Covid-19: quale insegnamento?

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Disclosures

Advisory committees, speaking and teaching:

AbbVie, Angelini, Gilead, Janssen, GSK, Merck, ViiV

Grant and research support:

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AGENDA

qualche premessa

i punti di svolta

appendice

Covid-19: qualche premessa

COVID-19 Epidemiological Update

Edition 166 published 12 April 2024

Table 1. Newly reported and cumulative COVID-19 confirmed cases and deaths, by WHO Region, as of 31 March 2024**

WHO Region	New cases in last 28 days (%)	Change in new cases in last 28 days *	Cumulative cases (%)	New deaths in last 28 days (%)	Change in new deaths in last 28 days *	Cumulative deaths (%)	Countries reporting cases in the last 28 days	Countries reporting deaths in the last 28 days
Europe	118 816 (43%)	-28%	279 243 990 (36%)	538 (13%)	-42%	2 271 451 (32%)	34/61 (56%)	22/61 (36%)
Western Pacific	114 586 (42%)	54%	208 379 324 (27%)	266 (6%)	-28%	420 714 (6%)	14/35 (40%)	4/35 (11%)
Americas	32 692 (12%)	-45%	193 361 300 (25%)	3 346 (79%)	-42%	3 015 459 (43%)	15/56 (27%)	6/56 (11%)
South-East Asia	7 636 (3%)	-5%	61 273 832 (8%)	76 (2%)	15%	808 583 (11%)	6/10 (60%)	5/10 (50%)
Eastern Mediterranean	1 040 (0%)	-24%	23 414 772 (3%)	4 (0%)	-73%	351 935 (5%)	3/22 (14%)	2/22 (9%)
Africa	783 (0%)	55%	9 577 797 (1%)	0 (0%)	-100%	175 505 (2%)	26/50 (52%)	0/50 (<1%)
Global	**275 553 (100%)**	**-11%**	**775 251 779 (100%)**	**4 230 (100%)**	**-41%**	**7 043 660 (100%)**	**98/234 (42%)**	**39/234 (17%)**

**Percent change in the number of newly confirmed cases/deaths in the past 28 days, compared to 28 days prior. Data from previous weeks are updated continuously with adjustments received from countries.*

***See Annex 1: Data, table, and figure notes*

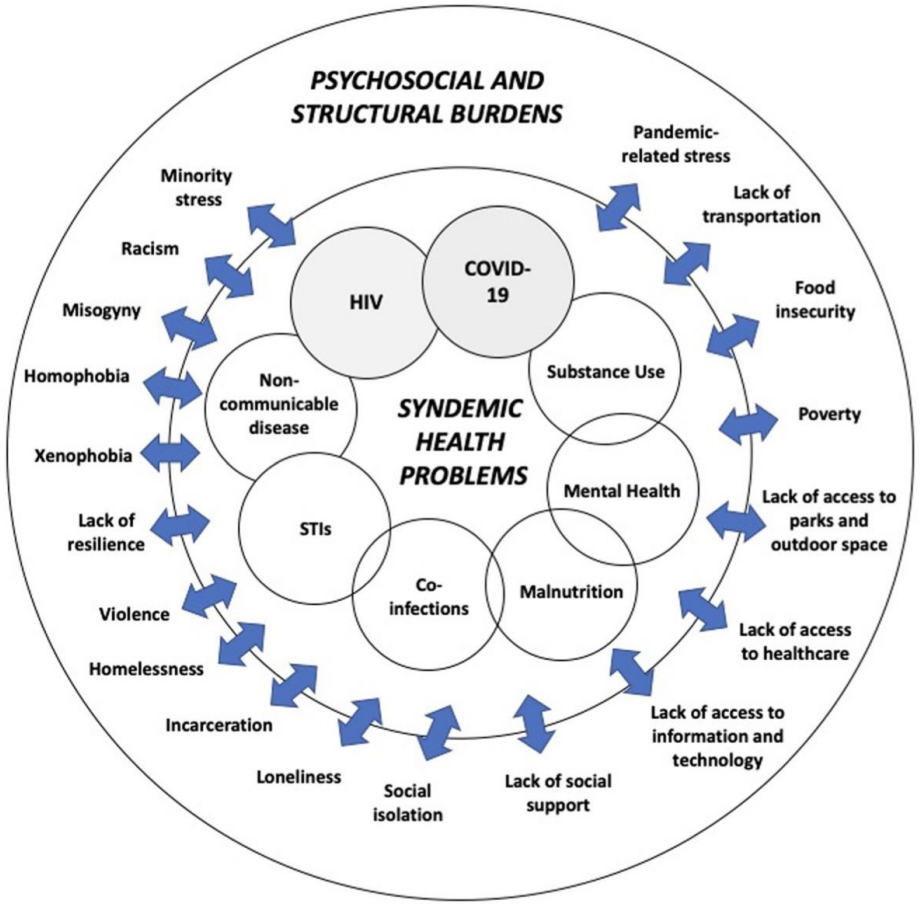
Offline: COVID-19 is not a pandemic

Richard Horton **The lancet Vol 396 September 26, 2020**

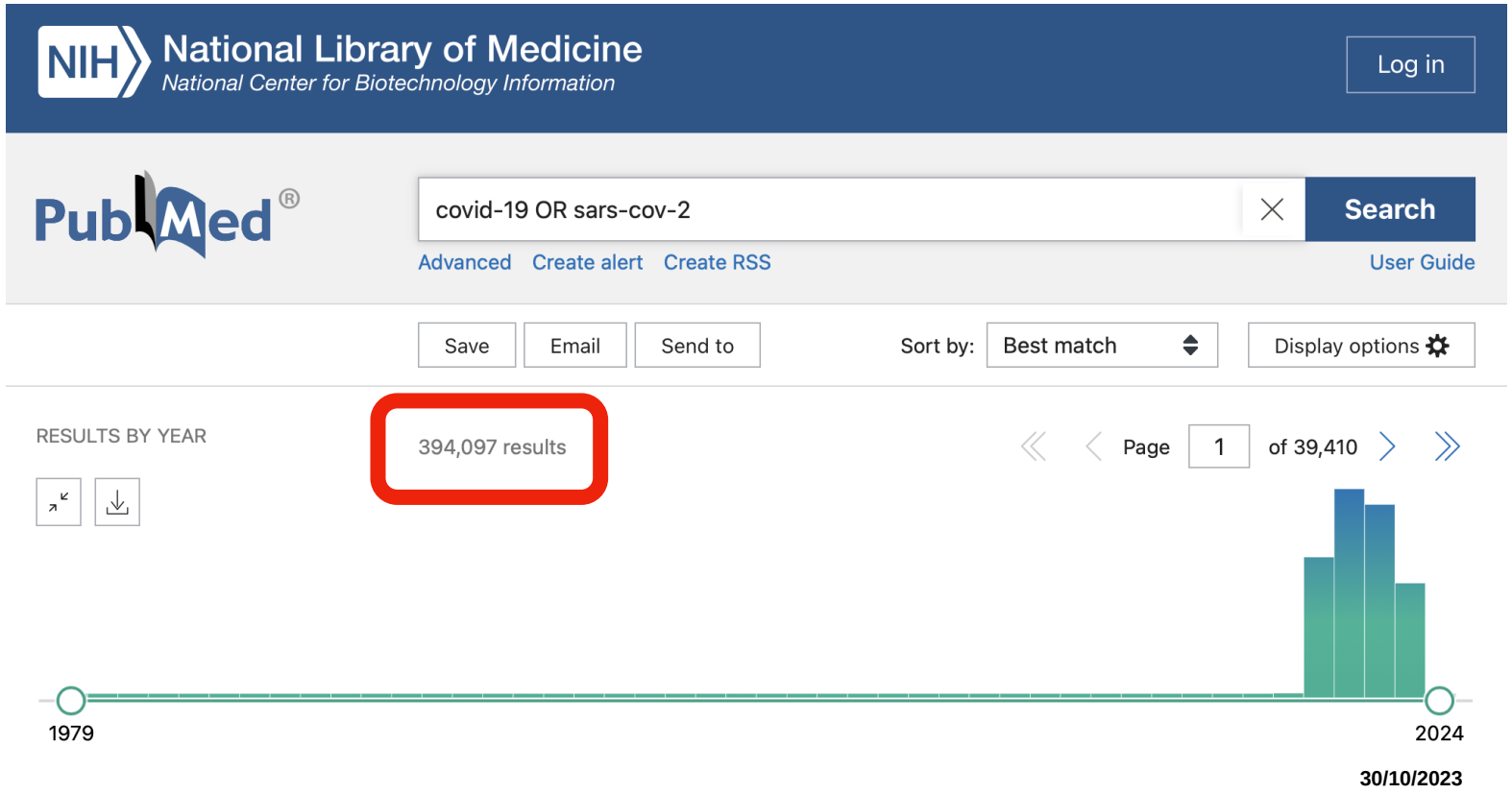
…..These conditions are clustering within social groups according to patterns of inequality deeply embedded in our societies. The aggregation of these diseases on a background of social and economic disparity exacerbates the adverse effects of each separate disease. ***COVID-19 is not a pandemic. It is a syndemic.*** *The syndemic nature of the threat we face means that a more nuanced approach is needed if we are to protect the health of our communities.*

SYNDEMIC

- The notion of a syndemic (from the greek συν and δήμος) was first conceived by Merrill Singer in the 1990s.
- ***"a syndemic approach reveals <u>biological and social interactions</u> that are important for prognosis, treatment, and health policy"***
- Limiting the harm caused by SARS-CoV-2 will demand far greater attention to NCDs and socioeconomic inequality than has hitherto been admitted.
- **A syndemic is not merely a comorbidity.**
- Syndemics are characterized by biological and social **interactions** between conditions and states, interactions that **increase a person's susceptibility to harm or worsen their health outcomes.**
- The total number of people living with chronic diseases is growing.



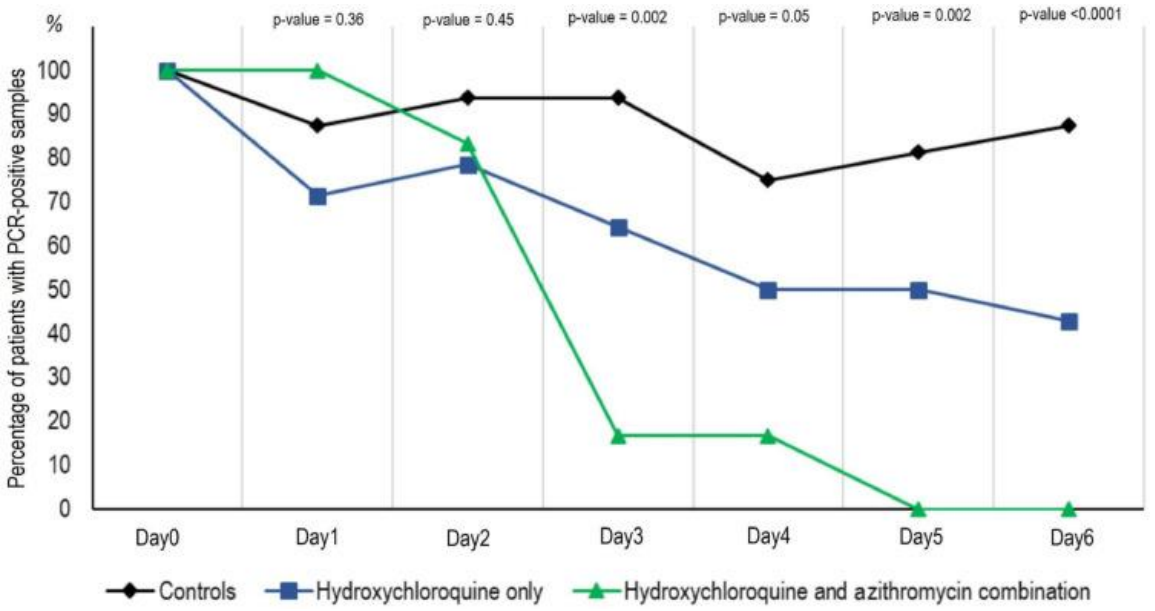
Shiau S et al. *AIDS Behav*. 2020;24(8):2244-2249. doi:10.1007/s10461-020-02871-9



Dal 1/1/2020 pubblicati in media circa 283 articoli (scientifici e non)al giorn

Il cortocircuito: "cattiva scienza – pessima stampa"

L'esempio Idrossiclorochina-Azitromicina



- Efficacia riportata inverosimile
- Esclusi i pazienti con deceduti/ricoverati in rianimazione
- Confronto tra diverse casistiche (molto piccole)

Gautret P et al, *IJAA 2020*

Il ruolo dell'A.O.Sacco nella gestione dell'emergenza infettivologica

In base all'Ordinanza della Presidenza del Consiglio dei Ministri n. 3285 del 30 aprile 2003, il Governo Italiano ha deciso di finanziare alcuni adeguamenti strutturali della A.O (già identificata come struttura per la risposta all' emergenza infettivologica per il nord Italia assieme allo Spallanzani indicato per il centro-sud), per migliorare gli standard necessari a fronteggiare eventi di bioterrorismo ed epidemie analoghe a quella della SARS.

20 febbraio 2020 ore 17
ospedale sacco milano:
il laboratorio di microbiologia
(in quel momento uno dei tre autorizzati da regione Lombardia e dall' ISS per la diagnostica per SARS CoV2)
comunica alla direzione strategica
sospetta positività per SARS CoV2 in paziente ricoverato ospedale di Codogno

20 febbraio 2020 ore 20
ospedale sacco milano:
laboratorio di microbiologia conferma positività per SARS CoV2 paziente ricoverato ospedale di Codogno

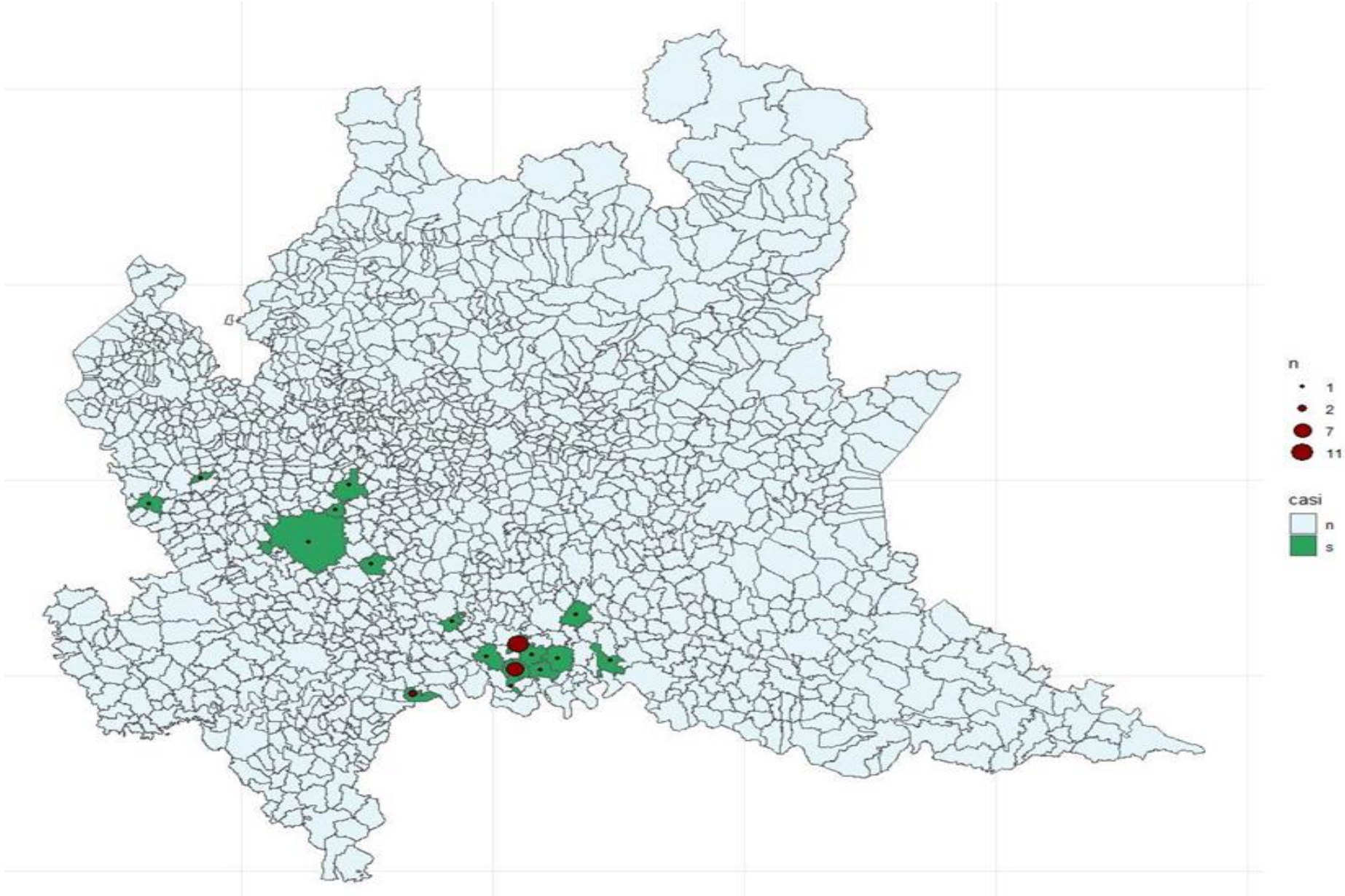
20 febbraio 2020 ore 21
ospedale sacco milano:

direzione strategica invia task force emergenza infettivologica a Codogno per trasferire paziente area di isolamento dedicata h Sacco (tre infettivologi, due rianimatori, un infermiere), secondo indicazioni regionali

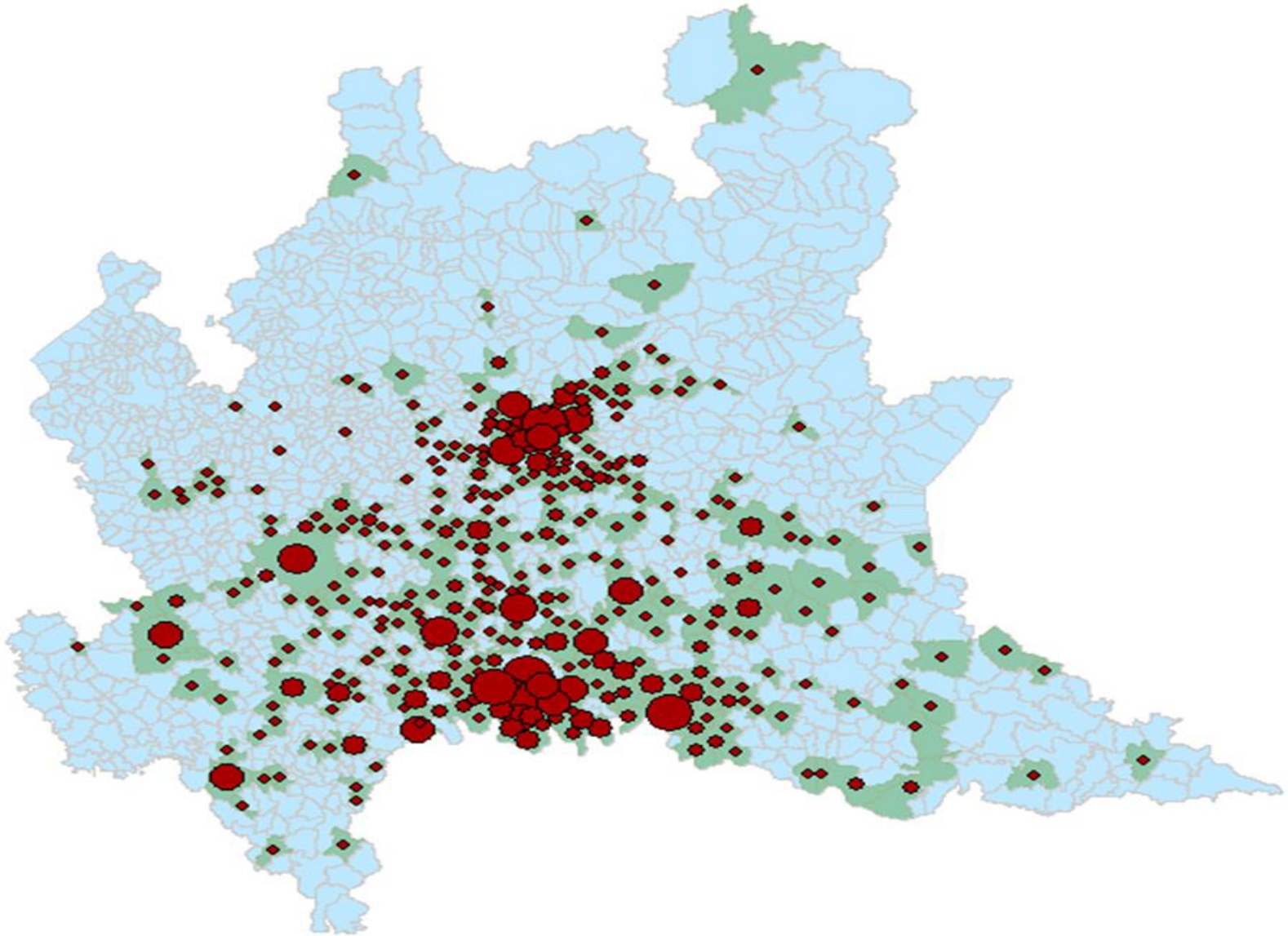
Nella notte tra il 20 e 21 febbraio 2020 vengono trasferiti al Sacco i primi tre pazienti da Codogno

