Pathophysiologic Basis and Clinical Rationale for Early Ambulatory Treatment of COVID-19 and Update on Vaccine Safety and Efficacy

Peter A. McCullough, MD, MPH

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Tagline: https://americaoutloud.com/the-mccullough-report/

December 25, 2021

Special Features

America Out Loud Talk Radio is featuring Christmas music on the network starting Christmas Eve thru Christmas Day. Listen on iHeart Radio or our Media Player.

Christmas Day

A Christmas Journey to Peace
Join Pastor Rick Stevens in a two-hour special from 10 to Noon ET.

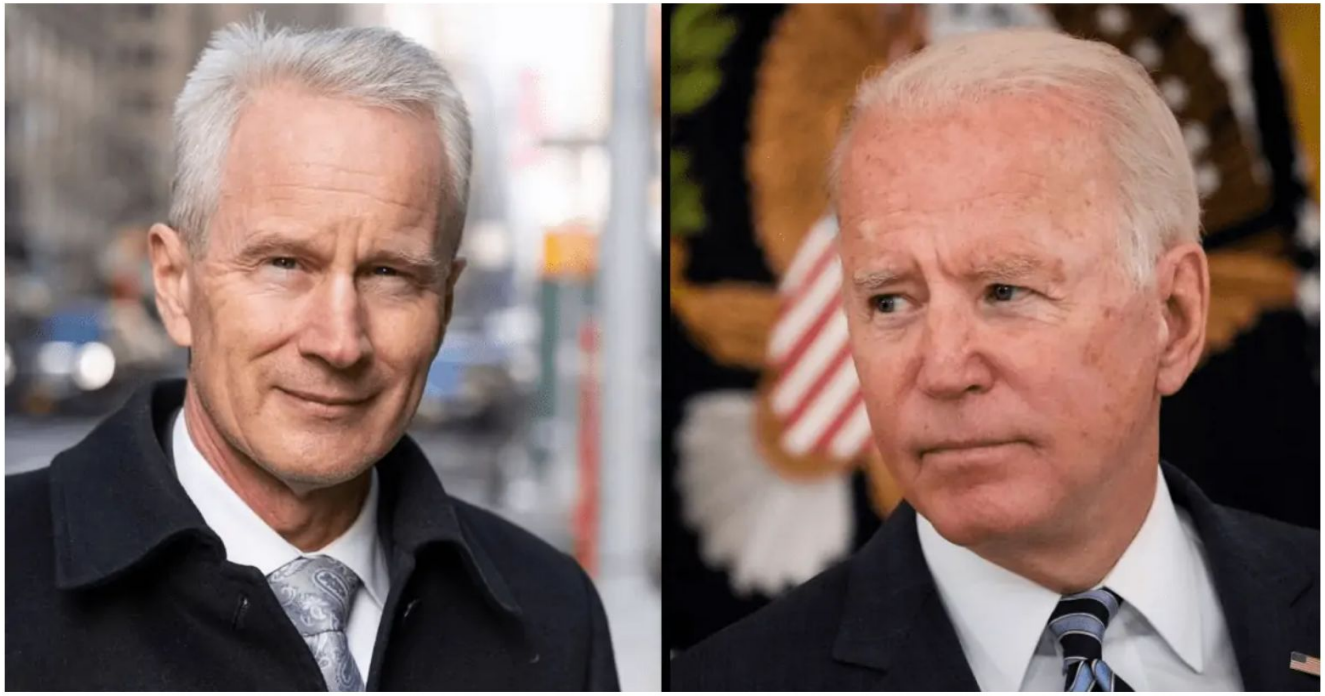
The Tales of Whynot?
Daniel Baranowski in a two-hour special from 4 to 6 PM ET.

Faith over Fear
Your Christmas Gift to YOU
DrLee4America provides a Biblical basis for the historical links between

Column

Dr. McCullough Counters Pres. Biden's Dark Holiday Message With Hope and Compassion

by **Dr. Peter McCullough** | Dec 24, 2021 | Healthcare, Politics




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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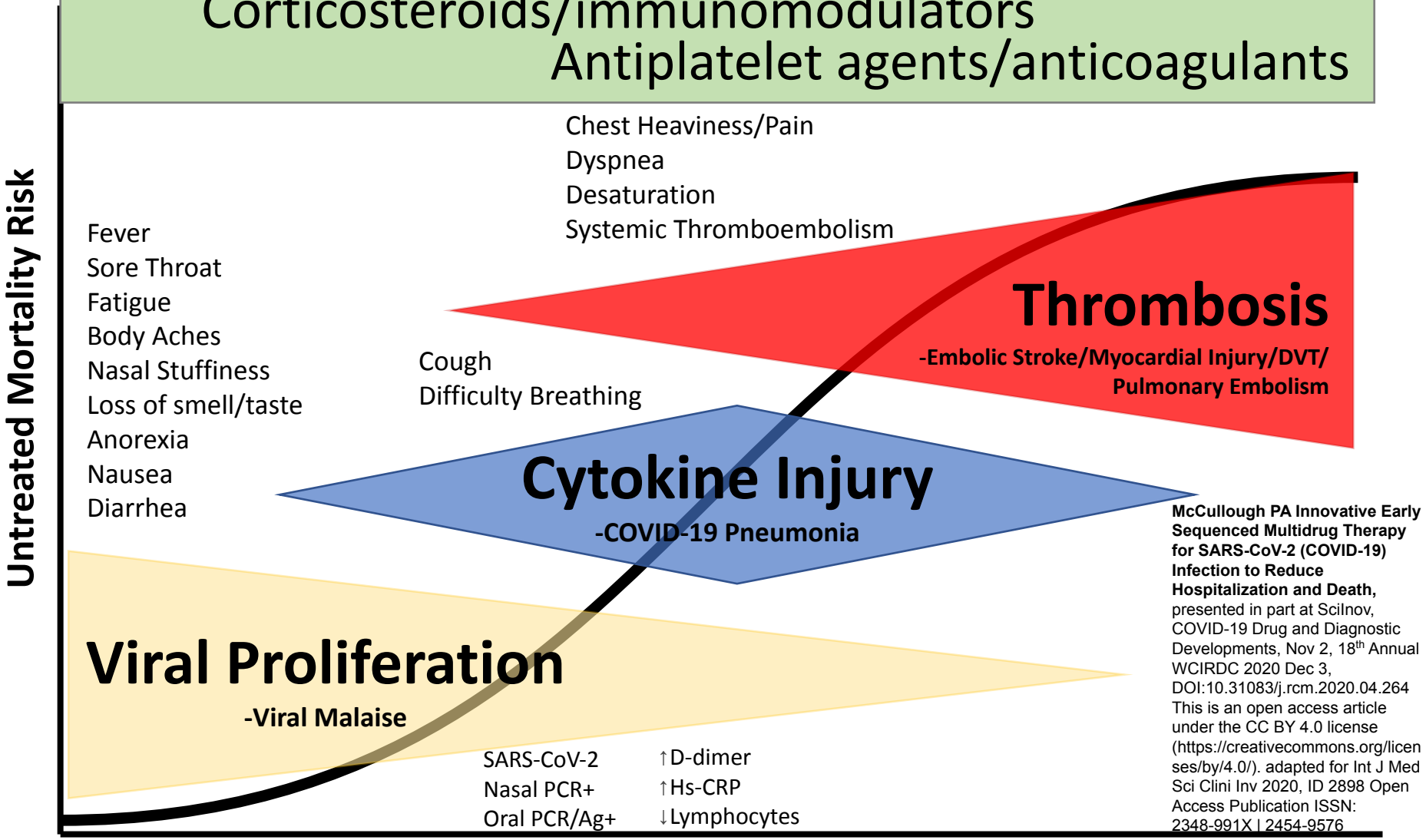
Therapeutic Response

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

September 17, 2021

Crushing the Lifeblood of Medical Science

by Dr. Peter McCullough

In this issue of The McCullough Report, we have some grave news about a concerning set of developments that have taken the COVID-19 crisis response and its consequences to the world to a whole new level. With the backdrop that free speech and scientific discourse is...

Treat the Viral Infection, Handle the Pandemic Crisis

by Dr. Peter McCullough | May 11, 2021 | Healthcare, Politics,

Sick COVID-19 patients don't feel better with masks and it's either too late or they have been failed by the vaccination. We need real doctors helping frightened patients in need to get through the crisis. We need to cut through all the fear, panic, hubris, and false narrative and getting to the truth of what is really going on during the pandemic...

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.

Review Article

Can povidone iodine gargle/mouthrinse inactivate SARS-CoV-2 and decrease the risk of nosocomial and community transmission during the COVID-19 pandemic? An evidence-based update

Aditi Chopra [a], Karthik Sivaraman [b], Raghu Radhakrishnan [c], Dhanasekar Balakrishnan [b], Aparna Narayana [b,*]

[a] Department of Periodontology, Manipal College of Dental Sciences, Manipal, Manipal Academy of Higher Education, Manipal 576104, India
[b] Department of Prosthodontics and Crown and Bridge, Manipal College of Dental Sciences, Manipal, Manipal Academy of Higher Education, Manipal 576104, India
[c] Department of Oral Pathology and Microbiology, Manipal College of Dental Sciences, Manipal, Manipal Academy of Higher Education, Manipal 576104, India

Table 2
Evidence confirming the efficacy of Povidone-Iodine (PVP-I) against SARS-CoV-2.

No	Study	Objective	Materials and methods	Results and conclusion	References
1.	In-vitro observational study	Virucidal activity of PVP-1 against SARS-CoV-2	Four products of PVP-I a. Antiseptic solution (PVP-I 10%) b. Skin cleanser (PVP-I 7.5%) c. Gargle and mouth wash (PVP-I 1%) d. Throat spray (PVP-I 0.45%) Tested for a contact time of 30 s for virucidal activity	All products of PVP-I inactivated the virus by ≥99.99% which corresponded to ≥4log$_{10}$ reduction of virus titre, within 30 s of contact	Anderson et al., 2020 [6]
2.	In-vitro observational study	Optimal contact time and concentration of oral PVP-I against SARS-CoV-2	a. PVP-I at a concentration of 0.5%, 1% and 1.5% compared with b. Ethanol (70%) and water for 15 and 30 s Tested against SARS-CoV-2-USAWA1/2020 strain	PVP-I (0.5%, 1% and 1.5%) inactivated SARS-CoV-2 completely within 15 s of contact 70% ethanol group did not inactivate SARS-CoV-2 after 15 s of contact, but was able to inactivate the virus at 30 s of contact	Bidra et al. [60]
3.	In-vitro observational study	Compare hydrogen peroxide (H_2O_2) and PVP-I oral antiseptic rinses against SARS-CoV-2	a. PVP-I (0.5%, 1.25% and 1.5%) and b. H_2O_2 aqueous solutions (3% and 1.5% concentrations) at contact periods of 15 s and 30 s Was tested against SARS-CoV-2	PVP-I (0.5%, 1% and 1.5%) inactivated SARS-CoV-2 completely at 15 s The H_2O_2 solutions (1.5% and 3.0%) showed minimal virucidal activity after 15 s and 30 s of contact time	Bidra et al. [61]
4.	Systematic review	To evaluate the specific efficacy of PVP-I against SARS-CoV-2	All protocols for nasal and oral PVP-I against COVID-19 were systematically reviewed	PVP-I can be safely administered for up to 5 months in the nasal cavity and 6 months in the oral cavity	Frank et al. [62]
5.	Short communication	The impact of PVP-I mouthwash on the salivary viral load of SARS-CoV-2	a. Nasopharyngeal swabs and salivary samples were tested for SARS-CoV-2 in patients before and after rinsing with 15 mL of 1% PVP-I for 1 min	PVP-I resulted in a significant drop in viral load, which remained for at least 3 h	Lamas et al. [53]

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

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

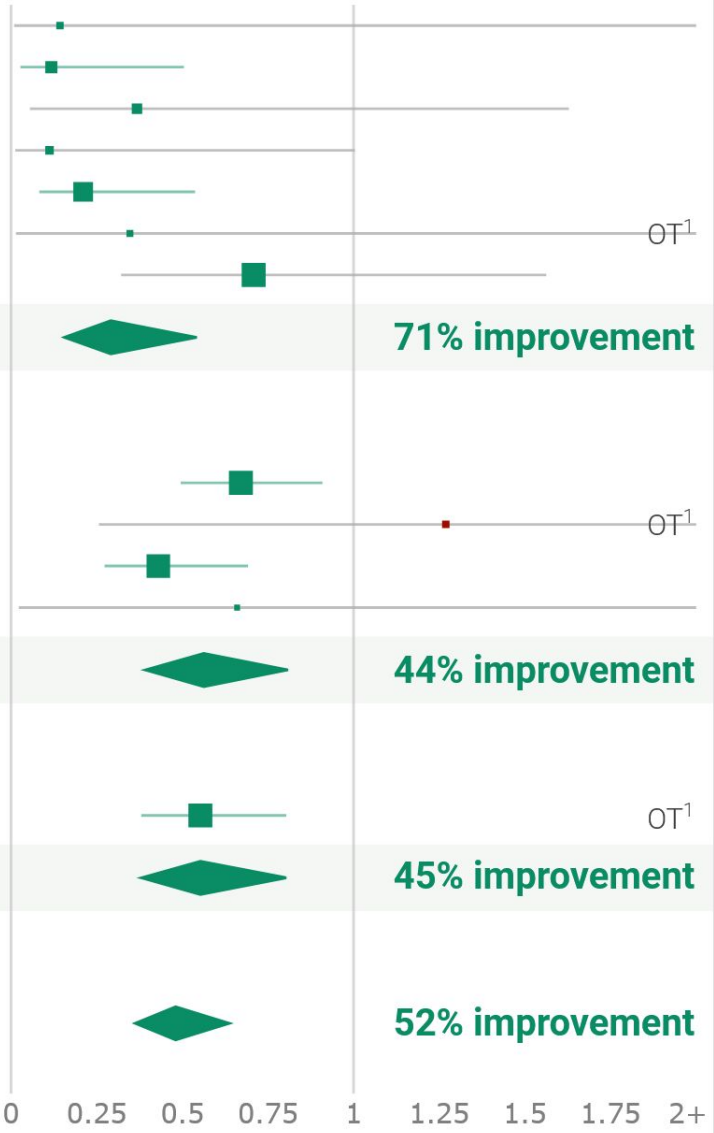
	Improvement, RR [CI]			Treatment	Control
Seneviratne (RCT)	33%	0.67 [0.50-0.91]	viral load	4 (n)	2 (n)
Zarabanda (RCT)	-27%	1.27 [0.26-6.28]	no recov.	3/13	2/11
Jamir	57%	0.43 [0.27-0.69]	death	39/163	62/103
Ferrer (RCT)	34%	0.66 [0.02-19.0]	viral load	9 (n)	12 (n)
Late treatment	44%	0.56 [0.39-0.81]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

A

Treating and Preventing Sinusitis with a Mouthwash/Gargle Solution

If you feel you are coming down with a sinus or throat infection and are without antibiotics here is a simple Mouthwash and Gargle solution you can make at home to help cure your self and prevent further infection. The main ingredient is 10% Povidone Iodine (e.g. Betadine) which is a known anti-fungal, anti-viral and anti-bacterial agent.

