Understanding the Covid Patient and a Comprehensive Approach to Early Treatment

Peter A. McCullough, MD, MPH

Chief Medical Advisor, Truth for Health Foundation
President, Cardiorenal Society of America
Editor-in-Chief, *Reviews in Cardiovascular Medicine*
Senior Associate Editor, *American Journal of Cardiology*
Tagline: https://americaoutloud.com/the-mccullough-report/


WASHINGTON, DC
SUNDAY
DEFEAT THE MANDATES
LET DOCTORS BE DOCTORS
FOX NEWS
TUCKER CARLSON TONIGHT

September 17, 2021

Governments Have Lost the War Against the Virus

by **Bryan Hyde** | Sep 17, 2021

The idea that the political class has leveraged fear over the Covid-19 pandemic into control over the public isn't just a conspiracy theory. Scott Morefield explains how this is evident to any person who recognizes that governments have lost the war against the virus....

This Den of Thieves is Full of Corrupted Government Officials

by **Susan Price** | Sep 16, 2021

Vaccinated or Not, Acute COVID-19 in High-Risk Patients Demands Early Treatment

by **Dr. Peter McCullough** | Aug 17, 2021 | Healthcare, Politics,

When COVID-19 deaths occur in the hospital the most common finding is blood clots in the lungs and elsewhere in the body due to inadequate anticoagulation. Hopefully with these tips, for those who have COVID-19 or will get it soon, whether vaccinated or not, will be useful in keeping the syndrome to a mild 4-day cold and a deliverance to natural immunity...

Outline

- SARS-CoV-2 infection (COVID-19)
- Pillars of pandemic response
- Role of early ambulatory treatment
  - Anti-spike protein antibody infusions
  - Hydroxychloroquine
  - Ivermectin
  - Paxlovid
  - Molnupiravir
  - Corticosteroids
  - Colchicine
  - Anticoagulants
- Early sequenced multidrug therapy
- COVID-19 vaccine safety and efficacy
- Conclusions

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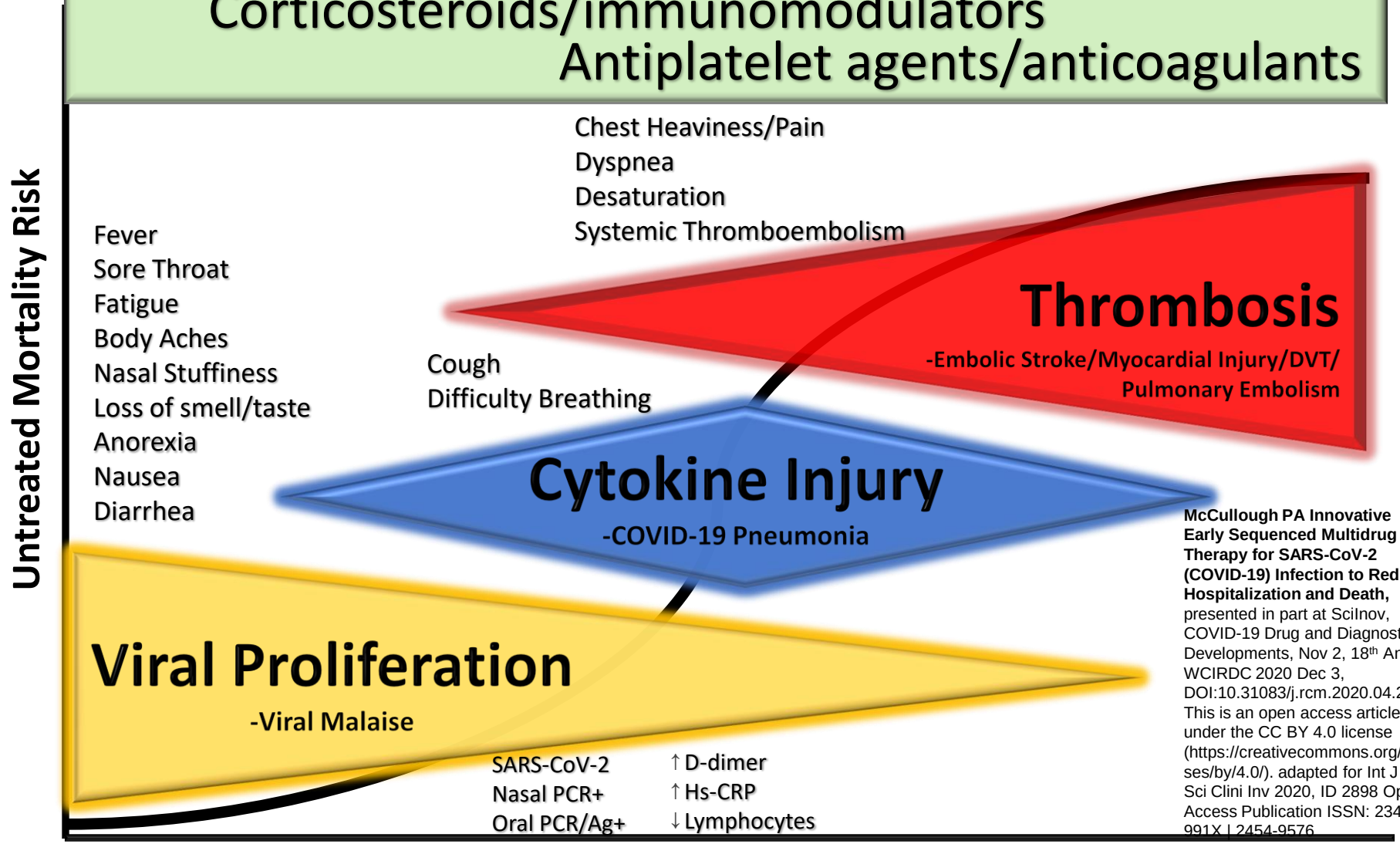
Therapeutic Response

Intracellular anti-infectives/antiviral antibodies
Corticosteroids/immunomodulators
Antiplatelet agents/anticoagulants



McCullough PA Innovative Early Sequenced Multidrug Therapy for SARS-CoV-2 (COVID-19) Infection to Reduce Hospitalization and Death, presented in part at SciInov, COVID-19 Drug and Diagnostic Developments, Nov 2, 18th Annual WCIRDC 2020 Dec 3, DOI:10.31083/j.rcm.2020.04.264

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Four Pillars of Pandemic Response

Contagion Control
"Stop the Spread"

Early Home Treatment
"↓ Hospitalizations/Death"

Late-Stage Treatment In-Hospital
"Safety Net for Survival"

Vaccination
"Herd Immunity"

*Correspondence: peteramccullough@gmail.com (Peter A. McCullough)
DOI:10.31083/j.rcm.2020.04.264

The Weekend

Listen on iHeart Radio
or our Media Player.

The McCullough Report
At-Home Management of COVID-19, Everyone Can Do 2 pm ET

Energetic Health Radio
The CDC's Dirty Little Secret w/ Dr. Henry Ealy 3 pm ET

The Frankly Daniel Show
A Fractured Biden COVID-19 Fairy Tale w/ Daniel Baranowski 4 pm ET

Dr. Henry Ealy
This Week In COVID: Vaccine Breakthrough Increases By 78.8% In Only 1 Month

Dr. Peter McCullough
Omicron Unleashes Mass Illness and a New Reality on podcast

A New Year Begins

New Year Brings New Hope

by DrLee4America

It is a New Year, and with that comes a feeling of new potential, new hope, and optimism – if you choose to change your outlook on what role you play in how you view each day.

Column

Dilute Povidone-Iodine Nasal/Oral Washes for the Prevention and Treatment of COVID-19

by Dr. Peter McCullough | Dec 30, 2021 | Feature 3, Healthcare

Print PDF

The SARS-CoV-2 virus is transmitted in the air and settles in the nose, and multiplies for days before it invades the body. When sick with nasal congestion, headache, fever, and body aches, the source of symptoms is the virus in the nose.

The virus must be killed in the nasal cavity at least twice a day after coming back home for prevention and up to every four hours during active treatment. This is very important with the Omicron variant, which multiplies 70 times faster than the prior strains of the virus.

Early treatment using this approach is associated with a 71% improvement, as shown in the figure. Also shown is a quick set up at home with povidone-iodine, which costs under $10 a bottle online.

Take 1/2 tsp mix in a shot glass 1.5 oz of water, squirt up nose, sniff back to the back of the throat and spit out. Do twice in each nostril, then gargle with the rest for 30 sec. Do not swallow. If iodine allergic or intolerant, can substitute hydrogen peroxide.

12 povidone-iodine COVID-19 studies

c19pvpi.com Dec 29, 2021

	Improvement	RR [CI]		Treatment	Control
Mohamed (RCT)	86%	0.14 [0.01-2.21]	viral+	0/5	3/5
Choudhury (RCT)	88%	0.12 [0.03-0.50]	death	2/303	17/303
Guenezan (RCT)	63%	0.37 [0.06-1.63]	viral load	12 (n)	12 (n)
Elzein (DB RCT)	89%	0.11 [0.01-1.00]	viral load	25 (n)	9 (n)
Arefin (RCT)	79%	0.21 [0.08-0.54]	viral+	4/27	19/27
Baxter (RCT)	65%	0.35 [0.01-8.27]	hosp.	0/37	1/42
Pablo-Marcos	29%	0.71 [0.32-1.56]	viral load	31 (n)	40 (n)
Early treatment	71%	0.29 [0.16-0.54]		6/440	40/438

$Tau^2 = 0.15$, $I^2 = 22.0\%$, $p = 0.00011$

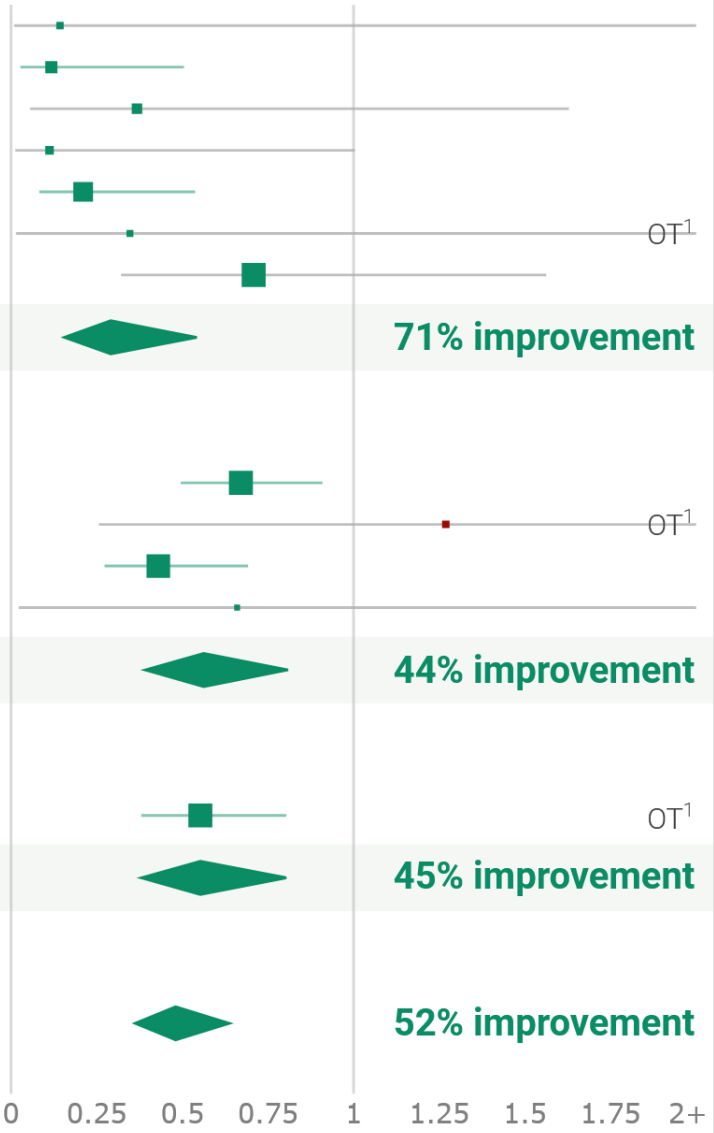
	Improvement	RR [CI]		Treatment	Control
Seneviratne (RCT)	33%	0.67 [0.50-0.91]	viral load	4 (n)	2 (n)
Zarabanda (RCT)	-27%	1.27 [0.26-6.28]	no recov.	3/13	2/11
Jamir	57%	0.43 [0.27-0.69]	death	39/163	62/103
Ferrer (RCT)	34%	0.66 [0.02-19.0]	viral load	9 (n)	12 (n)
Late treatment	44%	0.56 [0.39-0.81]		42/189	64/128

