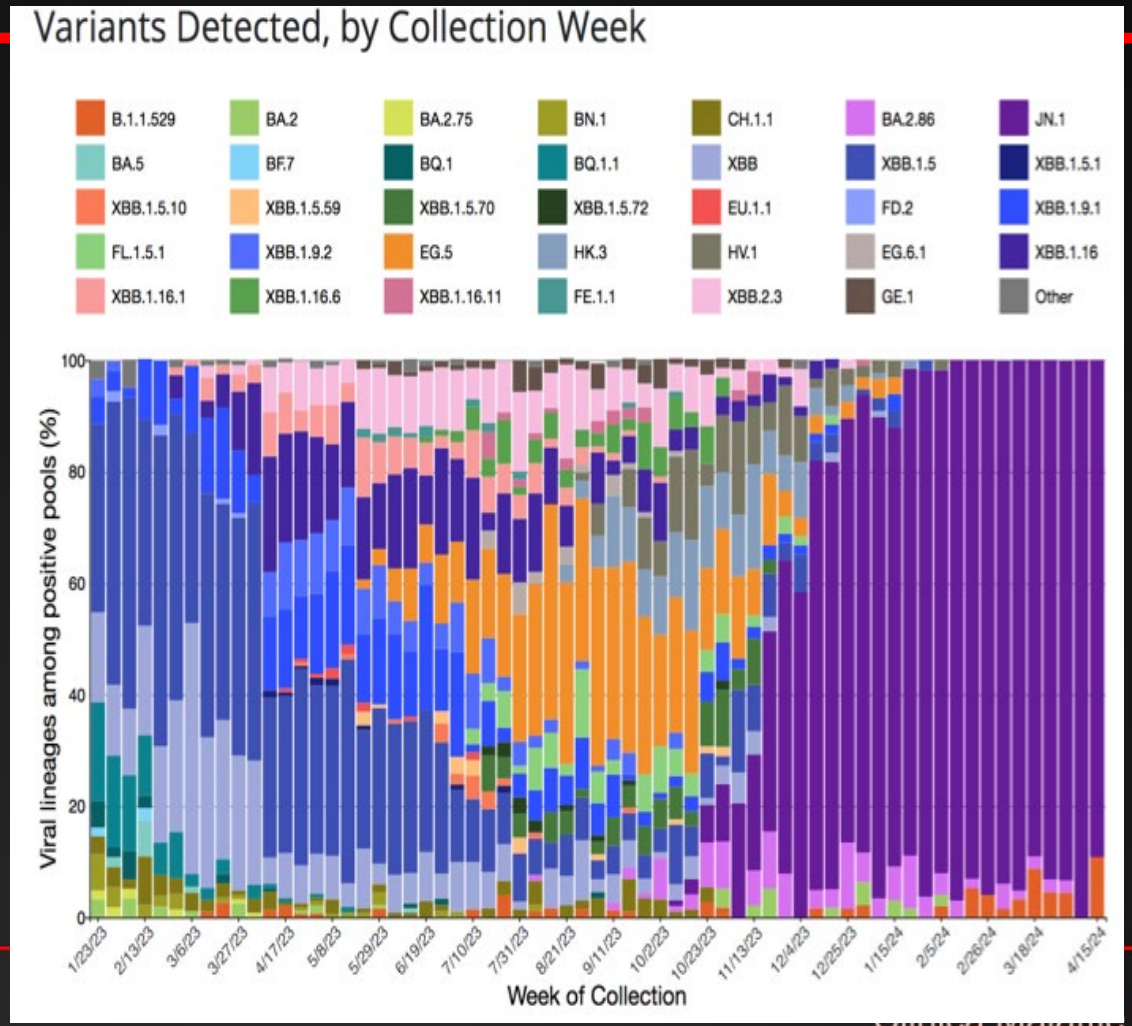
Submitted, in revision

SARS-COV-2: Variabilità sincrona delle varianti





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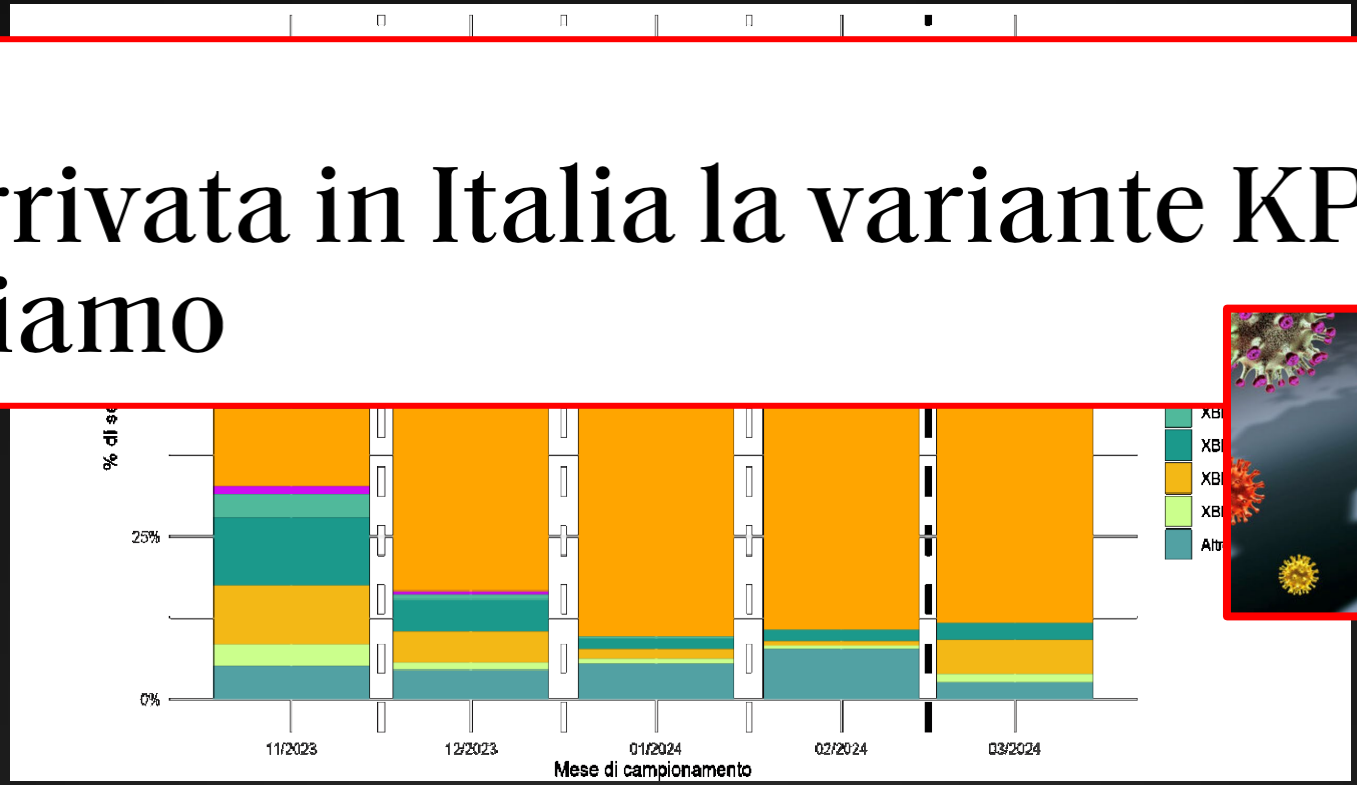
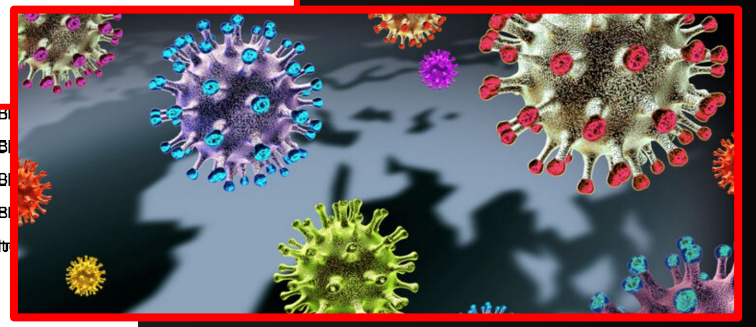
CDC 2024, May 07 Data tracker