Make the following two solutions with 10% Povidone Iodine (e.g. Betadine).

0.62% Dilute Solution
1 cup sterile water (this volume should be enough for 7 days)
1 Tablespoon of 10% **Povidone Iodine (PVD-I)**
¼ tsp salt

In the labs a 1% solution of Povidone Iodine has been shown to be 99.99% effective as an antiviral treatment in just 30 seconds.
0.50% solutions have also been shown to be effective especially with repeated treatments.

0.01% Very Dilute Solution
2 cups sterile water
¼ tsp of 10% **Povidone Iodine (PVD-I)**
½ tsp salt

This solution is purposely a weak disinfectant but much more of a soothing sterile wash that inhibits the growth of any pathogen

Use a Bulb Syringe for the Nasal Flush

Follow this daily regimen for a week to **eliminate** an established Sinusitis:

6 AM with 0.62% Dilute PVD-I flush Nose and Gargle. Take Allegra-D
12 Noon with 0.01% Very Dilute PVD-I flush Nose and Gargle.
6 PM with 0.01% Very Dilute PVD-I flush Nose and Gargle.
12 Midnight with 0.01% Very Dilute PVD-I flush Nose and Gargle. Take Mucinex-DM

Effect of 1% Povidone Iodine Mouthwash/Gargle, Nasal and Eye Drop in COVID-19 patient

Bioresearch Communications
Volume 7, Issue 1, January 2021

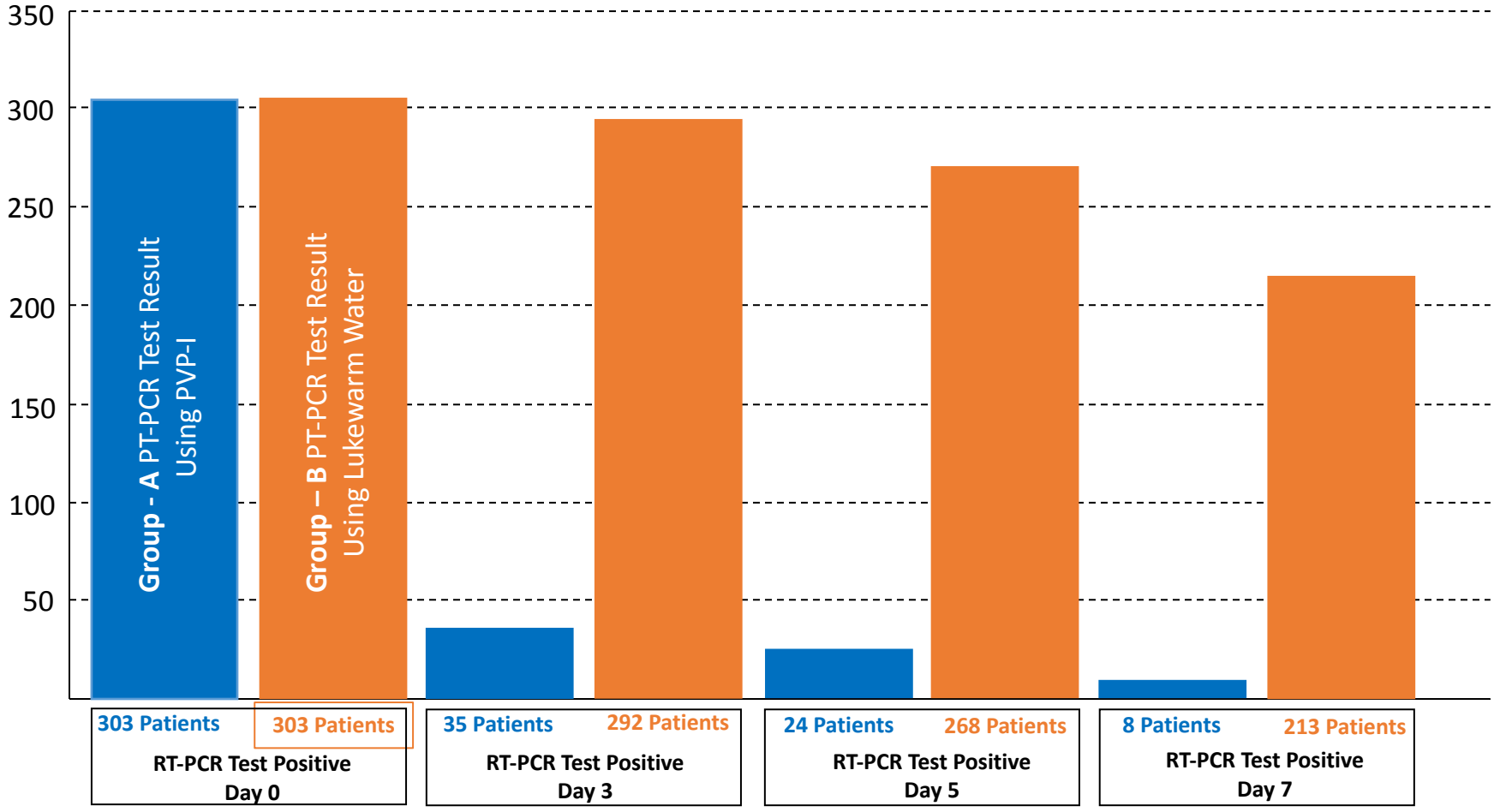
Md. Iqbal Mahmud Choudhury[1], Nilufar Shabnam[2], Tazin Ahsan[3], Md. Saiful kabir[4], Rashed Md. Khan[5], S.M. Abu Ahsan[6]

[1]Assistant professor, Plastic Surgery Unit, Department of Surgery, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh. [2] Assistant professor, Department of Surgery, BIRDEM Hospital & Ibrahim Medical College, Shahbag, Dhaka, Bangladesh. [3]Medical officer, Upazila Health Complex, Chowgacha, Jessore, Bangladesh. [4]Professor and Head, Department of Dermatology and Venereology, National Medical College, Dhaka, Bangladesh. [5]Professor and Head, Department of Dermatology and Venereology, Dhaka Medical College, Dhaka, Bangladesh. [6]Associate Professor and Head, Ad-din Sakina Medical college, Jessore, Bangladesh.

ABSTRACT: Background: The sudden onset of COVID-19 began in late 2019 caused by a novel coronavirus (SARS-COV2) and on 11th March, WHO declared it to have developed pandemic status. There is still no specific treatment and vaccine available for COVID-19; causing wide spread health problem and concern of the globe. Povidone iodine (PVP-I) is an antiseptic that has been used for over 150 years. It is already proved that different concentration of PVP-I can deactivate COVID-19 virus. **Methodology:** In this randomized controlled clinical trial, out of 1113 patients 606 patients were enrolled and divided in 2 groups by randomization after taken consents. In Gr-A, 303 patients underwent mouthwash/gargle, nasal drops and eye drops with 1% povidone iodine 4 hourly for 4 weeks as well as symptomatic treatment according to need. In Gr-B 303 patients were advised mouthwash/gargle, nasal cavity and eye wash with lukewarm water 4 hourly for 4 weeks and symptomatic treatment according to need. RT-PCR test done every 3rd, 5th and 7th day and Thyroid hormone level (TSH, T_3, T_4, FT_4) at 4th week for follow up. **Results:** The group of patients used 1% PVP-I have shown tremendously reduced mortality, morbidity and hospital as well as financial burden in this covid situation. **Conclusion:** Administration of 1% PVP-I as mouthwash/gargle, nasal or eye drop is simple, rapid and cost effective in reduction of mortality and morbidity by COVID-19.

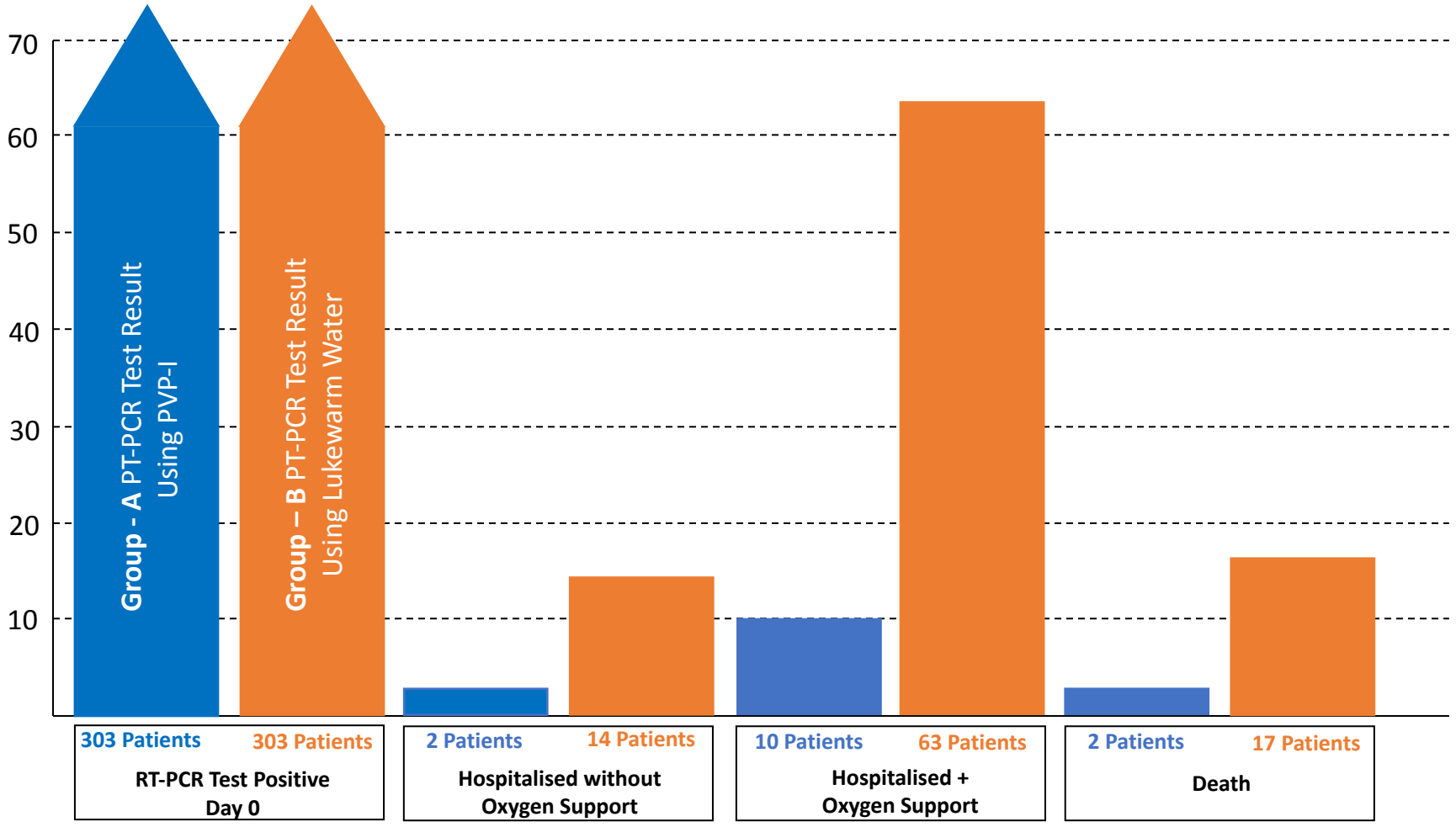
KEYWORDS: Povidone Iodine, 1Pq.s, COVID-19.

RCT: EFFECT OF 1% POVIDONE IODINE MOUTHWASH/GARGLE, NASAL AND EYE DROP IN COVID-19 PATIENTS



Bioresearch Communications
Volume 7, Issue 1, January 2021

RCT: EFFECT OF 1% POVIDONE IODINE MOUTHWASH/GARGLE, NASAL AND EYE DROP IN COVID-19 PATIENTS (OUTCOMES)



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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.

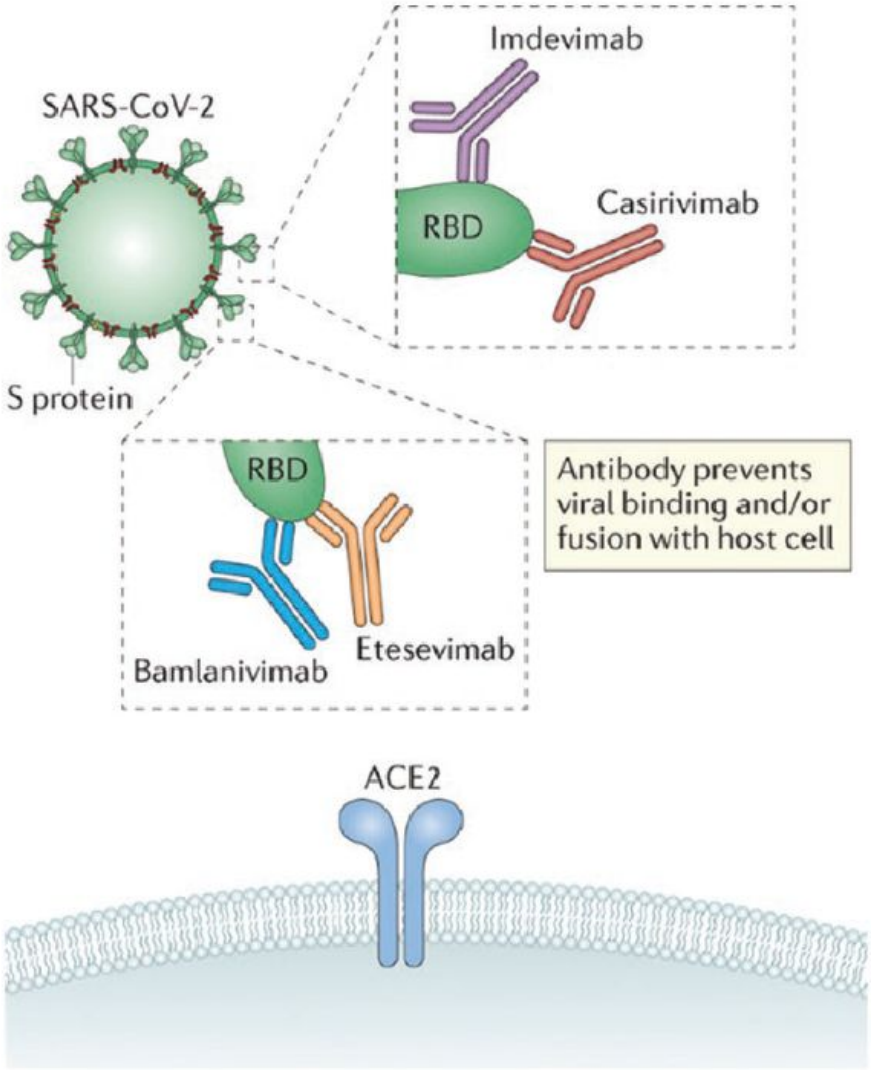


Figure 1. Schematic depiction of the potential mechanism of mAbs in COVID-19 infection. Reprinted with permission from reference [4]. Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; mAb, monoclonal antibody; RBD, receptor binding domain; S, spike; SARS-CoV-2, 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