….poi lo tsunami

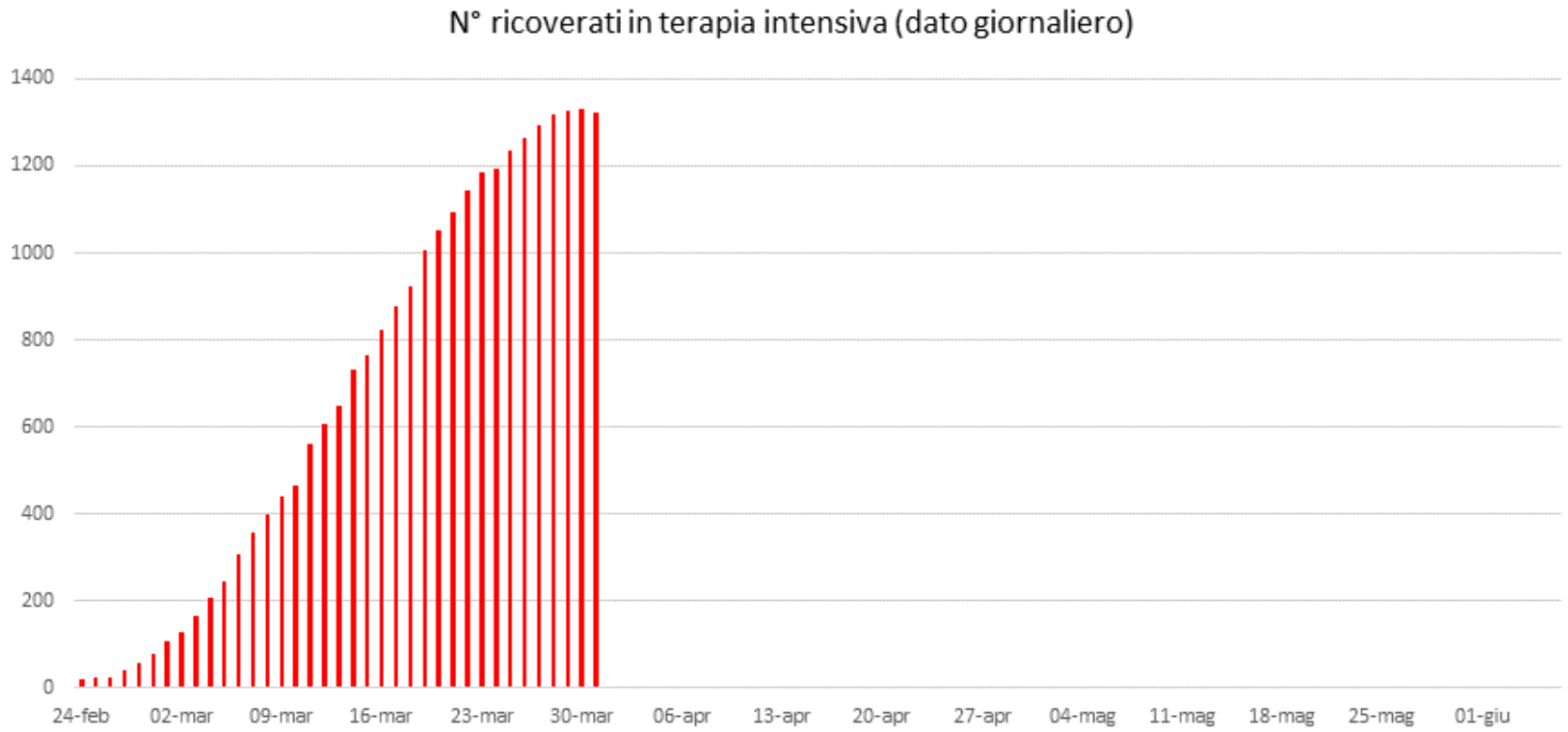
SABATO
22 FEBBRAIO 2020



MARTEDI'
3 MARZO 2020



Incremento pazienti in TI - marzo 2020

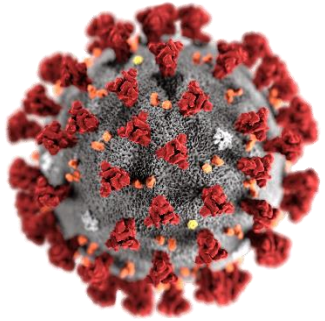


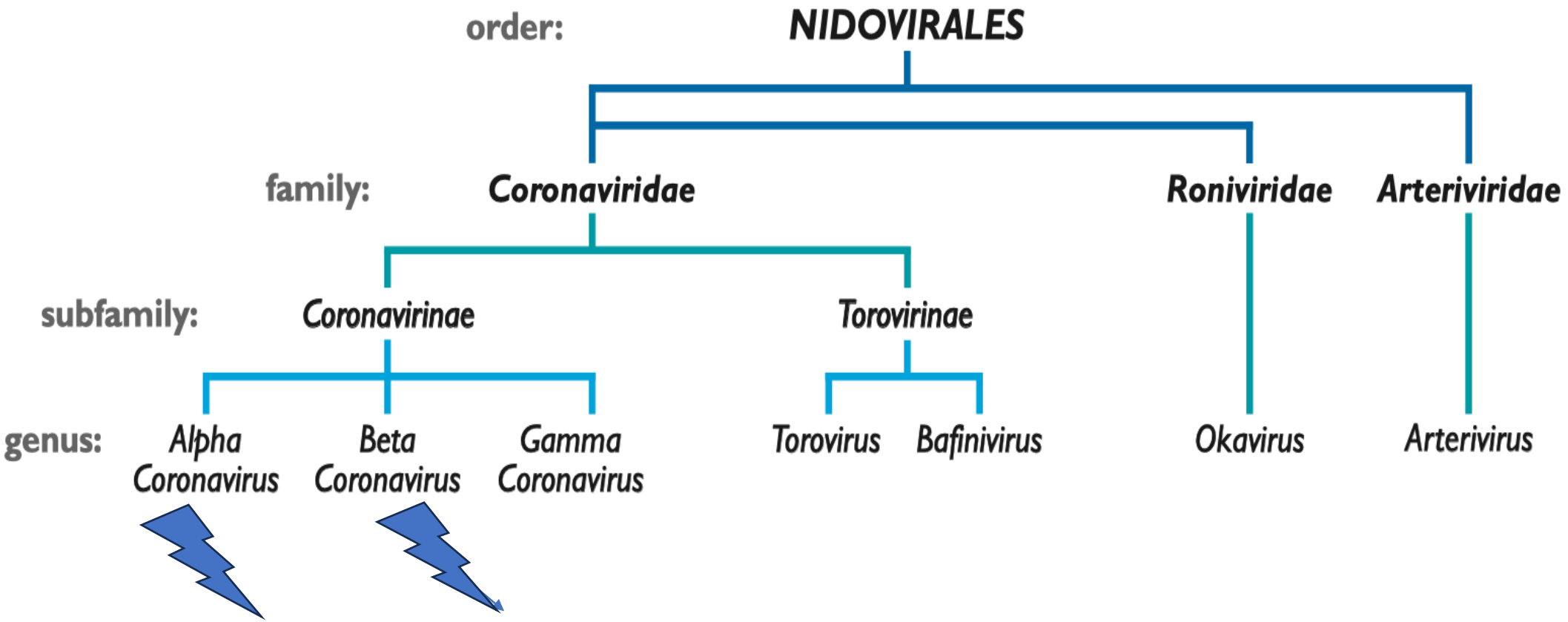
I punti di svolta nella lotta al SARS CoV-2

Punto di svolta 1:
il virus e le sue varianti

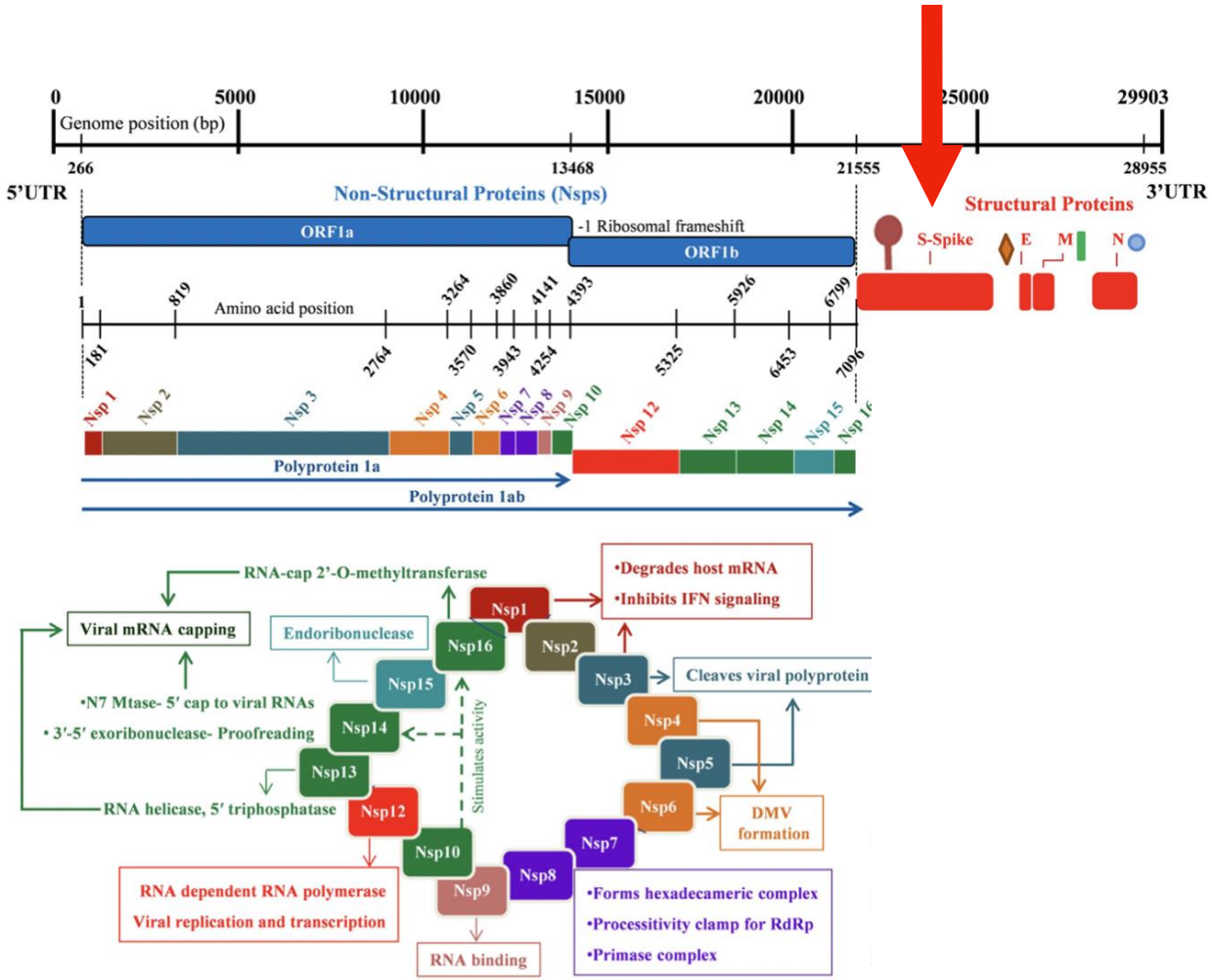
Il **31 dicembre 2019** le autorità sanitarie cinesi informavano la comunità internazionale relativamente a cluster di casi di polmonite ad eziologia sconosciuta diagnosticati a Wuhan nella provincia di Hubei. **Il 9 gennaio 2020** le Autorità sanitarie cinesi dichiaravano di aver individuato un nuovo ceppo di coronavirus mai identificato prima nell'uomo (provvisoriamente chiamato 2019-nCoV e poi classificato come SARS-CoV-2), quale agente causale di queste polmoniti. Una **settimana dopo** veniva pubblicata la sequenza genomica del virus. Più tardi, la malattia respiratoria causata da questo nuovo coronavirus veniva definita come COVID-19. Il **30 gennaio 2020**, dopo la seconda riunione del Comitato di sicurezza, il Direttore generale dell'Organizzazione Mondiale della Sanità (OMS) dichiarava il focolaio internazionale di COVID-19 un'emergenza di sanità pubblica di rilevanza internazionale (*Public Health Emergency of International Concern* – PHEIC), come sancito nel Regolamento sanitario internazionale (*International Health Regulations*, IHR, 2005). **L'11 marzo 2020** l' OMS dichiarava lo stato di pandemia da SARS-CoV-2.

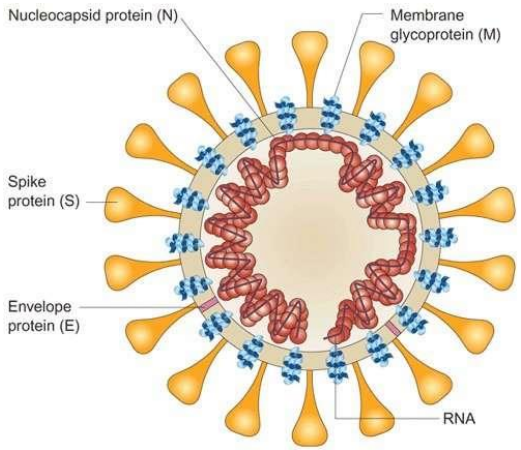
7 Human Coronaviruses:
4 normal; 3 "novel"





Alpha: **HCoV-229E**, **HCoV-NL63** Beta: **HCoV-HKU1**, **HCoV-OC43**, **MERS-CoV**, **SARS-CoV**, **SARS-CoV-2**





Genoma complesso

4 Proteine strutturali

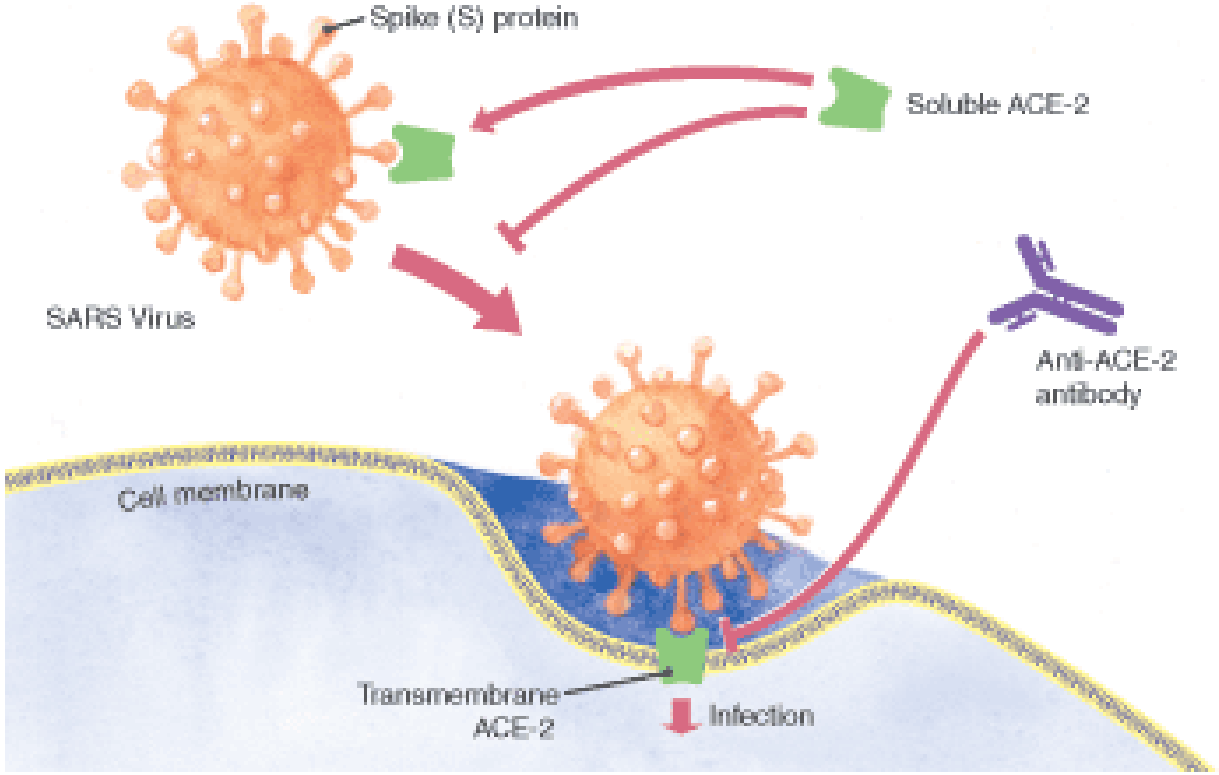
Fra le 4 proteine strutturali la principale è la proteina S (spike). Sulla quale è presente RBD. E che è risultata essere obiettivo vaccinale.

16 Proteine non strutturali

16 proteine non-strutturali NSPs che regolano la replicazione/trascrizione e possono avere funzioni diverse. Compresa la capacità di interferire con la risposta immunitaria dell'ospite

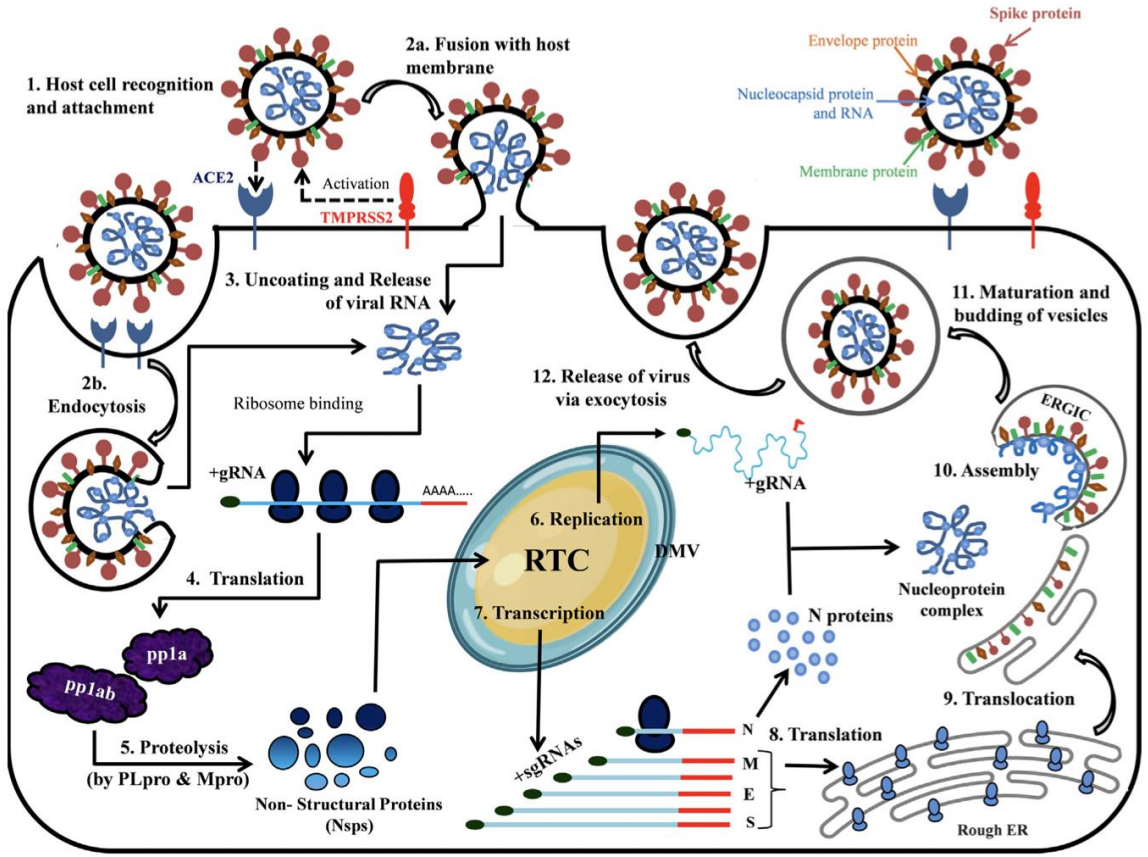
https://doi.org/10.1016/j.jmb.2020.11.024

Novel CoV attachment



- **ACE-2 Receptors**
  - Type 2 alveolar cells - highest
  - Bronchial epithelia
  - Tongue > buccal epithelia
  - Upper Intestinal epithelia
  - Myocardial cells
  - Kidney proximal tubule cells
  - Bladder urothelial cells
- **SARS-CoV-2 binds to ACE-2 Receptor 10-20x more strongly than SARS-CoV**
- Question of ADEs (Antibody Dependent Enhancement)
  - Antibodies can create a backdoor enhancement for viral replication
  - Implications on viral replication and vaccine development safety

Ciclo vitale



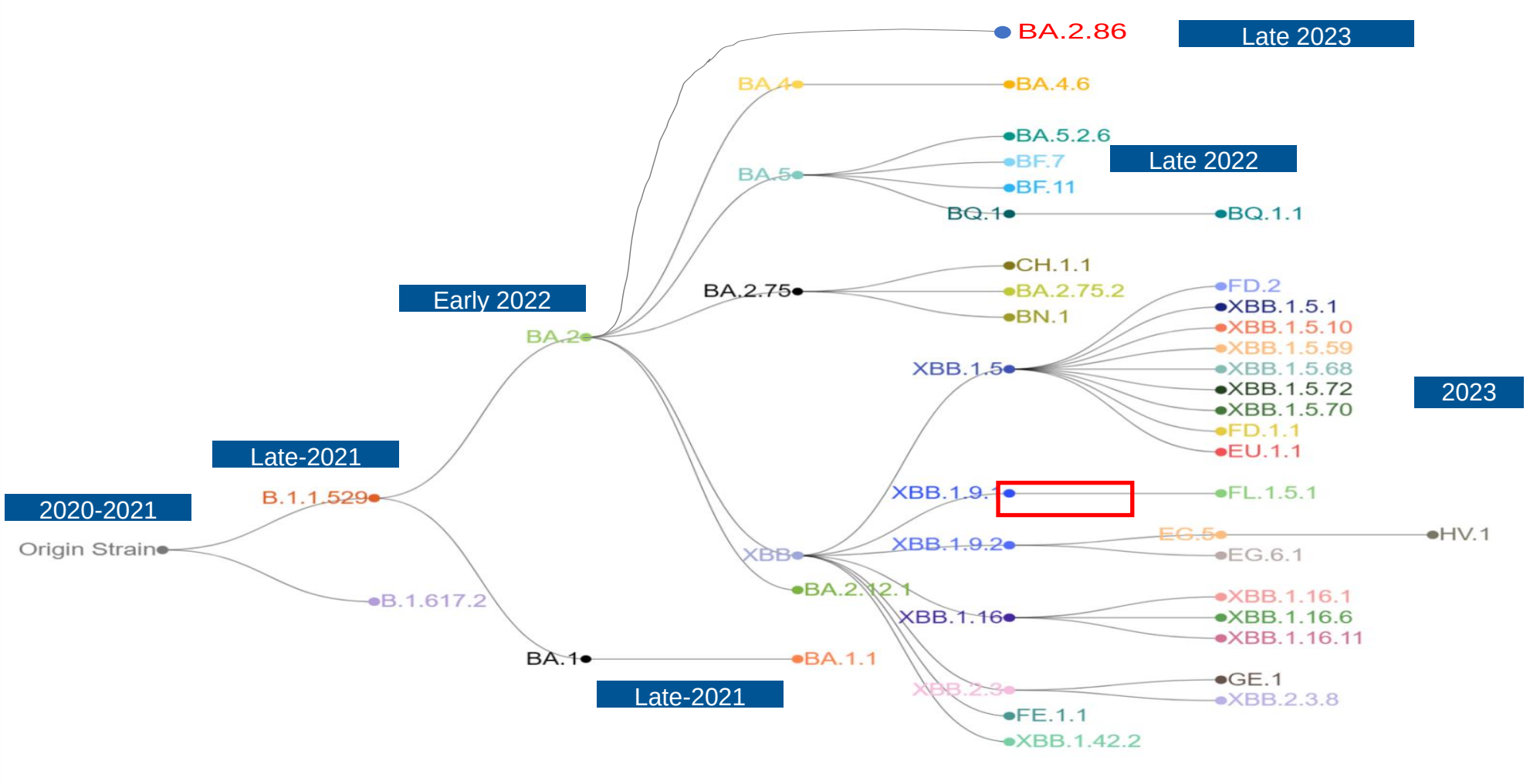
Legame tra Proteina S e complesso ACE-2/TMPRSS2

Formazione di un Replication-transcription complex (RCT) all'interno di Double-membrane vesicles (DMV)

https://doi.org/10.1016/j.jmb.2020.11.024

Evolution of COVID-19 variants

I virus evolvono nel tempo: SARS Cov-2 produce varianti, legate a mutazioni della proteina S.



https://covid.cdc.gov/covid-data-tracker/#variant-proportions

tracking SARS-CoV-2 variants

All viruses, including SARS-CoV-2, the virus that causes COVID-19, change over time. Most changes have little to no impact on the virus's properties. However, some changes may affect the virus's properties, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures. In late 2020, the emergence of variants that posed an increased risk to global public health prompted WHO to characterize some as variants of interest (VOIs) and variants under monitorig (VUMs) **in order to prioritize global monitoring and research, and to inform and adjust the COVID-19 response**.