$Tau^2 = 0.05$, $I^2 = 40.6\%$, $p = 0.0019$

	Improvement	RR [CI]		Treatment	Control
Seet (CLUS. RCT)	45%	0.55 [0.38-0.80]	severe case	42/735	64/619
Prophylaxis	45%	0.55 [0.38-0.80]		42/735	64/619

$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.002$

All studies	52%	0.48 [0.36-0.64]		90/1,364	168/1,185



[1] OT: comparison with other treatment

$Tau^2 = 0.06$, $I^2 = 33.5\%$, $p < 0.0001$

Effect extraction pre-specified, see appendix

Favors povidone-iodine

Favors control

A

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June 25, 2021 The Centers for Disease Control and Prevention (CDC) has identified that the combined frequencies of the SARS-CoV-2 P.1/Gamma variant (first identified in Brazil) and the B.1.351/Beta variant (first identified in South Africa) throughout the United States now exceed 11% and are trending upward (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html). Results from in vitro assays that are used to assess the susceptibility of viral variants to particular monoclonal antibodies suggest that bamlanivimab and etesevimab administered together are not active against either the P.1 or B.1.351 variants. These assays use "pseudotyped virus-like particles" that help determine likely susceptibility of the live SARS-CoV-2 variant viruses.

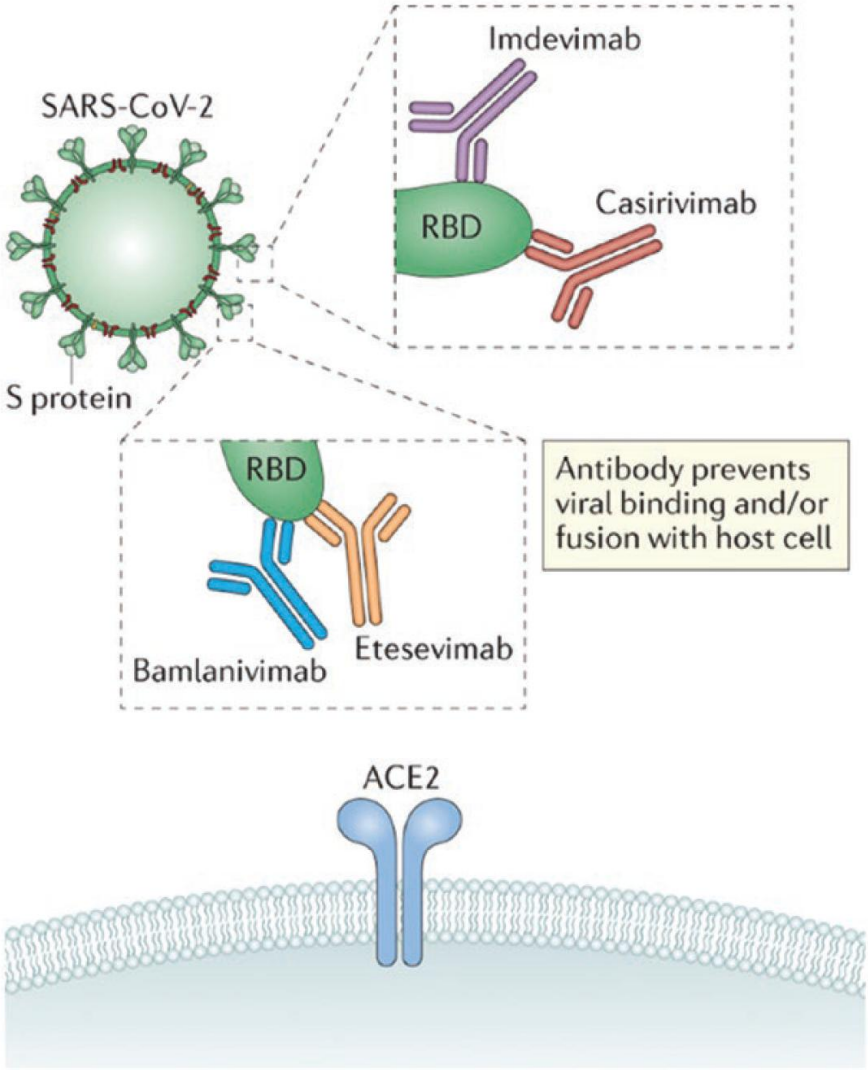


Figure 1. Schematic depiction of the potential mechanism of mAbs in COVID-19 infection. Reprinted with permission from reference [4]. Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; mAb, monoclonal antibody; RBD, receptor binding domain; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Reproduction permission was obtained from Rights Link. Taylor, P.C., Adams, A.C., Hufford, M.M. et al. (2021). https://doi.org/10.1038/s41577-021-00542-x.

https://doi.org/10.1093/cid/ciab579

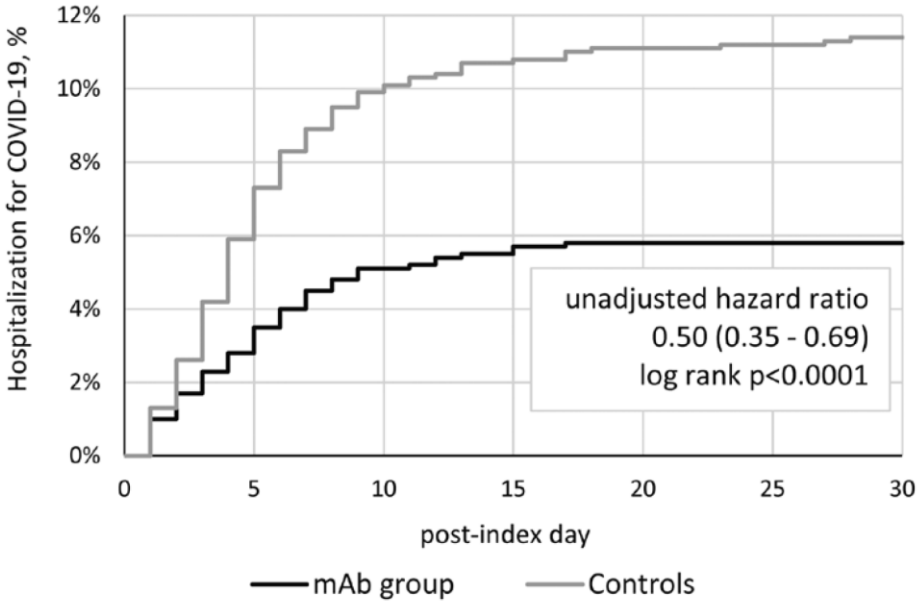
Clinical Infectious Diseases

MAJOR ARTICLE

Neutralizing Monoclonal Antibody Treatment Reduces Hospitalization for Mild and Moderate Coronavirus Disease 2019 (COVID-19): A Real-World Experience

John Paul Verderese,[1] Maria Stepanova,[1] Brian Lam,[1] Andrei Racila,[1] Andrej Kolacevski,[2] David Allen,[3] Erin Hodson,[1] Bahareh Aslani-Amoli,[1] Michael Homeyer,[1] Sarah Stanmyre,[1] Helen Stevens,[1] Stephanie Garofalo,[2] Linda Henry,[1] Chapy Venkatesan,[1] Lynn H. Gerber,[1,2,4] Steve J. Motew,[4] J. Stephen Jones,[4] and Zobair M. Younossi[1,2,4]

[1]Inova Medicine, Inova Health System, Falls Church, Virginia, USA; [2]Inova Office of Research, Inova Health System, Falls Church, Virginia, USA; [3]Department of Pharmacy, Inova Fairfax Medical Campus, Falls Church, Virginia, USA; and [4]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, Virginia, USA



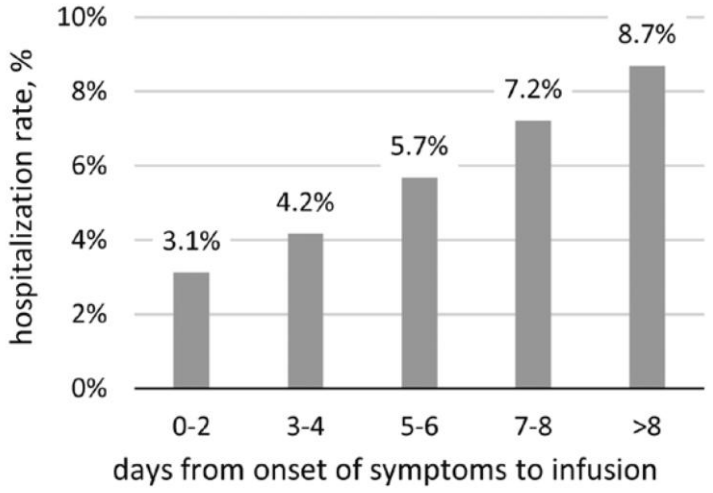


Figure 3. Distribution of hospitalization rates based on the number of days between the first onset of symptoms and NmAb infusion (n = 358). Abbreviation: NmAb, neutralizing monoclonal antibody.

Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab

This article was published on October 27, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2107934

Anil Gupta, M.D., Yaneicy Gonzalez-Rojas, M.D., Erick Juarez, M.D., Manuel Crespo Casal, M.D., Jaynier Moya, M.D., Diego R. Falci, M.D., Ph.D., Elias Sarkis, M.D., Joel Solis, M.D., Hanzhe Zheng, Ph.D., Nicola Scott, M.Sc., Andrea L. Cathcart, Ph.D., Christy M. Hebner, Ph.D., Jennifer Sager, Ph.D., Erik Mogalian, Pharm.D., Ph.D., Craig Tipple, M.B., B.S., Ph.D., Amanda Peppercorn, M.D., Elizabeth Alexander, M.D., Phillip S. Pang, M.D., Ph.D., Almena Free, M.D., Cynthia Brinson, M.D., Melissa Aldinger, Pharm.D., and Adrienne E. Shapiro, M.D., Ph.D., for the COMET-ICE Investigators*

- Sotrovimab targets Spike glycoprotein (↓mutagenic)
- 500 mg IV outpatient infusion in acute COVID-19 resulted in ↓85% hospitalization and death

Table 2. Efficacy Out… …g. Day 29 (Intention-to-Treat Population).*

Outcome	Sotrovimab (N = 291)	Placebo (N = 292)
Primary outcome		
Hospitalization for >24 hr for any cause or death from any cause — no. (%)	3 (1)	21 (7)
Hospitalization for >24 hr for any cause	3 (1)	21 (7)
Death from any cause	0	1 (<1)†

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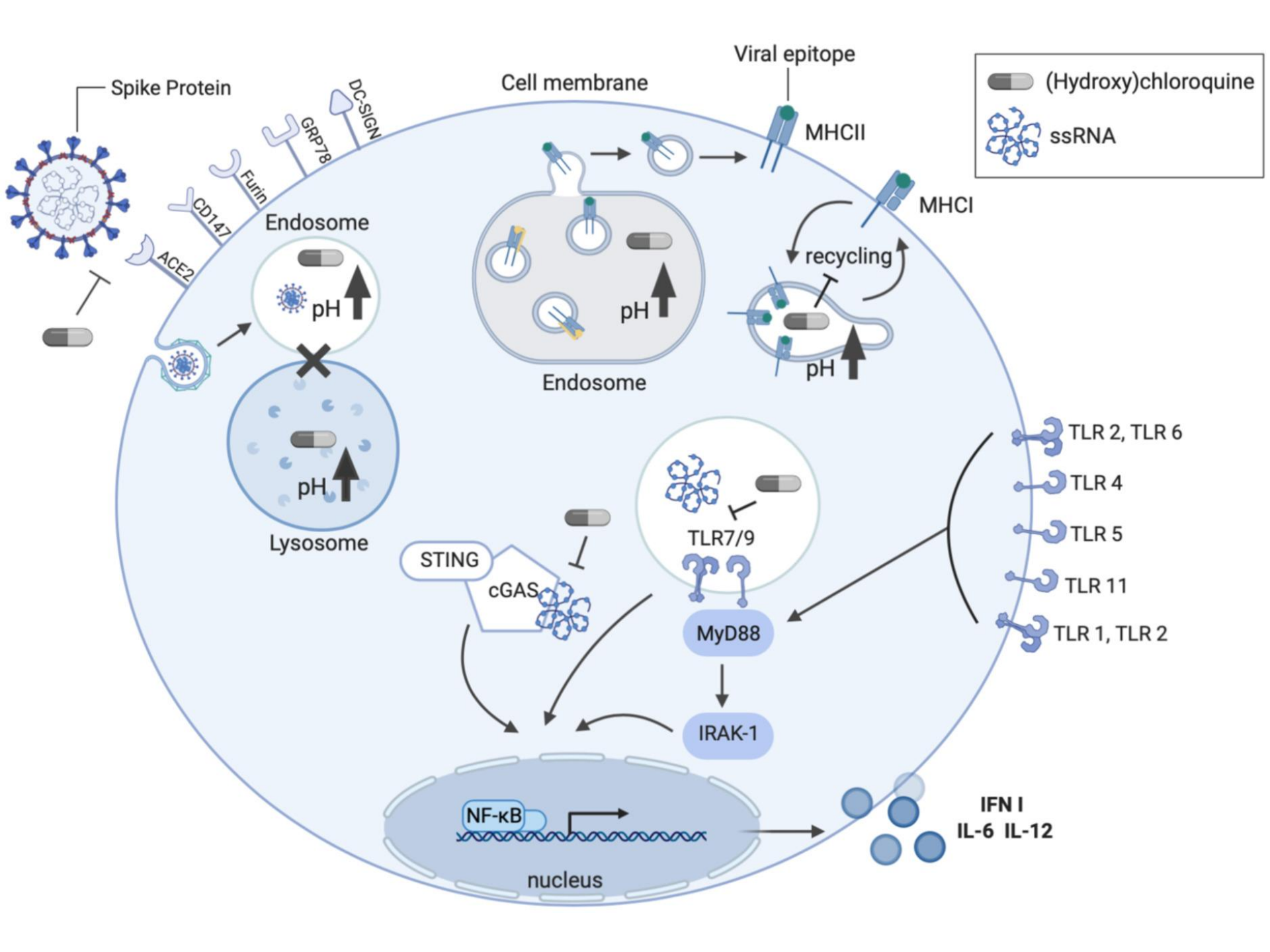
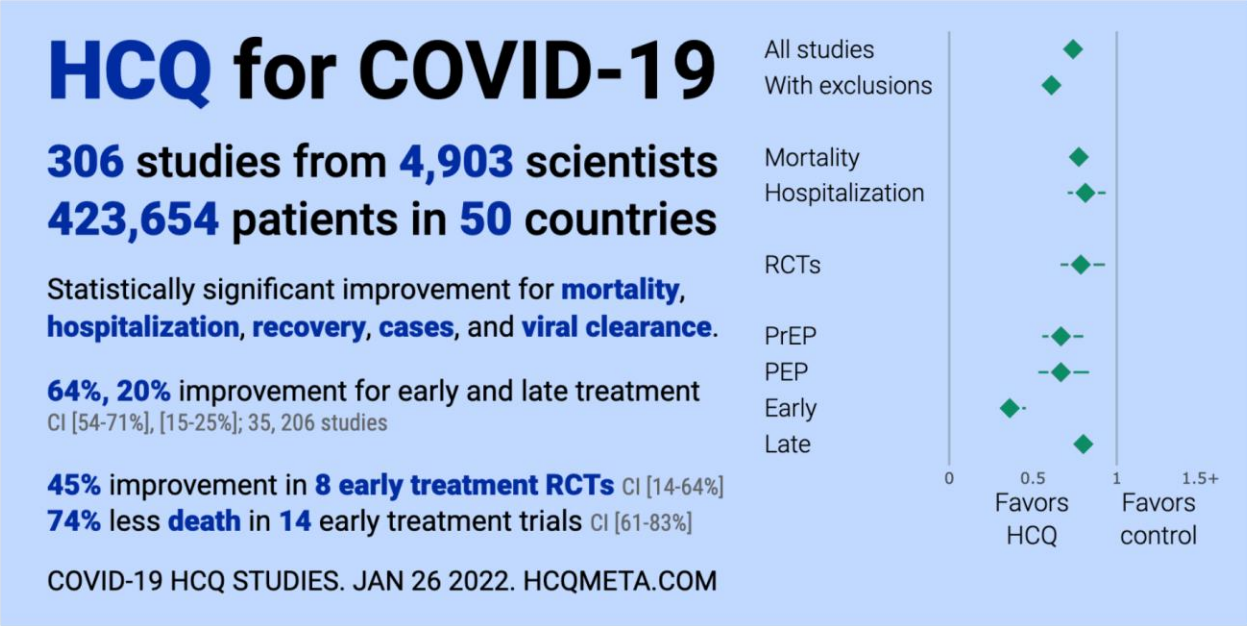

Spike Protein
ACE2
CD147
Furin
GRP78
DC-SIGN
Cell membrane
Viral epitope
MHCII
MHCI
recycling
Endosome
pH
Endosome
pH
pH
Lysosome
(Hydroxy)chloroquine
ssRNA
TLR 2, TLR 6
TLR 4
TLR 5
TLR 11
TLR 1, TLR 2
TLR7/9
STING
cGAS
MyD88
IRAK-1
NF-κB
nucleus
IFN I
IL-6 IL-12

https://c19hcq.com/



HCQ COVID-19 studies. 374 studies, 279 peer reviewed, 306 comparing treatment and control groups. HCQ is not effective when used very late with high dosages over a long period (RECOVERY/SOLIDARITY), effectiveness improves with earlier usage and improved dosing. Early treatment consistently shows positive effects. Negative evaluations typically ignore treatment time, often focusing on a subset of late stage studies. *In Vitro* evidence made some believe that therapeutic levels would not be attained, however that was incorrect, e.g. see *[Ruiz]*. Recently added: Corradini AbdelGhaffar Shousha Juneja Tyson Atipornwanich HCQ or CQ has been officially adopted for early treatment in all or part of 36 countries (53 including non-government medical organizations). Submit updates/corrections.

Journal Pre-proofs

Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting

N=28,759
COVID-19 early outpatients 25% treated
HCQ 200 bid x 5 days vs watchful waiting
Primary endpoint urgent visit or hospitalization
↓ 30% hospitalization, ↓60% death (p<0.001)

Accepted Date:

Please cite this article as: M. Mokhtari, M. Mohraz, M. Mehdi Gouya, H. Namdari Tabar, K. Tayeri, S. Aghamohamadi, Z. Rajabpoor, M. Karami, A. Raeisi, H. Rahmani, H. Khalili, Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting, *International Immunopharmacology* (2021), doi: https://doi.org/10.1016/j.intimp.2021.107636

IMR Press

Editorial

Role of hydroxychloroquine in multidrug treatment of COVID-19

Peter A. McCullough[1,*], Raphael B. Stricker[2], Harvey A. Risch[3]

[1] *Truth for Health Foundation, Tucson, AZ, USA*

[2] *Union Square Medical Associates, San Francisco, CA, USA*

[3] *Yale School of Public Health, New Haven, CT 06510, USA*

*Correspondence: Peteramccullough@gmail.com (Peter A. McCullough)

DOI:10.31083/j.rcm2203063

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Keywords

SARS-CoV-2; COVID-19; Hydroxychloroquine; Ambulatory treatment; Mortality

Hydroxychloroquine is the most widely prescribed intracellular anti-infective for human SARS-CoV-2 infection and COVID-19 syndrome. There have been 296 studies, 220 of which are peer reviewed, 246 comparing treatment and control groups [1]. This agent is successfully used in both prophylaxis and early therapy (Fig. 1). As a general principle, the earlier hydroxychloroquine is started in the course of illness, the larger treatment effects can be observed. These effects are greatly enhanced by the use of agents in combination to address SARS-CoV-2 replication, cytokine storm, and thrombosis [2, 3]. Early treatment of SARS-CoV-2 infection has the largest opportunity to control the outbreak since efforts

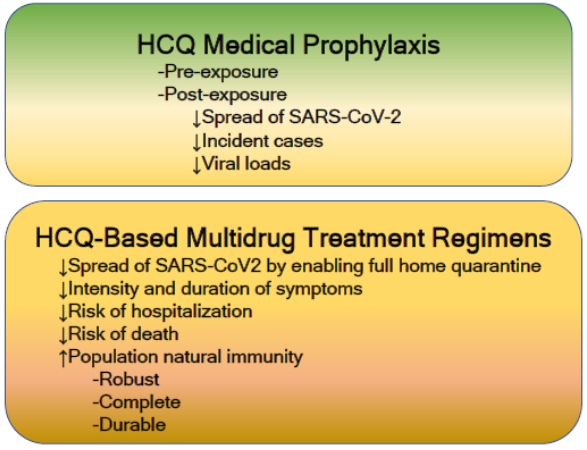

Fig. 1. Roles of hydroxychloroquine in the prevention and treatment of SARS-CoV-2 infection and the COVID-19 syndrome.