Monitoraggio delle varianti di SARS-CoV-2

ITALIA

Covid: è arrivata in Italia la variante KP.2, cosa sappiamo





ISS marzo-aprile 2024

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Virological characteristics of the SARS-CoV-2 KP.2 variant

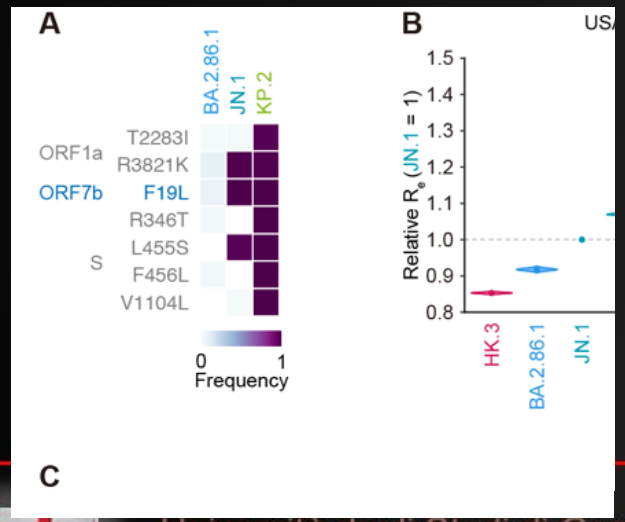
Yu Kaku, Keiya Uriu, Yusuke Kosugi et al.The Genotype to Phenotype Japan (G2P-Japan) Consortium, Jumpei Ito, Kei Sato
bioRxiv preprint version April 26,2024

Più trasmissibile

Relative effective reproduction number (Re) of KP.2 is 1.22-, 1.32-, and 1.26-times higher than JN.1 in USA, United Kingdom, and Canada

Più immunoevasiva

KP.2 shows the most significant resistance to the sera of monovalent XBB.1.5 vaccine without infection (3.1-fold) as well as those who with infection (1.8-fold).



These results suggest that KP.2 has higher viral fitness

Vince il più efficiente e non il più forte

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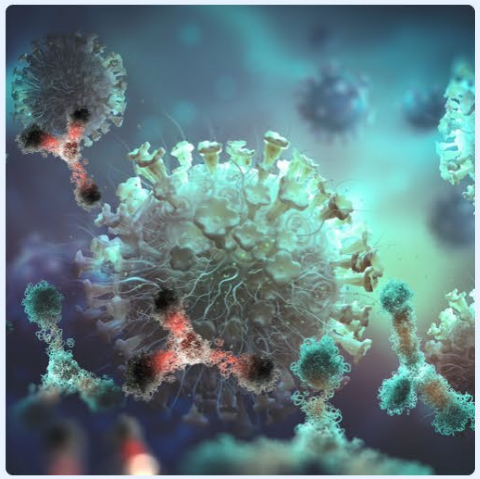

ETF recommends updating COVID-19 vaccines to target new JN.1 variant

Share

30 April 2024

Updated vaccines will help maintain protection against disease as virus continues to evolve.

News | Human | COVID-19 | Vaccines

EMA's Emergency Task Force (ETF) has recommended updating COVID-19 vaccines to target the new SARS-CoV-2 variant JN.1 for the 2024/2025 vaccination campaign.

Vaccinazione XBB .1.5 ha una copertura 2.5 volte inferiore versus JN1

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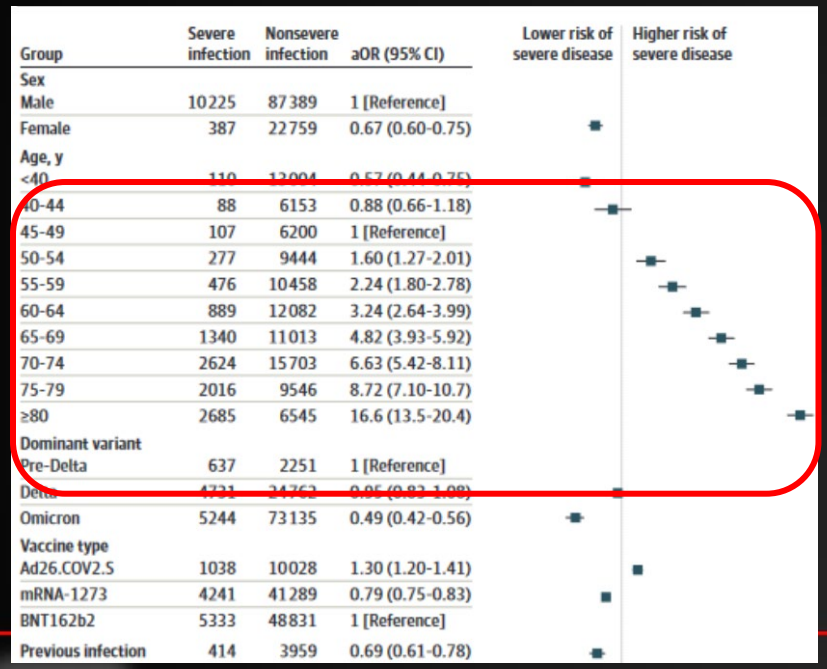
Viewpoint

September 12, 2023

COVID-19 in the Fall of 2023—Forgotten but Not Gone

5 maggio 2023: End of Emergency….but not COVID-19

Del Rio C and Malani PN, JAMA 2023

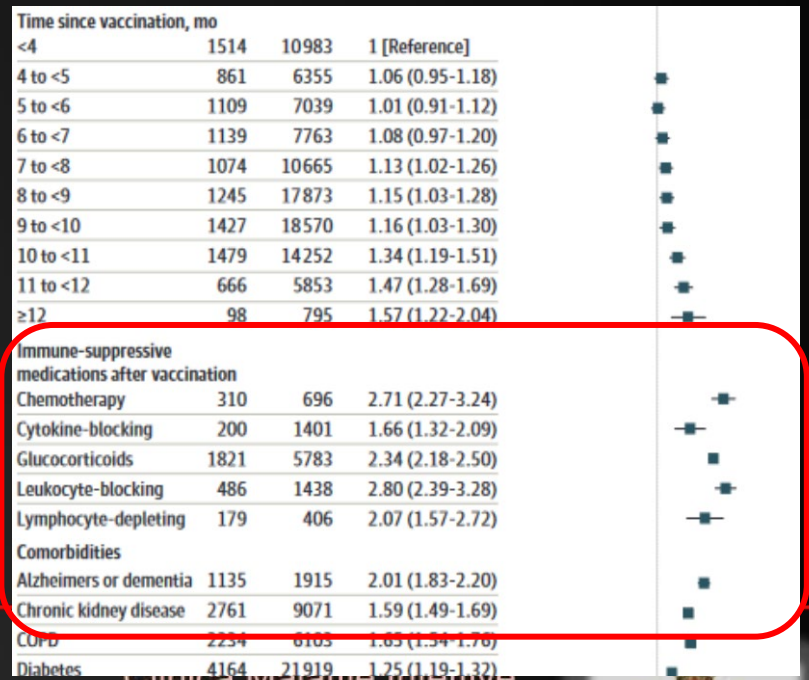


Group	Severe infection	Nonsevere infection	aOR (95% CI)
Sex			
Male	10225	87389	1 [Reference]
Female	387	22759	0.67 (0.60-0.75)
Age, y			
<40	110	13094	0.57 (0.44-0.75)
40-44	88	6153	0.88 (0.66-1.18)
45-49	107	6200	1 [Reference]
50-54	277	9444	1.60 (1.27-2.01)
55-59	476	10458	2.24 (1.80-2.78)
60-64	889	12082	3.24 (2.64-3.99)
65-69	1340	11013	4.82 (3.93-5.92)
70-74	2624	15703	6.63 (5.42-8.11)
75-79	2016	9546	8.72 (7.10-10.7)
≥80	2685	6545	16.6 (13.5-20.4)
Dominant variant			
Pre-Delta	637	2251	1 [Reference]
Delta	4731	34763	0.85 (0.82-1.08)
Omicron	5244	73135	0.49 (0.42-0.56)
Vaccine type			
Ad26.COV2.S	1038	10028	1.30 (1.20-1.41)
mRNA-1273	4241	41289	0.79 (0.75-0.83)
BNT162b2	5333	48831	1 [Reference]
Previous infection	414	3959	0.69 (0.61-0.78)

