Message

From: Alexander, Paul (HHS/ASPA) (VOL) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 5/17/2020 3:06:34 AM
To: Michael Caputo [redacted]
Subject: RE: Hello-follow up

Working on this and will have some nice things for you. Already got good data on excess cancer deaths over next 12 months...

I will pull it all together first then give you...

Dr. Paul E. Alexander, PhD
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US Department of Health and Human Services (HHS)
Washington, DC
Tel: [redacted] (Office)
Tel: [redacted] (Cellular)

Email: [redacted]

From: Michael Caputo [redacted]
Sent: Saturday, May 16, 2020 9:20 PM
To: Alexander, Paul (HHS/ASPA) (VOL) [redacted]
Subject: Re: Hello-follow up

You need to take ownership of these numbers. This is singularly important to what you and I want to achieve.

Michael Caputo
[redacted]

On May 16, 2020, at 8:18 PM, Alexander, Paul (HHS/ASPA) (VOL) [redacted] wrote:

Once there is data we will find it.

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Problem is with it being so new, not much of this type of information has accumulated. If it is there in any manner then do not worry we will tease it out.

Yes, please connect me with whomever.

Sent from my iPhone

On May 16, 2020, at 2:52 PM, Michael Caputo [redacted] wrote:

> An oped? Speech?
> I know the President wants us to enumerate the economic cost of not reopening.
> We need solid estimates to be able to say something like:
>
> 50,000 more cancer deaths!
> 40,000 more heart attacks!
> 25,000 more suicides!
> 155,000 more trauma deaths!
> 240,000 hospitals will close!
> 400,000 heath care workers jobless!
>
> 170,000 more high school dropouts!
>
> Etc
>
> Dr Redfield told me he has someone at CDC researching similar topics. Let me connect you.
>
> ------
> Michael Caputo
> [redacted]
>
> > On May 16, 2020, at 1:52 PM, Alexander, Paul (HHS/ASPA) (VOL) [redacted] wrote:
> >
> > We are doing work behind the scenes this weekend on this. See below.
> >
> > **From:** Alexander, Paul (HHS/ASPA) (VOL)
> > **Sent:** Saturday, May 16, 2020 1:49 PM
> > **To:** Brennan, Patrick (OS/ASPA) [redacted]
> > **Subject:** RE: Hello-follow up
> >
> > My man, sounds like a great plan. I looked at the preliminary and talked a little as to what is the key issue...the key issue people will have is this:
> >
> > - Why are you (governments, public health officials) saying now that it is safe for me to go out and slowly resume normal life activities?
> > - Message should include: We know you are scared for this virus that emerged from China has presented us with many unknowns and death to our most precious citizens. The

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omission by China and the World Health Organization (WHO) initially of key information such as human-to-human spread had a tremendous impact on global nations' ability and capacity to respond. However, over the last 3 months, evidence has accumulated and now we have more data about this virus and know that not everyone in the population is at equal risk. The elderly are at high risk, not younger healthy adults or children. The risk to our children approaches zero and is vanishingly small. While we open the country, we have to remain vigilant with social distancing, hand washing, heightened sanitation...so that we do not put the elderly at risk for getting this virus. It is them we sought initially and still seek now, to protect. We have taken measures to beef up our healthcare systems so as to handle surges at hospital emergency rooms. We have to continue to protect our frail and elderly population as they are the most hard hit from this virus. The rest of the population has to jointly play a role in this by reducing the spread to the elderly while going about your daily life activities. If you are younger and healthy, then your risk of severe illness or death is vanishingly small and thus we have to go on with living lives as we develop a vaccine (s) and effective therapeutics. The consequences of failing to do so will have far greater consequences on lives e.g. deaths of despair will accumulate, lack of vaccinations for traditional vaccine preventable illnesses for children due to fear of doctor office and institutional settings, depression, alcohol abuse, drug abuse, small and medium sized business failure, loss of jobs, loss of homes etc. and the consequences of these emotionally and psychologically to people, than COVID-19 on its own. We must get on with our lives now.