La piattaforma genomica di condivisione internazionale GISAI

The GISAID Data Science Initiative promotes the rapid sharing of data from priority pathogens. The Initiative ensures that open access to data in GISAID is provided free-of-charge to all individuals that agreed to identify themselves and agreed to uphold the GISAID sharing mechanism governed through its Database Access Agreement

Table 3. Weekly prevalence of SARS-CoV-2 VOIs and VUMs, epidemiological week 28 to week 32 of 2023

Lineage	Countries[§]	Sequences[§]	2023-28	2023-29	2023-30	2023-31	2023-32
VOIs							
XBB.1.5*	124	269 726	12.2	11.5	10.3	9.7	10.2
XBB.1.16*	109	52 868	22.9	23.8	22.7	24.5	22.7
EG.5*	57	12 895	15.4	18.6	22.1	22.9	26.1
VUMs							
BA.2.75*	125	123 914	2.3	1.6	1.4	1.3	0.9
BA.2.86[ǂ]	7	21					
CH.1.1*	96	43 112	0.6	0.7	0.7	0.9	0.8
XBB*	130	70 196	6.5	6.6	6.0	6.1	5.0
XBB.1.9.1*	107	58 606	12.6	12.4	12.7	11.8	13.2
XBB.1.9.2*	86	27 671	7.1	6.4	5.9	5.2	4.6
XBB.2.3*	76	10 754	4.9	5.0	5.4	4.9	5.5
Unassigned	95	152 492	3.3	1.8	0.7	0.1	0.1
Other[+]	209	6 772 234	11.4	11.1	11.5	12.1	10.7

[§] Number of countries and sequences are since the emergence of the variants.

* Includes descendant lineages, except those individually specified elsewhere in the table. For example, XBB* does not include XBB.1.5, XBB.1.16, EG.5, XBB.1.9.1, XBB.1.9.2, and XBB.2.3.

[+] "Other" represents other circulating lineages excluding the VOI, VUMs, BA.1*, BA.2*, BA.3*, BA.4*, BA.5*. Due to delays in or retrospective assignment of variants, caution should be taken when interpreting the prevalence of the "Other" category.

[ǂ] Prevalence for BA.2.86 cannot be calculated due to the very small numbers of sequences.

The VOI and the VUMs that have shown increasing trends are highlighted in yellow, those that have remained stable are highlighted in blue, while those with decreasing trends are highlighted in green.

Table 5. Weekly prevalence of SARS-CoV-2 VOIs and VUMs by WHO regions, week 10 to week 13 of 2024

Lineage (week 10-2024 to 13-2024)	AMRO	AFRO[¥]	EMRO[¥]	EURO	SEARO[¥]	WPRO
VOIs						
XBB.1.5*	↓			↓		↓
XBB.1.16*	↓			↓		↓
EG.5*	↓			↓		↓
BA.2.86*	↓			↓		↓
JN.1*	↑			↑		↑

↑ Increasing trend
↓ Decreasing trend
↔ Stable trend
Insufficient Data
Most Prevalent variant(s)

* Includes descendant lineages, except those individually specified elsewhere in the table. For example, XBB* does not include XBB.1.5, XBB.1.16, EG.5, XBB.1.9.1, and XBB.2.3.

¥ due to the small numbers of sequences submitted in these regions, it has not been possible to determine trends for the VOIs and VUMs in these regions; this is also represented by the shaded cells in the table.

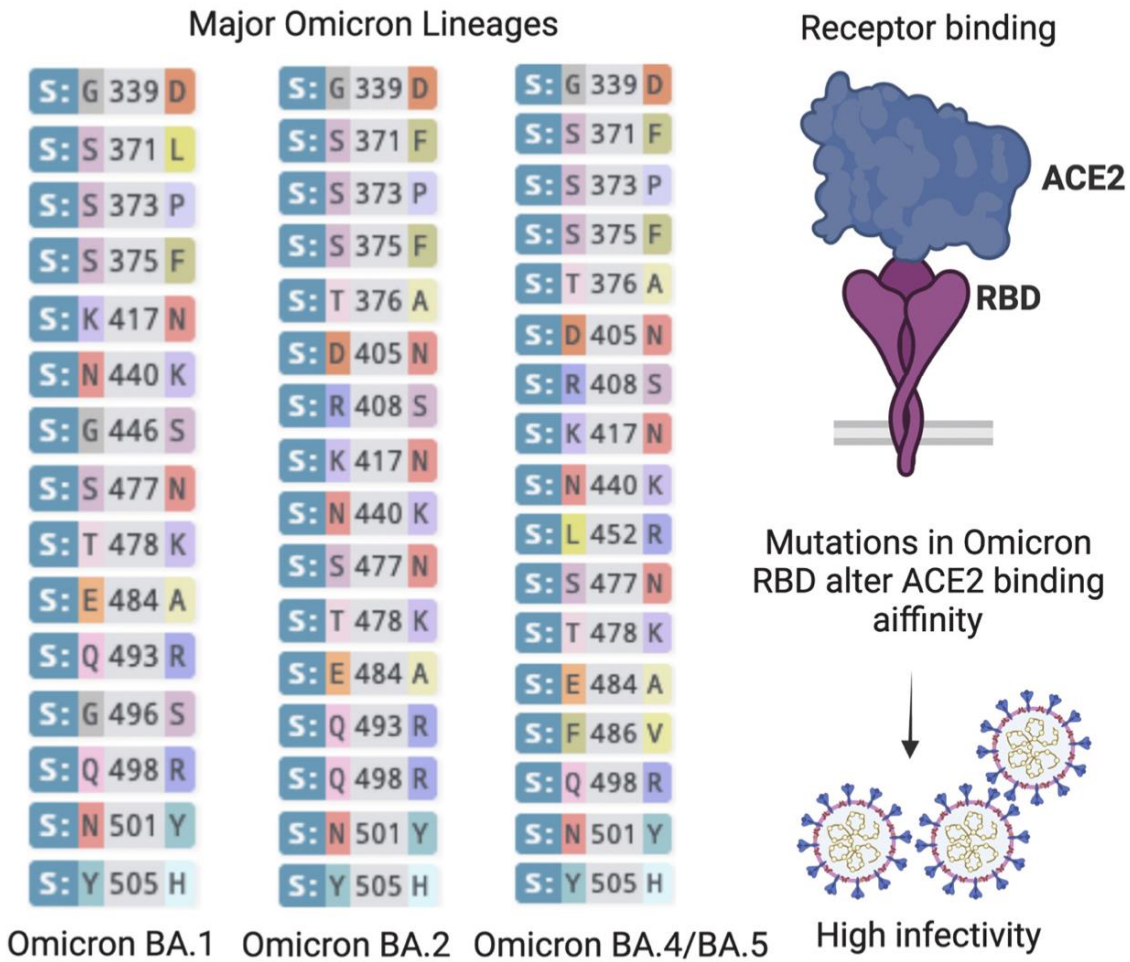
Variante omicron e sottpvarianti

Rispetto alle precedenti (delta):

- Vantaggio replicativo

- Escape immunologico

- Ridotta gravità di malattia.



https://doi.org/10.1016/j.jiph.2022.11.024

VIRUS: COSA SAPPIAMO E COSA ANCORA NO

Origine di SARS-CoV-2

2 possibilità:

- Spillover naturale da animale
- Fuga accidentale (o deliberata) da laboratorio

Irrespective of Covid's origins, future outbreaks could result from deliberate, accidental, or natural causes, and improving our ability to understand and prove theories will be critical.

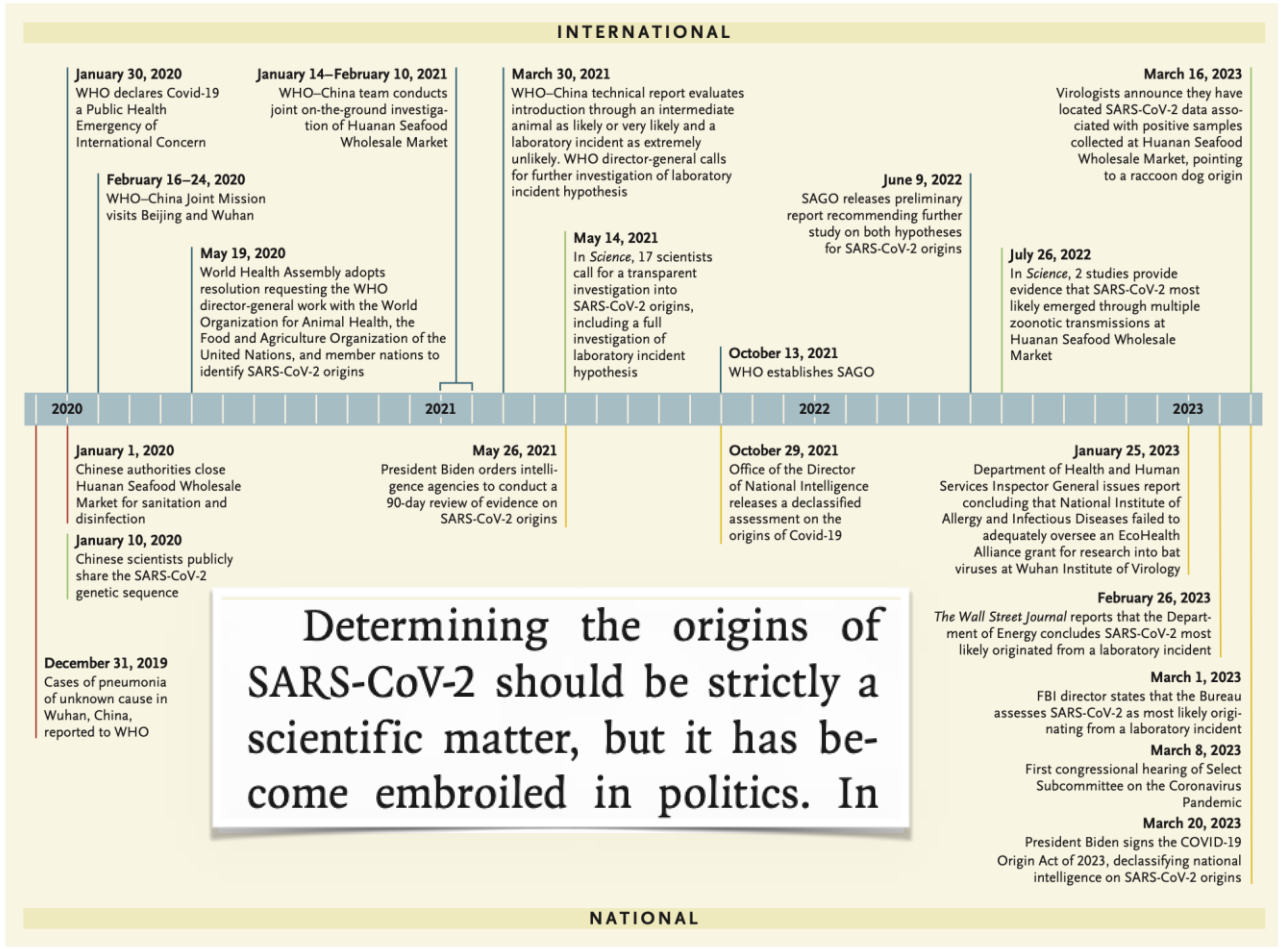
The NEW ENGLAND JOURNAL of MEDICINE

The Origins of Covid-19 — Why It Matters (and Why It Doesn't)

Perspective

JUNE 22, 2023

Lawrence O. Gostin, J.D., and Gigi K. Gronvall, Ph.D.

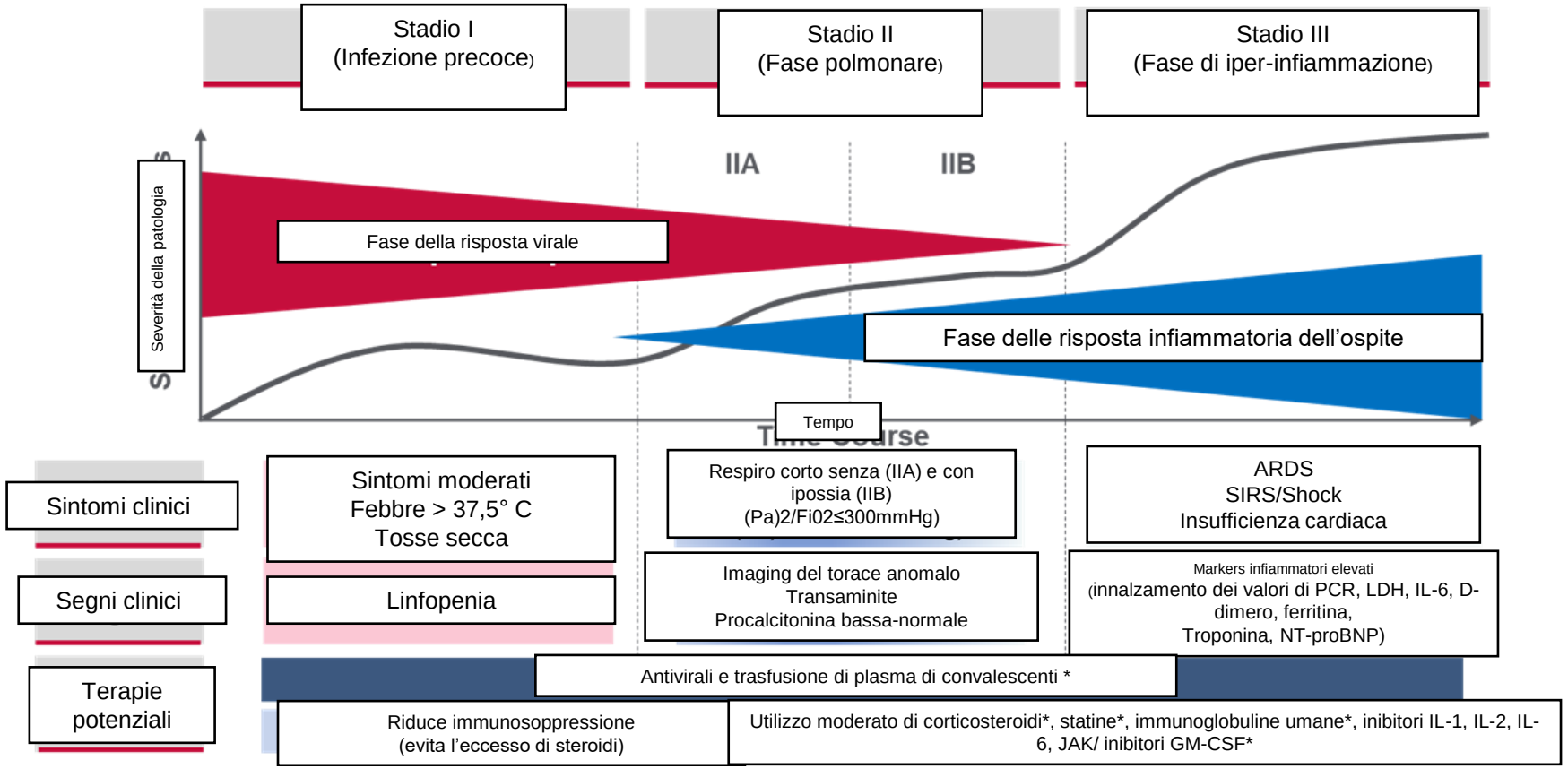


Key Events in the Effort to Determine the Origins of the Covid-19 Pandemic.

FBI denotes Federal Bureau of Investigation, SAGO Scientific Advisory Group for the Origins of Novel Pathogens, and WHO World Health Organization.

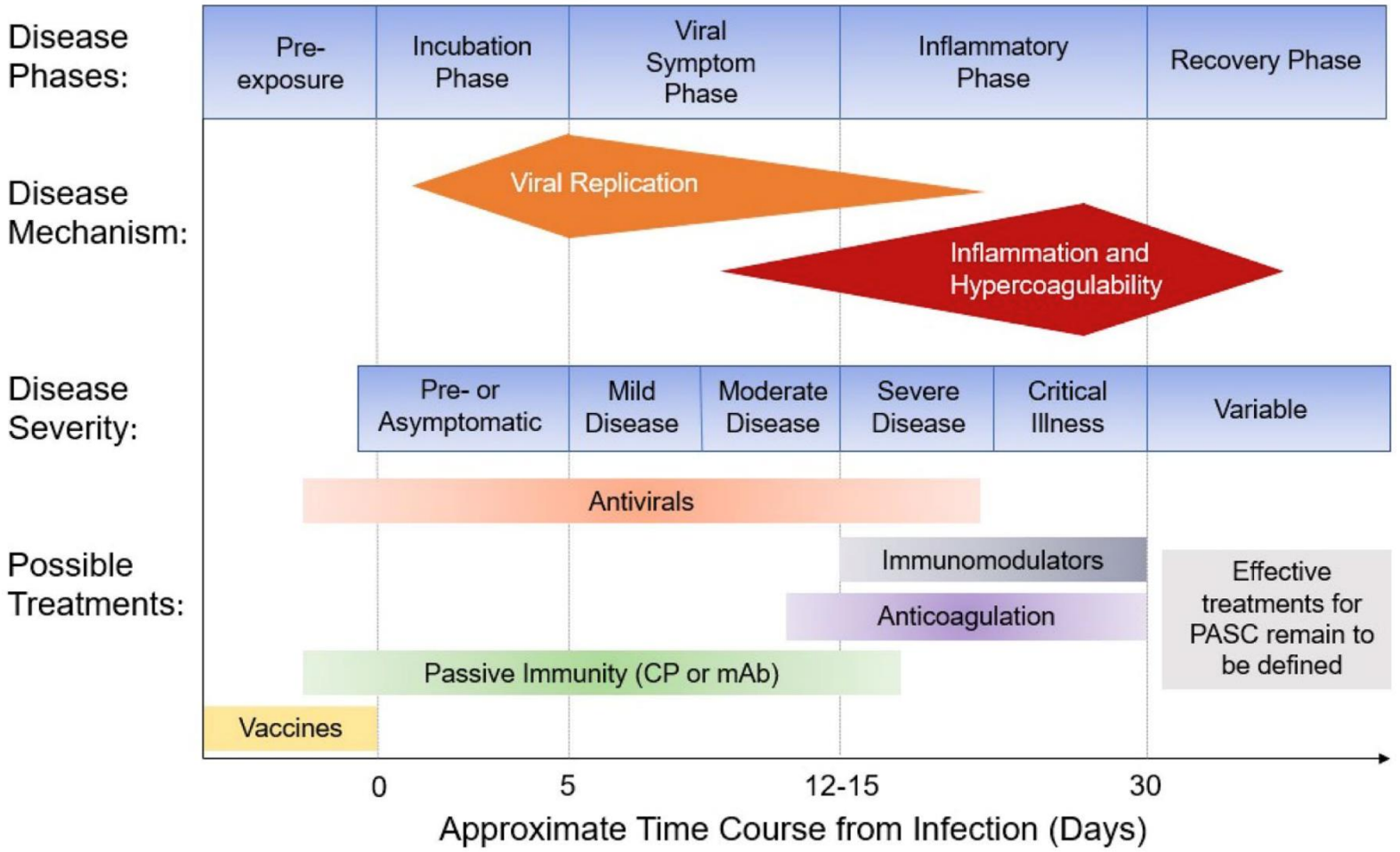
Punto di svolta 2: la comprensione della fisiopatologia della malattia