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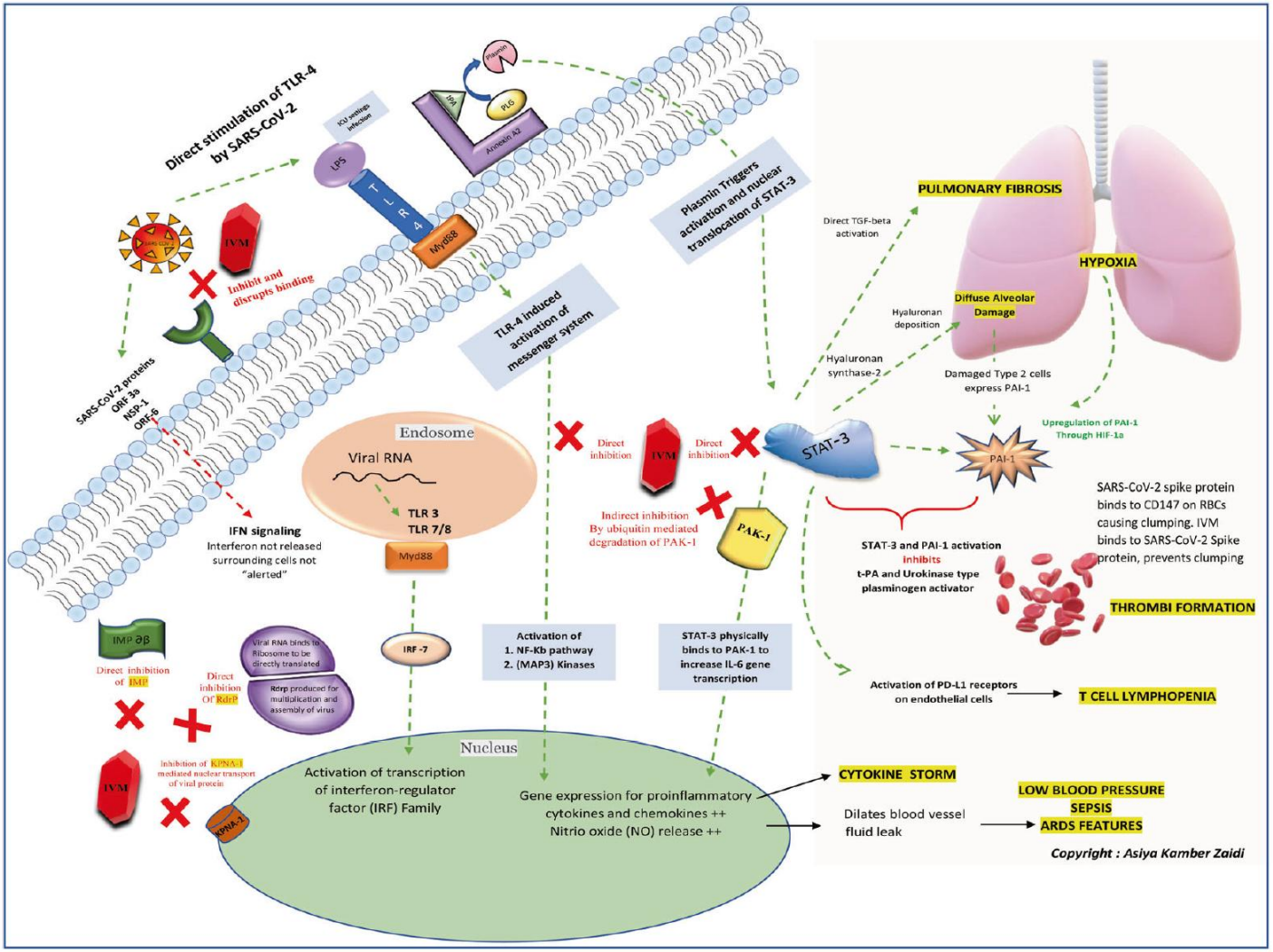
The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article

Asiya Kamber Zaidi [1,2] · Puya Dehgani-Mobaraki[3]

Received: 11 May 2021 / Revised: 17 May 2021 / Accepted: 20 May 2021

The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article



https://c19ivermectin.com/

Ivermectin for COVID-19

76 studies from 718 scientists
57,647 patients in 26 countries

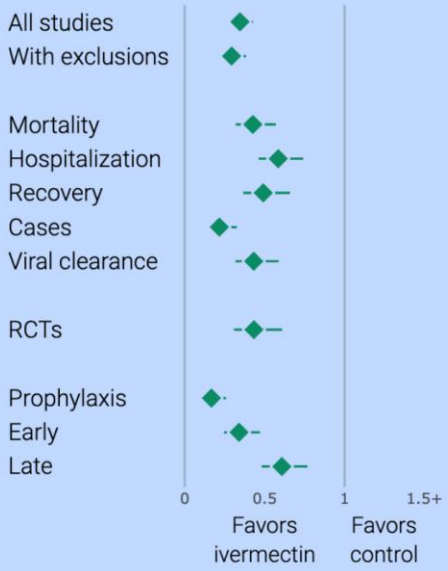
Statistically significant improvement for **mortality**, **ventilation**, **ICU**, **hospitalization**, **recovery**, **cases**, and **viral clearance**.

83%, 66%, 39% improvement for prophylaxis, early, and late treatment CI [74-89%], [53-75%], [23-52%]

57% improvement in **32 RCTs** CI [39-69%]

57% lower **mortality** from **37** studies CI [43-68%]

COVID-19 IVERMECTIN STUDIES. JAN 26 2022. IVMMETA.COM



Ivermectin COVID-19 studies. 144 studies, 94 peer reviewed, 76 with results comparing treatment and control groups. FLCCC provides treatment recommendations. Recently added: Liu Zubair Tyson Abbas Baguma Kerr Semiz Ivermectin has been officially adopted for early treatment in all or part of 22 countries (39 including non-government medical organizations). Submit updates/corrections.

frontiers

Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19

Pierre Kory, MD[1]*, G. Umberto Meduri, MD[2]†, Jose Iglesias, DO[3], Joseph Varon, MD[4], Keith Berkowitz, MD[5], Howard Kornfeld, MD[6], Eivind Vinjevoll, MD[7], Scott Mitchell, MBChB[8], Fred Wagshul, MD[9], Paul E. Marik, MD[10]

Figure 6. Meta-analysis of mortality outcomes from controlled trials of ivermectin treatment in COVID-19

Group by RCT-Obs	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Dead / Total Ivermectin	Dead / Total Control
OBS	Rajter	0.524	0.287	0.958	-2.099	0.036	26 / 173	27 / 107
OBS	Khan	0.121	0.015	0.969	-1.990	0.047	1 / 115	9 / 133
OBS	Gorial	0.842	0.039	18.393	-0.109	0.913	0 / 16	2 / 71
OBS	Budhiraja	0.118	0.007	1.932	-1.499	0.134	0 / 34	103 / 942
OBS		0.451	0.258	0.789	-2.793	0.005		
RCT	Mahmud	0.138	0.007	2.694	-1.306	0.192	0 / 183	3 / 180
RCT	Hashim	0.314	0.061	1.611	-1.389	0.165	2 / 70	6 / 70
RCT	Elgazzar	0.074	0.017	0.318	-3.502	0.000	2 / 200	24 / 200
RCT	Niaee	0.154	0.047	0.506	-3.080	0.002	4 / 120	11 / 60
RCT	Cadegiani	0.046	0.002	0.970	-1.980	0.048	0 / 585	2 / 137
RCT		0.136	0.064	0.288	-5.207	0.000		
Overall		0.294	0.188	0.461	-5.347	0.000		

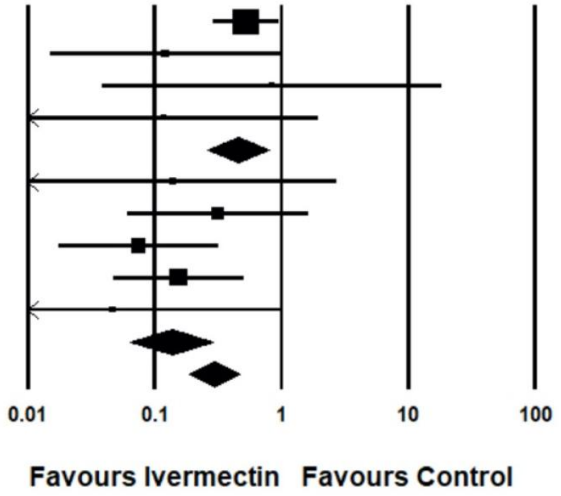


Figure 6 legend: OBS: Observational study, RCT: Randomized Controlled Trial. Symbols: Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

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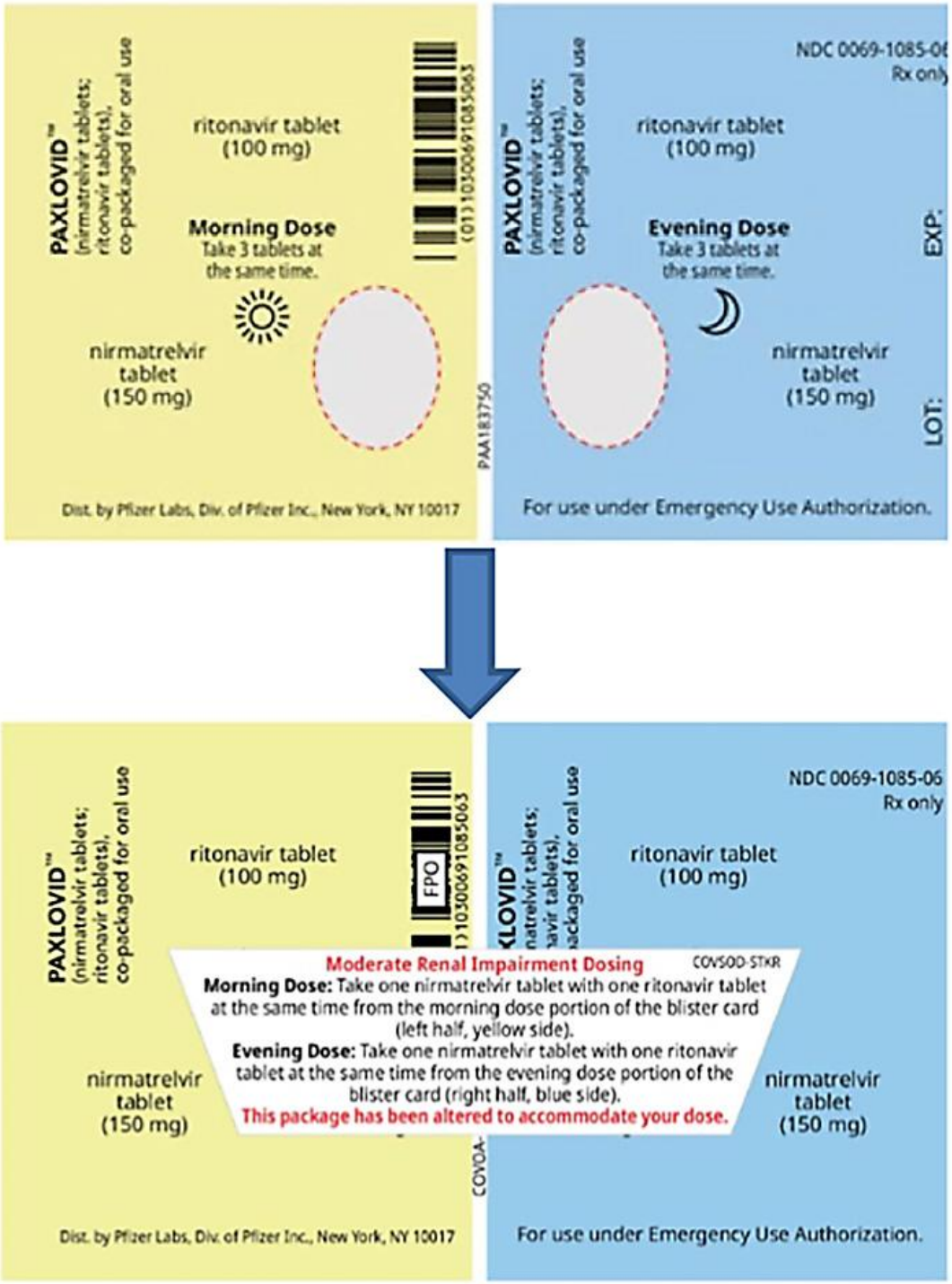
Pfizer Announces Additional Phase 2/3 Study Results Confirming Robust Efficacy of Novel COVID-19 Oral Antiviral Treatment Candidate in Reducing Risk of Hospitalization or Death