Something like this. We have to now 'unscare' people while as we re-open, we will see blips and spikes in cases and deaths. We must school them that we will respond to the spikes and hotspots as needed.

From: Brennan, Patrick (OS/ASPA) [redacted]
Sent: Saturday, May 16, 2020 9:22 AM
To: Alexander, Paul (HHS/ASPA) (VOL) [redacted]
Subject: Re: Hello-follow up

I think we may have what we need now — I just fwded you some great data that was pulled from databases HHS subscribes to (IQVIA stuff, you're probably familiar) which covers the slipper healthcare item very well. I am going to draft it today and see how it writes; I will send you a draft as soon as I've got it and we can see where, if anywhere, we need anymore data. Sound good?

Sent from my iPhone

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On May 16, 2020, at 5:16 AM, Alexander, Paul (HHS/ASPA) (VOL) [redacted] wrote:

Hi Patrick, so what do you think is the best model to approach this with? Do we wait for folk to come back with data points? Or do we generate some now beyond the ones we have? What types of data do you seek or do you think is optimal for this? In reality, this is not studied like the effects of the virus on health. What we seek are more socio economic data effects, psychological data etc. that will be more 'soft' narrative data.

But I am very keen on helping you and Paul etc. optimally so any heads up form you will be good.

Regards

From: Brennan, Patrick (OS/ASPA)
[redacted]
Sent: Friday, May 15, 2020 3:21 PM
To: Pollard, Ashton (OS/IOS) [redacted]
Cc: Alexander, Paul (HHS/ASPA) (VOL)
[redacted]
Subject: Re: Hello-follow up

Thank, Ashton.

Paul, I'm the guy with the office next to you haha, but haven't been in this week.

My understanding is that we should circle up with Paul to understand the ETA on data calls from parts of HHS.

I suspect that data won't be ready soon enough though — so what we should do is pull outside, existing data (although in some cases CDC and SAMHSA may have existing studies on health and employment etc.) I will build a draft of the op ed from that.

Paul, you have an existing document with some research pulled on this question, right? Can you send me that?

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On May 15, 2020, at 3:13 PM,
Pollard, Ashton (OS/IOS)
[redacted] wrote:

Great! Yes – that's what I thought we were discussing, but I needed a little additional context. I am adding Patrick Brennan here as a start and we can circle back with Paul. Patrick is the Secretary's speechwriter, so he will be the primary architect of those talking points. Hope this is helpful and let me know if you need anything else!

From: Alexander, Paul (HHS/ASPA) (VOL) [redacted]
Sent: Friday, May 15, 2020 3:11 PM
To: Pollard, Ashton (OS/IOS)
[redacted]
Subject: RE: Hello-follow up

Hi Ashton, thanks much and I sure am excited by this work for the President too. Very tough time but full of much hope. And being strong.

Anyway, yes, I think its Paul Mango etc. Not sure but yes, Patrick too as they are trying to put some talking point together to go out as per Judy. Has to do with the Health vs Health to focus on the impact of COVID outside of the infection and the short and long term effects of COVID that go beyond COVID.

Judy said she wanted something by Wed. Thus if they wanted my eye balls on the stuff, then I just wanted some link. I do not know any of these people.

From: Pollard, Ashton (OS/IOS)
[redacted]
Sent: Friday, May 15, 2020 3:06 PM
To: Alexander, Paul (HHS/ASPA) (VOL)
[redacted]
Subject: RE: Hello-follow up

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Paul,

Nice to meet you as well! Welcome to HHS.

Regarding linking you up with folks, since I came in a little late, are we referring to Paul Mango and Patrick Brennan? They were on the phone.

Let me know exactly who you mean and I'm happy to make the connection!