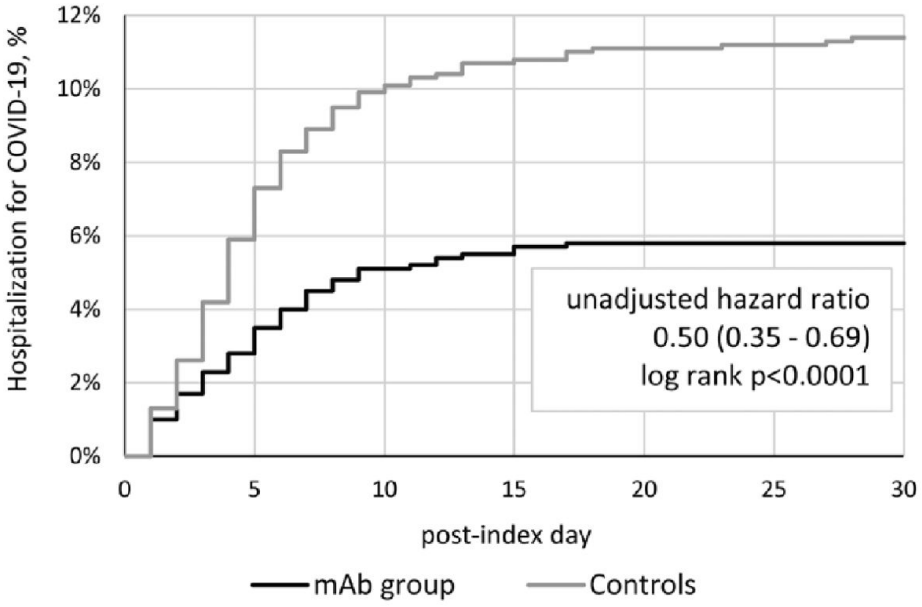
Clinical Infectious Diseases

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



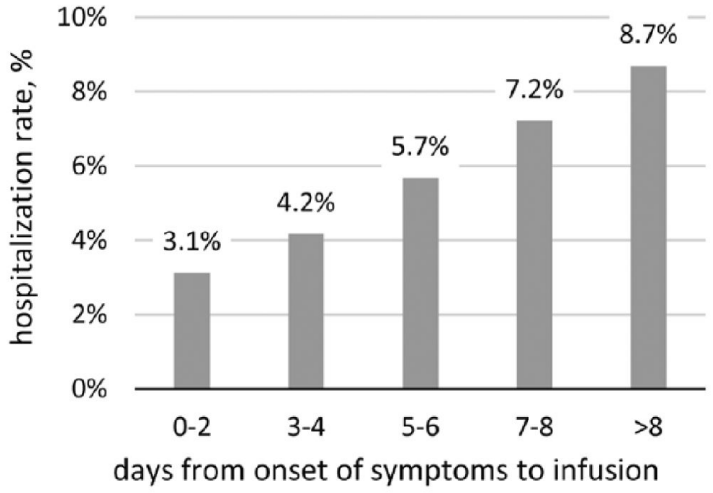


Figure 3. Distribution of hospitalization rates based on the number of days between the first onset of symptoms and NmAb infusion (n = 358). Abbreviation: NmAb, neutralizing monoclonal antibody.

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

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*

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

DOI: 10.1056/NEJMoa2107934

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

Table 2. Efficacy Out… …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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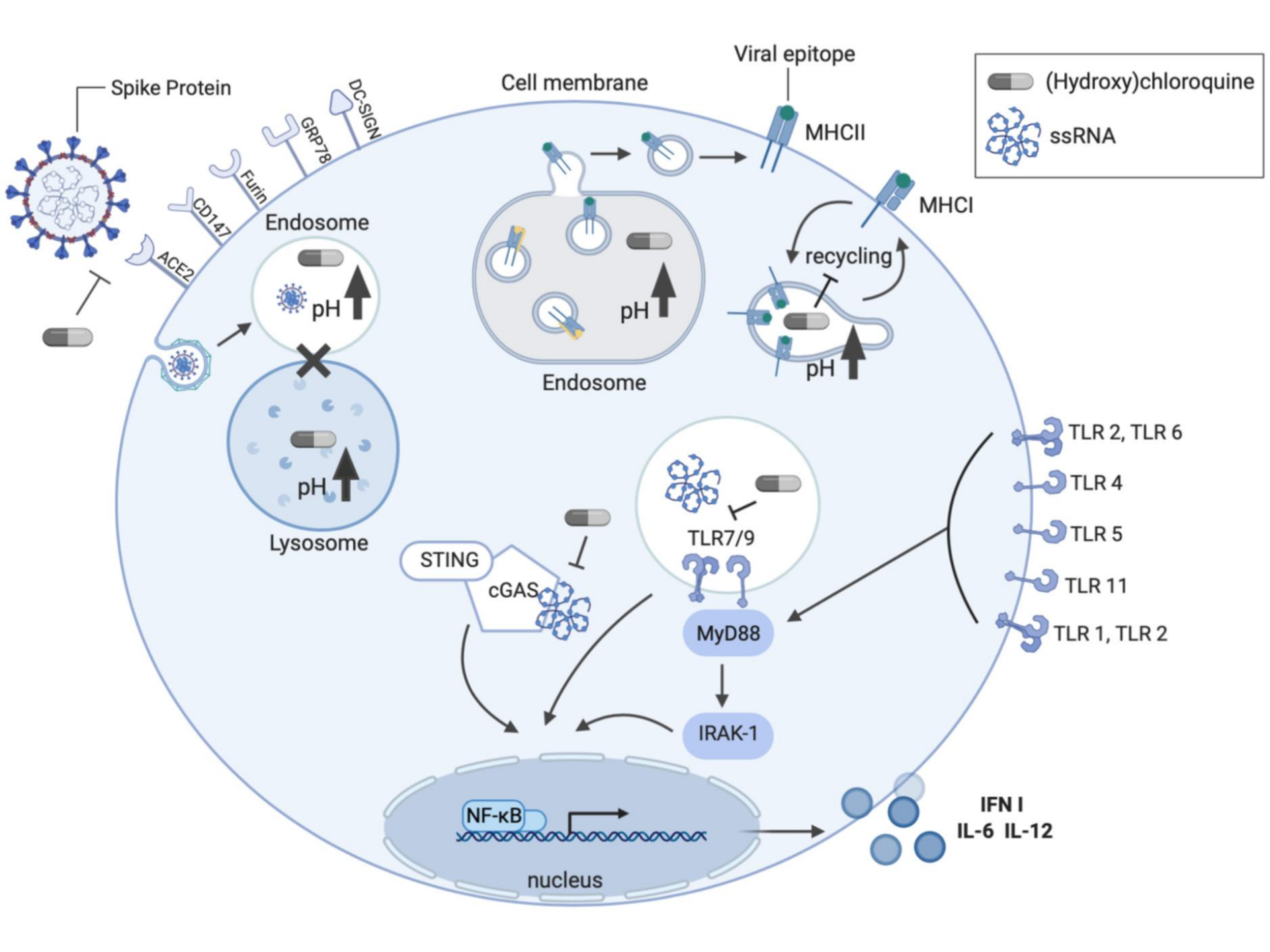
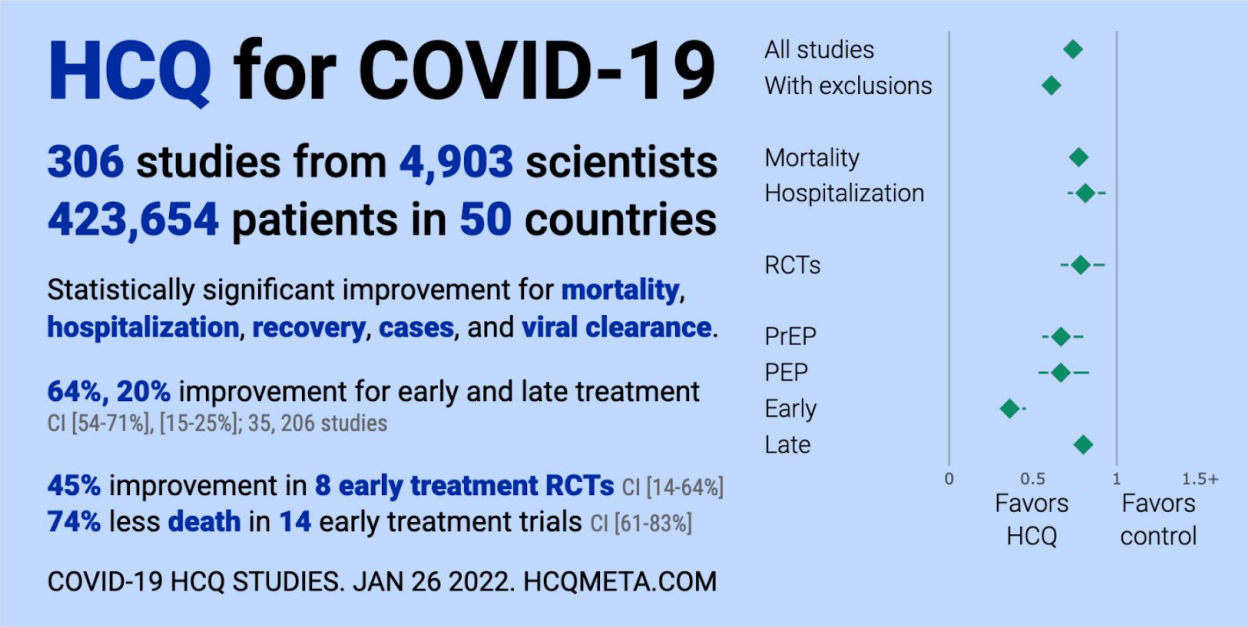
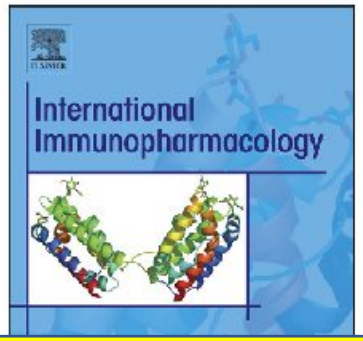

Spike Protein
ACE2
CD147
Furin
GRP78
DC-SIGN
Cell membrane
Viral epitope
MHCII
MHCI
recycling
Endosome
pH
Endosome
pH
pH
Lysosome
(Hydroxy)chloroquine
ssRNA
TLR 2, TLR 6
TLR 4
TLR 5
TLR 11
TLR 1, TLR 2
TLR7/9
STING
cGAS
MyD88
IRAK-1
NF-κB
nucleus
IFN I
IL-6 IL-12

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



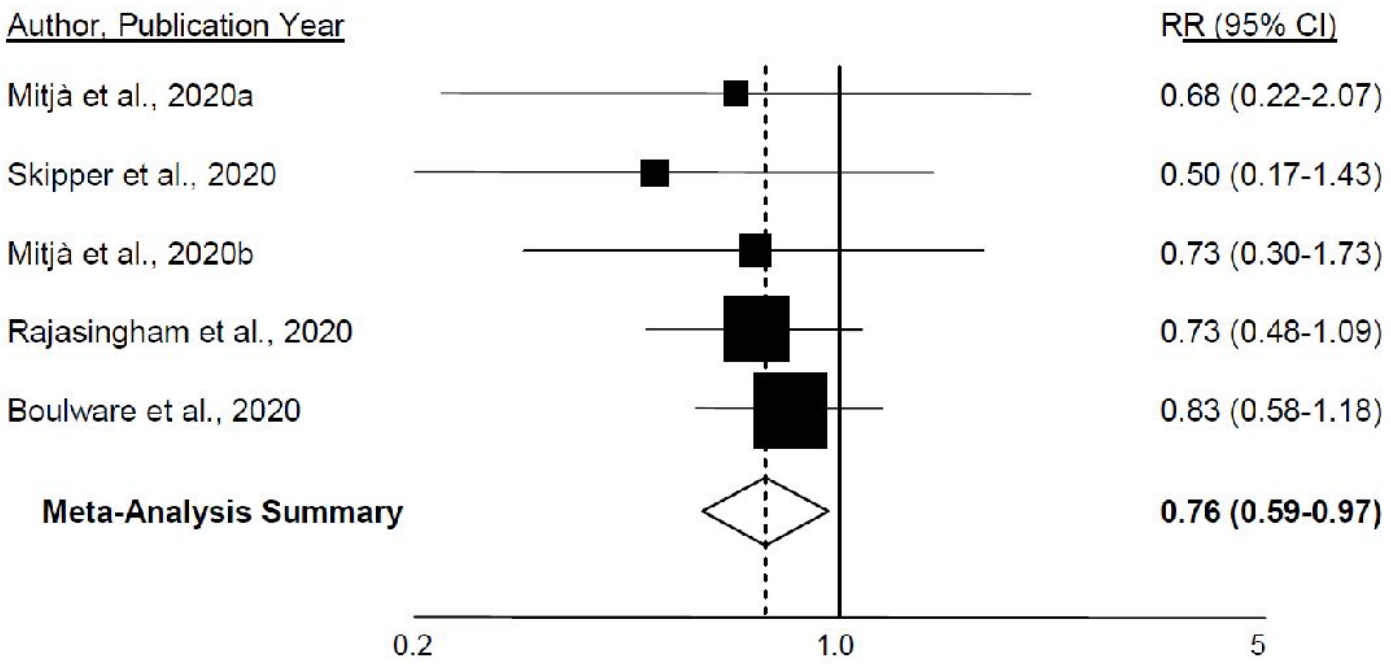
Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting

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

HCQ COVID-19 Efficacy in Outpatient RCTs



Outpatient RCT hydroxychloroquine treatment and risk of COVID-19 infection, hospitalization, or death

Figure 1

JAMA | Original Investigation

JAMA. doi:10.1001/jama.2020.22240
Published online November 9, 2020.

Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19
A Randomized Clinical Trial

Table 2. Outcomes, Systematically Collected Safety Events, and Serious Adverse Events

Outcome	Hydroxychloroquine (n = 242)	Placebo (n = 237)	Unadjusted absolute difference (95% CI)[a]	Adjusted odds ratio or odds ratio (95% CI)[b]
Primary outcome				
COVID Outcomes Scale score at 14 d, median (IQR)[c]	6 (4 to 7)	6 (4 to 7)	0[d]	1.02 (0.73 to 1.42)
Secondary outcomes				
COVID Outcomes Scale score, median (IQR)[c]				
At 2 d	4 (3 to 5)	4 (3 to 5)	0[d]	1.28 (0.90 to 1.81)
At 7 d	5 (4 to 7)	6 (3 to 6)	−1 (−2 to 0)	1.16 (0.84 to 1.61)
At 28 d	6 (6 to 7)	6 (6 to 7)	0 (−1 to 1)	0.97 (0.69 to 1.38)
All-cause, all-location death, No. (%)	n = 241	n = 236		
At 14 d	18 (7.5)	14 (5.9)	1.5 (−2.9 to 6.0)	1.56 (0.68 to 3.57)
At 28 d	25 (10.4)	25 (10.6)	−0.2 (−5.7 to 5.3)	1.07 (0.54 to 2.09)
Time to recovery in days, median (IQR)	5 (1 to 14)	6 (1 to 15)	−1 (−3 to 1)	0.97 (0.69 to 1.35)
Composite of death or ECMO through 28 d, No./total No. (%)	29/241 (12.0)	28/236 (11.9)	0.2 (−5.6 to 6.0)	1.13 (0.60 to 2.14)
Support-free days through day 28, median (IQR)				
Hospital-free days	21 (11 to 24)	20 (10 to 24)	1 (−1 to 3)	1.17 (0.85 to 1.61)
Oxygen-free days	21 (0 to 27)	20 (0 to 27)	1 (−2 to 4)	0.96 (0.68 to 1.34)
ICU-free days	28 (21 to 28)	28 (18 to 28)	0 (0 to 0)	1.26 (0.84 to 1.88)
Ventilator-free days	28 (28 to 28)	28 (28 to 28)	0[d]	1.26 (0.76 to 2.08)
Vasopressor-free days	28 (28 to 28)	28 (28 to 28)	0[d]	1.03 (0.61 to 1.72)
Systematically collected safety events, No. (%)[e]				
Cytopenia[f]	92 (38.0)	87 (36.7)	1.3 (−7.4 to 10.0)	1.06 (0.73 to 1.53)
AST or ALT ≥2 times upper limit of normal	50 (20.7)	65 (27.4)	−6.8 (−14.4 to 0.9)	0.69 (0.45 to 1.05)
Cardiac arrest treated with CPR[g]	10 (4.1)	4 (1.7)	2.5 (−0.8 to 5.6)	2.51 (0.78 to 8.12)
Symptomatic hypoglycemia[h]	10 (4.1)	8 (3.4)	0.8 (−2.8 to 4.3)	1.23 (0.48 to 3.18)
Ventricular tachyarrhythmia[i]	5 (2.1)	6 (2.5)	−0.5 (−3.4 to 2.4)	0.81 (0.24 to 2.70)
Seizure	1 (0.4)	0	0.4 (−1.0 to 1.8)	
Patients with ≥1 SAEs reported[j]	14 (5.8)	11 (4.6)	1.1 (−3.0 to 5.2)	1.26 (0.56 to 2.84)

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*

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DOI:10.31083/j.rcm2203063

Submitted: 16 September 2021 Accepted: 17 September 2021 Published: 24 September 2021

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

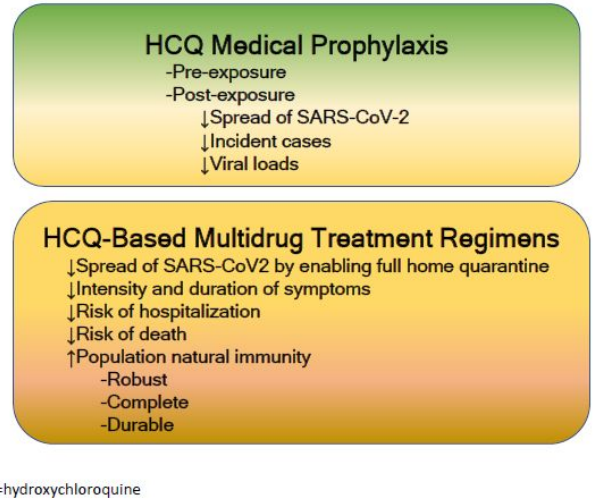


Fig. 1. Roles of hydroxychloroquine in the prevention and treatment of SARS-CoV-2 infection and the COVID-19 syndrome.

Outline

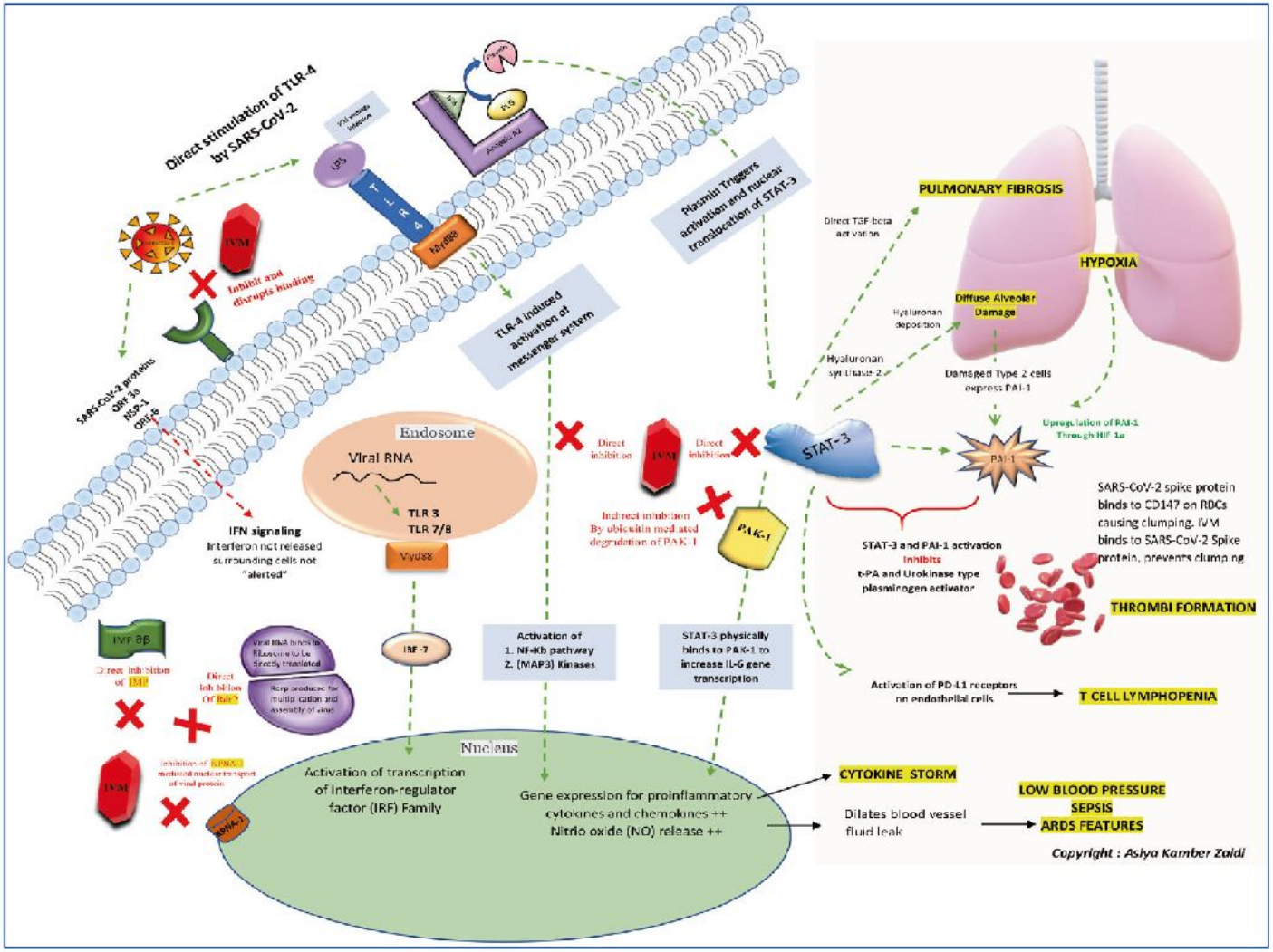
- SARS-CoV-2 infection (COVID-19)
- Pillars of pandemic response
- Role of early ambulatory treatment
  - Anti-spike protein antibody infusions
  - Hydroxychloroquine
  - Ivermectin
  - Paxlovid
  - Molnupiravir
  - Corticosteroids
  - Colchicine
  - Anticoagulants
- Early sequenced multidrug therapy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

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

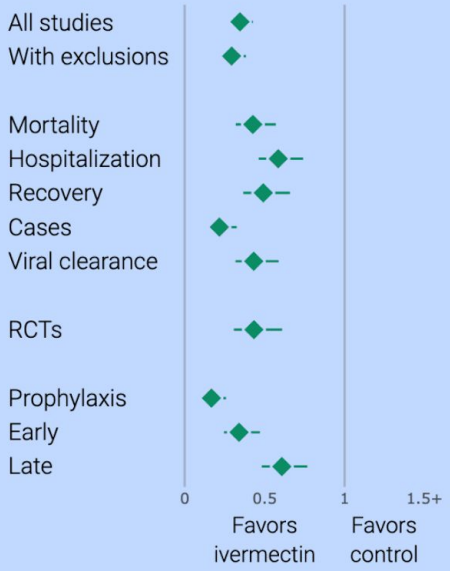
Statistically significant improvement for **mortality**, **ventilation**, **ICU**, **hospitalization**, **recovery**, **cases**, and **viral clearance**.

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		

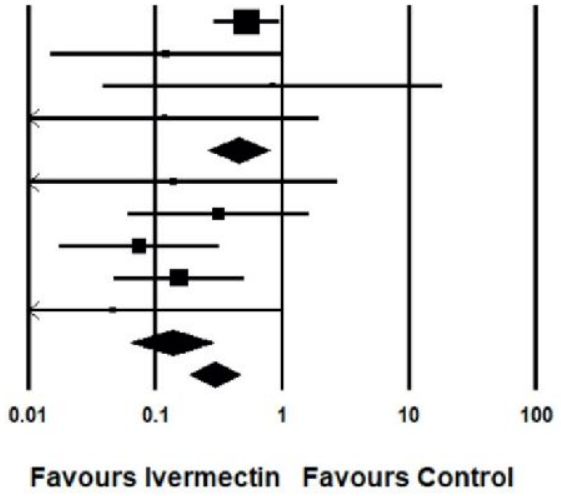


Figure 6 legend: OBS: Observational study, RCT: Randomized Controlled Trial. Symbols: Squares: indicate treatment effect of an individual study. Large diamond: reflect summary of study design immediately above. Small diamond: sum effect of all trial designs. Size of each symbol correlates with the size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

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- COVID-19 vaccine safety and efficacy
- Conclusions

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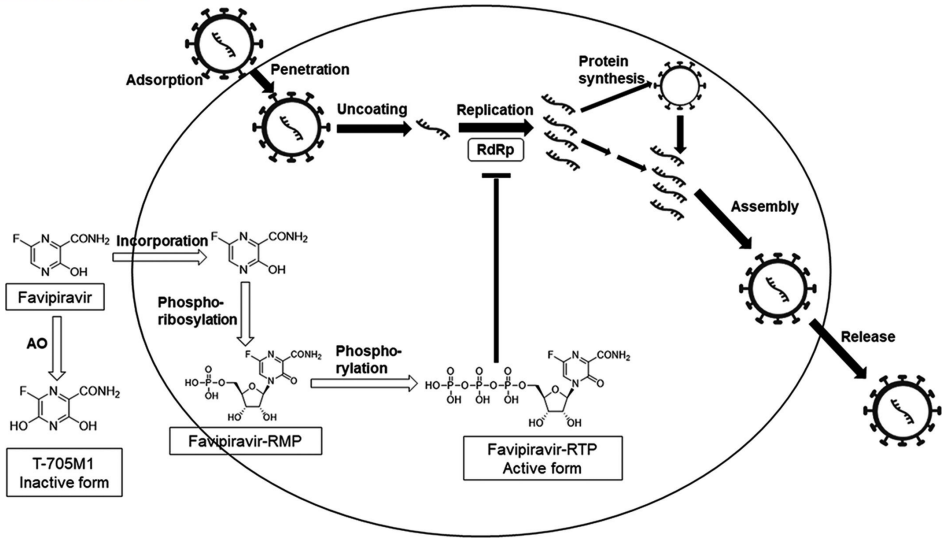
COMMENTARY

Favipiravir and the Need for Early Ambulatory Treatment of SARS-CoV-2 Infection (COVID-19)

Peter A. McCullough[a,b,c]

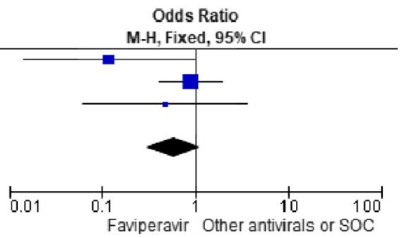
[a]Baylor University Medical Center, Dallas, Texas, USA
[b]Baylor Heart and Vascular Institute, Dallas, Texas, USA
[c]Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, Texas, USA

ABSTRACT It is becoming increasingly clear that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), like most human viral infections, will require multiple drugs in combination to treat COVID-19 illness. In this issue of the Journal, Doi and colleagues describe successful treatment of patients with early COVID-19 with favipiravir, an oral polymerase inhibitor, to rapidly and substantially clear SARS-CoV-2 from nasal secretions irrespective if it was started relatively early or later within the first week of infection. These data support the concept that favipiravir could be paired with at least one more off-target antiviral agent (doxycycline, azithromycin, or ivermectin) followed by corticosteroids and antithrombotics to prevent COVID-19



Study or Subgroup	Favipiravir Events	Total	Other antivirals or SOC Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Cai Q 2020 (1)	1	35	9	45	32.9%	0.12 [0.01, 0.98]
Chen C 2020 (2)	13	116	15	120	56.3%	0.88 [0.40, 1.95]
Ivashchenko AA 2020 (3)	2	40	2	20	10.9%	0.47 [0.06, 3.64]
Total (95% CI)		**191**		**185**	**100.0%**	**0.59 [0.30, 1.14]**
Total events	16		26			

Heterogeneity: Chi² = 3.28, df = 2 (P = 0.19); I² = 39%
Test for overall effect: Z = 1.57 (P = 0.12)