Comprensione fisiopatologia della malattia



Siddiqi HK et al, *J Heart Lung Transplant 2020*

Clinical management approach to COVID-19 based on disease phase and severity

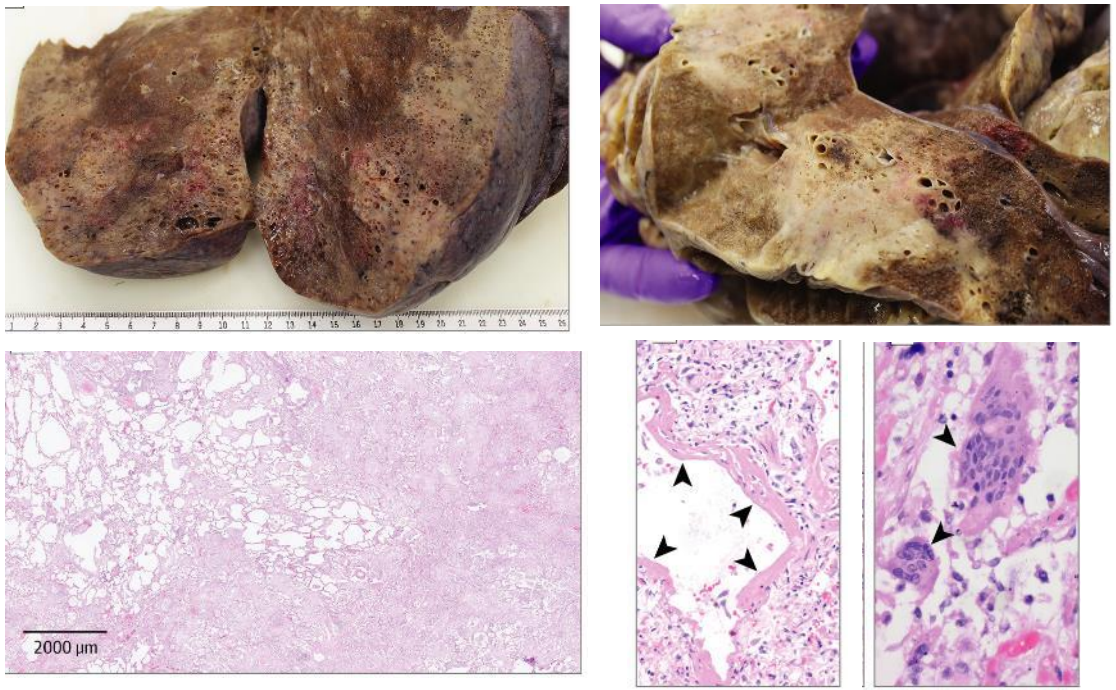


Bae YE et al, *Curr Infect Dis Rep 2021*

Pulmonary Sequelae

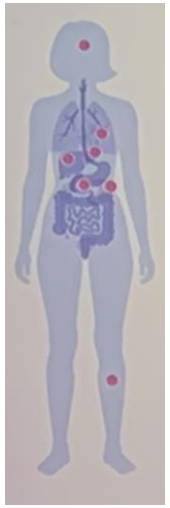
- Diffuse alveolar damage noted in multiple, small postmortem studies of COVID-19
  - N = 38 from northern Italy[1]
  - N = 10 from Germany[2]
- Platelet–fibrin thrombi indicative of coagulopathy observed in small arterial vessels of some patients[1]

Macroscopic and Histologic Lung Findings[2]



1. Carsana. Lancet Infect Dis. 2020;20:1135. 2. Schaller. JAMA. 2020;323:2518.

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 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 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

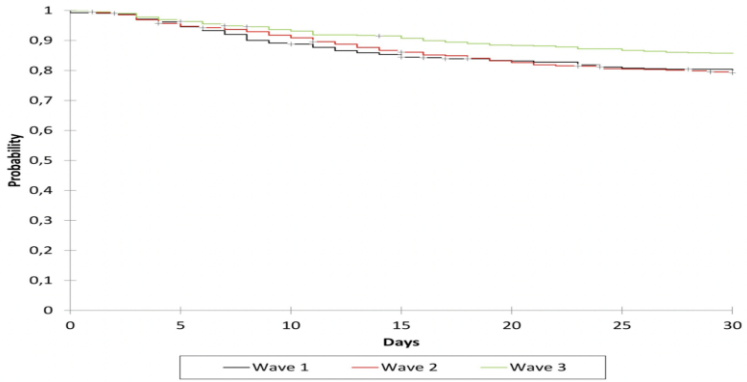
Vaccini e varianti hanno cambiato il decorso della malattia

PLOS ONE

RESEARCH ARTICLE

Mortality rates among COVID-19 patients hospitalised during the first three waves of the epidemic in Milan, Italy: A prospective observational study

Andrea Giacomelli[1☯*], Anna Lisa Ridolfo[1☯], Laura Pezzati[1,2], Letizia Oreni[1], Giorgia Carrozzo[1,2], Martina Beltrami[1,2], Andrea Poloni[1,2], Beatrice Caloni[1,2], Samuel Lazzarin[1,2], Martina Colombo[1,2], Giacomo Pozza[1,2], Simone Pagano[1,2], Stefania Caronni[1,2], Chiara Fusetti[1], Martina Gerbi[1], Francesco Petri[1], Fabio Borgonovo[1], Fabiana D'Aloia[2], Cristina Negri[1], Giuliano Rizzardini[1], Spinello Antinori[1,2]



Mortalità in pazienti ospedalizzati:
I ondata = 21,3%
II ondata = 23,7%
III ondata = 15,8%

https://doi.org/10.1371/journal.pone.0263548

Punto di svolta 3: fattori di rischio per un outcome peggiore di COVID-19

Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy

Characteristic[a]	No. of patients (n = 3988)	No. of deaths (n = 1926)	Mortality rate per 1000 patient-days	HR (95% CI)	*P* value
Age, y					
<56	997	245	4.5 (3.9-5.0)	1 [Reference]	NA
56-63	997	416	9.2 (8.3-10.1)	1.91 (1.63-2.24)	<.001
64-69	997	562	15.6 (14.3-16.9)	2.98 (2.56-3.46)	<.001
>69	997	703	25.2 (23.4-27.1)	4.25 (3.68-4.92)	<.001
Men	3188	1580	12.2 (11.6-12.9)	1.22 (1.08-1.37)	<.001
Women	800	346	9.9 (8.8-10.9)	0.73 (0.82-0.92)	<.001
Comorbidities					
None	1302	490	7.7 (7.0-8.4)	0.55 (0.49-0.61)	<.001
Hypertension	1643	962	15.8 (14.8 -16.8)	1.68 (1.53-1.84)	<.001
Hypercholesterolemia	545	376	22.4 (20.2-24.8)	1.90 (1.70- 2.14)	<.001
Heart disease[b]	533	342	19.4 (17.4-21.5)	1.66 (1.48- 1.87)	<.001
Type 2 diabetes	514	328	19.3 (17.3-21.5)	1.66 (1.47- 1.88)	<.001
Malignant neoplasm[c]	331	202	17.3 (15.0-19.8)	1.45 (1.25-1.68)	<.001
COPD	93	67	25.4 (19.7-32.2)	2.03 (1.59-2.59)	<.001
CKD	87	71	39.3 (30.7-49.6)	2.78 (2.19-3.53)	<.001
Liver disease	86	42	11.4 (8.3-15.5)	1.03 (0.76-1.39)	.87
Other disease	501	274	13.7 (12.1-15.4)	1.19 (1.04-1.35)	.01

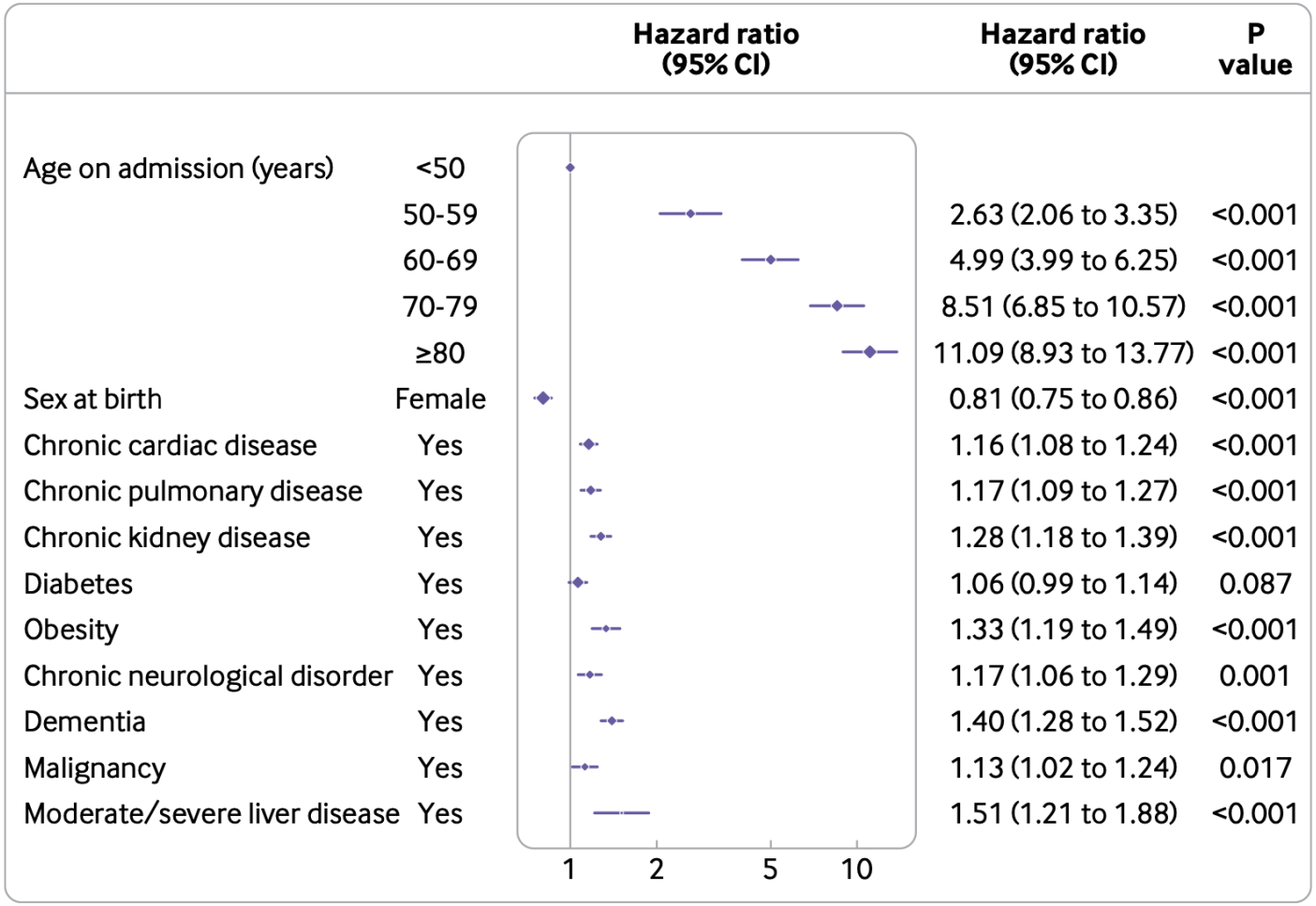
Table 2. Multivariable Cox Proportional Hazards Regression Analysis of Factors Associated With Mortality

Variable	Category (description)	Multivariable HR (95% CI)	*P* value[a]
Age in years	10-y Increments	1.75 (1.60-1.92)	<.001
Men	Men vs women	1.57 (1.31-1.88)	<.001
Respiratory support	Spontaneous breathing vs NIV	1.81 (0.57-5.76)	.32
	Invasive MV vs NIV	1.24 (1.00-1.55)	.052
Hypertension	Yes vs no	0.99 (0.81-1.22)	.93
Hypercholesterolemia	Yes vs no	1.25 (1.02-1.52)	.03
Heart disease	Yes vs no	1.08 (0.91-1.29)	.38
Type 2 diabetes	Yes vs no	1.18 (1.01-1.39)	.04
Malignancy	Yes vs no	1.09 (0.92-1.28)	.33
COPD	Yes vs no	1.68 (1.28-2.19)	<.001
ACE inhibitor therapy	Yes vs no	1.17 (0.97-1.42)	.10
ARB therapy	Yes vs no	1.05 (0.85-1.29)	.64
Statin	Yes vs no	0.98 (0.81-1.20)	.87
Diuretic	Yes vs no	1.10 (0.91-1.32)	.32
PEEP at admission	1-cm H_2O increments	1.04 (1.01-1.06)	.009
Fio_2 at admission	10% Increments	1.14 (1.10-1.19)	<.001
Pao_2/Fio_2 at admission	100-U increments	0.80 (0.74-0.87)	<.001

Grasselli G et al, *JAMA Intern Med 2020*

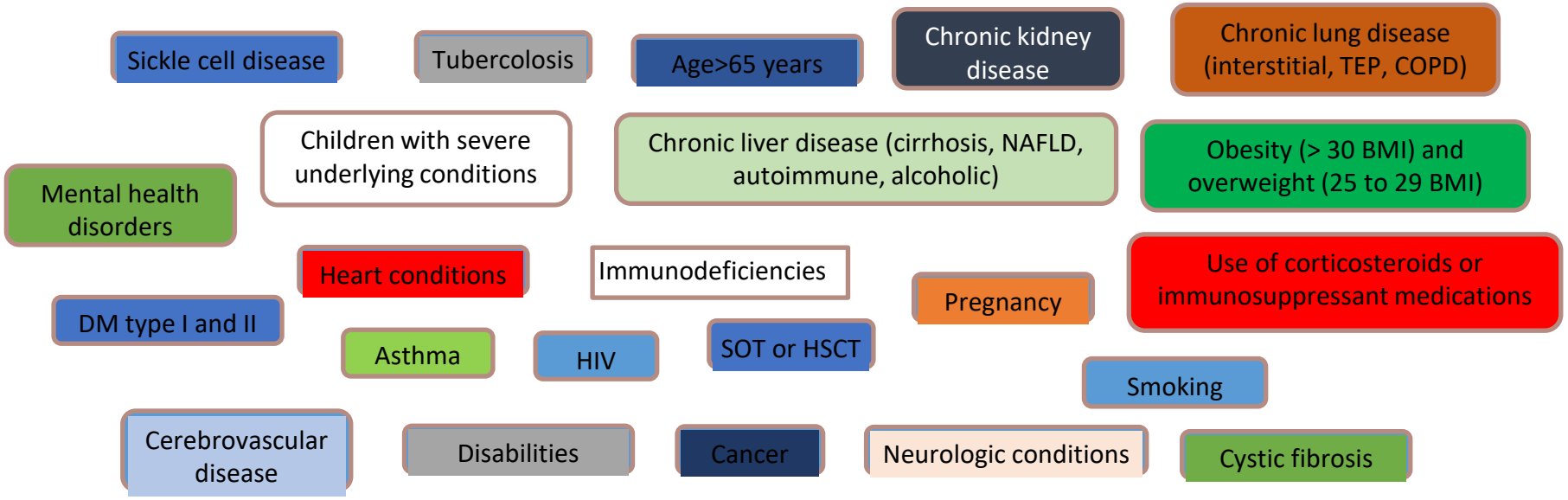
Predictors of Mortality Among COVID-19–Positive Hospitalized Patients in the UK

- Prospective observational cohort study of hospital admissions in England, Wales, and Scotland during February 6 - April 19, 2020 (N = 20,133)
- Significantly increased risk of mortality among **older patients, men, and those with chronic comorbidities**



Docherty AB et al, BMJ 2020;369:m1985.

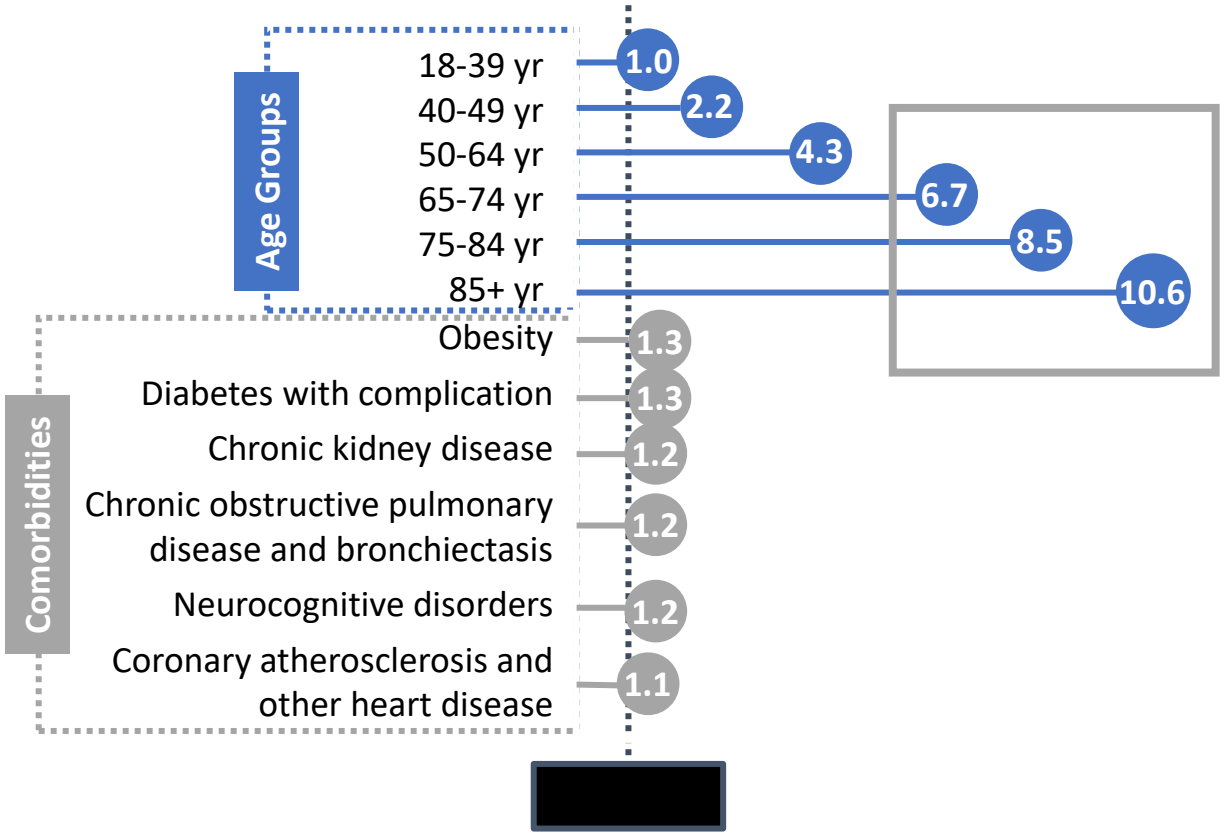
Comorbidities classified as risk factors for severe COVID-19 for CDC



www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions

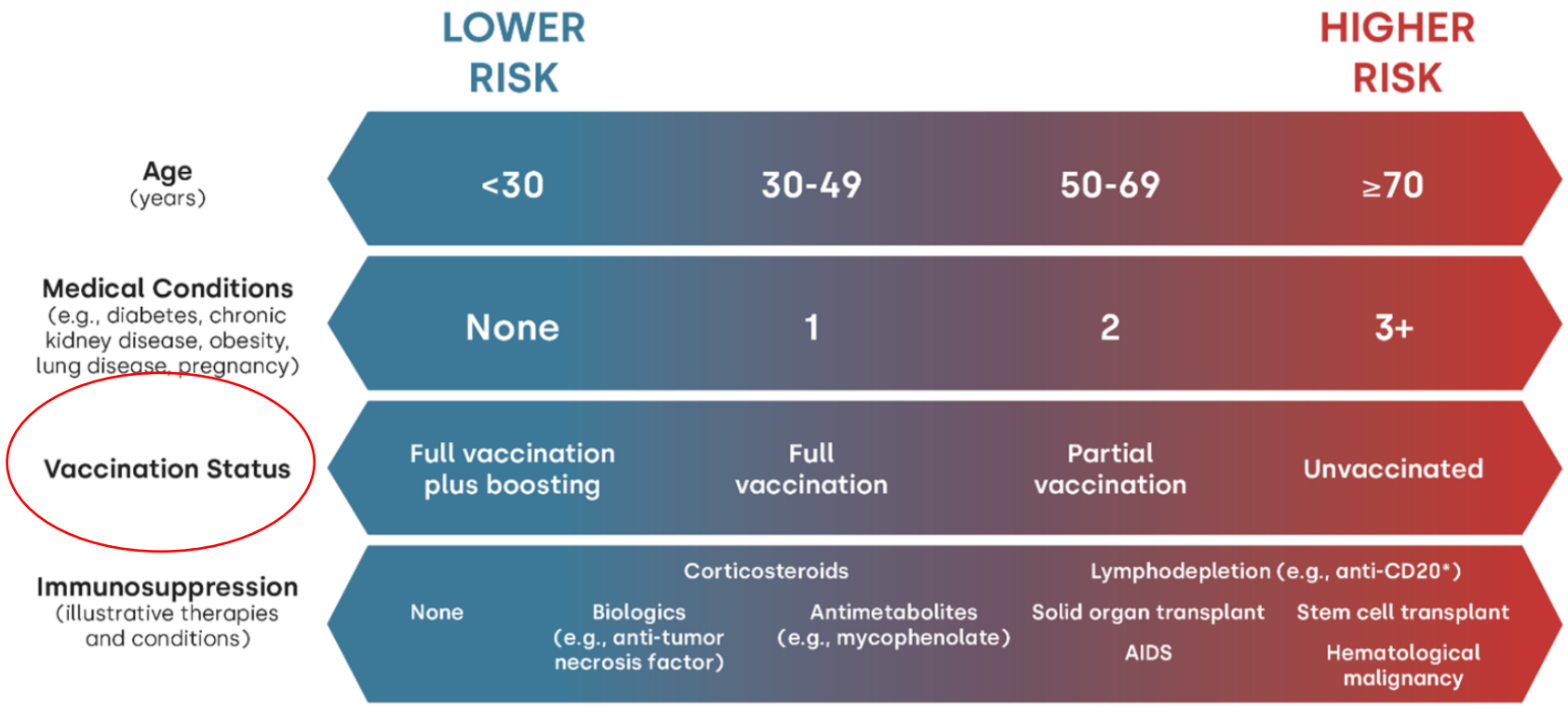
Age Is Strongest Rsk Factor for Severe COVID-19

COVID-19 Death Risk Ratio for
Select Age Group and Comorbid Conditions



cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Last updated December 5, 2022.