Tuesday, December 14, 2021 - 06:45am

- *Final data available from all high-risk patients enrolled in EPIC-HR study (n= 2,246) confirmed prior results of interim analysis showing PAXLOVID™ (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) reduced risk of hospitalization or death by 89% (within three days of symptom onset) and 88% (within five days of symptom onset) compared to placebo; no deaths compared to placebo in non-hospitalized, high-risk adults with COVID-19*
- *The above data have been shared with the U.S. Food and Drug Administration (FDA) as part of an ongoing rolling*


PAXLOVID™
(nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
ritonavir tablet (100 mg)
Morning Dose
Take 3 tablets at the same time.
nirmatrelvir tablet (150 mg)
(01)10350069108506 3
PAA183750
Dist. by Pfizer Labs, Div. of Pfizer Inc., New York, NY 10017
NDC 0069-1085-06
Rx only
PAXLOVID™
(nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
ritonavir tablet (100 mg)
Evening Dose
Take 3 tablets at the same time.
nirmatrelvir tablet (150 mg)
EXP:
LOT:
For use under Emergency Use Authorization.
PAXLOVID™
(nirmatrelvir tablets; ritonavir tablets), co-packaged for oral use
ritonavir tablet (100 mg)
FPO
(01)10350069108506 3
Moderate Renal Impairment Dosing
COVSOD-STKR
Morning Dose: Take one nirmatrelvir tablet with one ritonavir tablet at the same time from the morning dose portion of the blister card (left half, yellow side).
Evening Dose: Take one nirmatrelvir tablet with one ritonavir tablet at the same time from the evening dose portion of the blister card (right half, blue side).
This package has been altered to accommodate your dose.
nirmatrelvir tablet (150 mg)
COVDA-
Dist. by Pfizer Labs, Div. of Pfizer Inc., New York, NY 10017
NDC 0069-1085-06
Rx only
ritonavir tablet (100 mg)
nirmatrelvir tablet (150 mg)
For use under Emergency Use Authorization.

Outline

- SARS-CoV-2 infection (COVID-19)
- Pillars of pandemic response
- Role of early ambulatory treatment
  - Anti-spike protein antibody infusions
  - Hydroxychloroquine
  - Ivermectin
  - Paxlovid
  - Molnupiravir
  - Corticosteroids
  - Colchicine
  - Anticoagulants
- Early sequenced multidrug therapy
- COVID-19 vaccine safety and efficacy
- Conclusions

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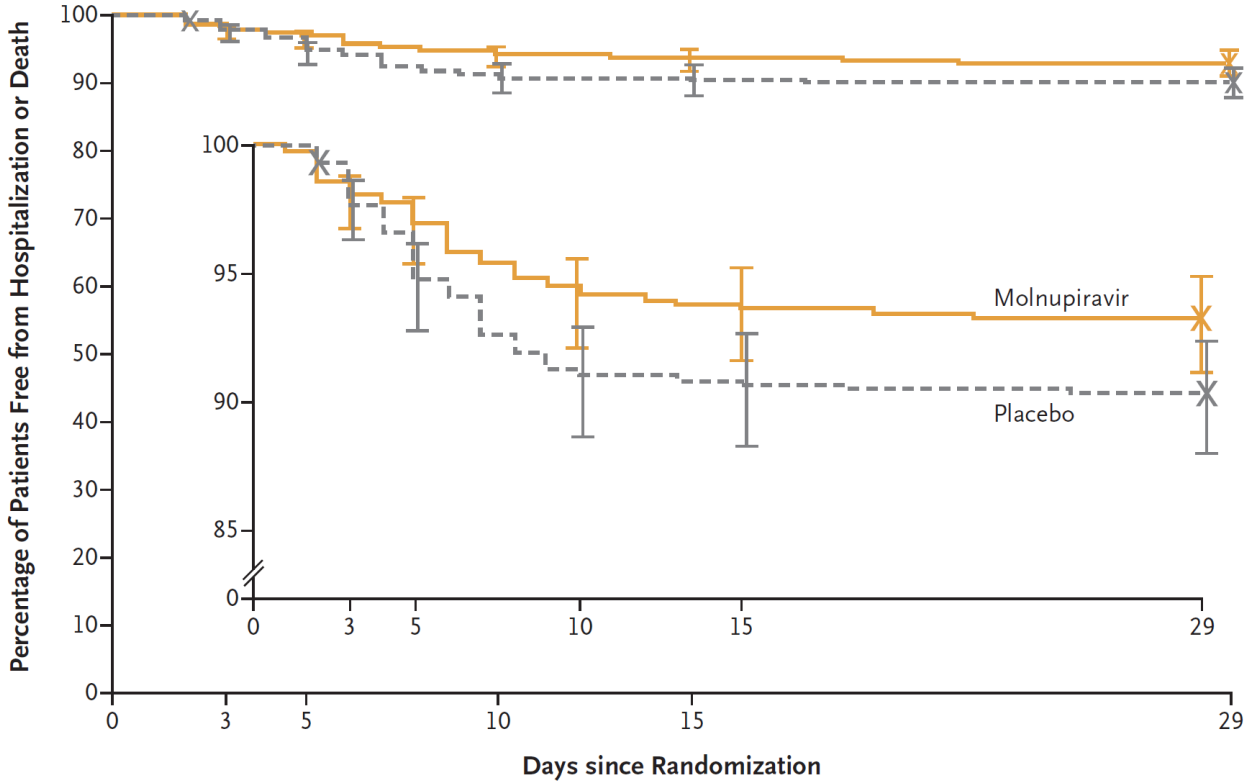
Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*



No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

ARTICLES
https://doi.org/10.1038/s41594-021-00651-0

nature structural & molecular biology

OPEN

Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis

Florian Kabinger[1,5], Carina Stiller[2,5], Jana Schmitzová[1,5], Christian Dienemann[1], Goran Kokic[1], Hauke S. Hillen[3,4], Claudia Höbartner[2]✉ and Patrick Cramer[1]✉

Molnupiravir is an orally available antiviral drug candidate currently in phase III trials for the treatment of patients with COVID-19. Molnupiravir increases the frequency of viral RNA mutations and impairs SARS-CoV-2 replication in animal models and in humans. Here, we establish the molecular mechanisms underlying molnupiravir-induced RNA mutagenesis by the viral RNA-dependent RNA polymerase (RdRp). Biochemical assays show that the RdRp uses the active form of molnupiravir, β-D-N^4-hydroxycytidine (NHC) triphosphate, as a substrate instead of cytidine triphosphate or uridine triphosphate. When the RdRp uses the resulting RNA as a template, NHC directs incorporation of either G or A, leading to mutated RNA products. Structural analysis of RdRp–RNA complexes that contain mutagenesis products shows that NHC can form stable base pairs with either G or A in the RdRp active center, explaining how the polymerase escapes proofreading and synthesizes mutated RNA. This two-step mutagenesis mechanism probably applies to various viral polymerases and can explain the broad-spectrum antiviral activity of molnupiravir.

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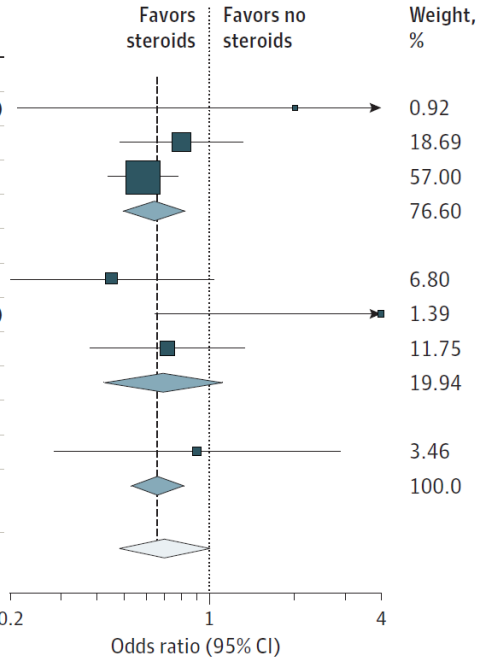
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)
Dexamethasone					
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)
Hydrocortisone					
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)
Methylprednisolone					
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)



Outpatient prednisone reported in
Szente Fonseca SN, de Queiroz Sousa A, Wolkoff AG, et al. Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis. *Travel Med Infect Dis*. 2020;38:101906. doi:10.1016/j.tmaid.2020.101906

Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial

Sanjay Ramakrishnan, Dan V Nicolau Jr*, Beverly Langford, Mahdi Mahdi, Helen Jeffers, Christine Mwasuku, Karolina Krassowska, Robin Fox, Ian Binnian, Victoria Glover, Stephen Bright, Christopher Butler, Jennifer L Cane, Andreas Halner, Philippa C Matthews, Louise E Donnelly, Jodie L Simpson, Jonathan R Baker, Nabil T Fadai, Stefan Peterson, Thomas Bengtsson, Peter J Barnes, Richard E K Russell, Mona Bafadhel*

STOIC Trial N=139
COVID-19 early outpatients
Inhaled budesonide vs usual care
800 mcg bid x 14 days
Primary endpoint urgent visit or hospitalization
↓87% primary endpoint (p=0.004)

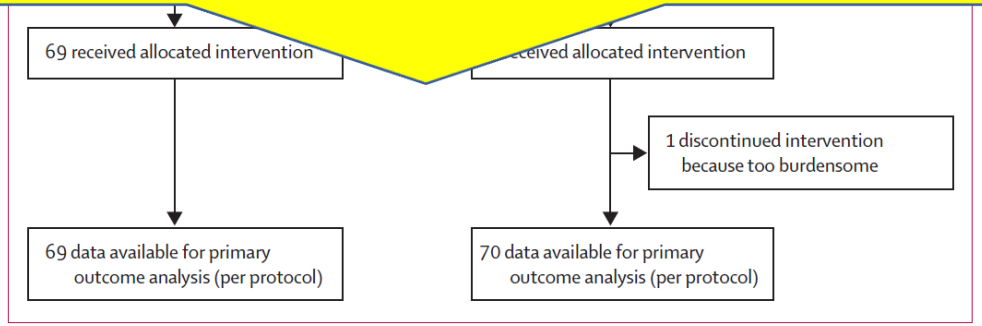


Figure 1: Trial profile

Nasal symptoms	3 (4%)	5 (7%)
Sore throat	0 (0%)	2 (3%)
Chest pain or tightness	4 (6%)	1 (1%)
Other	7 (10%)	8 (12%)
Highest temperature recorded, °C†‡	36·6 (36·2–37·1)	36·6 (35·5–38·3)
Lowest oxygenation recorded, percent saturation†‡	96% (95–97)	96% (95–97)
SARS-CoV-2 viral cycle threshold‡	32·6 (22·4–39·4)	31·8 (15·6–40·0)

Data are mean (SD) or n (%), unless stated otherwise. *Mean (range). †Median (IQR). ‡At randomisation.