Lower risk of severe disease

Higher risk of severe disease

The main risk factor
for severe COVID-19
<u>also in vaccinated patients</u>
is age and
immune suppressive therapy



Time since vaccination, mo			
<4	1514	10983	1 [Reference]
4 to <5	861	6355	1.06 (0.95-1.18)
5 to <6	1109	7039	1.01 (0.91-1.12)
6 to <7	1139	7763	1.08 (0.97-1.20)
7 to <8	1074	10665	1.13 (1.02-1.26)
8 to <9	1245	17873	1.15 (1.03-1.28)
9 to <10	1427	18570	1.16 (1.03-1.30)
10 to <11	1479	14252	1.34 (1.19-1.51)
11 to <12	666	5853	1.47 (1.28-1.69)
≥12	98	795	1.57 (1.22-2.04)
Immune-suppressive medications after vaccination			
Chemotherapy	310	696	2.71 (2.27-3.24)
Cytokine-blocking	200	1401	1.66 (1.32-2.09)
Glucocorticoids	1821	5783	2.34 (2.18-2.50)
Leukocyte-blocking	486	1438	2.80 (2.39-3.28)
Lymphocyte-depleting	179	406	2.07 (1.57-2.72)
Comorbidities			
Alzheimers or dementia	1135	1915	2.01 (1.83-2.20)
Chronic kidney disease	2761	9071	1.59 (1.49-1.69)
COPD	2234	6165	1.65 (1.54-1.76)
Diabetes	4164	21919	1.25 (1.19-1.32)

Sun J et al JAMA Intern med 2022

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Dosi successive fino al 24/09/2023

Dose addizionale/richiamo (booster)

40.494.455

84,89 % della popolazione potenzialmente oggetto di dose addizionale o booster che ha ultimato il ciclo vaccinale da almeno 4 mesi

Booster immuno / 2ª dose booster

6.731.575

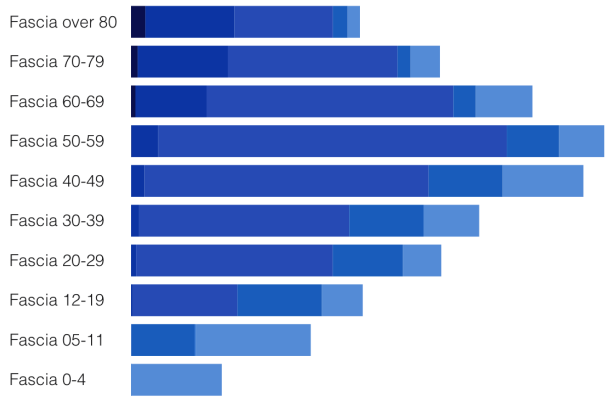
16,89 % della popolazione potenzialmente oggetto di dose booster/2ª booster cha ha ultimato il ciclo vaccinale da almeno 4 mesi

3ª dose booster

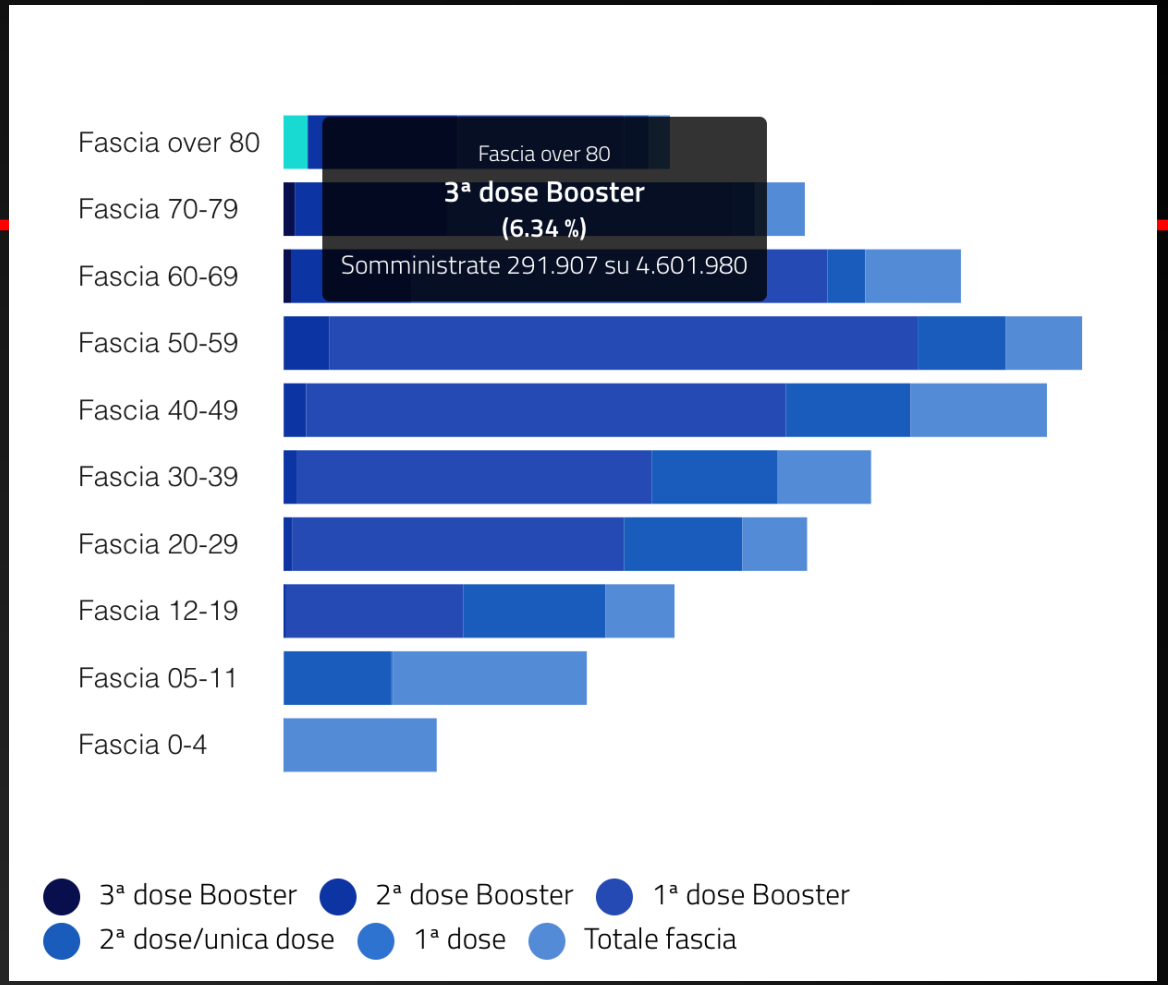
527.680

8,61 % della popolazione potenzialmente oggetto di 3ª dose booster cha ha ultimato il ciclo vaccinale da almeno 4 mesi