COVID-19 Risk Continuum



Sociodemographic factors and non-pharmaceutical interventions affect exposure risk

Original illustration by Dr. William Werbel. Adapted for the COVID-19 Real-Time Learning Network

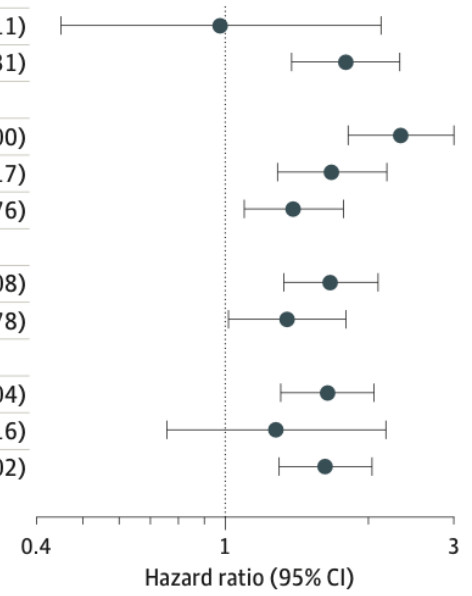
Brought to you by CDC and IDSA

Risk of Death in Patients Hospitalized for COVID-19 vs Seasonal Influenza in Fall-Winter 2022-2023

Electronic health databases of the US Department of Veterans Affairs (VA). Between October 2022 and January 2023. There were 8996 hospitalizations (538 deaths within 30 days) for COVID-19 and 2403 hospitalizations (76 deaths) for seasonal influenza

higher risk of death compared with seasonal influenza in fall-winter 2022-2023

	Death rate at 30 d, % (95% CI)		Excess deaths at 30 d, % (95% CI)	Hazard ratio (95% CI)	*P* value for interaction
	COVID-19	Influenza			
Age, y					
≤65	1.29 (0.77-1.82)	1.33 (0.46-2.20)	-0.04 (-1.06 to 0.98)	0.97 (0.45-2.11)	Reference
>65	6.42 (5.85-6.98)	3.66 (2.77-4.54)	2.76 (1.71 to 3.81)	1.78 (1.37-2.31)	.10
COVID-19 vaccination status					
Unvaccinated	8.75 (7.46-10.01)	3.86 (3.09-4.63)	4.88 (3.39 to 6.37)	2.32 (1.80-3.00)	Reference
1 or 2 doses of vaccine	6.23 (5.22-7.23)	3.79 (3.03-4.56)	2.44 (1.17 to 3.70)	1.66 (1.28-2.17)	.009
Boosted	5.18 (4.55-5.79)	3.77 (3.00-4.53)	1.41 (0.43 to 2.39)	1.38 (1.09-1.76)	<.001
SARS-CoV-2 infection					
Primary infection	6.14 (5.58-6.69)	3.76 (2.99-4.51)	2.38 (1.44 to 3.32)	1.65 (1.32-2.08)	Reference
Reinfection	5.11 (4.11-6.09)	3.85 (3.08-4.62)	1.26 (0.00 to 2.52)	1.34 (1.01-1.78)	.15
Outpatient COVID-19 antiviral treatment					
No	6.03 (5.53-6.53)	3.75 (2.99-4.51)	2.28 (1.37 to 3.19)	1.63 (1.30-2.04)	Reference
Yes	4.81 (2.49-7.07)	3.81 (3.04-4.57)	1.01 (-1.41 to 3.42)	1.27 (0.75-2.16)	.42
Overall	5.97 (5.48-6.46)	3.75 (2.98-4.50)	2.23 (1.32 to 3.13)	1.61 (1.29-2.02)	

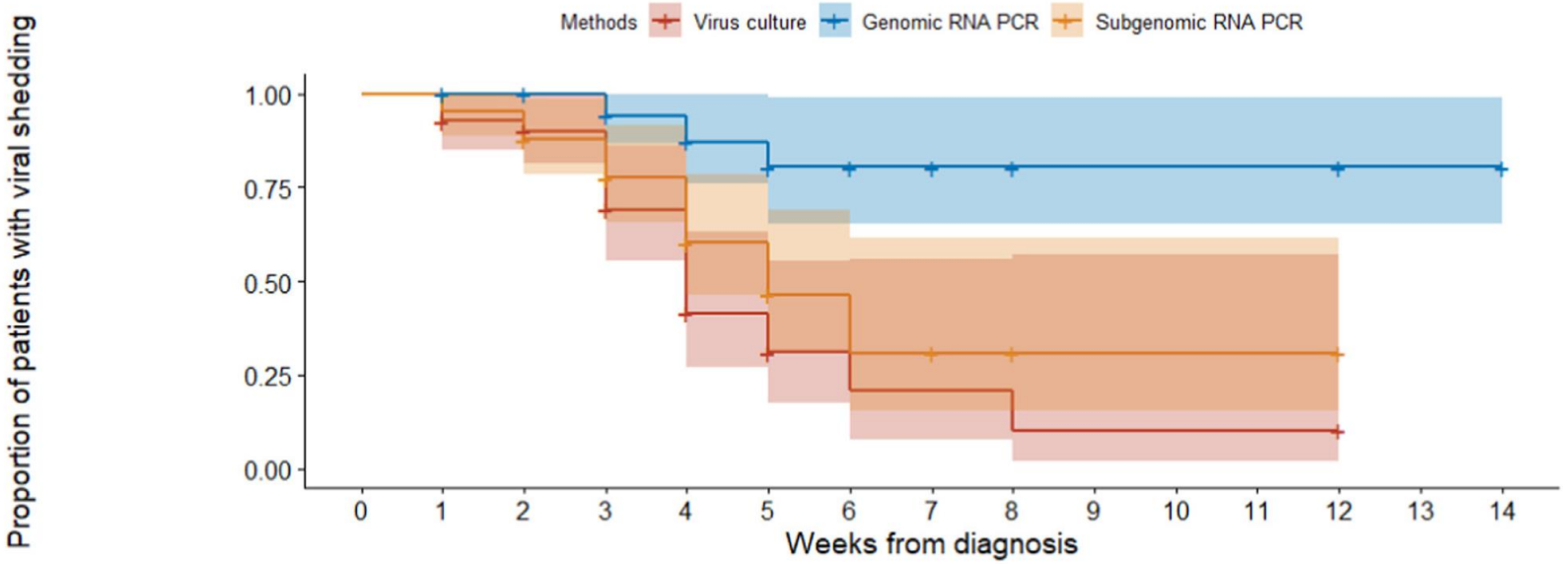


Xie Y et al, *JAMA 2023*

Characteristics and risk factors of prolonged viable virus shedding in immunocompromised patients with COVID-19

A total of **41 patients** were enrolled during the study period. Of these, **29 had hematologic malignancies**, and the remaining **12 underwent solid organ Tx.**

Of 142 saliva samples from the 41 patients, **102 (72%) gave positive culture results**. Survival analysis revealed **median of 4 weeks of viable virus shedding (IQR 3–6 weeks)**.



Variable	Total (n = 41)
Age, median years (IQR)	61 (47–65)
Male	27 (66)
Charlson's comorbidity index, median (IQR)	4 (2–5)
Hypertension	9 (22)
Diabetes mellitus	8 (20)
Solid cancer	3 (7)
Chronic kidney diseases	9 (22)
Chronic lung disease	1 (2)
Hematologic malignancy	29 (70)
Acute myeloid leukemia	8 (20)
Acute lymphoblastic leukemia	4 (10)
Myelodysplastic syndrome	3 (7)
Hodgkin's lymphoma	1 (2)
Non-Hodgkin's lymphoma	15 (37)
Solid organ transplantation	12 (30)
Kidney transplantation	9 (22)
Liver transplantation	2 (5)
Lung transplantation	1 (2)
Bone marrow transplantation	14 (34)
Allogenic	9 (22)
Autologous	5 (12)
Days since transplantation, median (IQR)	481 (181–4252)
B-cell depleting therapy[a]	10 (24)
Before COVID-19	4 (10)
After COVID-19	4 (10)
Before and after COVID-19	2 (5)
T-cell depleting therapy[b]	4 (10)
Initial Severity	
Asymptomatic	23 (56)
Mild	8 (20)
Moderate	6 (15)
Severe	4 (10)
Vaccination status	
None	12 (30)
Partial (1- or 2-dose)	15 (38)
Completion of primary series (3-dose)	14[c] (34)
Subvariants	
Omicron BA.1.	7 (17)
Omicron BA.2.	33 (80)
Undetermined	1 (2)

Kang SW, et al. Journal of Infection 86 (2023) 412–414

Punto di svolta 4: la terapia

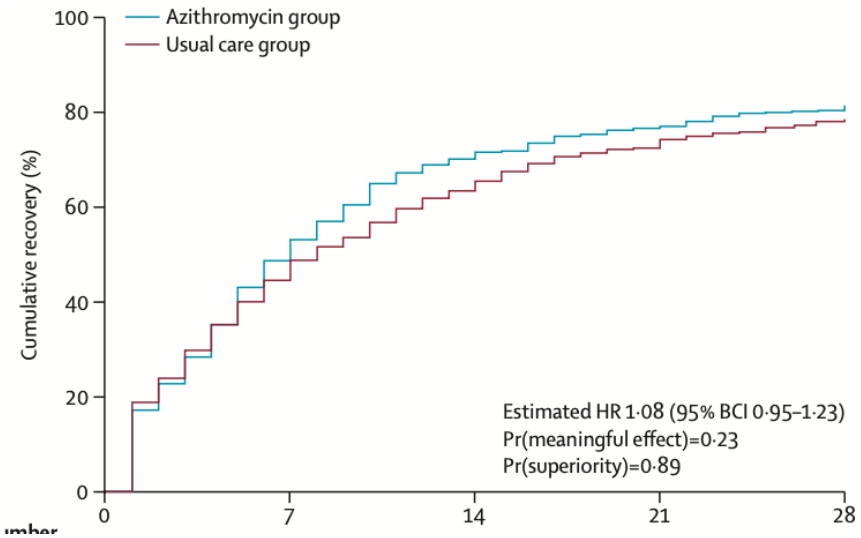
La Terapia di COVID-19: 2020

- **Farmaci antiretrovirali**
  - Lopinavir
  - Darunavir
- **Altri antivirali**
  - Remdesivir
  - Ribavirina
  - Favipiravir
- **Altri farmaci ad azione antivirale**
  - Clorochina
  - Idrossiclorochina
- **Farmaci immunomodulanti**
  - Corticosteroidi
  - Anti-IL6R (Tocilizumab, ecc)
  - Anti-IL1R (Anakinra, ecc)
  - Plasma iperimmune
- **Altri farmaci**
  - Eparine a basso peso molecolare o Eparina non frazionata
  - Antibiotici: Azitromicina

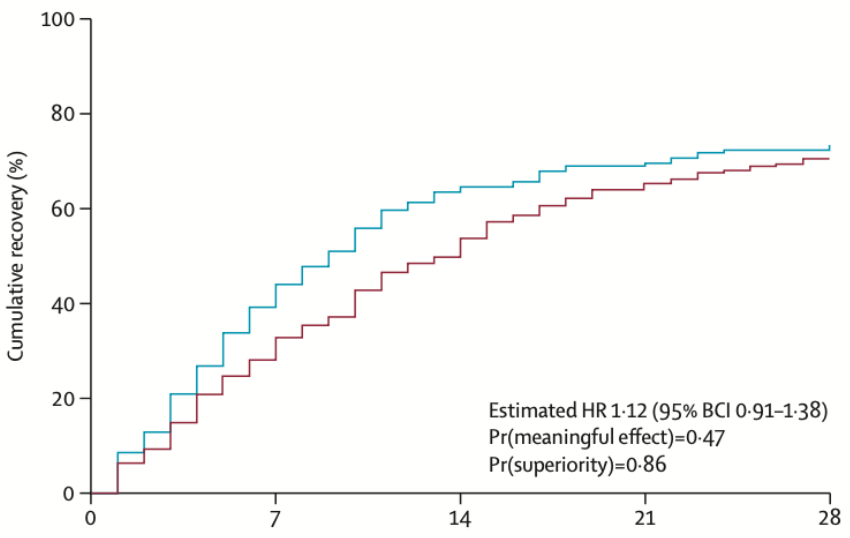
Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

*PRINCIPLE Trial Collaborative Group**

All



SARS-CoV-2 pos



Lancet 2021

Time to Stop Using Ineffective Covid-19 Drugs

Salim S. Abdool Karim, M.B., Ch.B., Ph.D., and Nikita Devnarain, Ph.D.

Time to stop using ineffective Covid-19 drugs

Salim S. Abdool Karim and Nikita Devnarain

Supplementary online Table 1: World Health Organisation recommendations on which medications should or should not be used to treat Covid-19 (adapted from the WHO living guidelines for therapeutics and Covid-19, 14 July 2022)[8]

	Strong recommendation against	Recommendation against	No recommendation for or against	Recommendation for	Strong recommendation for
Non-severe disease	• Convalescent plasma • Hydroxychloroquine • Lopinavir-ritonavir • Colchicine	• Corticosteroids[a] • Ivermectin[b] • Fluvoxamine[b] • Nirmatrelvir and ritonavir[a,c]	• Heparin • Metformin	• Molnupiravir[a,d] • Sotrovimab[a,d,e] • Remdesivir[a,d] • Casirivimab and imdevimab[a,d,f]	• Nirmatrelvir and ritonavir[d]
Severe disease	• Hydroxychloroquine • Lopinavir-ritonavir	• Ruxolitinib and tofacitinib[a] • Ivermectin[b] • Convalescent plasma[b]		• Casirivimab and imdevimab[a,f]	• Corticosteroids • IL-6 receptor blockers or Baricitinib

Note: Severe disease is defined as oxygen saturation <90% on room air, pneumonia or respiratory distress

[a] Conditional recommendation

[b] Only recommended for use within the context of a clinical trial

[c] In non-severe patients at low risk of hospitalization

[d] In non-severe patients at highest risk of hospitalization

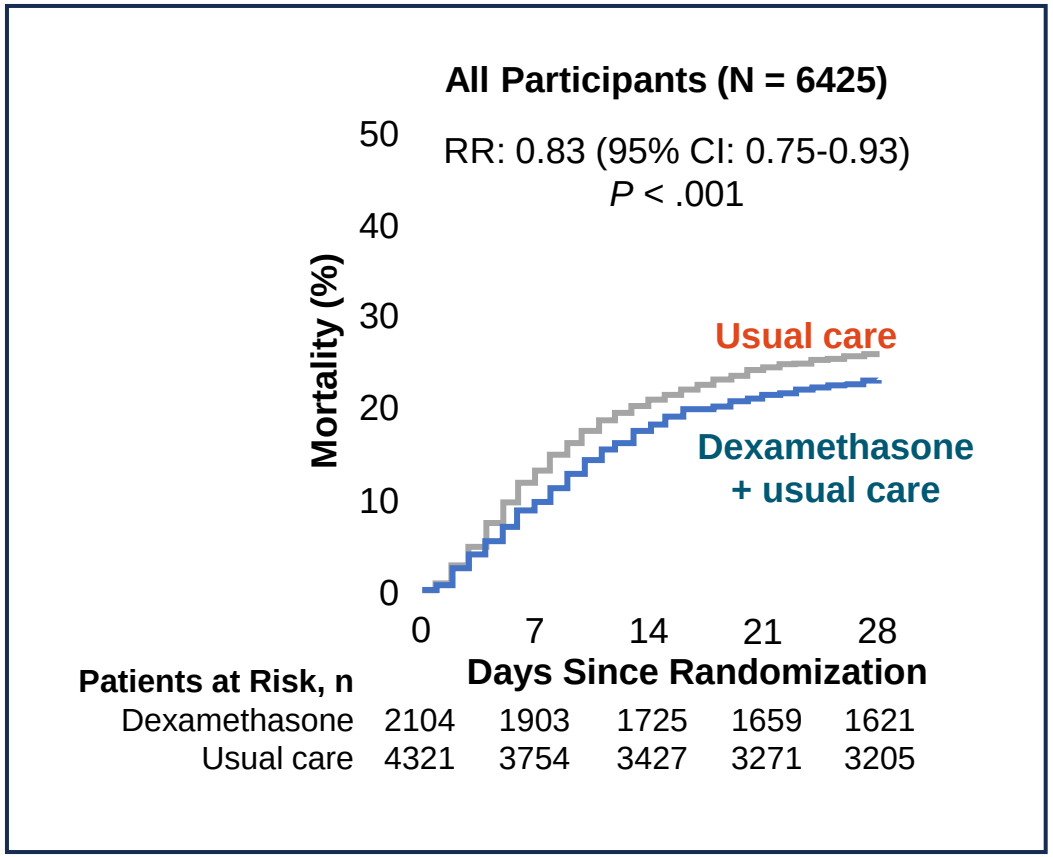
[e] Excluding pregnant or breastfeeding women, and children

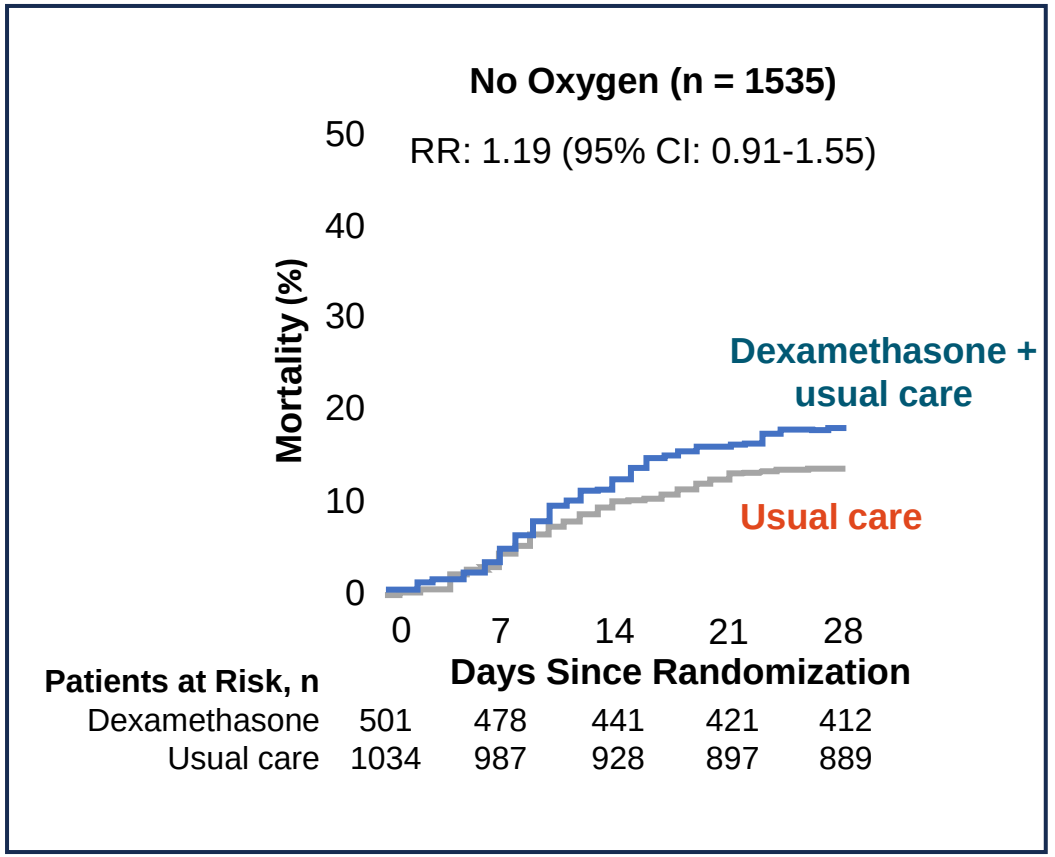
[f] If seronegative for SARS-CoV-2 antibodies (note: evidence of limited efficacy for omicron BA.1 variant)

[8]Agarwal A, Rochwerg B, Lamontagne F, Siemieniuk RA, Agoritsas T, Askie L, et al. A living WHO guideline on drugs for covid-19. BMJ. 2020;370:m3379.