Table: Characteristics of study participants in the per-protocol population at study enrolment

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Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded,

Planned sample N=6000
Global N=4488, early outpatients
Colchicine vs Placebo
0.5 (0.6) mg bid x 3 days then 0.5 qd x 30 d
N=4159 PCR+
↓25% Hospitalization or Death, p=0.04
↓44% Death, p=NS

www.thelancet. espiratory Published online May 27, 2021 https://doi.org/10.1016/S2213-2600(21)00222-8

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Early initiation of prophylactic anticoagulation for prevention of COVID-19 mortality: a nationwide cohort study of hospitalized patients in the United States

Christopher T Rentsch, PhD[1,2*&]; Joshua A Beckman, MD[3*]; Laurie Tomlinson, PhD[1]; Walid F Gellad, MD[4,5,6]; Charles Alcorn, BS[7]; Farah Kidwai-Khan, MS[2,8]; Melissa Skanderson, MSW[2]; Evan Brittain, MD[9]; Joseph T King, Jr, MD, MSCE[2,10]; Yuk-Lam Ho, MPH[11]; Svetlana Eden, PhD[12]; Suman Kundu, DSc[13]; Michael F Lann, MS[7]; Robert A Greevy, Jr, PhD[14]; P. Michael Ho, MD, PhD[15]; Paul A Heidenreich, MD[16,17]; Daniel A Jacobson, PhD[18]; Ian J Douglas, PhD[1]; Janet P Tate, ScD[2,8]; Stephen JW Evans, MSc[1]; David Atkins, MD[19]; Amy C Justice, MD, PhD[2,8,20†]; Matthew S Freiberg, MD[13,21†]

*These authors contributed equally to this work; †Joint principal investigators
&corresponding: christopher.rentsch@lshtm.ac.uk; @DarthCTR

Table 2. Absolute and relative risks associated with exposure to prophylactic doses of anticoagulation in the first 24 hours of hospitalization

			Unweighted	IPT-weighted	
Outcome	**N**	**No. events**	**HR (95% CI)**	**Cumulative incidence (95% CI)**	**HR (95% CI)**
30-day mortality					
Exposed	3627	513	0.85 (0.69-1.05)	14.3 (13.1-15.5)	0.73 (0.66-0.81)
Unexposed	670	109	ref	18.7 (15.1-22.9)	ref
Inpatient mortality					
Exposed	3627	418	0.82 (0.66-1.03)	11.7 (10.7-12.8)	0.69 (0.61-0.77)
Unexposed	670	92	ref	16.4 (13.0-20.5)	ref
Initiate therapeutic anticoagulation					
Exposed	3627	573	1.14 (0.91-1.42)	15.6 (14.4-16.8)	0.81 (0.73-0.90)
Unexposed	670	92	ref	18.8 (15.2-23.1)	ref

Abbreviations: PY, person-years; HR, hazard ratio; CI, confidence interval; IPT, inverse probability of treatment

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REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection

Peter A. McCullough, MD, MPH,[a,b,c] Ronan J. Kelly, MD,[a] Gaetano Ruocco, MD,[d] Edgar Lerma, MD,[e] James Tumlin, MD,[f] Kevin R. Wheelan, MD,[a,b,c] Nevin Katz, MD,[g] Norman E. Lepor, MD,[h] Kris Vijay, MD,[i] Harvey Carter, MD,[j] Bhupinder Singh, MD,[k] Sean P. McCullough, BS,[l] Brijesh K. Bhambi, MD,[m] Alberto Palazzuoli, MD, PhD,[n] Gaetano M. De Ferrari, MD, PhD,[o] Gregory P. Milligan, MD, MPH,[a] Taimur Safder, MD, MPH,[a] Kristen M. Tecson, PhD,[b] Dee Dee Wang, MD,[p] John E. McKinnon, MD,[p] William W. O'Neill, MD,[p] Marcus Zervos, MD,[p] Harvey A. Risch, MD, PhD[q]

[a]Baylor University Medical Center, Dallas, Tex; [b]Baylor Heart and Vascular Institute, Dallas, Tex; [c]Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, Tex; [d]Cardiology Division, Regina Montis Regalis Hospital, Mondovì, Cuneo, Italy; [e]Christ Advocate Medical Center, Chicago, Ill; [f]Emory University School of Medicine, Atlanta, Ga; [g]Johns Hopkins School of Medicine, Baltimore, Md;

1. Precautionary principle—mass casualty event
2. Signal of benefit—from all evidence
3. Acceptable safety
4. Drugs in combination

KEYWORDS: Ambulatory treatment; Anticoagulant; [illegible]; COVID-19; Critical care; Epidemiology; Hospitalization; Mortality; SARS-CoV-2

Funding: None.
Conflicts of Interest: None.
Authorship: All authors had access to the data and a role in writing this manuscript.

Requests for reprints should be addressed to Peter A. McCullough, MD, MPH, Baylor Heart and Vascular Institute, 621 N. Hall St, H030, Dallas, TX, 75226.
E-mail address: peteramccullough@gmail.com

The pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 [COVID-19]) is rapidly expanding across the world with each country and region developing distinct epidemiologic patterns in terms of frequency, hospitalization, and death. There has been considerable focus on 2 major areas of response to the pandemic: containment of the spread of infection and reducing inpatient mortality.

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Review

Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)

Peter A. McCullough[1,*], Paul E. Alexander[2], Robin Armstrong[3], Cristian Arvinte[4], Alan F. Bain[5], Richard P. Bartlett[6], Robert L. Berkowitz[7], Andrew C. Berry[8], Thomas J. Borody[9], Joseph H. Brewer[10], Adam M. Brufsky[11], Teryn Clarke[12], Roland Derwand[13], Alieta Eck[14], John Eck[14], Richard A. Eisner[15], George C. Fareed[16], Angelina Farella[17], Silvia N. S. Fonseca[18], Charles E. Geyer, Jr.[19], Russell S. Gonnering[20], Karladine E. Graves[21], Kenneth B. V. Gross[22], Sabine Hazan[23], Kristin S. Held[24], H. Thomas Hight[25], Stella Immanuel[26], Michael M. Jacobs[27], Joseph A. Ladapo[28], Lionel H. Lee[29], John Littell[30], Ivette Lozano[31], Harpal S. Mangat[32], Ben Marble[33], John E. McKinnon[34], Lee D. Merritt[35], Jane M. Orient[36], Ramin Oskoui[37], Donald C. Pompan[38], Brian C. Procter[39], Chad Prodromos[40], Juliana Cepelowicz Rajter[41], Jean-Jacques Rajter[41], C. Venkata S. Ram[42], Salete S. Rios[43], Harvey A. Risch[44], Michael J. A. Robb[45], Molly Rutherford[46], Martin Scholz[47], Marilyn M. Singleton[48], James A. Tumlin[49], Brian M. Tyson[50], Richard G. Urso[51], Kelly Victory[52], Elizabeth Lee Vliet[53], Craig M. Wax[54], Alexandre G. Wolkoff[55], Vicki Wooll[56] and Vladimir Zelenko[57]

[1] *Baylor University Medical Center, Baylor Heart and Vascular Institute, Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, 75226, TX, USA*
[2] *Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, L8S 4L8, Ontario, Canada*
[3] *Armstrong Medical Group, Texas City, 75510, TX, USA*
[4] *North Suburban Medical Center and Vibra Hospital, Thornton, 80229, Colorado, USA*
[5] *Chicago Health and Wellness Alliance, Chicago, 60603, IL, USA*
[6] *Recipient of the Texas HHS Meritorious Service Award, 78751, Texas, USA*
[7] *PianoPsych, LLC, Natick, 01760, MA, USA*
[8] *Division of Gastroenterology, Department of Medicine, Larkin Community Hospital, S. Miami, 33143, FL, USA*
[9] *Centre for Digestive Diseases, Five Dock, 2046, NSW, Australia*
[43] *University of Brasilia, Brasilia , 70910-900, DF, Brazil*
[44] *Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, 06510, CT, USA*
[45] *Robb Oto-Neurology Clinic, Phoenix, 85012, AZ, USA*
[46] *Bluegrass Family Wellness, Crestwood, 40014, KY, USA*
[47] *Heinrich Heine University, Düsseldorf, 40225, Germany*
[48] *Past Pres. Association of American Physicians and Surgeons, Tucson, 85716, AZ, USA*
[49] *NephroNet Clinical Trials Consortium, Buford, 30518, GA, USA*
[50] *All Valley Urgent Care, El Centro, 92243, CA, USA*
[51] *Houston Eye Associates, Houston 77025, TX, USA*
[52] *Victory Health, LLC., 80487, Colorado, USA*
[53] *Vive Life Center, 85728, Arizona & Texas, USA*
[54] *Family Medicine, Mullica Hill, 08062, NJ, USA*
[55] *CMO Emergency Hapvida Saude, HMO, Fortaleza, 60140-061, CE, Brazil*
[56] *National Healthcare Coalition, Family Medicine, Eagle, 83616, ID, USA*
[57] *Affiliate Physician, Columbia University Irving Medical Center, New York City, 10032, NY, USA*

*Correspondence: peteramccullough@gmail.com (Peter A. McCullough)
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Adapted from McCullough PA Innovative Early Sequenced Multidrug Therapy for SARS-CoV-2 (COVID-19) Infection to Reduce Hospitalization and Death, presented in part at Scilnov, COVID-19 Drug and Diagnostic Developments, Nov 2, 18th Annual WCIRDC 2020 Dec 3, DOI:10.31083/j.rcm.2020.04.264 adapted for Int J Med Sci Clini Inv 2020, ID 2898 Open Access Publication ISSN: 2348-991X | 2454-9576