Thanks,
Ashton

From: Alexander, Paul (HHS/ASPA) (VOL) [redacted]
Sent: Friday, May 15, 2020 3:02 PM
To: Pollard, Ashton (OS/IOS) [redacted]
Subject: Hello-follow up

Hi Ashton, so good meeting you today and thank you for willingness to help me this morning as the badge is taking long and so it's a drama each morning.

Anyway, based on what Judy was asking just now, please help if they want my role with Paul and the others...can you help link me up to the folk Judy was saying to get something in writing ready by Wednesday.

And please you all call me Paul. Not Dr. Alexander.

Grateful!

Dr. Paul E. Alexander, PhD
Senior Advisor to the Assistant Secretary

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[redacted]

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Message

From: Alexander, Paul (HHS/ASPA) (VOL) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 5/17/2020 10:52:00 PM
To: Paul Elias Alexander [redacted]
Subject: FW: COVID Lockdown - SUICIDE Impact

Dr. Paul E. Alexander, PhD
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Tel: [redacted] (Cellular)

Email: [redacted]

From: Alexander, Paul (HHS/ASPA) (VOL)
Sent: Sunday, May 17, 2020 6:52 PM
To: Caputo, Michael (HHS/ASPA) [redacted]; Traverse, Brad (HHS/ASPA) [redacted]
Subject: COVID Lockdown - SUICIDE Impact

300,000 additional deaths for 2020 based on the lockdown and deaths of despair due to COVID-19; this is 90.1 deaths per 100,000 US population

Michael, I have given Patrick stuff he is using for Peter Navvaro e.g. 40,000 cancer deaths for 2020 etc.; do I give him this too or do you want this for the President?

Below is the modelling approach for the suicide deaths for 2020 (additional deaths of despair).

Paul

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Researchers warn the COVID-19 lockdown will take its own toll on health:

https://www.reuters.com/investigates/special-report/health-coronavirus-usa-cost/

https://protect2.fireeye.com/url?k=21573c75-7d0235a5-21570d4a-0cc47a6a52de-a6ff85176f49c7d9&u=https://wellbeingtrust.org/wp-content/uploads/2020/05/WBT_Deaths-of-Despair_COVID-19-FINAL-FINAL.pdf

References:

Phillips, Julie A., and Colleen N. Nugent. 2014. "Suicide and the Great Recession of 2007-2009: The Role of Economic Factors in the 50 U.S. States." Social Science & Medicine (1982) 116 (September): 22–31.

Luo, Feijun, Curtis S. Florence, Myriam Quispe-Agnoli, Lijing Ouyang, and Alexander E. Crosby. 2011. "Impact of Business Cycles on US Suicide Rates, 1928-2007." American Journal of Public Health 101 (6): 1139–46.

We are modelling deaths of despair as a consequence of COVID-19 and based on drugs, alcohol, and suicidal causes

- I am modelling based on 1% increase in unemployment yields 1.6 % deaths of despair/suicide (Phillips and Nugent, 2014); note WBT models based on this assumption of 1%:1.6%

- We are modelling due to COVID-19

- We are modelling due to the effects of lockdown and isolation/uncertainty and the resulting uptick in deaths of despair

- Based on that and accepting a "medium" recovery rate of economy (this is based on the exceptional impact the President's policies had pre- COVID-19 lockdown getting the economy to 3.5% unemployment; note that we could have modeled as due to a 'slow recovery' or 'fast' but we handicapped and chose the middle group.

-We will use a US 2018 population of 327,167,434, and so rounded to 330,000,000

- Therefore, for 2020, for a medium rate of recovery, there are 15, 000 deaths projected per 1.6 % increase in deaths of despair (WBT based model)

- Therefore, assuming the employment rate was 4% when lockdown started (but it was 3.5 %), then as of May 17, 2020, the unemployment rate hovers at around 15%

- Therefore, this means an 11% point increase

- Some suggest it will get to 20%, some to 32%

- We will split the difference of 32% - 15% = 17 % /2 = 8.5 %

- 11% (present rise from 4% unemployment fbefore COVID-19 lockdown)+ 8.5 % = approx 20%