N Engl J Med 2022

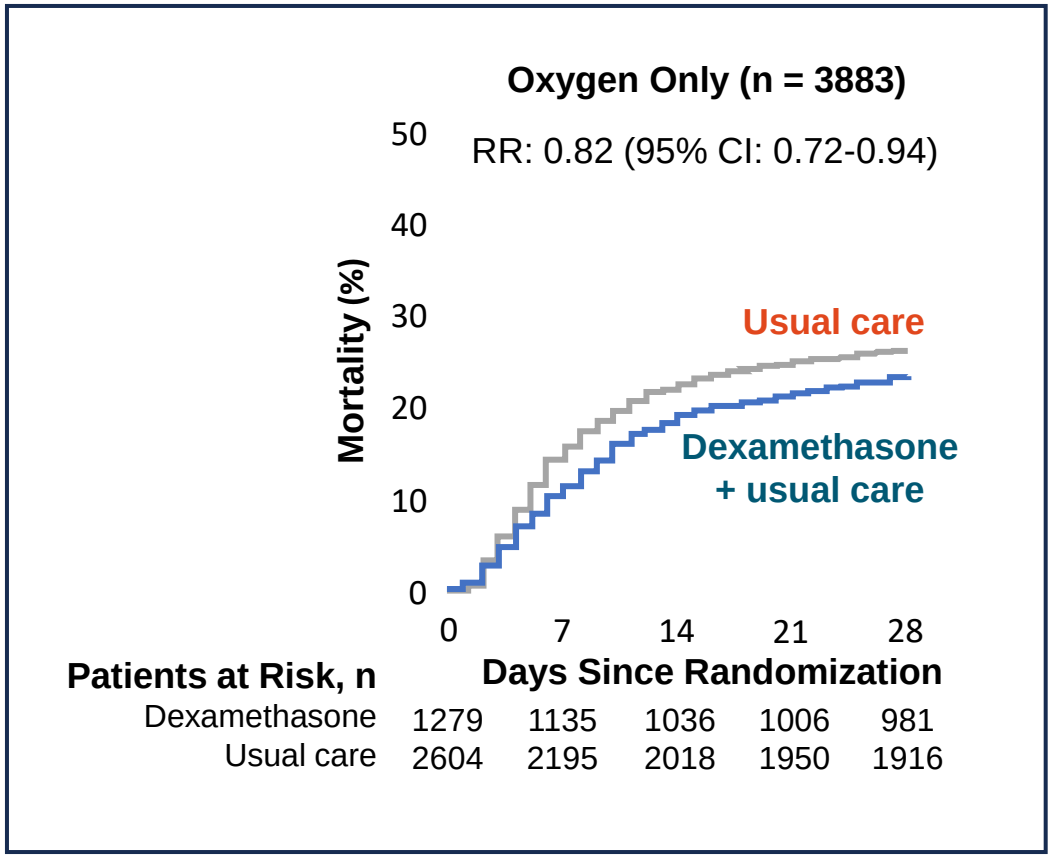
RECOVERY Trial: Mortalità con desametasone + cure usuali vs cure usuali da sole

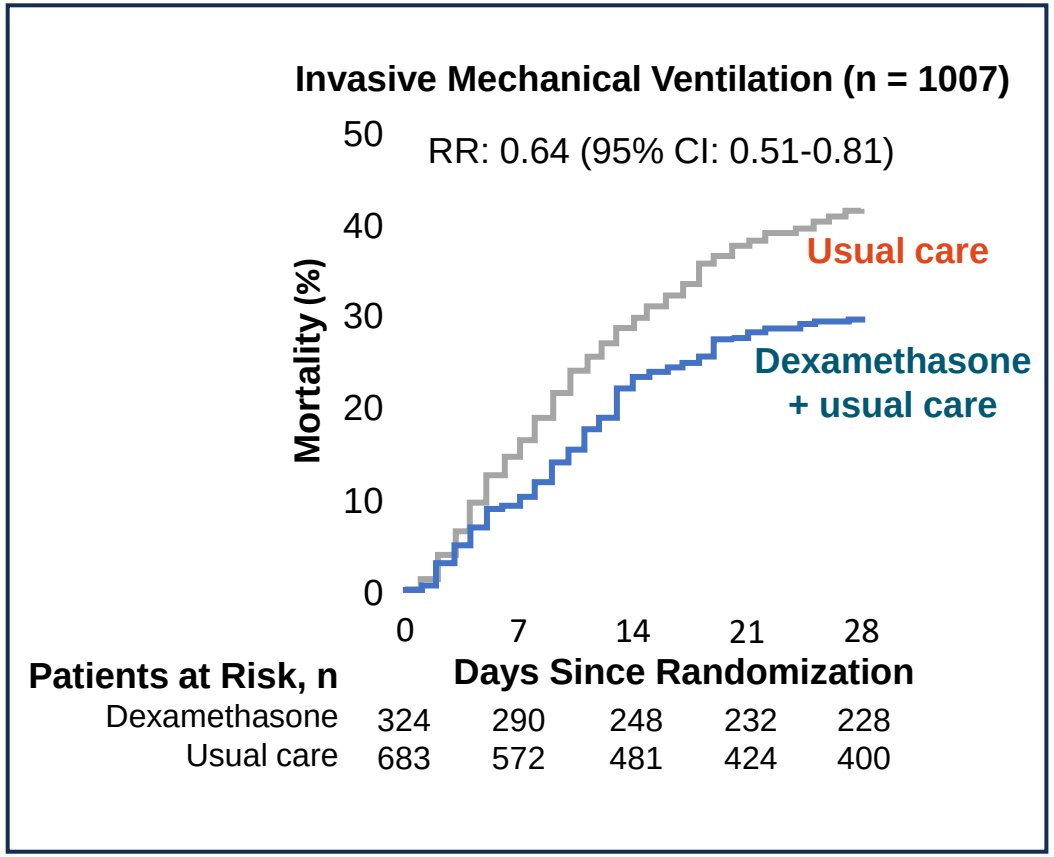




RECOVERY Collaborative Group. N Engl J Med 2021;384:693.

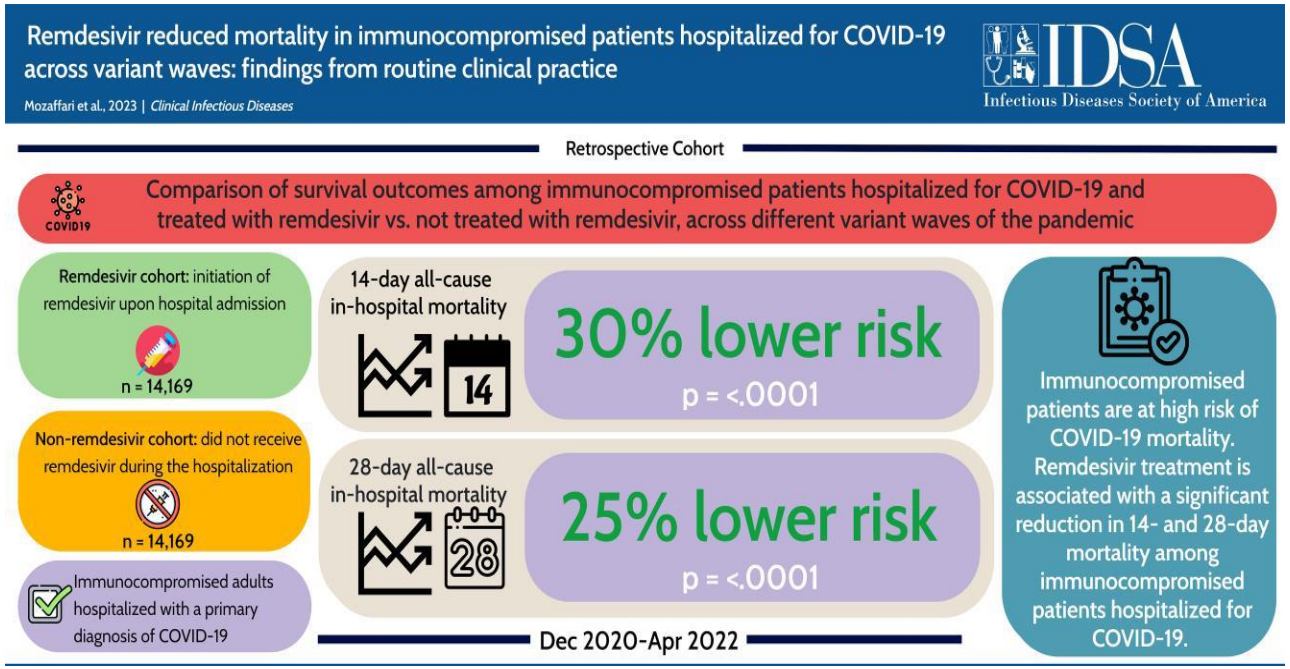
RECOVERY Trial: Mortalità nei pazienti con ossigeno o ventilazione meccanica ± desametasone





RECOVERY Collaborative Group. N Engl J Med 2021;384:693.

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



Patients who received remdesivir **within 2 days of hospitalization** were matched 1:1 using propensity score matching to patients who did not receive remdesivir.

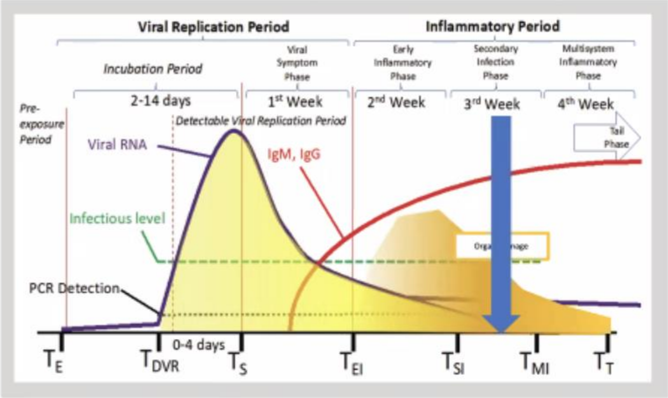
Remdesivir Tx: 11.1% and 17.7% patients died within 14 and 28 days,
Non Remdesivir: 15.4% and 22.4%
Reduction in mortality at 14 (HR, 0.70; 95% CI, .62–.78) and 28 days (HR, 0.75; 95% CI, .68–.83).

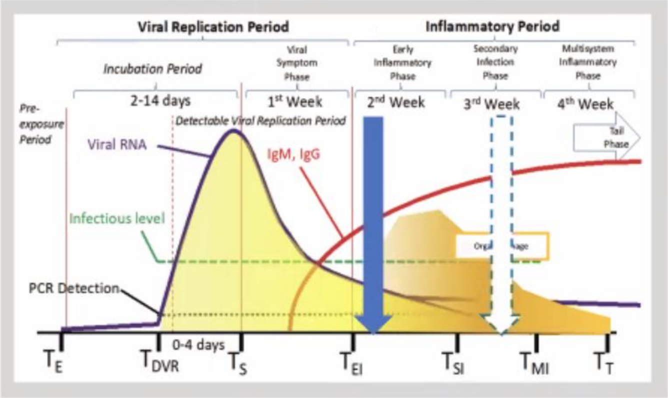
Characteristic		Before Matching, %		After Matching, %	
		Non-Remdesivir n = 11 213	Remdesivir n = 19 184	Non-Remdesivir n = 14 169	Remdesivir n = 14 169
Immunocompromised conditions	Cancer	25	22	23	23
	Solid organ and hematopoietic stem cell transplant	10	7	8	8
	Hematologic malignancies	18	16	18	17
	Moderate or severe primary immunodeficiencies	33	34	33	34
	Immunosuppressive medications	35	43	42	43
	Asplenia	3	3	3	3
	Bone marrow failure/Aplastic anemia	21	16	18	16
	Human immunodeficiency virus	2	2	1	2
	Toxic effects of antineoplastics	5	4	4	4
Comorbidities	Obesity	30	36	36	35
	Chronic obstructive pulmonary disease	31	34	34	34
	Cardiovascular disease	86	82	84	84
	Diabetes mellitus	41	39	40	40
	Renal disease	40	26	30	28

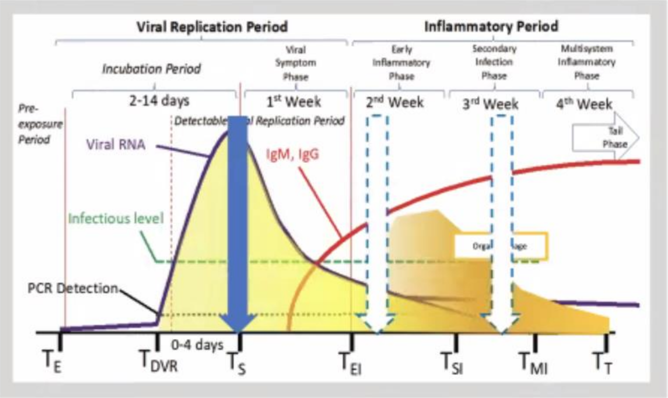
Mozaffari E, et al. CID 2023

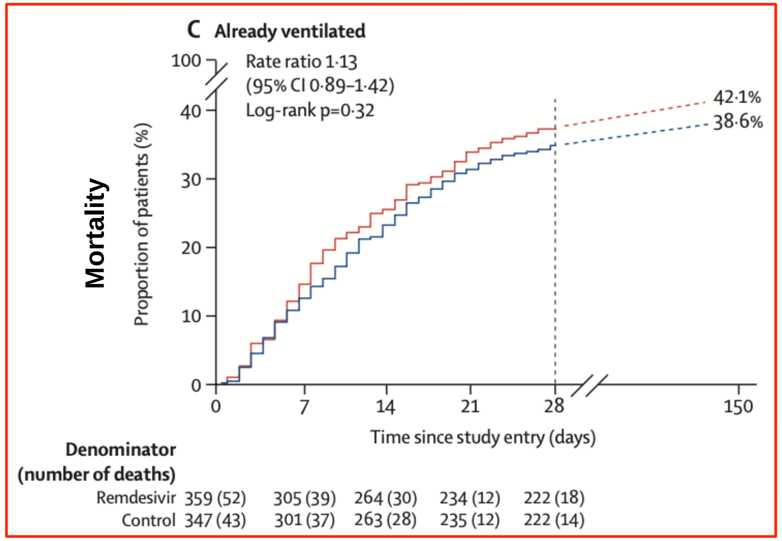
Remdesivir:

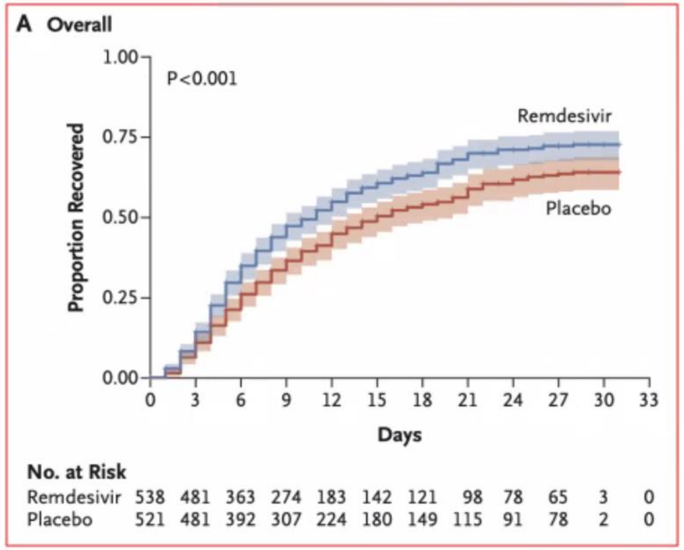
the Importance of Understanding the Stages of COVID-19 in treatment

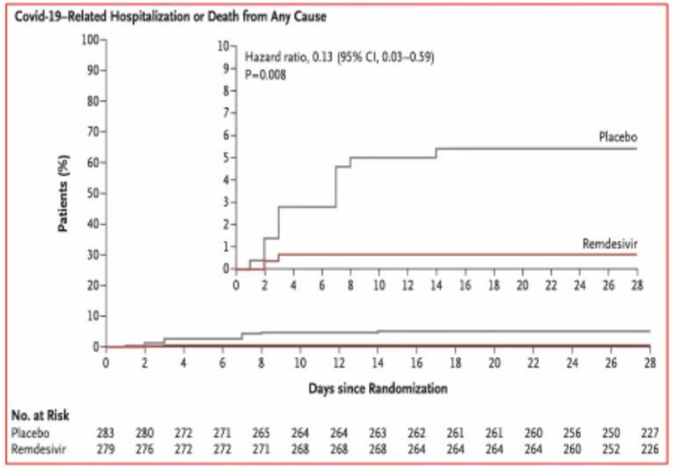












WHO Solidarity Trial Consortium, *Lancet 2022*

Beigel JH et al, N Engl J Med 2020

Gottlieb RL, et al, *N Engl J Med 2021*

Therapeutic Management of Hospitalized Adults with COVID-19

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a,b]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
Hospitalized but Does Not Require Supplemental Oxygen	All patients	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other systemic corticosteroids **(AIII)** for the treatment of COVID-19.[c]	
	Patients who are at high risk of progressing to severe COVID-19[a,b]	**Remdesivir**[d] **(BIIb)** for patients who are immunocompromised; **(BIII)** for other high-risk patients	
Hospitalized and Requires Conventional Oxygen[e]	Patients who require minimal conventional oxygen	**Remdesivir**[d,f] **(BIIa)**	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[h] **(CIIa)** For other patients: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[f] **(BIIa)**. If remdesivir cannot be obtained, use **dexamethasone (BI)**.	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add 1 of the following immunomodulators:[g] *Preferred* • **PO baricitinib (BIIa)** • **IV tocilizumab (BIIa)** *Alternatives* • **IV abatacept (CIIa)** • **IV infliximab (CIIa)**	
Hospitalized and Requires HFNC Oxygen or NIV	All patients	**Dexamethasone** should be administered to all patients **(AI)**. If not already initiated, promptly add 1 of the following immunomodulators: *Preferred* • **PO baricitinib**[g,i] **(AI)** *Preferred Alternative* • **IV tocilizumab**[g,i] **(BIIa)** *Additional Alternatives (Listed in Alphabetical Order)* • **IV abatacept**[g,i] **(CIIa)** • **IV infliximab**[g,i] **(CIIa)** Add remdesivir to 1 of the options above in certain patients (for examples, see footnote).[j]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation **(BIII)**.
Hospitalized and Requires MV or ECMO	All patients	**Dexamethasone** should be administered to all patients **(AI)**. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): • **PO baricitinib**[i,k] **(BIIa)** • **IV tocilizumab**[i,k] **(BIIa)**	

COVID-19 Treatment Guidelines 2023 - NIH

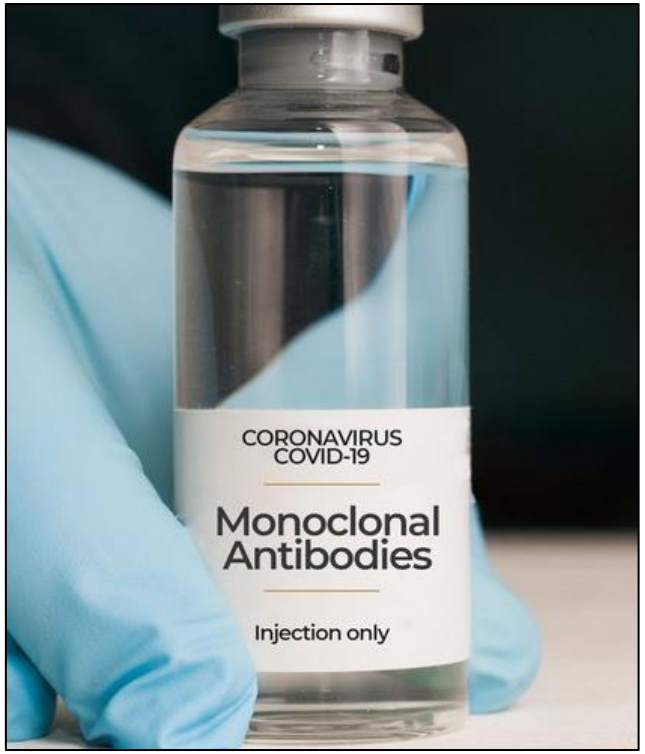
La terapia precoce

EGFR < 30
INTERAZIONI
PK
CAPSULE

EGFR < 30
TERATOGENICI
TA’
CAPSULE

EGFR < 30
EV su 3 GG

ANTIVIRALI



MONOCLONALI

Outpatient Antivirals: Reduced Hospitalization or Death

- Early use of antiviral agents significantly reduces risks of hospitalization or death compared with placebo
- Important to test and treat in timely fashion to maximize benefit

Study (Drug)	Start Date After Symptom Onset (Days)	RRR in Hospitalization or Death (%) Compared With Placebo	*P* Value
MOVe-OUT (molnupiravir)[1]	5	30	.0218
EPIC-HR (nirmatrelvir/ritonavir)[2]	3	89	<.001
	5	88	
PINETREE (remdesivir)[3]	7	87	.008

1. Bernal. NEJM. 2022;386:509. 2. Hammond. NEJM. 2022;386:1397. 3. Gottlieb. NEJM. 2022;386:305.

CRITERI AIFA

Il paziente presenta almeno uno fra questi fattori di rischio associati all'evoluzione in malattia grave *:	☐ Patologia oncologica/oncoematologica in fase attiva ☐ Insufficienza renale cronica ☐ Broncopneuomopatia cronica ostruttiva e/o altra malattia respiratoria cronica (ad es. soggetti affetti da asma, fibrosi polmonare o che necessitano di ossigenoterapia per ragioni differenti da SARS-CoV-2) ☑ Immunodeficienza primaria o acquisita ☑ Obesità (BMI >=30) ☐ Malattia cardio-cerebrovascolare (scompenso cardiaco, malattia coronarica, cardiomiopatia, ipertensione con concomitante danno d'organo, ictus) ☐ Diabete mellito non compensato (HbA1c>9.0% 75 mmol/mol) o con complicanze croniche ☐ Età >65 anni ☐ Epatopatia cronica ☐ Emoglobinopatie ☐ Patologie del neurosviluppo e patologie neurodegenerative

La terapia precoce

EGFR < 30
INTERAZIONI
PK
CAPSULE

EGFR < 30
TERATOGENICI
TA'
CAPSULE

EGFR < 30
EV su 3 GG

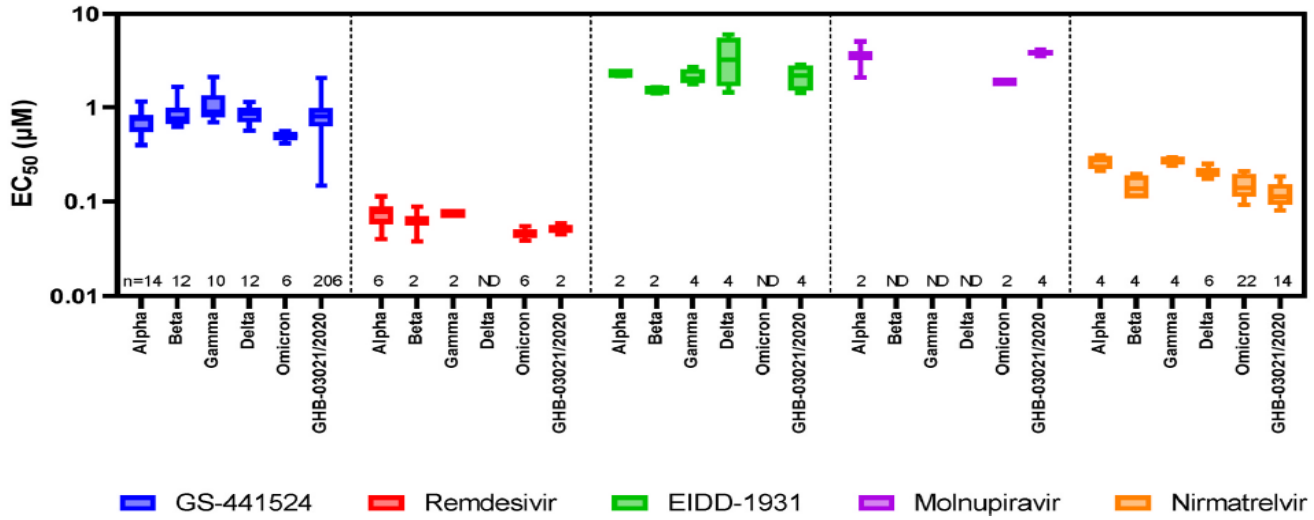
ANTIVIRALI

MONOCLONALI

Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern

Laura Vangeel [a], Winston Chiu [a], Steven De Jonghe [a], Piet Maes [b], Bram Slechten [c], Joren Raymenants [c,d], Emmanuel André [c,d], Pieter Leyssen [a], Johan Neyts [a,1,**], Dirk Jochmans [a,1,*]

[a] KU Leuven, Department of Microbiology, Immunology and Transplantation, Rega Institute, Laboratory of Virology and Chemotherapy, Leuven, Belgium
[b] KU Leuven, Department of Microbiology, Immunology and Transplantation, Rega Institute, Laboratory of Clinical and Epidemiological Virology, Leuven, Belgium
[c] University Hospitals Leuven, Department of Laboratory Medicine, Leuven, Belgium
[d] KU Leuven, Department of Microbiology, Immunology and Transplantation, Rega Institute, Laboratory of Clinical Bacteriology and Mycology, Leuven, Belgium



GS-441524, remdesivir, EIDD-1931, molnupiravir and nirmatrelvir retain their activity against all current VOCs including Omicron

Antiviral Research 198 (2022) 105252

Notably, these clinical trials were conducted before the omicron variant became prevalent, and in unvaccinated population

Real-world evidence of oral antiviral use in patients infected with the SARS-CoV-2 omicron variant is needed.