Footnotes
(1) 1 Day 14 CT worsening
(2) 2 Day 7 clinical deterioration (new dyspnea)
(3) Day 15; worsening in CT findings

Fig. 5 Forest plot for odds ratios regarding clinical deterioration among FVP group versus other antivirals

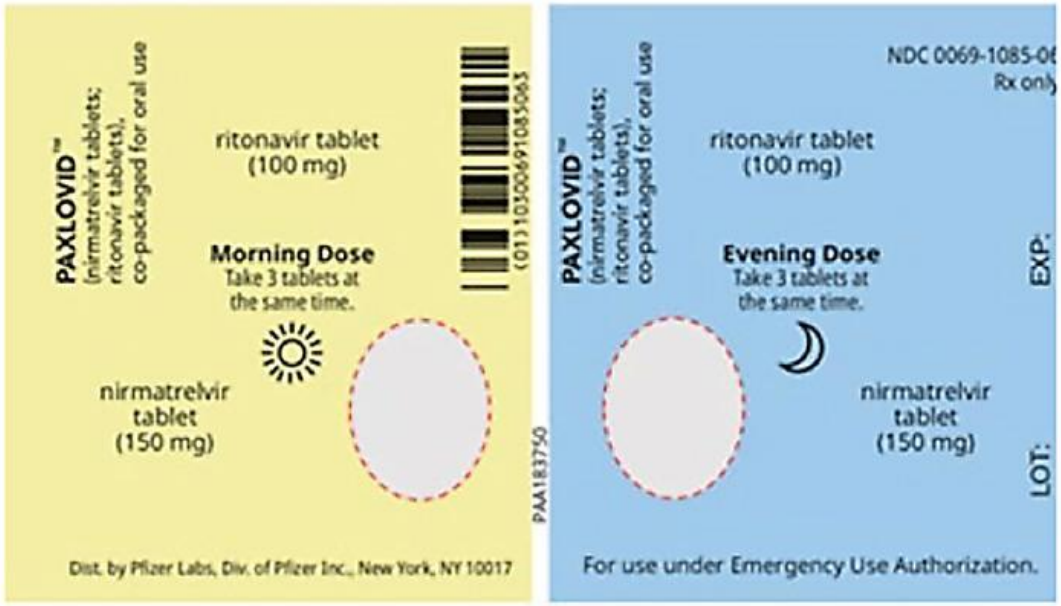
Japan, Russia, Saudi Arabia, Thailand, Kenya, 4 India states approved oral favipiravir for mild-moderate COVID-19 in guidelines. The Japanese Association for Infectious Diseases indicate 3600 mg (1800 mg BID) on day 1 and 1600 mg (800 mg BID) from day 2 onwards, for up to 14 days (http://www.sukl.cz/file/92991_1_1/2020).

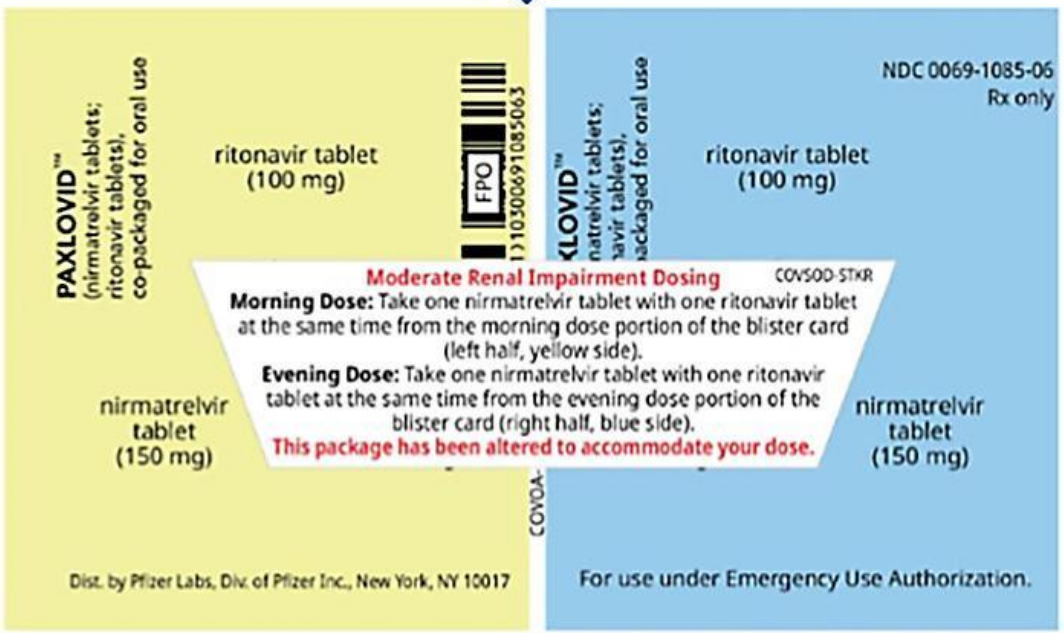
Shrestha *et al. Virol J* (2020) 17:141
https://doi.org/10.1186/s12985-020-01412-z

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
nirmatrelvir tablet (150 mg)
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.
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)
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  - Corticosteroids
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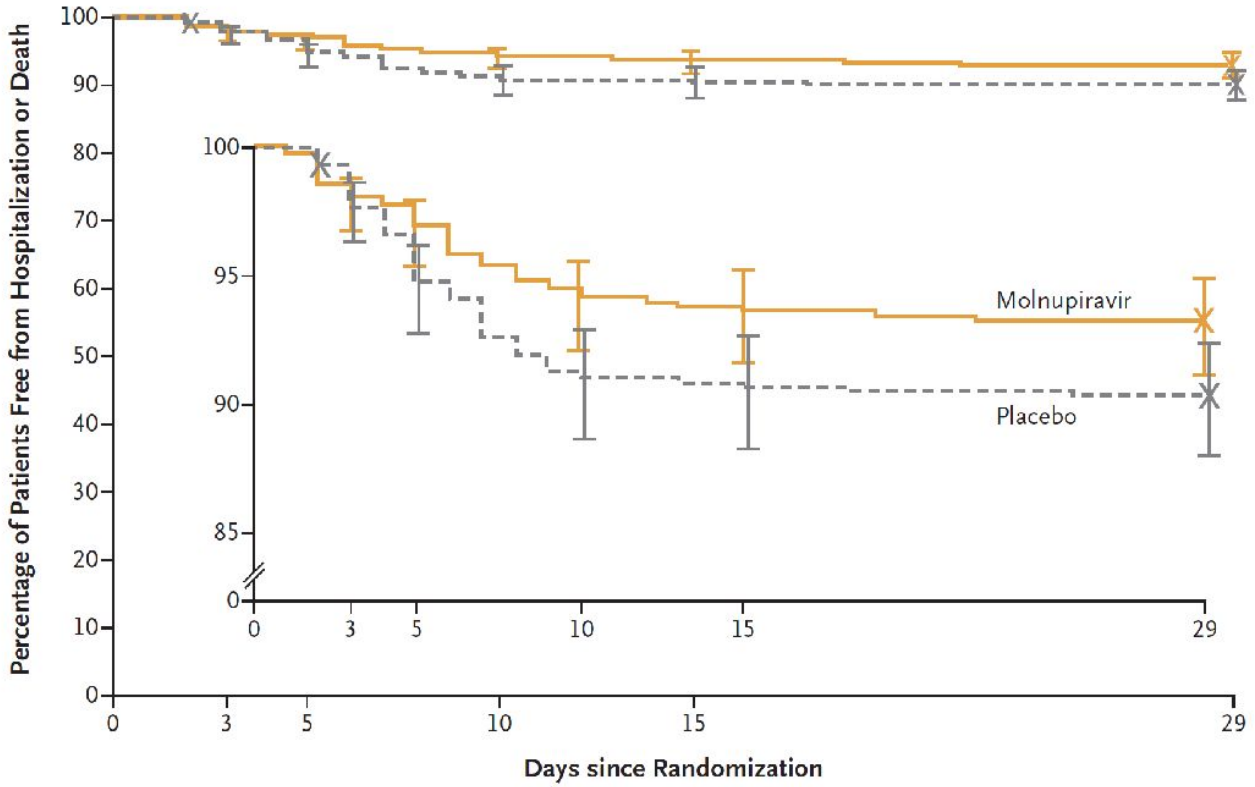
- Early sequenced multidrug therapy
- COVID-19 vaccine safety and efficacy
- Conclusions

This article was published on December 16, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2116044

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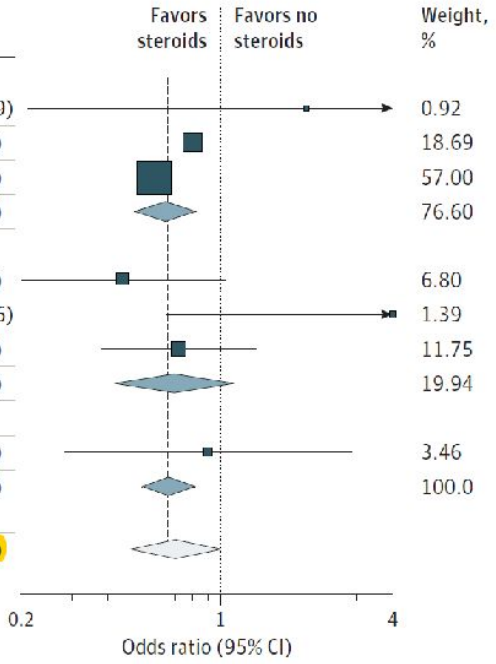
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

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)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
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)

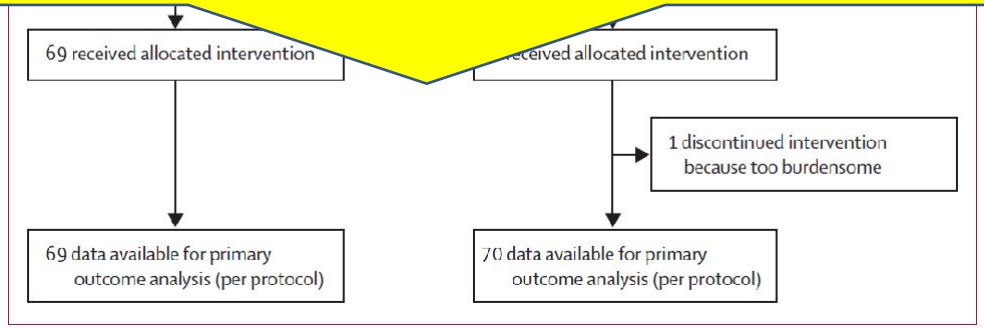


Figure 1: Trial profile

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 (36·7–37·1)	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**

www.thelancet.com/respiratory **Published online April 9, 2021** https://doi.org/10.1016/S2213-2600

Outline

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  - Ivermectin
  - Paxlovid
  - Molnupiravir
  - Corticosteroids
  - Colchicine
  - Anticoagulants
- Early sequenced multidrug therapy
- COVID-19 vaccine safety and efficacy
- Conclusions

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

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
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- Conclusions

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†]

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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

Outline

- SARS-CoV-2 infection (COVID-19)
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  - Anti-spike protein antibody infusions
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- Early sequenced multidrug therapy
- COVID-19 vaccine safety and efficacy
- Conclusions

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]

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KEYWORDS: Ambulatory treatment; Anticoagulant; ...; 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.

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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.

https://doi.org/10.1016/j.amjmed.2020.07.003

Published online: ?? xx, xxxx

IMR Press

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 High[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]

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DOI:10.31083/j.

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

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

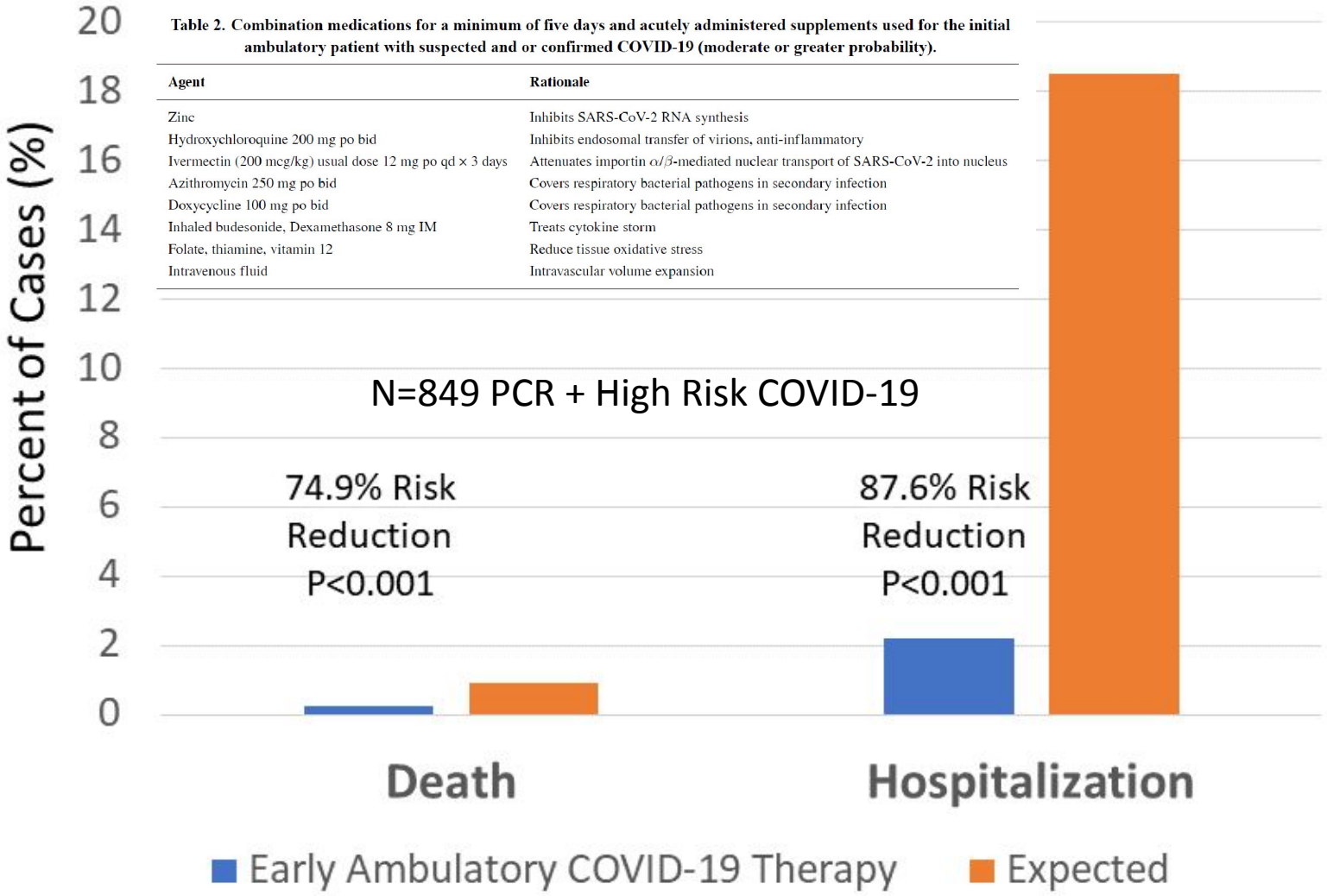
BMI=body mass index, Dz=disease, DM=diabetes mellitus, CVD=cardiovascular disease, CKD=chronic kidney disease, yr=years, HCQ=hydroxychloroquine, AZM=azithromycin, DOXY=doxycycline, IVM=Ivermectin, VTE=venous thrombo-embolic, EUA=Emergency Use Authorization (U.S. administration)

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.