- Thus with a 20 point increase, and based on a 1.6 % increase or 15K deaths per point increase

- Therefore 20 x 15,000 = 300,000 additional deaths for 2020 based on the lockdown and deaths of despair due to COVID-19; this is 90.1 deaths per 100,000 US population

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Message

From: Alexander, Paul (HHS/ASPA) (VOL) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 5/18/2020 4:23:02 PM
To: Brennan, Patrick (OS/ASPA) [redacted] Murphy, Ryan (OS/ASPA) [redacted] ASPA-Deputies [redacted]
Subject: RE: health vs. health op-ed draft for review

Yes, correct. My approach is simple...no doubt crude and based on the published data...a 1% increase in unemployment (for whatever reason but in this case it is driven by COVID-19 based on their analysis), translates to a 1.3% increase in additional deaths which is approx. 12.5 K (using a medium rate of recovery). This is approx.

Any so if we modelled lockdown lets say for 12 months, that's 150 K deaths (crude) and termed 'additional' deaths. And so assuming unemployment goes to 24% fast using figures out there, then that's a 20% increase in unemployment from baseline where it was Feb 2020 of 4% (approx.)...so 20 x 12 K =240 K approx. for the year...so approx. 20 K per month.

And so today, the model assumes that 50 K deaths have occurred (additional) since lockdown started. We cant do anything about that. But I play with the data and model it assuming lets say 240 K deaths could happen now if the unemployment gets to 24% (as it being suggested, it is already 15%)...

So assuming its about 20 K additional deaths per month (240 K per year), then I model removing the 20 K per month each additional month it stays closed...so I ask how many lives could we save...so if we opened the entire economy today, in full, those 240 K additional deaths that would likely occur if unemployment hits 24% which it looks like it will if lockdown persists, would not occur and we could save 190 K lives (I remove the 50 K that likely have occurred already using their model)....

So all this to say, yes, unemployment will continue and what we are talking about is 'additional' deaths'.

Their WBT model projects 154,000 deaths using different assumptions...there are several projections now...CDC 65 K, CNN 75 K and all seem to be using the same data I am using...

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Email: [redacted]

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From: Brennan, Patrick (OS/ASPA) [redacted]
Sent: Monday, May 18, 2020 11:59 AM
To: Alexander, Paul (HHS/ASPA) (VOL) [redacted]; Murphy, Ryan (OS/ASPA) [redacted]; ASPA-Deputies [redacted]
Subject: RE: health vs. health op-ed draft for review

Thank you, Paul.

My understanding of the Wellbeing Trust estimates is that they track elevated deaths from elevated unemployment in the coming years, which, of course, is increased if the lockdown makes the recession worse and deeper. Does your model assume ending the lockdown ends the elevated deaths of despair right away? But unemployment will continue to be elevated, just less so without the lockdown.

From: Alexander, Paul (HHS/ASPA) (VOL) [redacted]
Sent: Monday, May 18, 2020 11:50 AM
To: Murphy, Ryan (OS/ASPA) [redacted]; Brennan, Patrick (OS/ASPA) [redacted]; ASPA-Deputies [redacted]
Subject: RE: health vs. health op-ed draft for review

See this crude modeling I did...

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Email: [redacted]

From: Alexander, Paul (HHS/ASPA) (VOL)
Sent: Sunday, May 17, 2020 9:51 PM
To: Murphy, Ryan (OS/ASPA) [redacted]; Brennan, Patrick (OS/ASPA) [redacted]; ASPA-Deputies [redacted]
Subject: RE: health vs. health op-ed draft for review

This is quite good.