Ministero della salute.gov/vaccinazionecovid



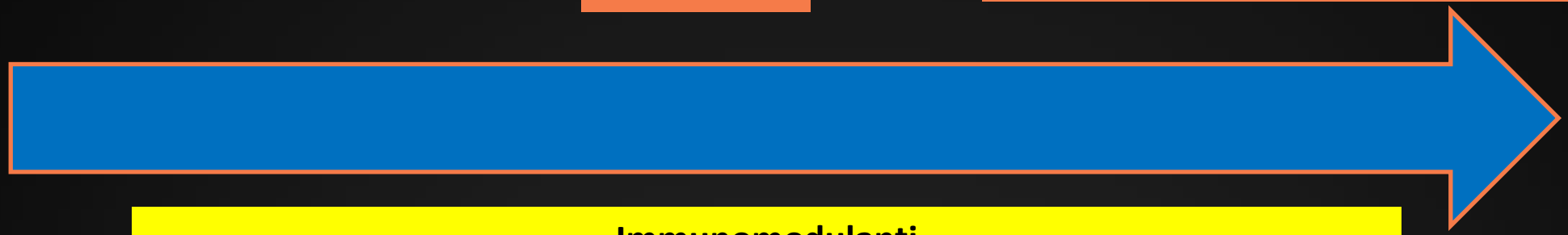
Over 80 anni:
3° dose booster 6,3%



The Next Future….

May 2024

Ottobre 2024…….Gennaio 2025



Immunomodulanti

Remdesivir

Nirmatrelvir/ritonavir

Terapia di combinazione

Nuovi mAbs Pre-esposizione

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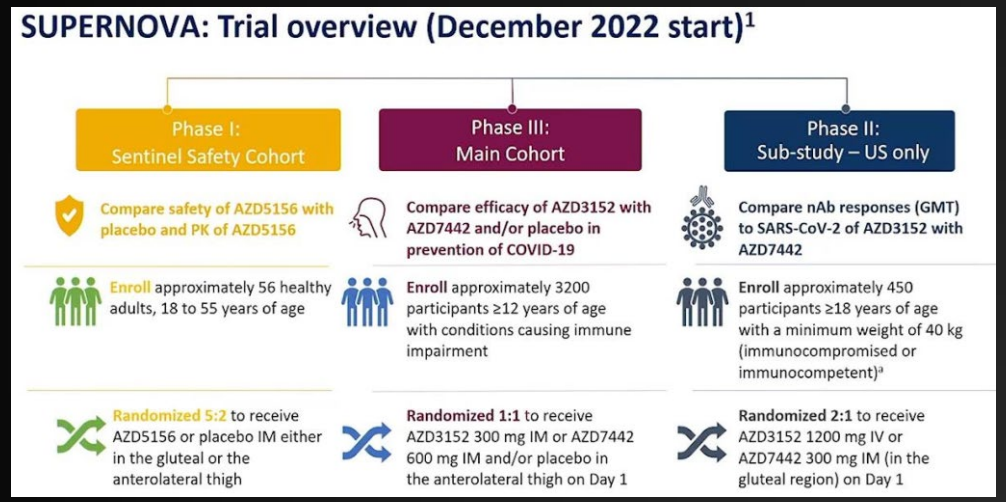
U.S. National Library of Medicine
ClinicalTrials.gov

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



Phase III RCT
AZD3152
Participants with immune impairement

Uso compassionevole in Francia

AZD5156
(cilga+AZD3152)

AZD7158
(AZD3152+AZD3959)
Under evaluation
EMA

gli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

ica Malattie Infettive
San Martino IRCCS
Genoa, Italy

INVIVYD

March 2024 FDA granted EUA

Invivyd Announces FDA Authorization for Emergency Use of PEMGARDATM (Formerly VYD222) for Pre-exposure Prophylaxis (PrEP) of COVID-19

Data from the CANOPY clinical trial along with ongoing in vitro neutralizing activity against major SARS-CoV-2 variants, including JN.1 (and XBB.1.5 and EG.5.1)

CANOPY is an ongoing Phase 3 clinical trial of VYD222 (PEMGARDA) for the pre-exposure prophylaxis of COVID-19 which enrolled adults ≥18 years of age in two cohorts.

Cohort A is a single-arm, open-label trial in adults who have moderate-to-severe immune compromise (n=306);

Cohort B is a 2:1 randomized, placebo-controlled trial in which adults who do not have moderate- to-severe immune compromise received VYD222 (n=317) or placebo (n=162).

Dosage 4500 mg ev > 1 h (+ dose at 3 months)

A hypersensitivity or infusion-related reaction in 9% and **anaphylaxis was observed in four of 623 (0.6%) participants in CANOPY, all in Cohort A.**

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The Medical Letter

Because the source matters.

The Medical Letter on Drugs and Therapeutics

FROM ISSUE 1702

May 13, 2024

COVID-19 Update: An EUA for Pemivibart (Pemgarda) for Pre-Exposure Prophylaxis

Download PDF: US English

The FDA has issued an Emergency Use Authorization (EUA) for the long-acting investigational IV monoclonal antibody pemivibart (*Pemgarda* – Invivyd) for pre-exposure prophylaxis of COVID-19 in persons ≥12 years old (weight ≥40 kg) who have moderate to severe immune compromise and are unlikely to respond adequately to COVID-19 vaccination (see Table 1).[1] *Pemgarda* is the only drug that is currently authorized in the US for pre-exposure prophylaxis of COVID-19. Tixagevimab/cilgavimab *(Evusheld)* was previously available under an EUA for this indication, but it lacks activity against currently circulating SARS-CoV-2 variants.[2]

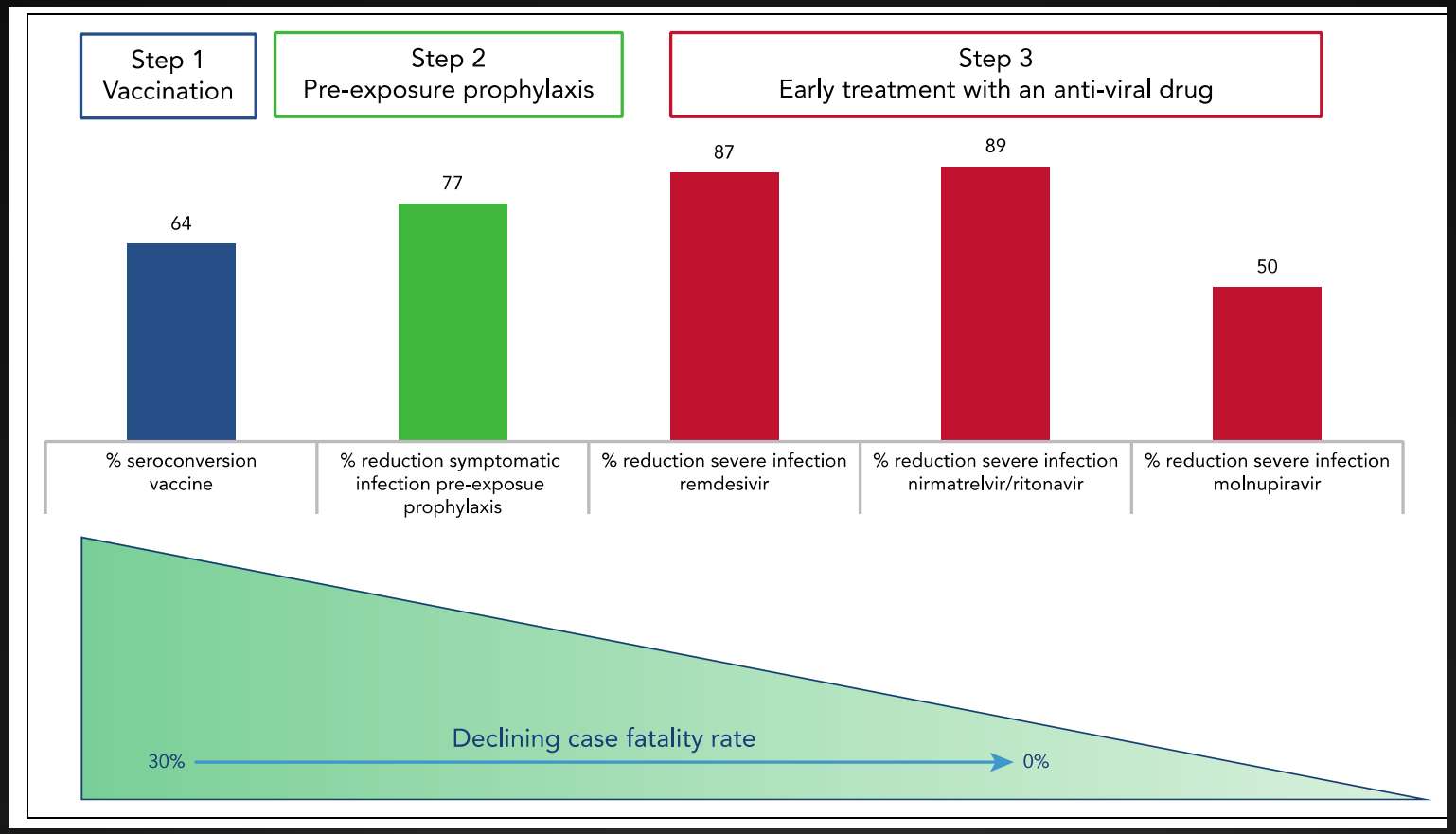
Table 1. Some Immunocompromising Conditions[1]

- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection
- Active treatment for a solid-tumor or hematologic malignancy
- Hematologic malignancy associated with poor vaccine response (e.g., acute leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma)
- Use of immunosuppressive therapy after a solid-organ or islet transplant
- Receipt of CAR T-cell therapy or hematopoietic stem cell transplant within previous 2 years
- Active treatment with other immunosuppressive or immunomodulatory drugs, such as high-dose corticosteroids (≥20 mg/day of prednisone or equivalent for ≥2 weeks) and tumor necrosis factor (TNF) inhibitors

1. FDA. Fact sheet for healthcare providers: Emergency Use Authorization for Pemgarda (pemivibart). March 2024. Available at: https://bit.ly/3Q3K5AL. Accessed April 25, 2024.

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

Scarfò L and Cuneo A. Blood 2023



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COVID-19: 4 anni dopo
Cosa possiamo fare ancora?

1. Adattarsi al cambiamento supportato da evidenze scientifiche

2. Individuare e trattare precocemente i pazienti a rischio

3. Modello vaccinazione ospedaliera e intrareparto

4. Profilassi pre esposizione (appena disponibile)

5. Considerare sempre oltre a virus e varianti, anche i fattori di rischio dell'ospite per una tailored therapy (quale, quando e per quanto tempo)

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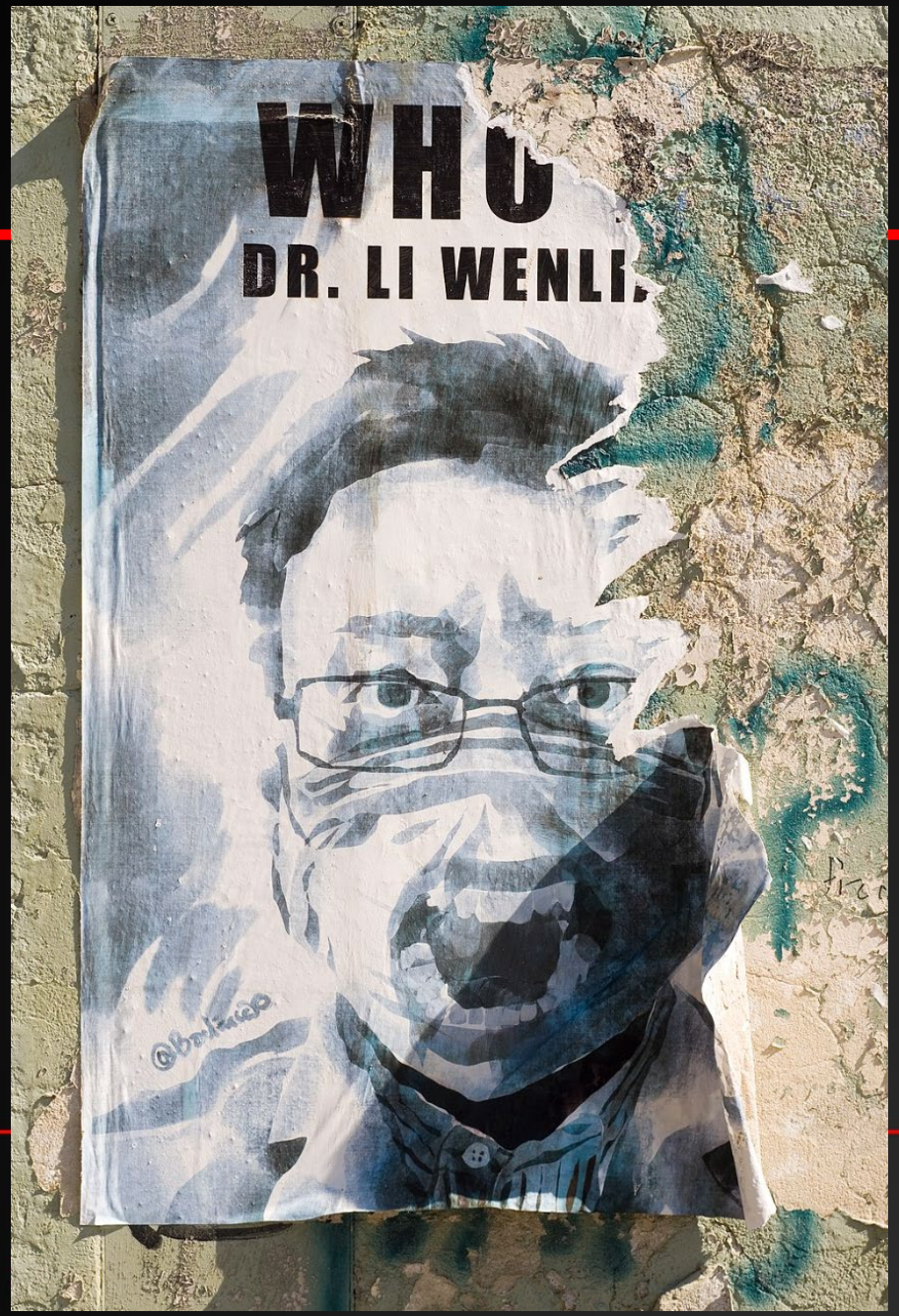

Li Wenliang (李文亮; Beizhen 12/10/1985-Wuhan 7/02/2020)
oculista cinese presso il Wuhan Central Hospital

30 dicembre 2019 inviò un messaggio ai colleghi medici in una chat di gruppo avvisandoli di indossare DPI per un'infezione che assomigliava molto, troppo alla SARS.

Fu accusato dalle autorità cinesi per aver diffuso commenti falsi
Il dott. Li contrasse la polmonite nel gennaio 2020
e morì all'età di 34 anni.