Permanent link to preprint on Authorea: https://doi.org/10.22541/au.161000355.54720791/v1

VIEWPOINT

COVID-19 Therapeutics for Nonhospitalized Patients

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Supplemental content

Published online January 14, 2022

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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

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.

JAMA Network Open

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.

terapia domiciliare covid19

Outline

- SARS-CoV-2 infection (COVID-19)
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The BMJ

Cite this as: *BMJ* 2021;375:n3151
http://dx.doi.org/10.1136/bmj.n3151
Published: 24 December 2021

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]

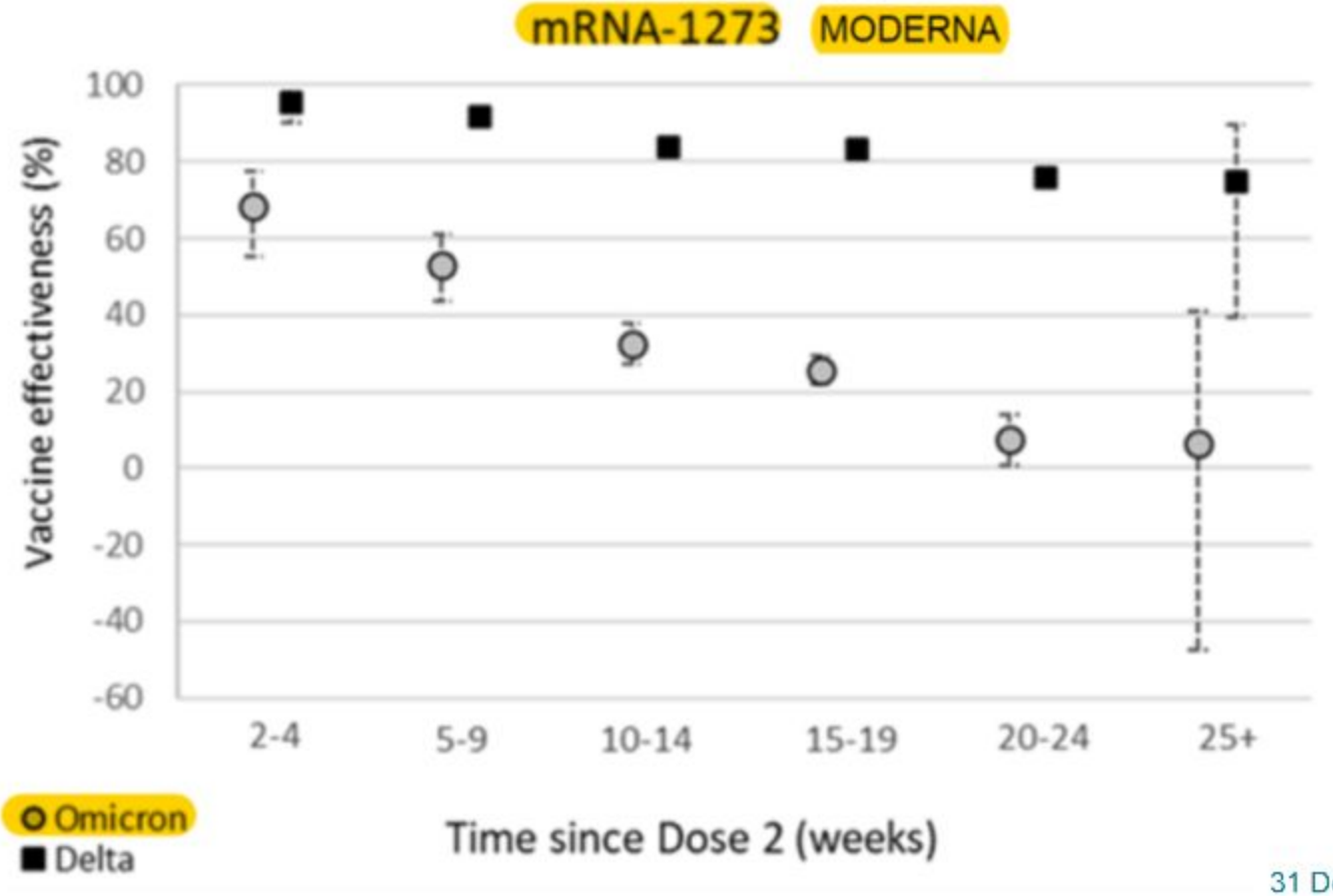
1 UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England: technical briefing 33. Dec 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043680/technical-briefing-33.pdf.

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

UK Health Security Agency

SARS-CoV-2 variants of concern and variants under investigation in England

Technical briefing: Update on hospitalisation and vaccine effectiveness for Omicron VOC-21NOV-01 (B.1.1.529)



Science, Public Health Policy, and the Law

Volume 3:100-129
September, 2021
Clinical and Translational Research

An Institute for Pure and Applied Knowledge (IPAK)

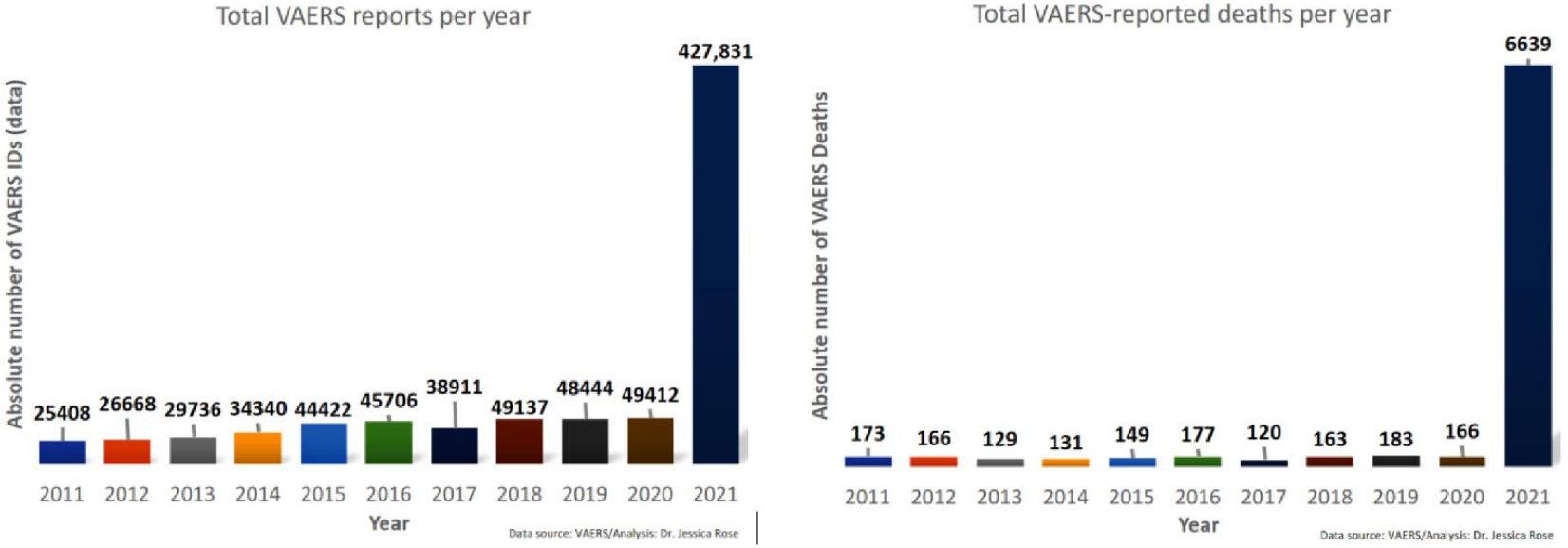
Public Health Policy Initiative (PHPI)

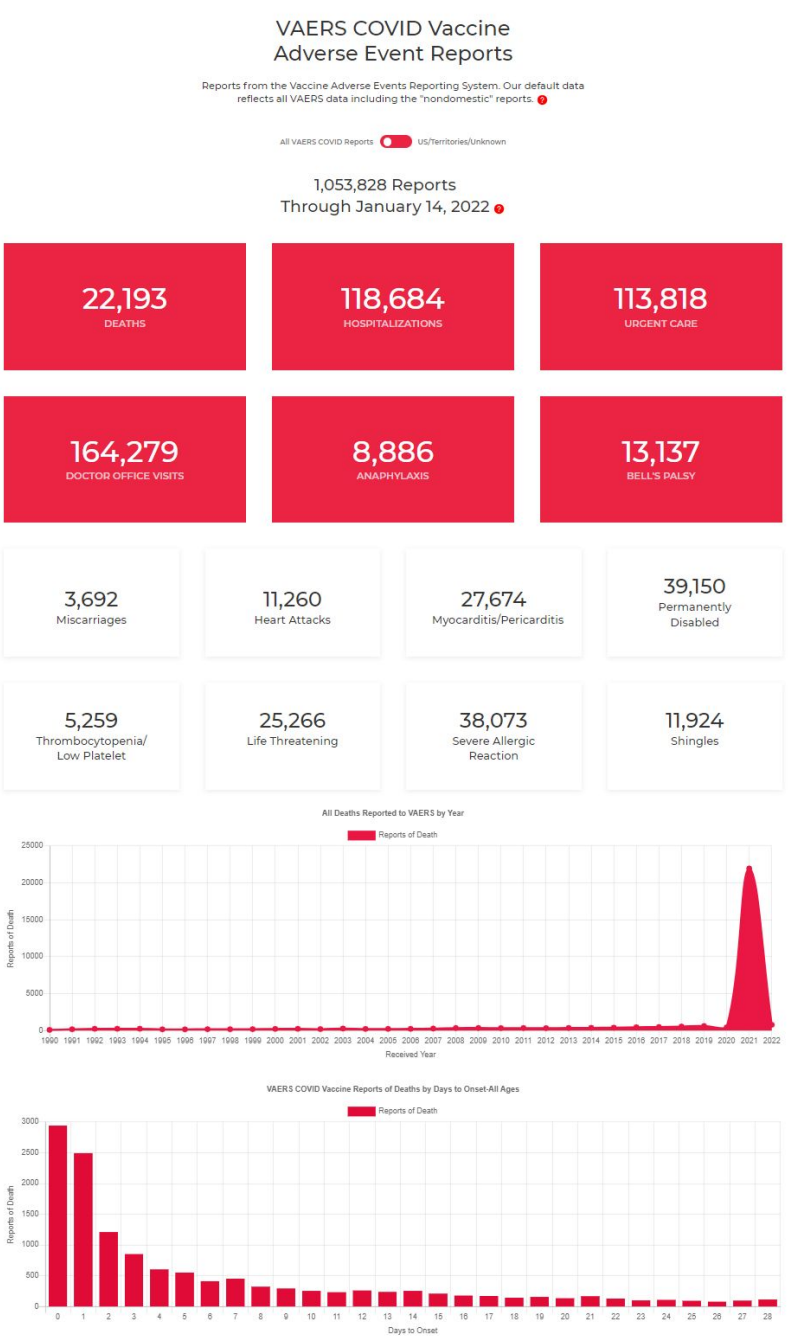
IPAK PHPI

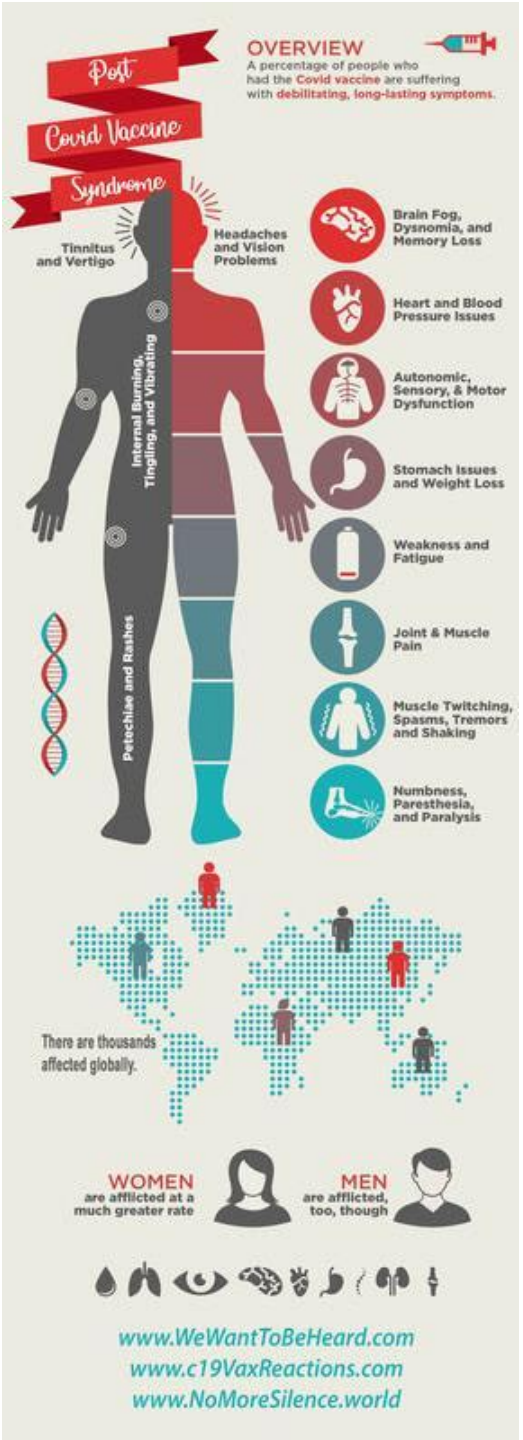
Critical Appraisal of VAERS Pharmacovigilance: Is the U.S. Vaccine Adverse Events Reporting System (VAERS) a Functioning Pharmacovigilance System?

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.)