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Two issues:

I have this for it resonates with parents:

School attendance and graduation

https://www.reuters.com/investigates/special-report/health-coronavirus-usa-cost/
https://www.rwjf.org/en/library/research/2016/09/the-relationship-between-school-attendance-and-health.html

High school students who miss 3 days school per month are 7 times more likely to drop out before graduating and live nine years less than their peers

Also, I did my own modelling on suicides and my figure comes out at 300,000 additional deaths due to despair. I see CNN has a figure of 75,000 and then the attached suggested 65,000. I used the WBT as the source data and modelled a base 4% prior to COVID-19 lockdown and the now 15%, and then modeled folk who say it will get to 20% and others that say 32%...so I split the difference for a % increase of 20 points...the WBT suggests a high of 154 K deaths and so I know my model is correct...

But it is a model and we each can build our own assumptions.

Anyway, good job on those points how they are crafted.

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Email: [redacted]

From: Murphy, Ryan (OS/ASPA) [redacted]
Sent: Sunday, May 17, 2020 3:24 PM
To: Brennan, Patrick (OS/ASPA) [redacted] ASPA-Deputies [redacted] Alexander, Paul (HHS/ASPA) (VOL) [redacted]
Subject: RE: health vs. health op-ed draft for review

Some edits in the attached. Thanks.

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From: Brennan, Patrick (OS/ASPA) [redacted]
Sent: Saturday, May 16, 2020 8:32 PM
To: ASPA-Deputies [redacted]; Alexander, Paul (HHS/ASPA) (VOL) [redacted]
Subject: health vs. health op-ed draft for review

<< File: 5 16 20 op-ed draft.docx >>

This incorporates a couple non-public numbers we have from Admiral Giroir's work.

Patrick Brennan
Director of Speechwriting
Department of Health and Human Services
Office: [redacted] | Cell: [redacted]

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Message

From: Alexander, Paul (HHS/ASPA) [redacted]

Sent: 7/13/2020 12:43:37 AM

To: Birx, Deborah L. EOP/NSC [redacted]; Kent, Charlotte (CDC/DDPHSS/CSELS/OD) [redacted]; Redfield, Robert R. (CDC/OD) [redacted]; Schuchat, Anne MD (CDC/OD) [redacted]; Galatas, Kate (CDC/OD/OADC) [redacted]; Bunnell, Rebecca (CDC/DDPHSS/OS/OD) [redacted]; Richards, Chesley MD (CDC/DDPHSS/OD) [redacted]; Iademarco, Michael (CDC/DDPHSS/CSELS/OD) [redacted]; Caputo, Michael (HHS/ASPA) [redacted]