COVID-19-like or COVID-19-confirmed illness:
- -Self-quarantine at home
- -Povidone iodine oral/nasal washes 6x day
- -Contact tracing
- -Contagion control
- -Ventilate fresh air-reduce reinoculation

Room Air

Age < 50 yr. Healthy

Age ≥ 50 yr. or a Single Comorbidity BMI > 30 kg/m^2, Pulmonary Dz, DM, CVD, CKD, Cancer

Age ≥ 50 yr. with ≥1 Comorbidities

OTC bundle: Zinc 50 mg, vitamin D_3 20,000 IU, Vitamin C 3000 mg, Quercetin 500 mg po bid, Famotidine 80 mg (5-30 days)

If feasible: Sotrovimab Infusion EUA Dosing

Watchful Waiting

Immediately ≥ 2 Anti-Infective Agents (5-30 days)

HCQ 200 mg po bid + AZM 250 mg po bid or +DOXY 100 mg po bid	IVM 600 mcg/kg po qd x 5 doses + AZM 250 mg po bid or +DOXY 100 mg po bid	Paxlovid bid or Molnupiravir bid EUA dosing + AZM 250 mg po bid or +DOXY 100 mg po bid

Pulse Ox
Deliver
Home 0_2
If Needed

If Symptoms Worsen

Respiratory Symptoms Develop or Day 5 of illness

Inhaled budesonide 1 mg/2 mL nebulization/Dexamethasone 6 mg/Prednisone 1 mg/kg qd x 5 days ± taper/Colchicine 0.6 (0.5) mg po bid x 3 d then qd x 30 d

Complete Self-quarantine

Underlying Serious Medical Condition, ↑VTE Risk, Suspect micro- or overt thrombosis

Aspirin 325 mg po qd ± Low-molecular weight heparin or Apixaban, Rivaroxaban, Dabigatran, Edoxaban in Standard doses (5-30 days)

Re-evaluate
Hospitalize

Escalate Clinically

Consolidate

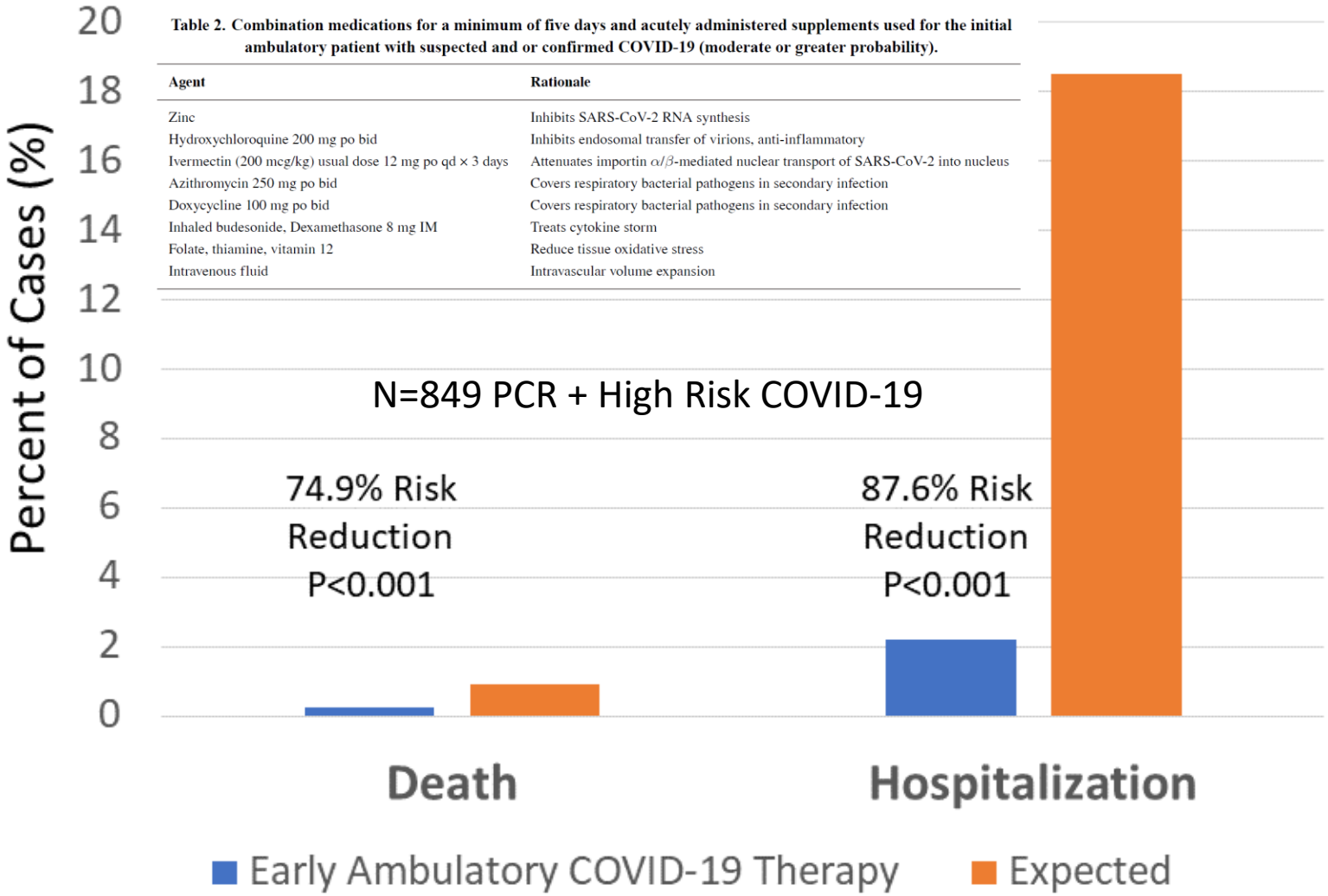
BMI=body mass index, Dz=disease, DM=diabetes mellitus, CVD=cardiovascular disease, CKD=chronic kidney disease, yr=years, HCQ=hydroxychloroquine, AZM=azithromycin, DOXY=doxycycline, IVM=Ivermectin, VTE=venous thrombo-embolic, EUA=Emergency Use Authorization (U.S. administration)

Early Ambulatory Multidrug Therapy Reduces Hospitalization and Death in High-Risk Patients with SARS-CoV-2 (COVID-19)

Brian Procter[1], Casey Ross[1], Vaness Pickard[1], Erica Smith[1], Cortney Hanson[1], and Peter A. McCullough[2]

Table 2. Combination medications for a minimum of five days and acutely administered supplements used for the initial ambulatory patient with suspected and or confirmed COVID-19 (moderate or greater probability).

Agent	Rationale
Zinc	Inhibits SARS-CoV-2 RNA synthesis
Hydroxychloroquine 200 mg po bid	Inhibits endosomal transfer of virions, anti-inflammatory
Ivermectin (200 mcg/kg) usual dose 12 mg po qd × 3 days	Attenuates importin α/β-mediated nuclear transport of SARS-CoV-2 into nucleus
Azithromycin 250 mg po bid	Covers respiratory bacterial pathogens in secondary infection
Doxycycline 100 mg po bid	Covers respiratory bacterial pathogens in secondary infection
Inhaled budesonide, Dexamethasone 8 mg IM	Treats cytokine storm
Folate, thiamine, vitamin 12	Reduce tissue oxidative stress
Intravenous fluid	Intravascular volume expansion



Procter BC, Ross C, Pickard V, Smith E, Hanson C, McCullough PA. Clinical outcomes after early ambulatory multidrug therapy for high-risk SARS-CoV-2 (COVID-19) infection. Rev Cardiovasc Med. 2020 Dec 30;21(4):611-614. doi: 10.31083/j.rcm.2020.04.260. PMID: 33388006.

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VIEWPOINT

COVID-19 Therapeutics for Nonhospitalized Patients

Rajesh T. Gandhi, MD
Massachusetts General Hospital, Harvard Medical School, Boston.

Preeti N. Malani, MD, MSJ
Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Health System, Ann Arbor; and Associate Editor, *JAMA*.

Carlos del Rio, MD
Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Georgia Grady Health System, Atlanta, Georgia.

Supplemental content

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Substantial progress has been made in therapeutics for nonhospitalized patients with COVID-19, but supply of and access to treatment remain limited. This Viewpoint summarizes currently available therapeutics for nonhospitalized patients in the setting of the Omicron variant including principles for equitable allocation.

Patients with mild or moderate COVID-19 are those who have respiratory and systemic symptoms but not hypoxia, tachypnea, or other complications that necessitate hospitalization.[1] During this early phase of illness, viral replication is occurring and antiviral therapies are used to prevent disease progression, hospitalization, and death.

Antivirals target different stages of the SARS-CoV-2 life cycle. Anti-SARS-CoV-2 monoclonal antibodies bind to the viral spike protein, preventing attachment and entry into cells. Nirmatrelvir-ritonavir inhibits the SARS-CoV-2 main protease, which cleaves viral polyproteins into nonstructural proteins essential for replication. Molnupiravir and remdesivir target SARS-CoV-2 RNA replication: the former induces RNA mutagenesis leading to virus that is unable to replicate and the latter is a nucleotide prodrug that inhibits viral RNA polymerase. Because of mutations in the viral spike protein of the Omicron variant, most currently available anti-SARS-CoV-2 monoclonal antibodies have reduced activity. Nirmatrelvir-ritonavir, remdesivir, and molnupiravir, which target more conserved viral regions, are expected to remain active against Omicron.

Treatment Options in the Omicron Era

Sotrovimab. Three antispike monoclonal antibody products are currently authorized in the US for treatment of high-risk nonhospitalized patients with mild to moderate COVID-19 who are within 10 days of symptom onset: bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab.[2] A preliminary non–peer-reviewed laboratory study demonstrated marked reduction in the activity of bamlanivimab/etesevimab and casirivimab/imdevimab against Omicron; by contrast, sotrovimab remained active.[3] As a result, the National Institutes of Health (NIH) COVID-19 treatment guidelines recommend that sotrovimab, but not bamlanivimab/etesevimab or casirivimab/imdevimab, be used in areas with a high prevalence of Omicron.[4]

Nirmatrelvir-Ritonavir. Nirmatrelvir is co-formulated with ritonavir to inhibit CYP3A metabolism of nirmatrelvir and achieve therapeutic levels.[5] In a phase 2/3 trial, 2246 nonhospitalized participants with COVID-19 who were at high risk of progression and within 5 days of symptom onset were randomly assigned to receive nirmatrelvir-ritonavir or placebo.[6] Participants who received nirmatrelvir-ritonavir had an 88% reduction in hospitalization or death compared with the placebo group: 8 of 1039 (0.8%) vs 66 of 1046 (6.3%). On December 22, 2021, the US Food and Drug Administration (FDA) issued Emergency Use Authorization of nirmatrelvir-ritonavir for treatment of mild to moderate COVID-19 in adult and pediatric patients (age ≥12 years and ≥40 kg) who are at high risk for progression and within 5 days of symptom onset.

Because ritonavir inhibits CYP3A, it alters the metabolism of many other drugs. Nirmatrelvir-ritonavir should not be administered with medications such as amiodarone (and several other antiarrhythmic drugs), rifampin, or rivaroxaban. Other medications, such as calcineurin inhibitors, may need dose reduction or close monitoring. Medications such as statins may be temporarily stopped. Prior to prescribing nirmatrelvir-ritonavir for patients taking other medications, clinicians should consult with an experienced pharmacist to assess potential drug interactions.