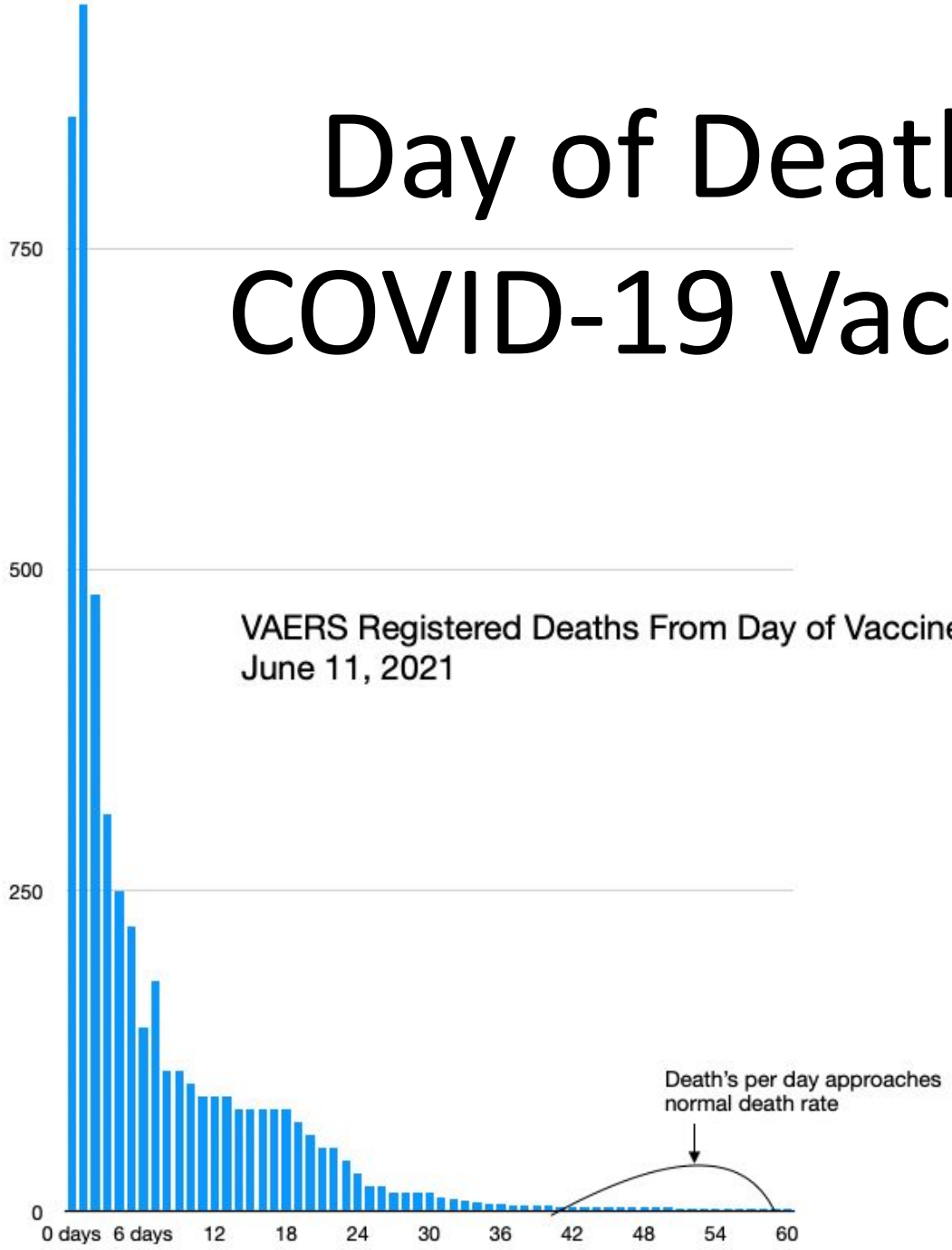




Historical P[illegible] injections/year?

All ~70 vaccines average expected 16,320 VAERS total reports/yr, ~158 total deaths/yr

Day of Death after COVID-19 Vaccination



Analysis of COVID-19 vaccine death reports from the Vaccine Adverse Events Reporting System (VAERS) Database

ResearchGate

86% of deaths had no other explanation other than the vaccine

McLachlan, Scott & Osman, Magda & Dube, Kudakwashe & Chiketero, Patience & Choi, Yvonne & Fenton, Norman. (2021). Analysis of COVID-19 vaccine death reports from the Vaccine Adverse Events Reporting System (VAERS) Database Interim Results and Analysis. 10.13140/RG.2.2.26987.26402.

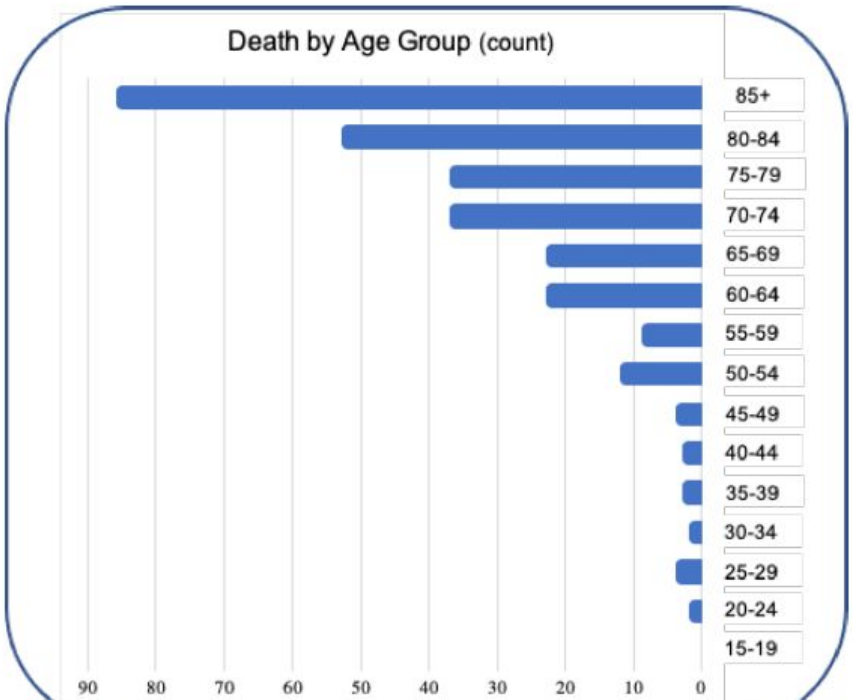


Figure 3: Death by Age Group

Much has been made in the media and academic literature about the need for protection and early vaccination of those aged 65 years and over. We believe this focus is the primary reason that 80% of the post-vaccination decedents reported are in this age group. Almost one-tenth (9%) expired within only 6 hours of their vaccination and 18% died in less than 12 hours. Over one third (36%) did not survive through to the following day.

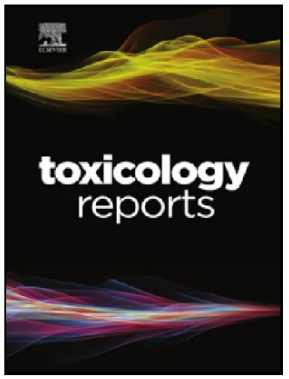
Mclachlan, Scott & Osman, Magda & Dube, Kudakwashe & Chiketero, Patience & Choi, Yvonne & Fenton, Norman. (2021). Analysis of COVID-19 vaccine death reports from the Vaccine Adverse Events Reporting System (VAERS) Database Interim Results and Analysis. 10.13140/RG.2.2.26987.26402.

https://www.researchgate.net/publication/352837543_Analysis_of_COVID-19_vaccine_death_reports_from_the_Vaccine_Adverse_Events_Reporting_System_VAERS_Database_Interim_Results_and_Analysis

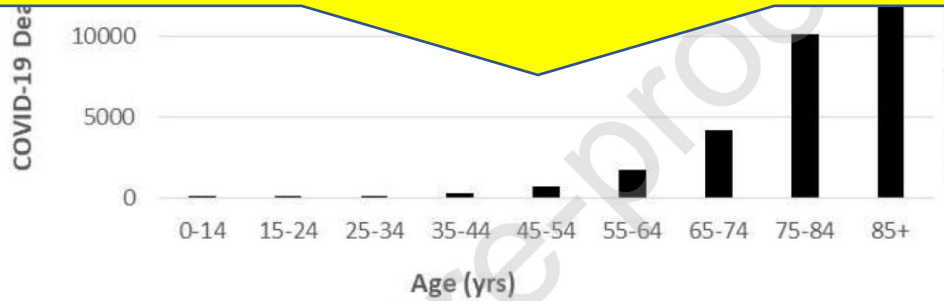
Journal Pre-proof

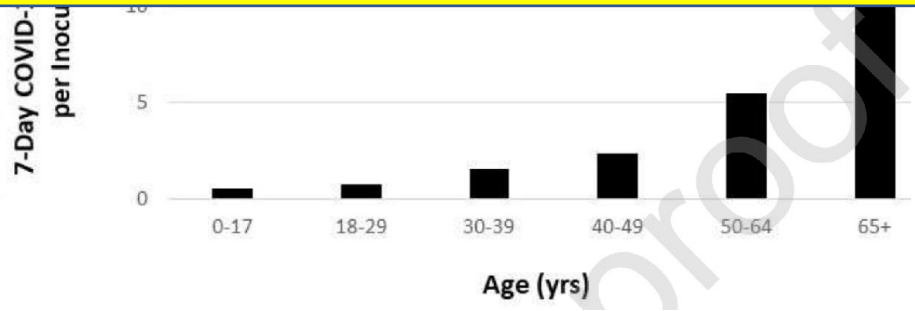
Why are We Vaccinating Children against COVID-19?

Ronald N. Kostoff, Daniela Calina, Darja Kanduc, Michael B. Briggs, Panayiotis Vlachoyiannopoulos, Andrey A. Svistunov, Aristidis Tsatsakis



"A novel best-case scenario cost-benefit analysis showed very conservatively that there are five times the number of deaths attributable to each inoculation vs those attributable to COVID-19 in the most vulnerable 65+ demographic"





September 17, 2021

Money Can Buy You A Seat In Congress

by Rob and Andrew | Sep 17, 2021

Some would argue that money and one's last name are not contributing factors when it comes to an election. However, oftentimes regardless of a candidate's experience, money and having the right last name can make the difference between winning and losing an election....

What to Expect if the Tyranny in Australia Hits Home

by Cathi Chamberlain | Sep 17, 2021

If you aren't stockpiling food and supplies right now, you may be in for a very uncomfortable future. Just ask Australians. Like a thief in

By Pushing Mass Vaccination, Governments Have Created Evolutionary Pressures on SARS-CoV-2

by Dr. Peter McCullough | Jul 20, 2021 | Healthcare, Politics,

Now fully vaccinated persons are contracting COVID-19 in large numbers, probably with the Delta variant. They cover vaccine safety, and when considering the failure of efficacy and the fatal and nonfatal serious safety concerns with all of the vaccines, Dr. McCullough concludes that we should shut down the ill-fated mass vaccination program...

Shedding of Infectious SARS-CoV-2 Despite Vaccination when the Delta Variant is Prevalent - Wisconsin, July 2021

Kasen K. Riemersma, DVM, PhD[1]; Brittany E. Grogan, MPH[2]; Amanda Kita-Yarbro, MPH[2]; Peter Halfmann, PhD[1]; Anna Kocharian, MS[3]; Kelsey R. Florek, PhD[4]; Ryan Westergaard, MD, PhD[3,5]; Allen Bateman, PhD[4]; Gunnar E. Jeppson, BS[6]; Yoshihiro Kawaoka, DVM, PhD[1]; David H. O'Connor, PhD[7]; Thomas C. Friedrich, PhD[1]; Katarina M. Grande, MPH[2]

[1] Department of Pathobiological Sciences, University of Wisconsin-Madison, Madison, WI, USA; [2] Public Health Madison & Dane County, Madison, WI, USA; [3] Wisconsin Department of Health Services; [4] Wisconsin State Laboratory of Hygiene; [5] Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; [6] Exact Sciences, Madison, WI, USA; [7] Department of Pathology and Laboratory Medicine, University of Wisconsin-Madison, Madison, WI, USA.

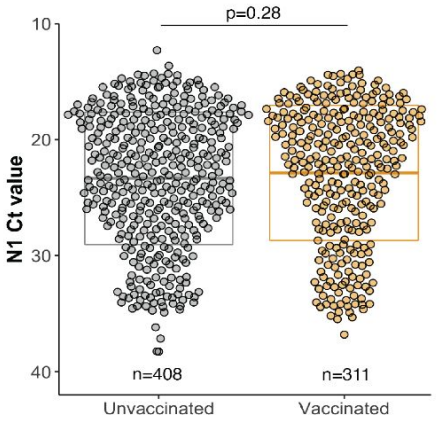


Figure 1. Distributions of SARS-CoV-2 PCR cycle threshold (Ct) values at the time of testing do not differ by vaccination status. N1 PCR Ct values for SARS-CoV-2-positive specimens grouped by vaccination status. Boxplots represent mean N1 Ct values +/- one standard deviation. P-values were calculated by comparing mean Ct values between the groups by Welch two-sample t-test.

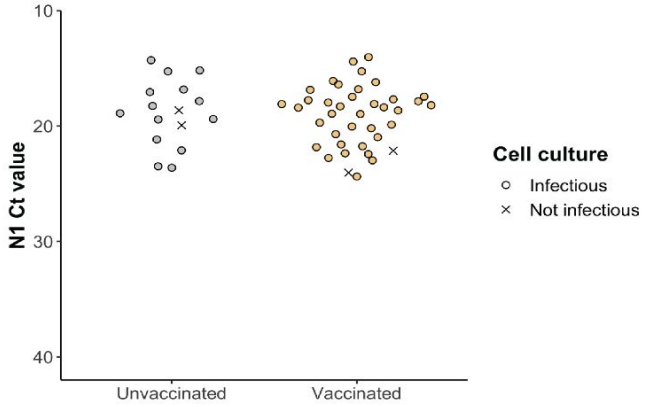


Figure 2. Infectious virus detected in nasal swab specimens from unvaccinated and fully vaccinated cases with Ct values < 25. Infectiousness was determined by the presence of cytopathic effects (CPE) after 5 days of replication in Vero E6 TMPRSS2 cells. Specimens with visually apparent CPE under a light microscope are represented by filled circles, and specimens without apparent CPE are represented by 'X'.