CC: Cono, Joanne (CDC/DDPHSS/OS/OD) [redacted]; OADS Clearance (CDC) [redacted]; Simone, Patricia (Pattie) (CDC/DDPHSS/CSELS/DSEPD) [redacted] Stephens, James W. (CDC/DDPHSS/CSELS/OD) [redacted]; Clark, David W. (CDC/DDPHSS/CSELS/OD) [redacted]; Clark, Cynthia K. (CDC/OD/OCS) [redacted] Caudwell, Kerry M. (CDC/OD/OCS) [redacted] Blowe, April R. (CDC/OD/OCS) [redacted] King, Veronnica (CDC/DDPHSS/CSELS/OD) [redacted] Phifer, Victoria (CDC/DDPHSS/CSELS/OD) [redacted]; Mitchell, Donyelle R. (CDC/DDPHSS/CSELS/OD) [redacted] Tumpey, Abbigail (CDC/DDPHSS/CSELS/OD) [redacted]; Brower, Melissa (CDC/DDPHSS/CSELS/OD) [redacted]; Bonds, Michelle E. (CDC/OD/OADC) [redacted]; Heldman, Amy B. (CDC/OD/OADC) [redacted]; Haynes, Benjamin (CDC/OD/OADC) [redacted]; Gaines-McCollom, Molly (CDC/OD/OADC) [redacted] Bedrosian, Sara (CDC/OD/OADC) [redacted] DeNoon, Daniel (CDC/OD/OADC) (CTR) [redacted]; Gindler, Jacqueline (CDC/DDPHSS/CSELS/OD) [redacted]; Rutledge, Terisa (CDC/DDPHSS/CSELS/OD) [redacted]; Weatherwax, Douglas (CDC/DDPHSS/CSELS/OD) [redacted] Hood, Teresa M. (CDC/DDPHSS/CSELS/OD) [redacted] Dunworth, Soumya (CDC/DDPHSS/CSELS/OD) [redacted]; Damon, Glenn (CDC/DDPHSS/CSELS/OD) (CTR) [redacted]; Meadows, Donald (ATSDR/OCOM/WE) [redacted]; Boyd, Martha F. (CDC/DDPHSS/CSELS/OD) [redacted]; Dott, Mary (CDC/DDPHSS/CSELS/OD) [redacted]; Branam, Ian (CDC/DDPHSS/CSELS/OD) [redacted]; Hoo, Elizabeth (CDC/OD/OCS) [redacted] Dennehy, Heather (CDC/OD/OCS) [redacted] Lepore, Loretta (CDC/OD/OCS) [redacted]; Campbell, Amanda (CDC/OD/OCS) [redacted] Warner, Agnes (CDC/OD/OCS) [redacted]; Harmon, Carrie E. (CDC/OD/OADC) [redacted] Messonnier, Nancy (CDC/DDID/NCIRD/OD) [redacted] Jernigan, Daniel B. (CDC/DDID/NCIRD/ID) [redacted] Shefer, Abigail (CDC/DDPHSIS/CGH/GID) [redacted]; Harris, Susan (CDC/DDID/NCIRD/DBD) [redacted] Emergency Clearance-2 [redacted] Eastham, Laura (CDC/DDID/NCHHSTP/DHPSE) [redacted]; CDC IMS 2019 NCOV Response Policy [redacted] Eisenberg, Emily (CDC/DDID/NCIRD/ID) [redacted] CDC IMS 2019 NCOV Response Incident Manager [redacted]; Walke, Henry (CDC/DDID/NCEZID/DPEI) [redacted]; CDC IMS 2019 NCOV Response Deputy Incident Manager [redacted]; Fitter, David J. (CDC/DDPHSIS/CGH/GID) [redacted] Beach, Michael J. (CDC/DDID/NCEZID/DFWED) [redacted]; CDC IMS 2019 NCOV Response ADS [redacted] CDC IMS 2019 NCOV Response MMWR and Publications [redacted]; Myers, Brad (CDC/OD/OADC) [redacted]; CDC IMS JIC Lead -2 [redacted] CDC IMS JIC Media -2 [redacted] CDC IMS JIC OADC LNO -2 [redacted] Khabbaz, Rima (CDC/DDID/NCEZID/OD) [redacted] Jernigan, Daniel B. (CDC/DDID/NCIRD/ID) [redacted] McGuffee, Tyler A. [redacted] Pence, Laura (HHS/IOS) [redacted] Steele, Danielle (HHS/IOS) [redacted]; Giroir, Brett (HHS/OASH) [redacted] Abel, Vadm Daniel (HHS/IOS) [redacted]; Bresee, Joseph (CDC/DDID/NCIRD/ID) [redacted] Thompson, Betsy (CDC/DDNID/NCCDPHP/DHDSP) [redacted]; Sanders, Michelle A. (CDC/DDID/NCEZID/DFWED) [redacted] Honein, Margaret (Peggy) (CDC/DDNID/NCBDDD/DBDID) [redacted] Carter, Melissa (CDC/DDNID/NCEH/DLS) [redacted]; Marandet, Angele G. (CDC/DDID/NCHHSTP/DHPIRS) [redacted]; Raziano, Amanda J. (CDC/DDID/NCEZID/DPEI) [redacted]; Walker, Misha (Nikki) (CDC/DDNID/NCBDDD/OD) [redacted] Philip, Celeste M. (CDC/DDNID/OD) [redacted]; Rose, Dale A. (CDC/DDID/NCEZID/DPEI) [redacted]; CDC IMS 2019 NCOV Response MMWR and Publications [redacted]

Subject: RE: (CUI/SBU): Two MMWR COVID-19 Response Early Releases Scheduled for - Tuesday, July 14, 2020

Hi everyone, and these are timely and quite good articles with key messages. For the second one, please see my red inserted suggestion below for your consideration.