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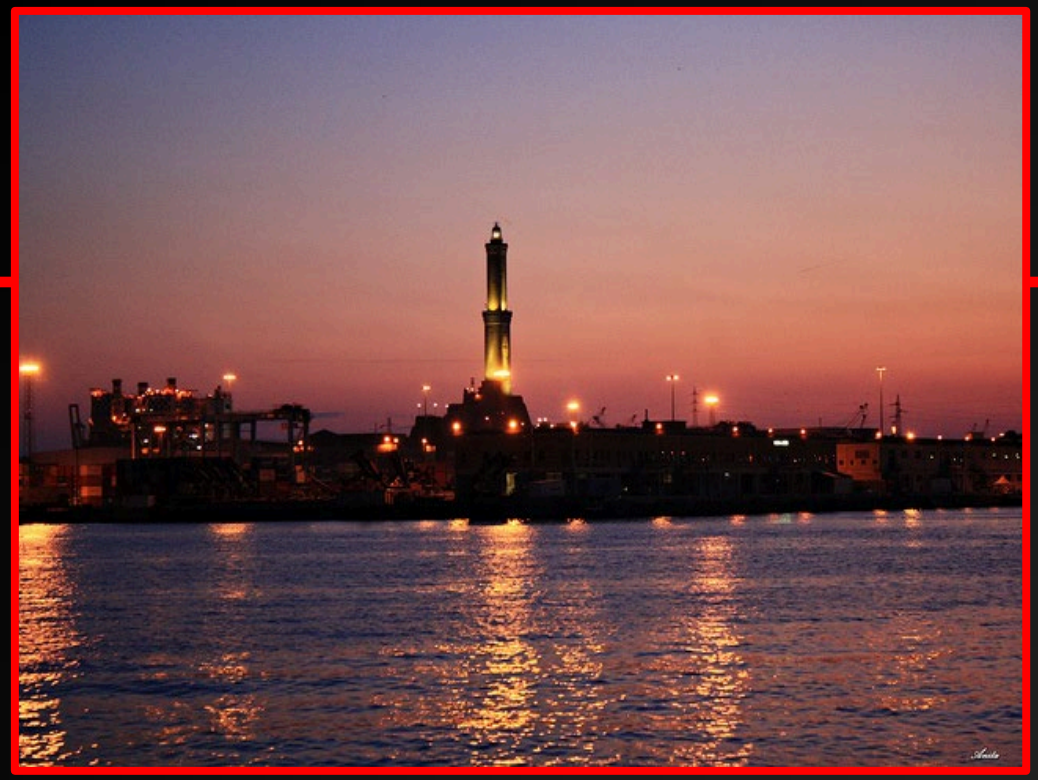

Grazie per l'attenzione….

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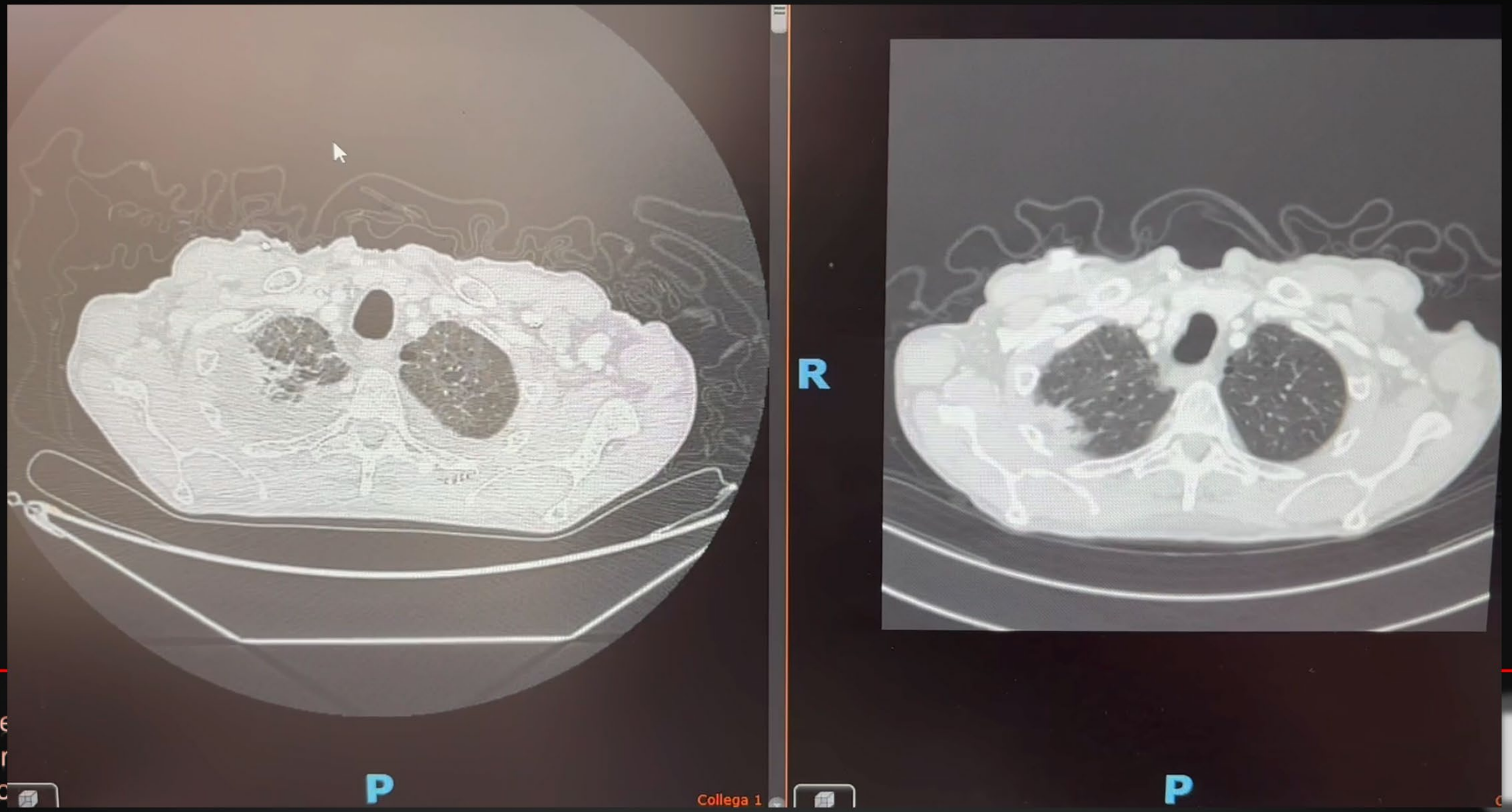
Uomo di 74 aa, 09/22 LNH (follicolare 3Ain remissione) PET 01/23 neg, mantenimento obinotuzumab (ultima somm 09.23).
4 dosi vaccinali. 08/2023 infezione paucisintomatica non trattata. 11/23 febbre e tosse. TNF negativi. 03/24 BAL positivo SARS-CoV-2 >>> HFNC

28.02.2024: estesi addensamenti a vetro smerigliato con consolidazione apicale al lobo sup destro
versamento pleurico bilaterale

15.03.2024: sfumate aree a vetro smerigliato in netta riduzione rispetto alla TC di febbraio
Non più dimostrabile versamento pleurico bilaterale