Prime conclusioni

- **Dati real life**:
  - efficacia di PAX (anziani ancorché vaccinati) 
  - efficacia di MOL (non vaccinati) 
- **Dati RCT**
  - PAX non dà vantaggio in basso rischio (EPIC-SR) 
  - MOL non dà vantaggio su *endpoint* forti, ma riduce durata sintomi di 4 giorni (PANORAMIC: soggetti a basso rischio, omicron, perlopiù vaccinati, trial non in cieco) 

Terapia di combinazione

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

The combination mAb and antiviral prevent the escape mutans virus and help to reduce viral burden

Copin R, et al. Cell 2021

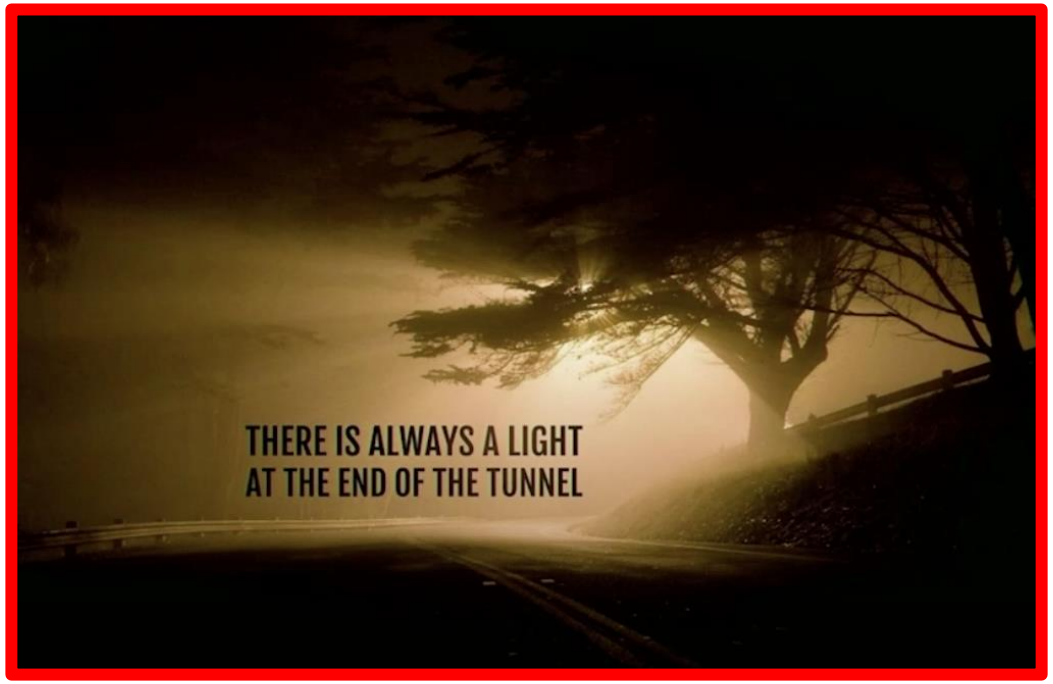
Baum A, et al. Science 2020

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)*

Non solo strategie di combinazione, ma per quanto tempo….

Punto di svolta 5:
il vaccino

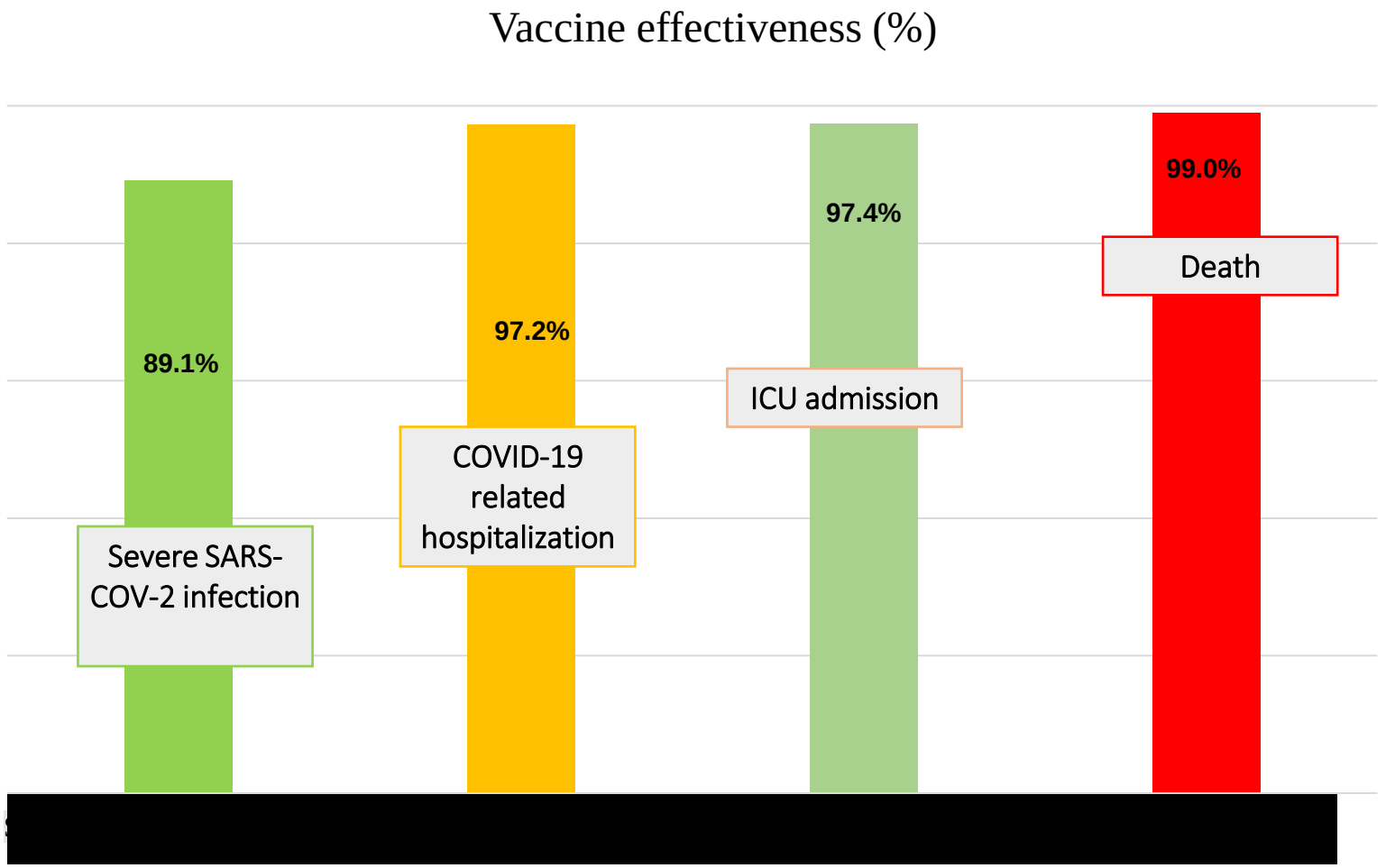
la svolta



Nobel Medicina 2023 a Karikó e Weissman per vaccino anti Covid

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.



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

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.

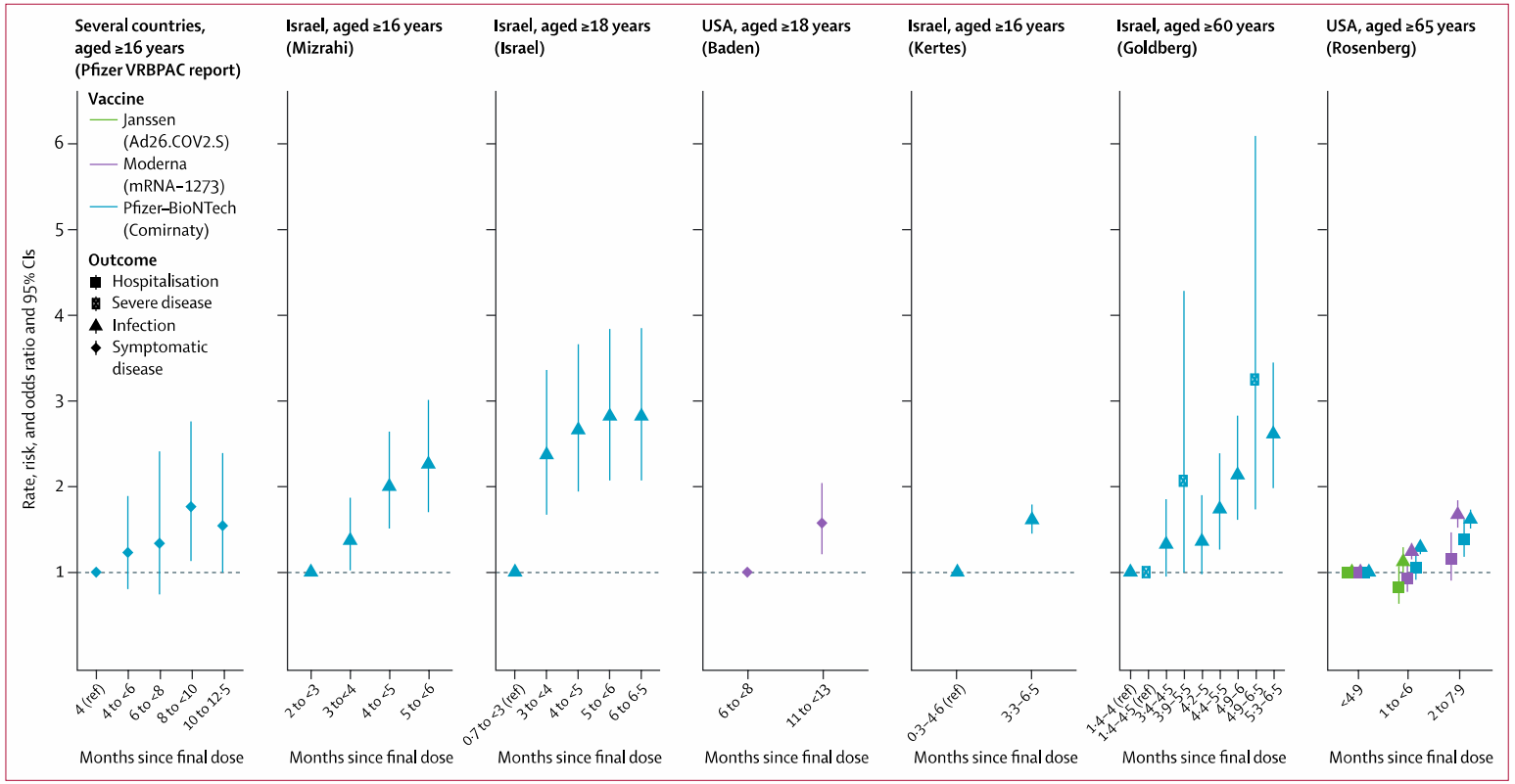


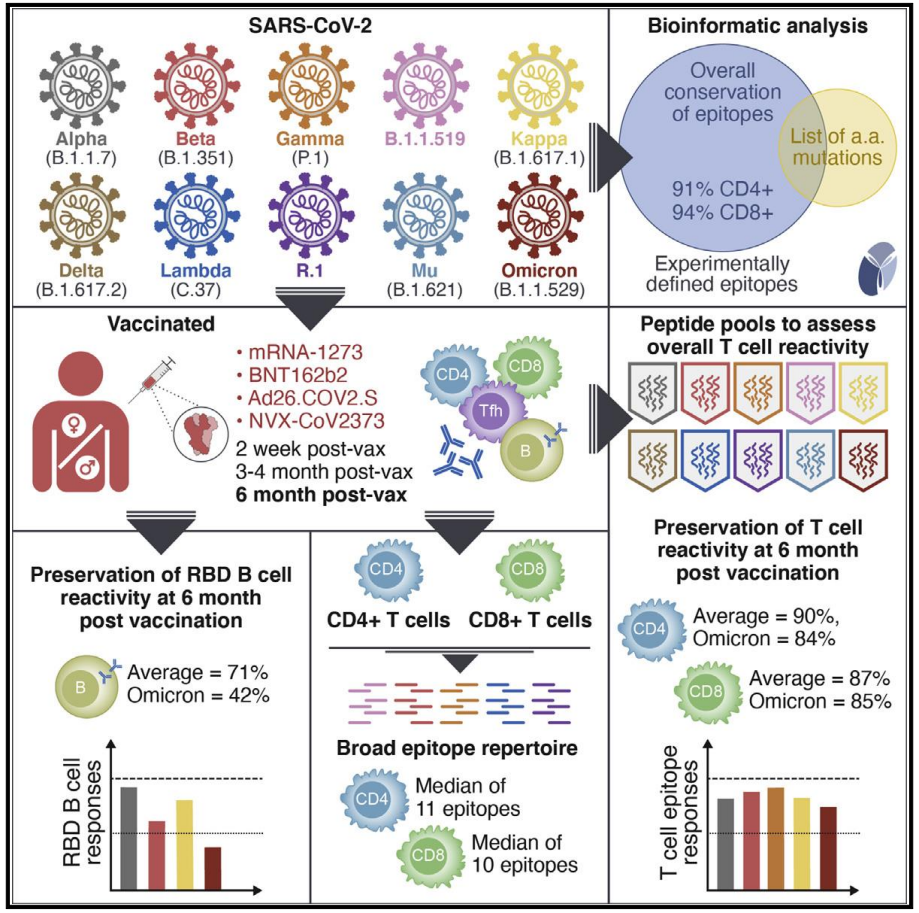
Figure 3: Rate, risk, and odds ratios of COVID-19 breakthrough cases caused by the delta variant by time of vaccination

Cell

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

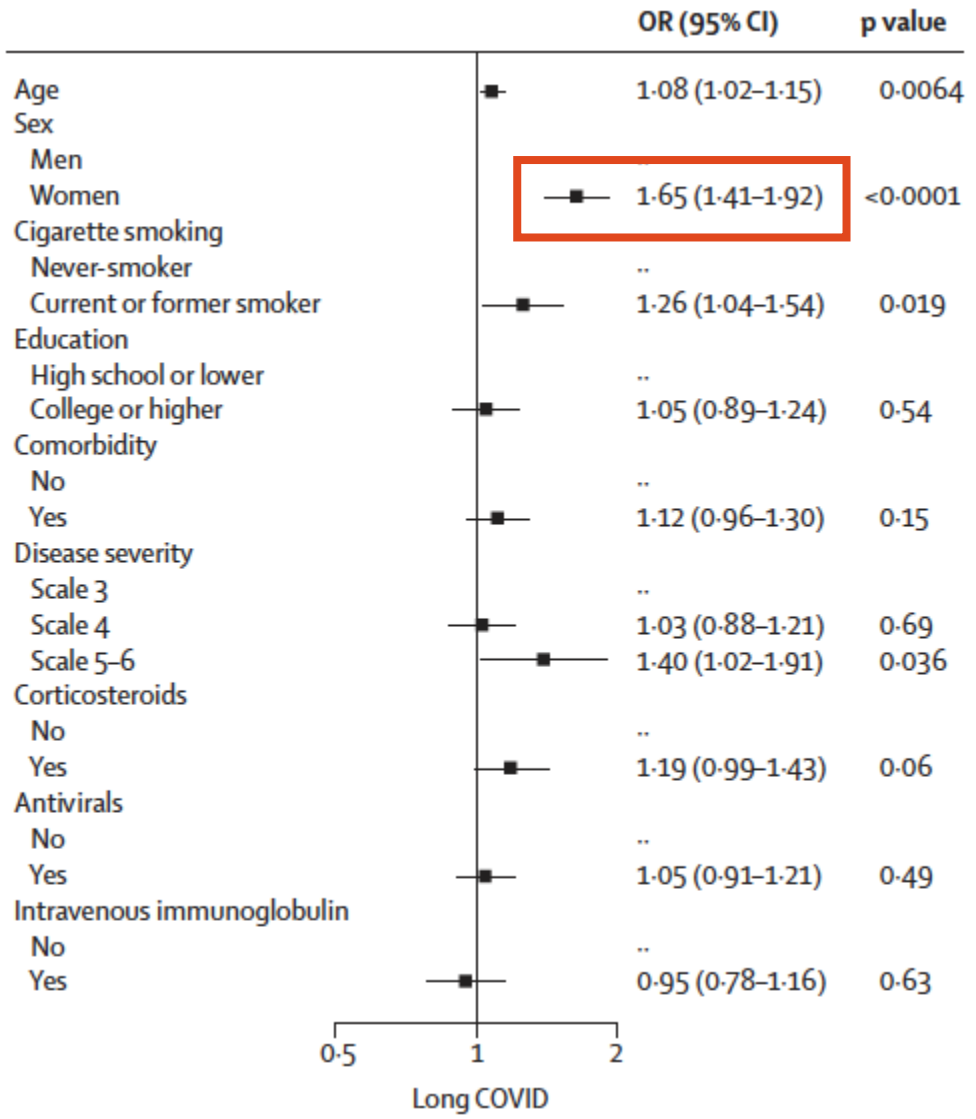
In brief

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

Appendice:
il long covid

COVID-19 survivors had a remarkably lower health status than the general population at 2 years

- **2,469 patients with COVID-19 were discharged from Jin Yin-tan Hospital between Jan 7 and May 29, 2020.**
- 1192 COVID-19 survivors completed assessments at the three follow-up visits and were included in the final analysis.
- The proportion of COVID-19 survivors with at least one sequelae symptom decreased significantly from **777 (68%) of 1149 at 6 months** to **650 (55%) of 1190 at 2 years** (p<0·0001)
- **Fatigue or muscle weakness** always being the most frequent.
- **COVID-19 survivors still had more prevalent symptoms and more problems in pain or discomfort, as well as anxiety or depression, at 2 years than did controls.**



Huang L, et al. Lancet Respir Med 2022; 10: 863–76

Long COVID Incidence and Prevalence

- ≥65 million individuals worldwide have long COVID (10% of >651 million documented COVID-19 cases)
  - Actual incidence likely much higher because of undocumented cases
- Occurs at all ages and acute phase disease severities
  - Highest percentage of diagnoses in those aged 36-50 yr
- Incidence rates by hospitalization and vaccination status
  - 10%-30% of nonhospitalized cases
  - 50%-70% of hospitalized cases
  - 10%-12% of vaccinated cases

Davis. Nat Rev Microbiol. 2023;21:133.