Effectiveness of Covid-19 vaccination against risk of symptomatic infection, hospitalization, and death up to 9 months: a Swedish total-population cohort study

842,974 pairs (N=1,684,958)

Preprints with THE LANCET

Peter Nordström, MD, PhD, Marcel Ballin, MSc., Anna Nordström, MD, PhD

Pfizer/BNT 30 mcg mRNA/injection

Symptomatic Infection
Fully Vaccinated (VE)

22 studies show waning vaccine efficacy over 3-6 months for all vaccines against all variants

Dr. Paul Alexander, Brownstone Institute Oct 29 2021

>180 days (N=22,755)	32	0·8	15	2·4	69 (44-83)	59 (18-79)

Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study

Anika Singanayagam*, Seran Hakki*, Jake Dunning*, Kieran J Madon, Michael A Crone, Aleksandra Koycheva, Nieves Derqui-Fernandez, Jack L Barnett, Michael G Whitfield, Robert Varro, Andre Charlett, Rhia Kundu, Joe Fenn, Jessica Cutajar, Valerie Quinn, Emily Conibear, Wendy Barclay, Paul S Freemont, Graham P Taylor, Shazaad Ahmad, Maria Zambon, Neil M Ferguson†, Ajit Lalvani†, on behalf of the ATACCC Study Investigators†

Summary

Background The SARS-CoV-2 delta (B.1.617.2) variant is highly transmissible and spreading globally, including in populations with high vaccination rates. We aimed to investigate transmission and viral load kinetics in vaccinated and unvaccinated individuals with mild delta variant infection in the community.

Lancet Infect Dis 2021
Published Online
October 28, 2021
https://doi.org/10.1016/

39% of transmission from fully vaccinated to fully vaccinated

for uninfected individ… 001). SAR among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (25% [95% CI 15–35] for vaccinated *vs* 23% [15–31] for unvaccinated). 12 (39%) of 31 infections in fully vaccinated household contacts arose from fully vaccinated epidemiologically linked index cases, further confirmed by genomic and virological analysis in three index case–contact pairs. Although peak viral load did not differ by vaccination status or variant type, it increased modestly with age (difference of 0·39 [95% credible interval −0·03 to 0·79] in peak $\log_{10}$ viral load per mL between those aged 10 years and 50 years). Fully vaccinated individuals with delta variant infection had a faster (posterior probability >0·84) mean rate of viral load decline (0·95 $\log_{10}$ copies per mL per day) than did unvaccinated individuals with pre-alpha (0·69), alpha (0·82), or delta (0·79) variant infections. Within individuals, faster viral load growth was correlated with higher peak viral load (correlation 0·42 [95% credible interval 0·13 to 0·65]) and slower decline (−0·44 [−0·67 to −0·18]).

Interpretation Vaccination reduces the risk of delta variant infection and accelerates viral clearance. Nonetheless, fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection in household settings, including to fully vaccinated contacts. Host–virus interactions early in infection may shape the entire viral trajectory.

J Cutajar BSc, V Quinn BSc, E Conibear MSc, Prof A Lalvani DM), **Department of Infectious Disease** (A Singanayagam, Prof W Barclay PhD, Prof G P Taylor DSc, M A Crone MBBCh, Prof P S Freemont PhD), **NIHR Health Protection Research Unit in Modelling and Health Economics, MRC Centre for Global Infectious Disease Analysis, Jameel Institute** (Prof N M Ferguson DPhil), and **UK Dementia Research Institute Centre for Care Research and Technology** (M A Crone, Prof P S Freemont),

JAMA | Original Investigation

Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity

Mark W. Tenforde, MD, PhD; Wesley H. Self, MD, MPH; Katherine Adams, MPH; Manjusha Gaglani, MBBS; Adit A. Ginde, MD, MPH; Tresa McNeal, MD; Shekhar Ghamande, MD; David J. Douin, MD; H. Keipp Talbot, MD, MPH; Jonathan D. Casey, MD, MSci; Nicholas M. Mohr, MD, MS; Anne Zepeski, PharmD; Nathan I. Shapiro, MD, MPH; Kevin W. Gibbs, MD; D. Clark Files, MD; David N. Hager, MD, PhD; Arber Shehu, MD; Matthew E. Prekker, MD, MPH; Heidi L. Erickson, MD; Matthew C. Exline, MD, MPH; Michelle N. Gong, MD; Amira Mohamed, MD; Daniel J. Henning, MD, MPH; Jay S. Steingrub, MD; Ithan D. Peltan, MD, MSc; Samuel M. Brown, MD, MS; Emily T. Martin, PhD; Arnold S. Monto, MD; Akram Khan, MD; Catherine L. Hough, MD; Laurence W. Busse, MD; Caitlin C. ten Lohuis, ACNP-BC; Abhijit Duggal, MD; Jennifer G. Wilson, MD; Alexandra June Gordon, MD; Nida Qadir, MD; Steven Y. Chang, MD, PhD; Christopher Mallow, MD, MHS; Carolina Rivas, BS; Hilary M. Babcock, MD, MPH; Jennie H. Kwon, DO, MSci; Natasha Halasa, MD, MPH; James D. Chappell, MD, PhD; Adam S. Lauring, MD, PhD; Carlos G. Grijalva, MD, MPH; Todd W. Rice, MD, MSci; Ian D. Jones, MD; William B. Stubblefield, MD, MPH; Adrienne Baughman, BS; Kelsey N. Womack, PhD; Jillian P. Rhoads, PhD; Christopher J. Lindsell, PhD; Kimberly W. Hart, MA; Yuwei Zhu, MD, MS; Samantha M. Olson, MPH; Miwako Kobayashi, MD; Jennifer R. Verani, MD, MPH; Manish M. Patel, MD; for the Influenza and Other Viruses in the Acutely Ill (IVY) Network

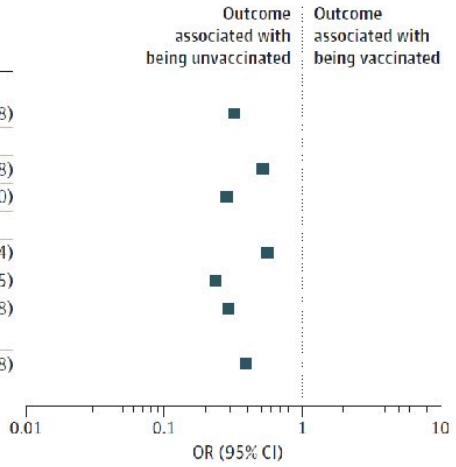
Participants

During March 11, 2021, to August 15, 2021, 5479 patients were enrolled from 21 hospitals; 966 patients were excluded from this analysis, with the most common reasons for exclusion being receipt of at least 1 mRNA vaccine but not being fully vaccinated (n = 547) and receipt of a COVID-19 vaccine other than an mRNA vaccine (n = 194) (**Figure 1**). The analytic population included 4513 patients (median age, 59 years [IQR, 45-69]; 2202 [48.8%] women; 23.0% non-Hispanic Black individuals, 15.9% Hispanic individuals, and 20.1% with an immunocompromising condition), including 1983 cases with COVID-19 and 2530 controls without it (1359 test-negative controls and 1171 syndrome-negative controls).

3/21 to 8/21 45% Delta

Figure 3. Association Between Progression to Severe Disease and Prior Vaccination Among Adults Hospitalized With COVID-19

Subgroup	Fully vaccinated case patients/total breakthrough cases (%)	Unvaccinated case patients/total unvaccinated (%)	Absolute difference (95% CI), %	Adjusted odds ratio (95% CI)[a]
Progression to death or invasive mechanical ventilation				
Overall	17/142 (12.0)	261/1055 (24.7)	-12.8 (-18.7 to -6.8)	0.33 (0.19 to 0.58)
By immunocompromising condition[b]				
Yes (immunocompromised)	8/61 (13.1)	31/146 (21.2)	-8.1 (-18.9 to 2.6)	0.54 (0.21 to 1.38)
No (immunocompetent)	9/81 (11.1)	230/909 (25.3)	-14.2 (-21.6 to -6.8)	0.29 (0.14 to 0.60)
By age group, y				
18-64	9/57 (15.8)	188/814 (23.1)	-7.3 (-17.2 to 2.6)	0.57 (0.27 to 1.24)
≥65	8/85 (9.4)	73/241 (30.3)	-20.9 (-29.4 to -12.4)	0.24 (0.11 to 0.55)
Hypoxemic within 24 h of admission[c]	13/96 (13.5)	227/806 (28.2)	-14.6 (-22.1 to -7.1)	0.30 (0.16 to 0.58)
Progression to death				
Overall	9/142 (6.3)	91/1055 (8.6)	-2.3 (-6.6 to 2.1)	0.41 (0.19 to 0.88)



Death occured 9 of 142 (6.3%) vaccine break-through cases and 91 of 1055 (8.6%) unvaccinated cases, p=0.36

An adjusted odds ratio (aOR) less than 1.0 indicated that progression to death or invasive mechanical ventilation after hospital admission for COVID-19 was associated with being unvaccinated compared with being vaccinated.

[a] Models were adjusted for age group (18-49, 50-64, and ≥65 years), sex, self-reported race and ethnicity, and number of chronic medical comorbidities (0, 1, 2, 3, and ≥4). Models stratified by age group were adjusted for continuous age in years.

[b] Immunocompromising conditions are defined in the Table.

[c] Analysis restricted to COVID-19 case patients with hypoxemia within 24 hours of admission, defined as receiving supplemental oxygen or having an oxygen saturation less than 92% as measured by pulse oximetry.

Cite as: B. A. Cohn *et al.*, *Science*
10.1126/science.abm0620 (2021).

SARS-CoV-2 vaccine protection and deaths among US veterans during 2021

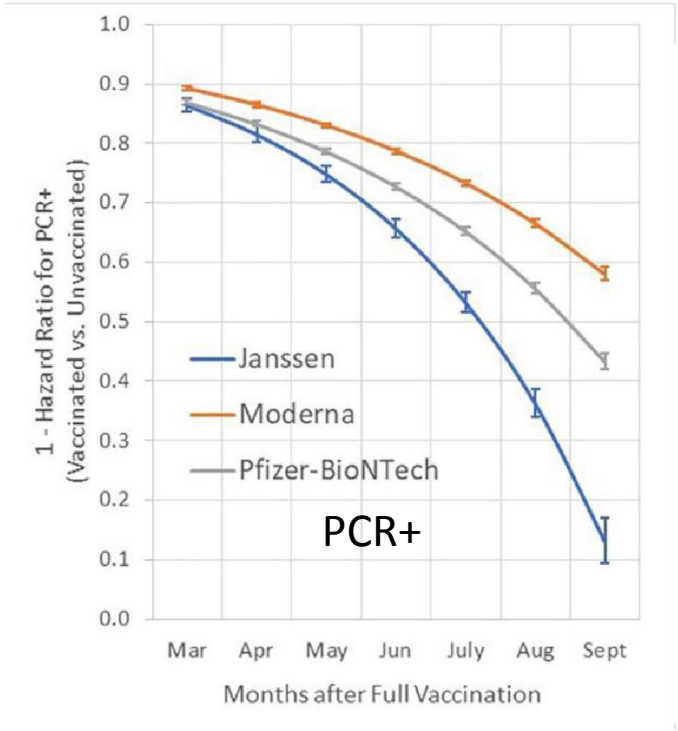
Barbara A. Cohn[1]†, Piera M. Cirillo[1,2]†, Caitlin C. Murphy[3]†, Nickilou Y. Krigbaum[1,2], Arthur W. Wallace[2,4]*

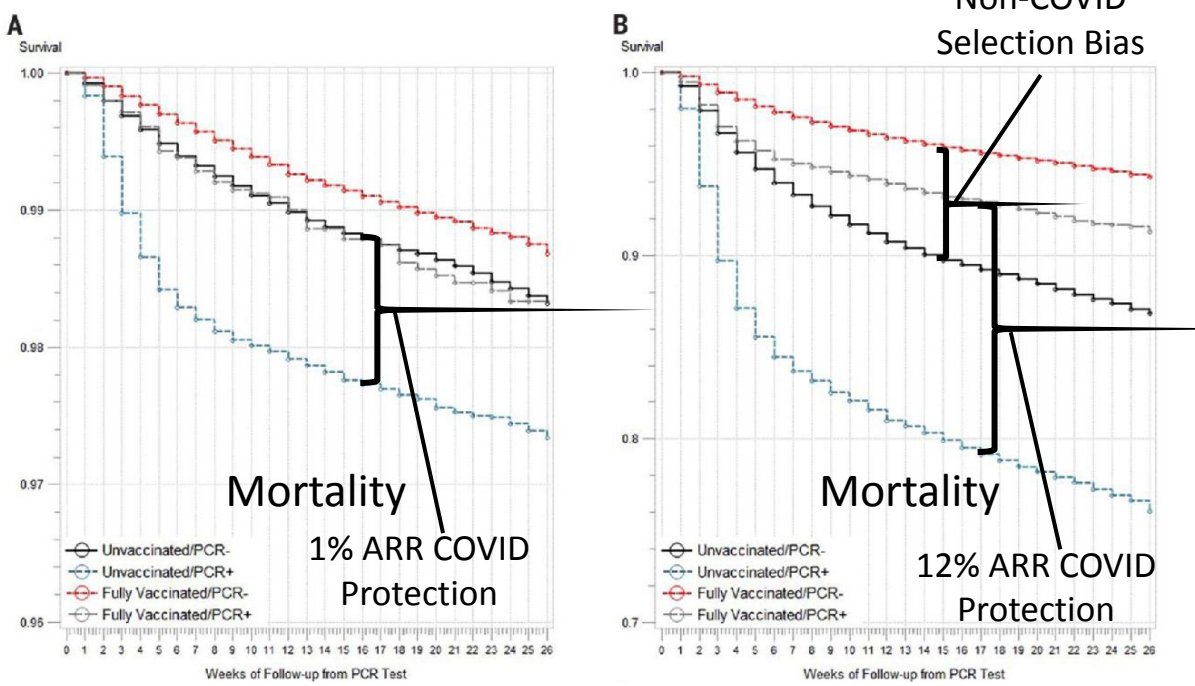
[1]Public Health Institute; Oakland, CA, USA. [2]Veterans Affairs Medical Center in San Francisco; San Francisco, CA, USA. [3]School of Public Health, University of Texas Health Science Center at Houston; Houston, TX, USA. [4]University of California, San Francisco; San Francisco, CA, USA.

We report SARS-CoV-2 vaccine effectiveness against infection (VE-I) and death (VE-D) by vaccine type (*n* = 780,225) in the Veterans Health Administration, covering 2.7% of the U.S. population. From February to October 2021, VE-I declined from 87.9% to 48.1%, and the decline was greatest for the Janssen vaccine resulting in a VE-I of 13.1%. Although breakthrough infection increased risk of death, vaccination remained protective against death in persons who became infected during the Delta surge. From July to October 2021, VE-D for age 65 years was 73.0% for Janssen, 81.5% for Moderna, and 84.3% for Pfizer-BioNTech; VE-D for age ≥65 years was 52.2% for Janssen, 75.5% for Moderna, and 70.1% for Pfizer-BioNTech. Findings support continued efforts to increase vaccination, booster campaigns, and multiple, additional layers of protection against infection.

Age <65 yrs

Age >65 yrs





ARR=absolute risk reduction

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

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