Remdesivir. Remdesivir is FDA approved for treatment of hospitalized patients with COVID-19. In a randomized trial, 562 nonhospitalized patients with COVID-19 who were within 7 days of symptom onset and had at least 1 risk factor for disease progression were randomly assigned to receive intravenous remdesivir or placebo on 3 consecutive days.[7] Participants who received remdesivir had a decreased risk of hospitalization compared with the placebo group: 2 of 279 (0.7%) receiving remdesivir and 15 of 283 (5.3%) receiving placebo. There were no deaths in either group. Based on these results, the NIH and Infectious Diseases Society of America COVID-19 treatment guidelines suggested remdesivir as an option for high-risk, nonhospitalized patients who are within 7 days of symptom onset.[4,8] This outpatient use of remdesivir is currently off-label.

Molnupiravir. In a phase 3 trial, 1433 nonhospitalized adults with mild to moderate COVID-19 who had at least 1 risk factor for severe disease and who were within 5 days of symptom onset were randomly assigned to receive molnupiravir or placebo twice daily for 5 days.[9] In the final analysis, participants who received molnupiravir had a 30% reduction in hospitalization or death compared with the placebo group (6.8% and 9.7%, respectively). This efficacy was lower than that observed in an interim analysis; the reasons for this difference are not clear.

Because of its mechanism of action, there have been theoretical concerns that molnupiravir may cause mutations in human DNA[10] or hasten development of new viral variants. The FDA concluded that the drug has a "low risk for genotoxicity" but is requiring the manufacturer to develop a process to evaluate genomic databases for new viral variants.

On December 23, 2021, the FDA issued an Emergency Use Authorization for molnupiravir for treatment of adults with mild to moderate COVID-19 who are at high risk for progression and within 5 days of symptom onset but only if other authorized therapeutic options are not "accessible or clinically appropriate." Molnupiravir is not recommended during pregnancy and is not authorized for children. The FDA recommends that individuals of child-bearing potential should use contraception during treatment and for 4 days after the last dose, and that

Corresponding Author: Rajesh T. Gandhi, MD, Massachusetts General Hospital, Cox 548, Boston, MA 02114 (rgandhi@mgh.harvard.edu).

A Guide to Home-Based COVID Treatment

Step-By-Step Doctors' Plan That Could Save Your Life

Editors: Jane M. Orient, M.D. &
Elizabeth Lee Vliet, M.D.

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Original Investigation | Medical Journals and Publishing

Adherence of Clinical Practice Guidelines for Pharmacologic Treatments of Hospitalized Patients With COVID-19 to Trustworthy Standards
A Systematic Review

Karen E. A. Burns, MD, MSc (Epid); Matthew Laird, BMSc; James Stevenson, BSc; Kimia Honarmand, MD; David Granton, MD; Michelle E. Kho, PT, PhD; Deborah Cook, MD; Jan O. Friedrich, MD; Maureen O. Meade, MD; Mark Duffett, PhD; Dipayan Chaudhuri, MD; Kuan Liu, PhD; Frederick D'Aragon, MD; Arnav Agarwal, MD; Neill K. J. Adhikari, MD; Hayle Noh, BSc; Bram Rochwerg, MD; for the Academy of Critical Care: Development, Evaluation, and Methodology (ACCADEMY)

Recommendations

Six CPGs (18.8%)[15,20,27,32,34,44] adhered (score of 4 or 5) to the requirement to provide a grade or rating of the level of confidence or certainty in the quality or strength of the evidence underpinning each recommendation. Similarly, 6 CPGs (18.8%)[15,23,27,32,34,44] adhered (all with a score of 5) to the requirement to provide a clear description of the potential benefits and harms and link this

External Review and Plans for Updating

Only 3 CPGs (9.4%)[32,34,44] adhered (score of 4 or 5) to the requirement to describe an external review process by specifying (name and description) relevant stakeholders (ie, scientific and clinical experts, organizations, agencies, patients, and representatives) and a process for external review.

Conclusions

Few COVID-19 CPGs met NAM standards for trustworthy guidelines. Approaches that prioritize engagement of a methodologist and multidisciplinary collaborators from at least 2 WHO regions may lead to the production of fewer, high-quality CPGs that are poised for updates as new evidence emerges.

Outline

- SARS-CoV-2 infection (COVID-19)
- Pillars of pandemic response
- Role of early ambulatory treatment
  - Anti-spike protein antibody infusions
  - Hydroxychloroquine
  - Ivermectin
  - Paxlovid
  - Molnupiravir
  - Corticosteroids
  - Colchicine
  - Anticoagulants
- Early sequenced multidrug therapy
- COVID-19 vaccine safety and efficacy
- Conclusions

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Covid-19: Hospital admission 50-70% less likely with omicron than delta, but transmission a major concern

Elisabeth Mahase

Someone infected with the omicron variant of SARS-CoV-2 is estimated to be between 31% and 45% less likely to attend emergency care than if they had been infected with the delta variant and 50-70% less likely to be admitted to hospital, analysis by the UK Health Security Agency has shown.[1]

But the agency said the findings, which exclude people with previous SARS-CoV-2 infection, are preliminary and highly uncertain because of the small numbers of hospital cases of omicron, an inability to effectively measure all previous infections, and the limited spread of omicron into older age groups.

It also emphasised that although a smaller proportion of people with omicron could end up in hospital than with previous variants, the actual number becoming seriously ill and needing hospital care could be huge, because of the variant's increased transmissibility.

The agency's chief executive, Jenny Harries, said, "Cases are currently very high in the UK, and even a relatively low proportion requiring hospitalisation could result in a significant number of people becoming seriously ill. The best way that you can protect yourself is to come forward for your first two doses of vaccine, or your booster jab, and do everything you can to stop onward transmission of the infection."

As at 20 December 132 people with confirmed omicron had been admitted to or transferred from hospital emergency departments. Notably, over 40% of hospital admissions were in London. Of the 132 patients, 17 had received a booster vaccine (three vaccine doses in total), 74 had received two doses, and 27 were not vaccinated. The vaccination status of six people was unknown, while eight had received a single dose. Within 28 days of an omicron diagnosis, 14 people were reported to have died, ranging in age from 52 to 96 years old.

It's still too early to estimate vaccine effectiveness against hospital admissions, but the agency said that this was more likely to be sustained, particularly after a booster.

England's health and social care secretary, Sajid Javid, said, "Hospital admissions are increasing, and we cannot risk the NHS being overwhelmed. This is early stage analysis, and we continue to monitor the data hour by hour."

The agency's findings are consistent with three recent studies, not yet peer reviewed, from researchers in England, Scotland, and South Africa, which all concluded that omicron carried a lower risk of hospital admission than delta.[2]

1 UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England: technical briefing 33. Dec 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043680/technical-briefing-33.pdf.

2 Christie B. Covid-19: Early studies give hope omicron is milder than other variants. *BMJ* 2021;375doi: 10.1136/bmj.n3144.

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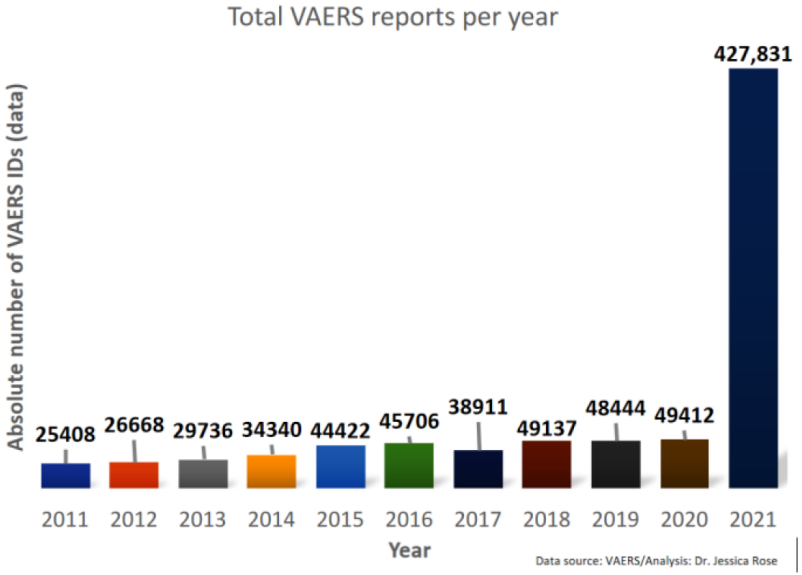
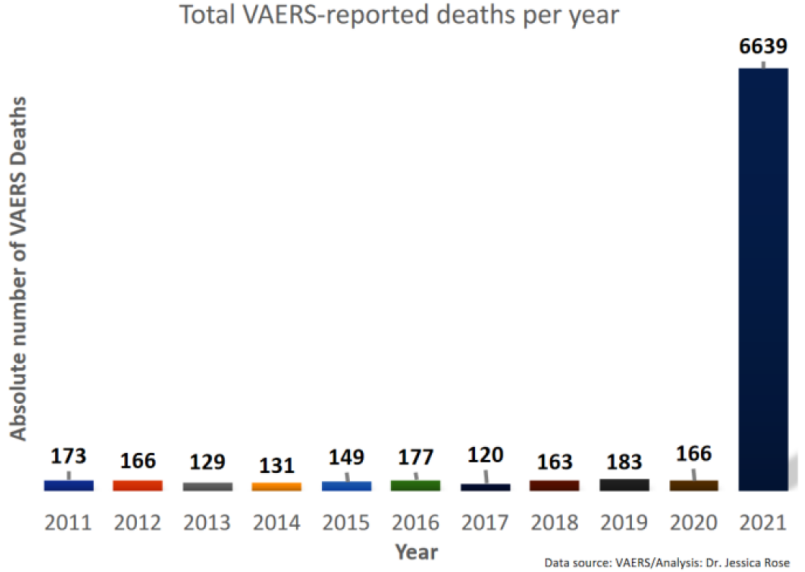
IPAK PHPI

Critical Appraisal of VAERS Pharmacovigilance: Is the U.S. Vaccine Adverse Events Reporting System (VAERS) a Functioning Pharmacovigilance System?

Jessica Rose, PhD, MSc, BSc

Figure 1: Bar plots showing the number of VAERS reports (left) and reported deaths (right) per year for the past decade. (2021 is partial data set.)





Outline

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Conclusions

- COVID-19 pandemic is a global disaster
- Pathophysiology is complex—not amenable to single drug
- Despite contagion control efforts, there have been two poor outcomes: hospitalization and death
- The prehospital phase is the time of therapeutic opportunity
- Hospitalization and late treatment form an inadequate safety net with unacceptably high mortality
- Early ambulatory therapy with a sequenced, multi-drug regimen is supported by available sources of evidence and has a positive benefit-to-risk profile
  - Reduce the risk of hospitalization and death
  - More safely temporize to close the crisis with vaccination and natural herd immunity
- COVID-19 genetic vaccines have an unfavorable safety profile and are not clinically effective, thus they cannot be generally supported in clinical practice at this time