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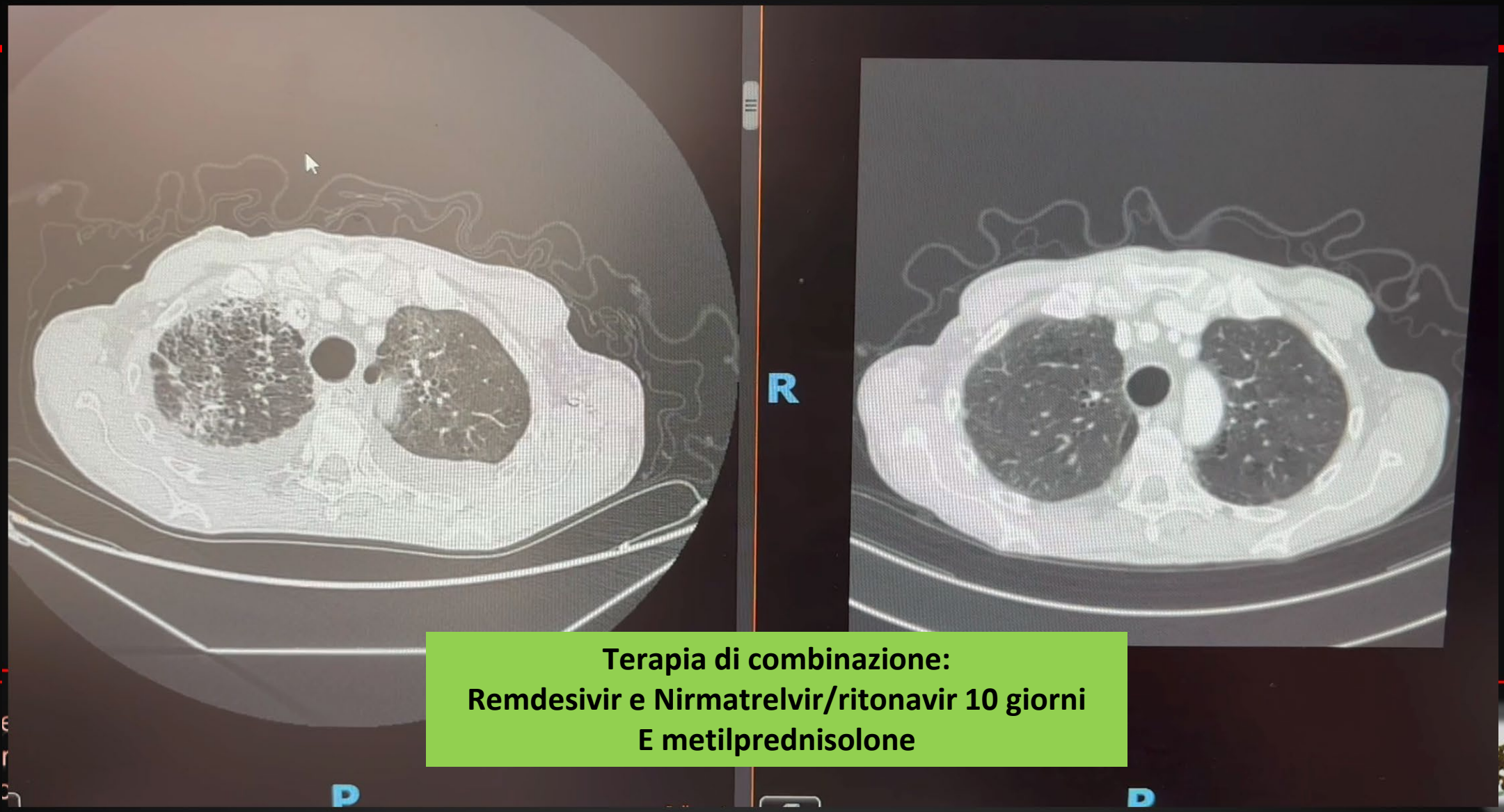


Terapia di combinazione:
Remdesivir e Nirmatrelvir/ritonavir 10 giorni
E metilprednisolone

Triple antiviral treatment for COVID-19 in an immunocompromised patient

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

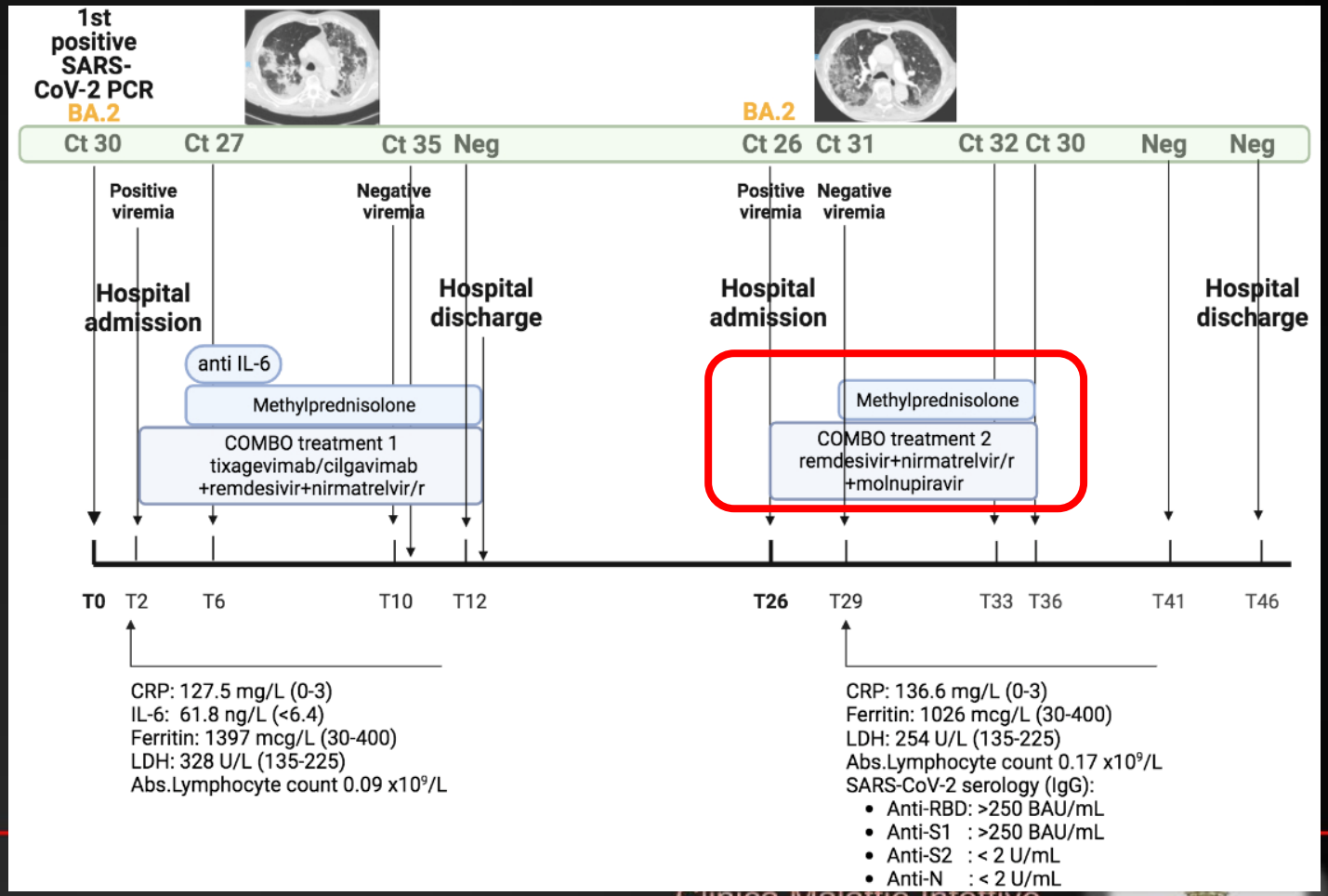
Chiara Dentone [1], Malgorzata Mikulska[1,2], Chiara Sepulcri [2*], Elisa Balletto[1,2], Vanessa De Pace[3], Sabrina Beltramini[4] and Matteo Bassetti[1,2]

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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Original Investigation | Infectious Diseases

Severity of Respiratory Syncytial Virus vs COVID-19 and Influenza Among Hospitalized US Adults

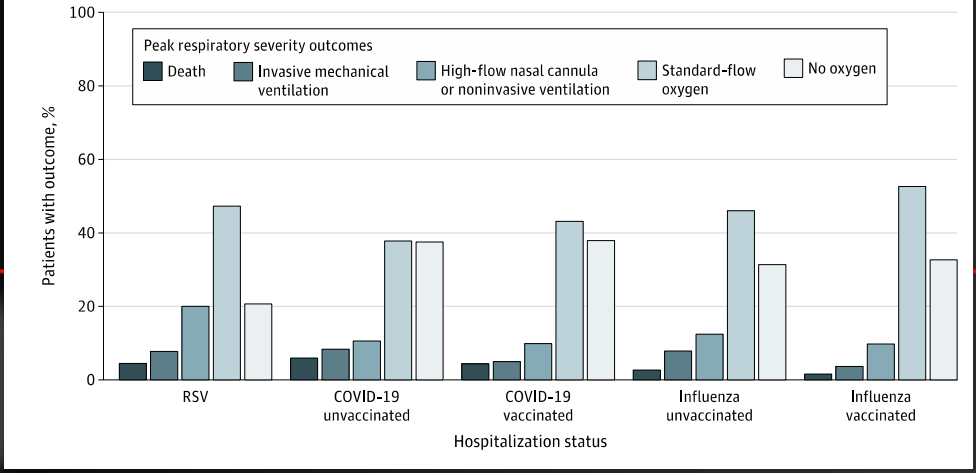
JAMA Network Open

Surie D, et al JAMA Network Open. April 2024;