I also wanted to raise an issue that is heavily discussed by lay people who are the subject of the recommendations by the Task Force. Again, for consideration and I write in blue and it surrounds the issue of face masks in public. It has to do with folk who wear the masks indoors due to questionable social distancing, and then continue outdoors but then toss it

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due to it being hot and cumbersome etc. This then eventually precludes them putting it back on when they return to a less ventilated indoor environment. I think to get the masks to work more effectively, we need to let people make their best common-sense judgement but offer guidance on use of masks in indoor, less ventilated spaces versus outdoors where there is more air circulation. People are confusing the term 'public space' with anything outdoors and thinking 'public space' means only when outdoors...this is not so and needs to be emphasized...the message has to be crystal clear and descriptive yet simple enough to help people think and differentiate. Importantly, you do not want them to get fed up with the masks and make it onerous and they toss it aside...for this pandemic (or similar), they must get to a place mentally where it is simple..."if I am outside and there is appropriate social distancing, then no mask, but once I hit the door of any indoor environment (retail store, taxi, airplane, office building etc....), where there is less air circulation and social distancing is not always possible, then a mask is needed":

Guidance on use of masks should indicate that (again, my suggestion based on talking to various folk)

"When you are outdoors in the open-air, provided that there is proper ventilation and appropriate social distancing is possible, then masks become less needed. However, once you enter any setting that is confined or does not have clear ventilation or you think there is not a free flow of air, then a face mask (some mask) is highly recommended. The need to wear an adequate face mask is greater when indoors with less air circulation and social distancing is a problem to practice. This as oposed to being outdoors when there is likely free flow of air and adequate social distancing is possible".

People are so very confused now and I fear it is why when we get to the place of 'mandating' face masks the discussion breaks down. For really there are situations when a mask is not needed and people know this intuitively for it is cumbersome and hot and a distress for some and they are in the open air and so we got to make it easier and simple. And people will comply but the message has to be clear. For example, I see people in their cars driving alone in the hot sun, with masks on and windows down and fresh air blowing through the car. In this case, a mask is not needed but folk are so scared and confused now. They don't know what is optimal now. So we have to be clear but simple and it must make sense to people. Some of it makes no sense and confuses them and so I ask that we consider. It did not help in the beginning when public health leaders said face masks were not needed etc., and I think this caused a set back that is still difficult to address. But with these experts here like Dr. Birx, I think the message can be made clear. Once it makes sense to people, they will do anything for the public good. Lets make it make 'sense'.

Thank you for the chance to share my thoughts.

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Produced to House Select Subcommittee on Coronavirus Crisis Pursuant to Oversight Request. Do Not Disclose Without Permission from Dep't of Health and Human Services

From: Birx, Deborah L. EOP/NSC [redacted]
Sent: Sunday, July 12, 2020 2:20 PM
To: Kent, Charlotte (CDC/DDPHSS/CSELS/OD) [redacted]; Redfield, Robert R. (CDC/OD) [redacted]; Schuchat, Anne MD (CDC/OD) [redacted]; Galatas, Kate (CDC/OD/OADC) [redacted]; Bunnell, Rebecca

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Subject: Re: (CUI/SBU): Two MMWR COVID-19 Response Early Releases Scheduled for - Tuesday, July 14, 2020

Thank you for sharing these are critical important and hopefully will get press next week. Deb