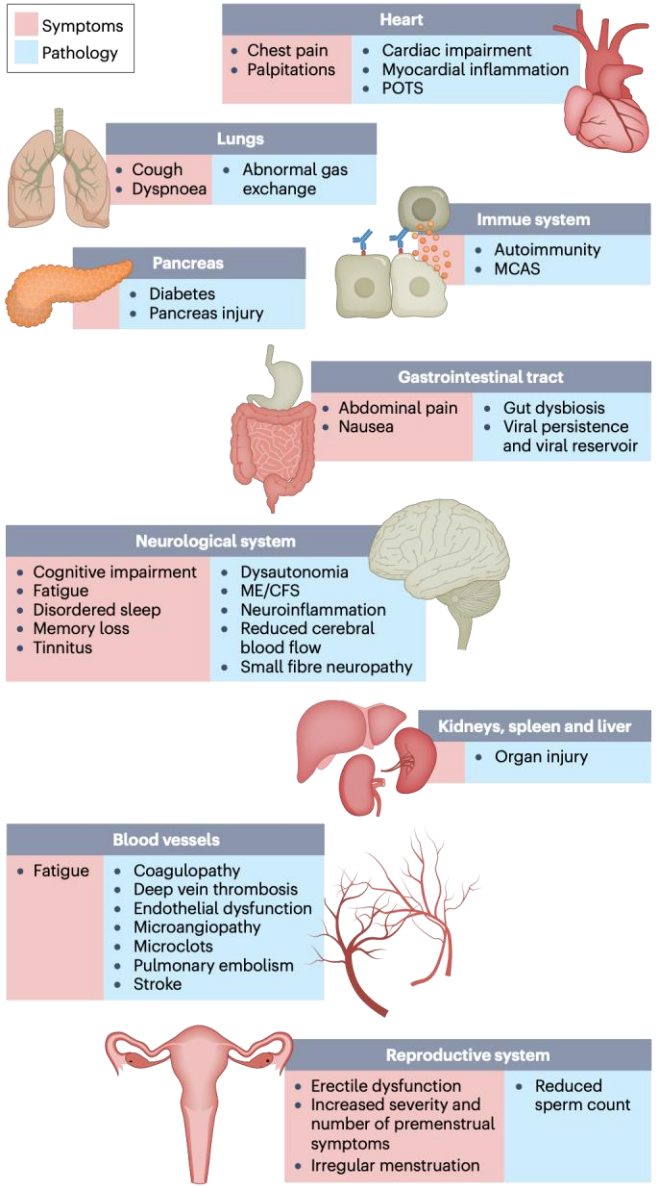
Severity of PASC

- Incidence of severe forms of PASC is **6% to 18%**
  - Higher among hospitalized and older patients
- PASC should be recognized as severe manifestation of COVID-19
  - High morbidity, mortality, and **strain to health systems**

Author	Cohort Size, N	Time Period, Mo	Overall PASC Incidence, %	Estimated Severe PASC, %
Zhang	2433	12	50	12
Taquet	273,618	6	57	7-11
Groff	250,000	6	55	15-18
Ziaudeen	3000	6	64-80	17
Logue	237	6	30	6
Bull-Otterson	353,164	30	21-27	8-11
Wulf Hanson	1,300,000	12	3.7	15

Lehman. The Open COVID Journal. 2022;e266695872209160.

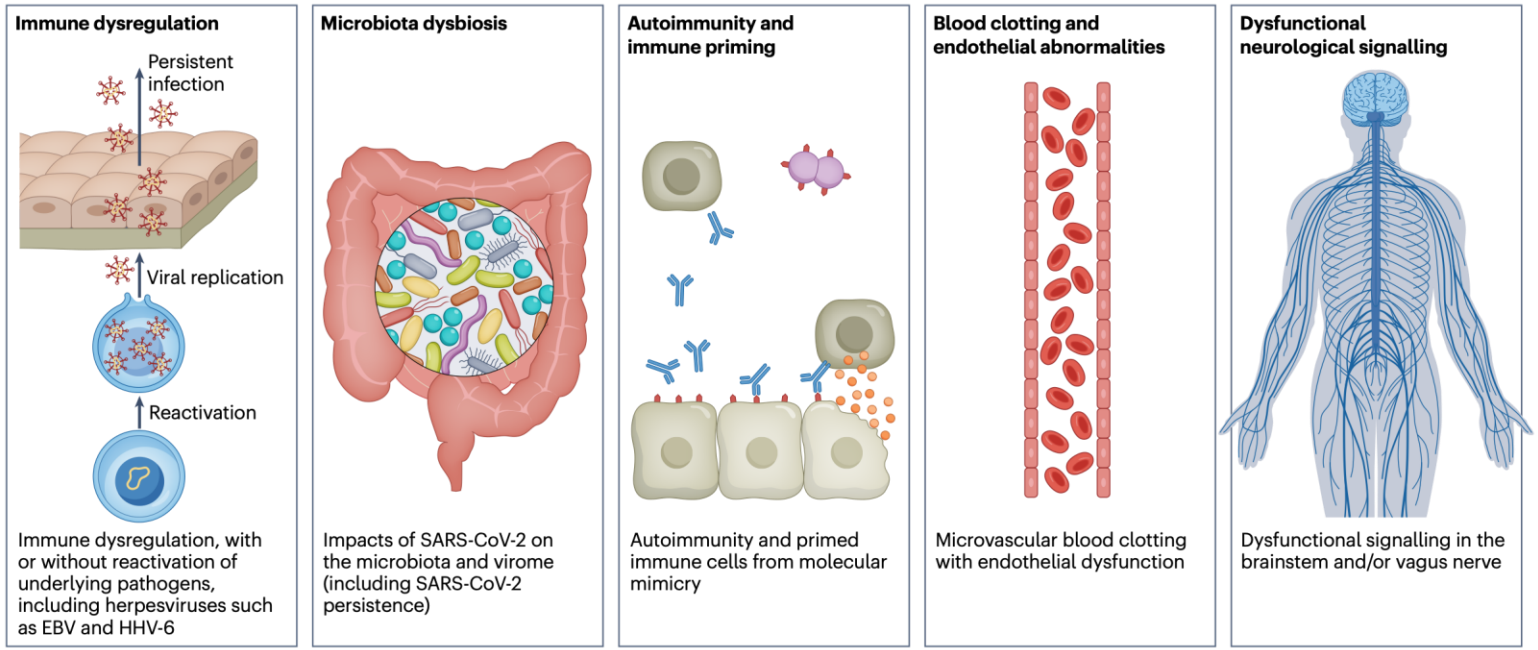
Long Covid



Persistenza o sviluppo di nuovi sintomi 3 mesi dopo l'infezione primaria da Sars-CoV-2. I sintomi devono perdurare per almeno 2 mesi senza altre cause evidenti.

(OMS)

65 milioni di pazienti stimati nel mondo (10%)

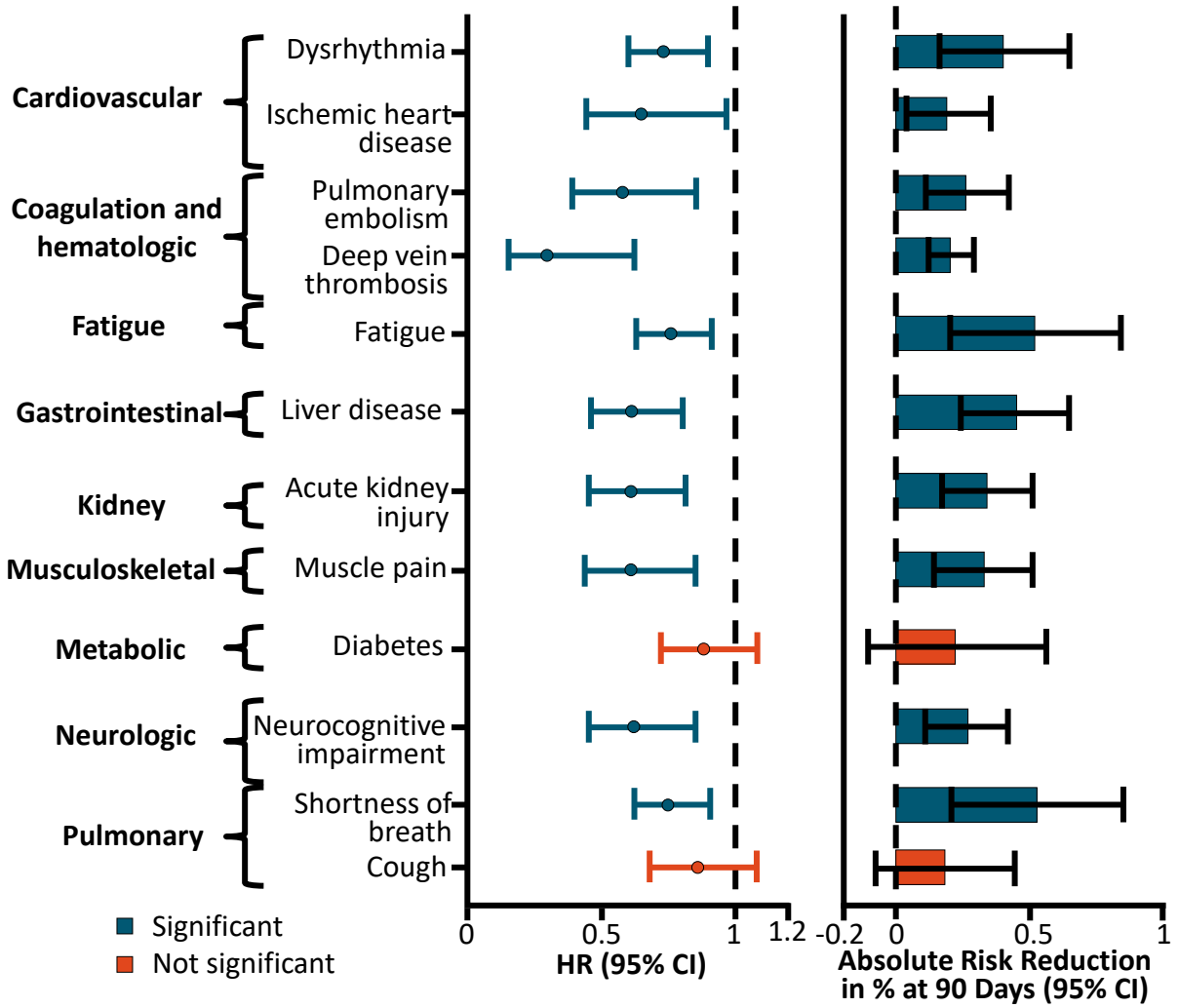


https://doi.org/10.1038/s41579-022-00846-2

Nirmatrelvir + Ritonavir Impact on PASC Symptoms

- VA Study of nonhospitalized patients with 1 comorbidity from May 2022 to June 2022
  - 56% vaccinated and boosted; 24% with 2-vaccine series; 16% no vaccination
  - 9217 taking nirmatrelvir + ritonavir; 47,123 untreated

Reduced Risk of:	% Reduction
PASC	26
Post acute COVID-19 hospitalization	30
Post acute COVID-19 death	49



Xia. MedRxiv. 2022;[Preprint].

Slide credit: clinicaleducationalliance.com:

Long COVID Treatments Under Consideration

- Investigational agents for long COVID
  - LYT-100
    - Deuterated pirfenidone
  - Leronlimab
    - CCR5 antagonist
  - LMWF5A
    - Anti-inflammatory peptide
  - SNG001
    - Inhaled interferon beta

- Currently available drugs being studied to treat long COVID
  - Budesonide (inhaled)
  - Colchicine
  - Fluvoxamine
  - Monoclonal antibodies
  - NSAIDS
  - SARS-CoV-2 vaccination
  - Sirolimus
  - Statins
  - Vitamin D

Schmidt. Nat Biotechnol. 2021;39:908.

VIEWPOINT

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

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Since the end of the US Public Health Emergency on May 11, 2023, there has been a desire from elected officials and the public to put COVID-19 in the rearview mirror. However, the emergence of new variants and a summer wave of infections remind us that SARS-CoV-2 is here for the foreseeable future. This Viewpoint addresses the current state of COVID-19 in the US and summarizes key clinical information for health care professionals and patients.

Current State of COVID-19 in the US

With the end of the Public Health Emergency, COVID-19 surveillance in the US is no longer performed using case counts. Instead, wastewater surveillance and tracking of hospitalizations and deaths are the major indicators being used to understand trends. Since late June 2023, there has been a steady increase in the detection of SARS-CoV-2 in wastewater, a change that correlates with a bump in reported hospitalizations and deaths.

However, these increases are small compared with those seen early in the pandemic when most of the population lacked any protective immunity to the virus and infection not uncommonly led to severe illness and even death for a substantial proportion of those infected. As a result of vaccination and infection, population immunity has increased. By the end of 2022, an estimated 97% of people aged 16 years or older had infection or vaccination-induced antibodies,[1] and the estimated age-adjusted COVID-19–associated death rate decreased 47%, from 115.6 per 100 000 persons in 2021 to 61.3 per 100 000 persons in 2022.[2]

> How disruptive these [COVID-19 waves] are will depend on the behavior of the virus but also, more importantly, on the behavior of humans.

Hybrid immunity (vaccination plus infection) provides the most robust protection against severe disease, hospitalization, and death.[1] However, the prevalence of hybrid immunity appears to be lowest among those aged 65 years and older, and immunity from vaccines wanes over time and that decrease is faster among older adults. This is why the US Centers for Disease Control and Prevention (CDC) has recommended that those 65 years and older receive an additional booster.[3]

Viral Evolution After Omicron

Since the initial emergence of the Omicron variant in November 2021, the virus has continued to rapidly evolve, acquiring mutations that provide it with increasing immune escape. The XBB.1.5 variant was first detected in the US in October 2022 and by January 2023 it had become the dominant variant observed. This prompted the US Food and Drug Administration (FDA) to recommend that the fall 2023 COVID-19 vaccine be a monovalent preparation targeting XBB.1.5. However, since then, 3 additional variants have emerged, EG.5, FL.1.5.1, and now BA.2.86. XBB.1.5 shares a nearly identical spike amino acid profile with EG.5 and FL.1.5.1, so there is confidence that the new monovalent vaccine will be protective. However, the large number of mutations in the spike protein of BA.2.86 raises concerns for greater immune escape from existing immunity from vaccines and prior infection and the possibility of a massive wave of cases as occurred with Omicron.[4] It is currently unknown if the BA.2.86 variant is highly transmissible or if the monovalent XBB.1.5 vaccine will provide protection. However, there is also no evidence that infection with BA.2.86 is more severe or that the mutations present in this variant will affect the utility of diagnostic tests or antivirals.

Limiting Transmission of SARS-CoV-2

The need for nonpharmacologic interventions (NPIs) was greatest early in the pandemic when the population was immunologically naive. As population immunity increased through vaccination, infection, or both, the relative importance of NPIs decreased, but their value may differ depending on the medical vulnerability of individual patients (eg, someone who is highly immunocompromised) and populations (eg, older adults living in a nursing home). Face coverings (masks) have become politicized and their role poorly understood. Not all face masks are the same, and mask quality and proper use are both essential to overall effectiveness. In general, older adults and those who are immunocompromised should strongly consider masking during influenza, respiratory syncytial virus (RSV), and COVID-19 surges while in crowded indoor public spaces. For everyone else, the decision to use a mask depends on their risk tolerance. In health care settings, masking remains a highly effective intervention during periods of peak respiratory virus transmission.[5] Ventilation is also an important measure to reduce risk of transmission not only of SARS-CoV-2 but other respiratory viruses and bacteria.[6]

What Is the Current Role of Vaccination?

COVID-19 vaccination is recommended for everyone 6 months and older in the US. Vaccination is safe and effective and protects against the most serious effects of SARS-CoV-2 infection, specifically hospitalization and death. However, protection against symptomatic infection is limited, and waning of immunity is a reality with the currently available vaccines. Among adults who are otherwise healthy ("immunocompetent"), recent estimates of vaccine effectiveness of a bivalent vaccine against hospitalization for COVID-19 were 62% compared with no vaccination in the 2 months after the bivalent dose but decreasing to 24% 4 to 6 months after the bivalent dose.[7] The CDC considers an individual who has completed a primary series and received a single booster as "up to date" in their COVID-19 vaccination. If they have completed a primary series and are not yet eligible for a booster, they are also up to date. However, an individual who has completed a primary series and is eligible for a booster but has not received a booster is not up to date.[3] For people aged 65 years and older, there is the option to receive 1 additional bivalent mRNA vaccine dose if it has been at least 4 months since their first bivalent vaccine dose.

Pfizer/BioNTech and Moderna have filed applications with the FDA for their XBB.1.5 monovalent COVID-19 vaccine for individuals 6 months of age and older. The CDC is expected to issue recommendations on who should receive this updated vaccine by mid-September. Given that there is unlikely to be much protection against symptomatic infection, it may be that the CDC recommendations will focus on providing additional protection to more vulnerable populations (older adults and individuals who are immunocompromised), but it is likely that the recommendation will be for everyone 6 months and older to be up to date in their immunizations and thus receive this vaccine.

When to Test and When to Use Antivirals?

Diagnostic testing and antiviral medications are additional tools to manage COVID-19. Antigen tests ("home tests") are less likely to detect the virus than polymerase chain reaction (PCR) assays, but antigen tests are readily available and thus used most frequently. All currently approved tests can detect circulating variants. When a person is symptomatic, a single negative antigen test result cannot rule out infection and another test should be done 48 hours later.

Nirmatrelvir-ritonavir (Paxlovid), which received full FDA approval in May 2023, is the preferred outpatient antiviral medication and the drug prescribed most frequently. This medication reduces the risk of severe illness, including hospitalization and death, by about half in those at high risk (older persons, those who are immunocompromised, and patients with underlying neurological and cardiovascular disease) regardless of vaccination status.[8] However, despite its effectiveness, many who are at increased risk of severe illness are not being prescribed this medication. Several reasons are thought to be causing this underutilization of nirmatrelvir-ritonavir, but drug-drug interactions and the fear of a rebound are commonly cited. Improving education among the public as well as among prescribing clinicians about the benefits of antivirals is essential to limit severe outcomes among the most medically vulnerable.

Conclusions

COVID-19 may be forgotten but it is not gone. As the US continues to emerge from the pandemic it is essential that clinicians and patients keep SARS-CoV-2 on the list of viral pathogens that cause major respiratory illness. Protecting the most vulnerable populations should be a priority. This includes making vaccinations, high-quality masks, testing, and antivirals easily available. Finally, perhaps the most important way to limit transmission is self-isolation of those who are infected. Regardless of test results, any person with symptoms of a respiratory infection should remain home and avoid going to school or work. While COVID-19 is no longer a public health threat, waves of infection will occur for the foreseeable future. How disruptive these are will depend on the behavior of the virus but also, more importantly, on the behavior of humans.

ARTICLE INFORMATION

Published Online: September 12, 2023. doi:10.1001/jama.2023.19049

Conflict of Interest Disclosures: Dr del Rio reported receiving grants from NIH/NIAID via the Emory Vaccine and Treatment Evaluation Unit during the conduct of this work. No other disclosures were reported.

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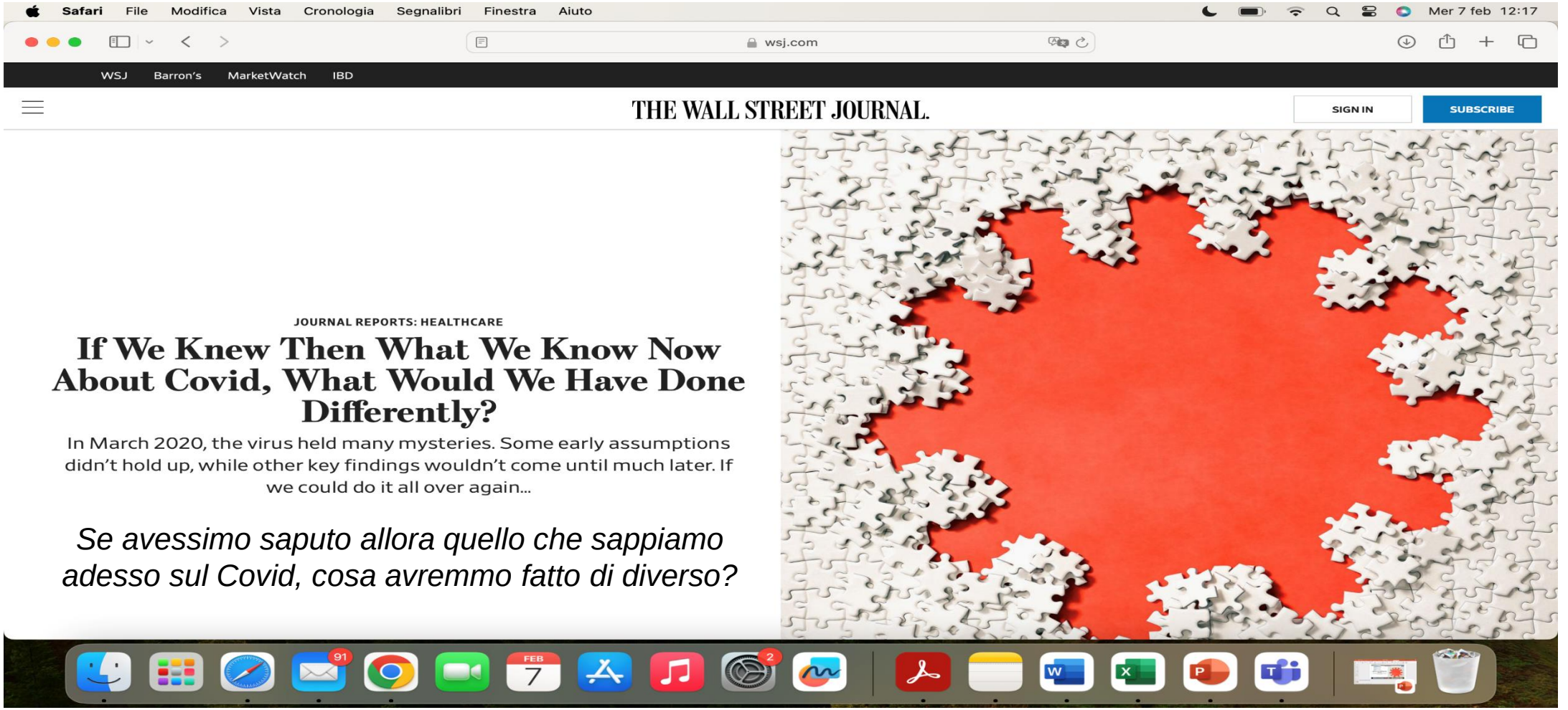

"Humanity's memory is short, and what is not ever-present fades quickly"

"La memoria dell'umanità è breve e ciò che non è sempre presente svanisce rapidamente"