DESIGN,SETTING,ANDPARTICIPANTS Inthiscohortstudy,adultsaged18yearsandolder admitted to the hospital with acute respiratory illness and laboratory-confirmed RSV, SARS-CoV-2, or influenza infection were prospectively enrolled from 25 hospitals in 20 US states from February 1, 2022, to May 31, 2023. Clinical data during each patient's hospitalization were collected using standardized forms. Data were analyzed from August to October 2023.

Conclusion: AmongadultshospitalizedinthisUScohortduringthe16 months before the first RSV vaccine recommendations, RSV disease was less common but similar in severity compared with COVID-19 or influenza disease among unvaccinated patients and more severe than COVID-19 or influenza disease among vaccinated patients for the most serious outcomes of IMV or death.

Peak Respiratory Severity of Adults Hospitalized With Respiratory Syncytial Virus (RSV), COVID-19, or Influenza by Vaccination Status



RESULTS Of7998adults(median[IQR]age,67[54-78]years;4047[50.6%]female)included,484 (6.1%) were hospitalized with RSV, 6422 (80.3%) were hospitalized with COVID-19, and 1092 (13.7%) were hospitalized with influenza. Among patients with RSV, 58 (12.0%) experienced IMV or death, compared with 201 of 1422 unvaccinated patients with COVID-19 (14.1%) and 458 of 5000 vaccinated patients with COVID-19 (9.2%), as well as 72 of 699 unvaccinated patients with influenza (10.3%) and 20 of 393 vaccinated patients with influenza (5.1%). In adjusted analyses, the odds of IMV or in-hospital death were not significantly different among patients hospitalized with RSV and unvaccinated patients hospitalized with COVID-19 (adjusted odds ratio [aOR], 0.82; 95% CI, 0.59-1.13; *P* = .22) or influenza (aOR, 1.20; 95% CI, 0.82-1.76; *P* = .35); however, the odds of IMV or death were significantly higher among patients hospitalized with RSV compared with vaccinated patients hospitalized with COVID-19 (aOR, 1.38; 95% CI, 1.02-1.86; *P* = .03) or influenza disease (aOR, 2.81; 95% CI, 1.62-4.86; *P* < .001).

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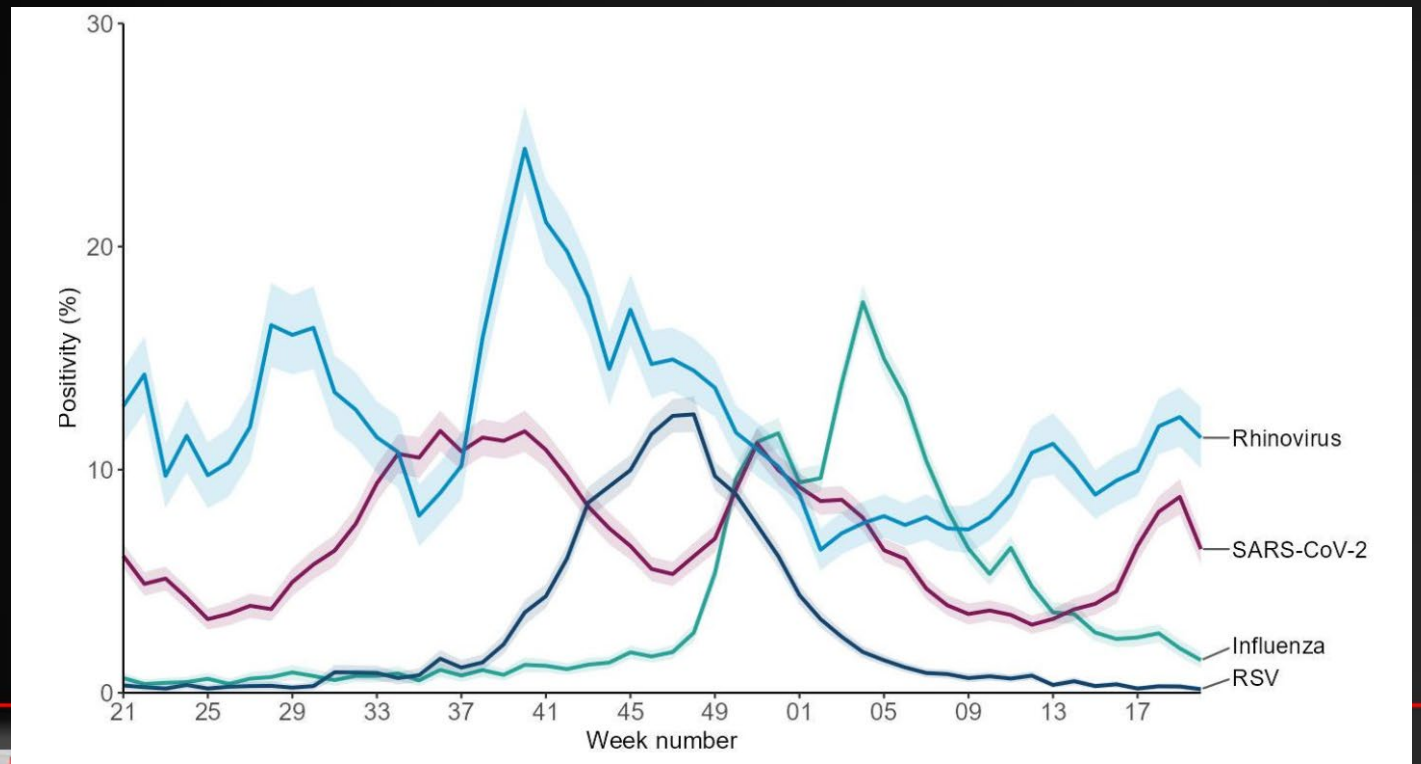
National influenza and COVID-19 surveillance report

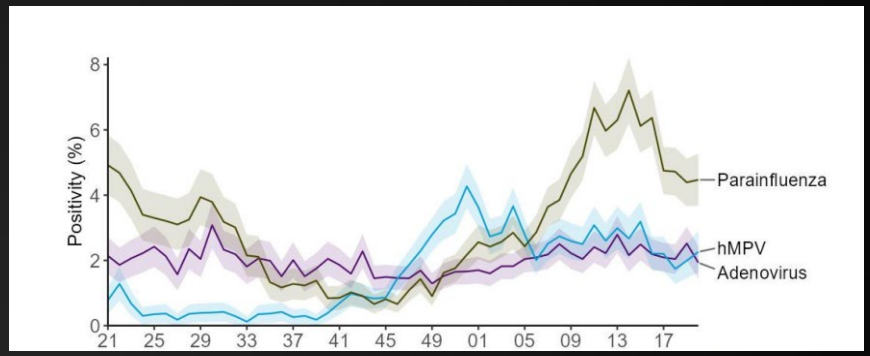
Week 21 report
(up to week 20 2024 data)
23 May 2024

UK Health Security Agency

Respiratory DataMart weekly positivity (%) for influenza, SARS-CoV-2, RSV and rhinovirus, England



Respiratory DataMart weekly positivity (%) for adenovirus, hMPV and parainfluenza, England



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