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From: "Kent, Charlotte (CDC/DDPHSS/CSELS/OD)" [redacted]
Date: Sunday, July 12, 2020 at 2:14 PM
To: Robert Redfield [redacted] "Schuchat, Anne MD (CDC/OD)" [redacted] "Galatas, Kate (CDC/OD/OADC)" [redacted] "Bunnell, Rebecca (CDC/DDPHSS/OS/OD)" [redacted] "Richards, Chesley MD (CDC/DDPHSS/OD)" [redacted] "Iademarco, Michael (CDC/DDPHSS/CSELS/OD)" [redacted]
Cc: "Cono, Joanne (CDC/DDPHSS/OS/OD)" [redacted] "OADS Clearance (CDC)"

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Subject: (CUI/SBU): Two MMWR COVID-19 Response Early Releases Scheduled for - Tuesday, July 14, 2020

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Produced in Response to Congressional Request
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Pursuant to Congressional Oversight of Health and Human Services

Two *MMWR* Early Releases related to the COVID-19 Response are scheduled for Tuesday, July 14, with the planned embargo lifting at 1 pm. Please note that the title, content, and timing might change. In addition, there are no CDC authors on the Springfield, Missouri report.

Absence of Apparent Transmission of SARS-CoV-2 from Two Stylists after Exposure at a Hair Salon with a Universal Face Covering Policy — Springfield, Missouri, May 2020

On May 12, 2020 (day 0), a stylist at salon A in Springfield, Missouri (stylist A), developed respiratory symptoms and continued working with clients until day 8 when the stylist tested positive for SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19). A second stylist (stylist B), exposed to stylist A, developed respiratory symptoms on May 15, 2020 (day 3), and worked with clients at salon A until day 8 before seeking testing for SARS-CoV-2, which returned positive on day 10. Both stylists were required to wear masks in the salon only while working with clients. Nearly 140 clients were directly serviced by stylists A and B from the time they developed symptoms until they took leave from work. Other stylists at salon A who worked closely with stylists A and B were identified, quarantined, and monitored daily for 14 days after their last exposure to stylists A or B. No other stylists reported COVID-19 symptoms. Stylists A and B were excluded from work after receiving positive test results for SARS-CoV-2. Salon A closed for three days following diagnosis of stylist B on day 10 to disinfect frequently touched and contaminated areas. Stylists A and B and the clients who were exposed to the two stylists followed the City of Springfield ordinance and salon A policy recommending the use of face coverings (surgical masks, N95 respirators, or cloth face coverings) to both stylists and clients during their interactions. After public health contact tracings and two weeks of follow-up, no COVID-19 symptoms were identified among the exposed clients or their secondary contacts. The city-wide ordinance and company policy might have played a role in preventing spread of COVID-19 during these exposures. These findings support the role of source control in preventing transmission and can inform the development of public health policy during the COVID-19 pandemic.

Factors Associated with Cloth Face Covering Use Among Adults During the COVID-19 Pandemic — United States, April and May 2020

On April 3, 2020, the White House Coronavirus Task Force and CDC announced a new behavioral recommendation to help slow the spread of coronavirus disease 2019 (COVID-19) by encouraging the use of a cloth face covering when out in public. There have been limited study of widespread use of cloth face coverings among the U.S. population, and therefore, little is known about encouraging the public to adopt this behavior. Immediately following the recommendation, an Internet survey sampled 503 adults during April 7–9 to assess their use of cloth face coverings and the behavioral and sociodemographic factors that might influence adherence to this recommendation. The same survey was administered 1 month later, during May 11–13, to another sample of 502 adults to assess changes in the prevalence estimates of use of cloth face coverings from April to May. Within days of the release of the first national recommendation for use of cloth face coverings, the majority of persons who reported leaving their home in the previous week reported using a cloth face covering. Prevalence of use increased to approximately 75% 1 month later, primarily associated with greater use among white, non-Hispanic persons, persons aged ≥65 years, and persons residing in the Midwest. The use of a cloth face covering was associated with theory-derived constructs that indicate a favorable attitude toward them, intention to use them, ability to use them, social support for using them, and beliefs that they offered protection for self, others, and the community. The results suggests that minority groups that are experiencing a greater force of severe illness and mortality from COVID-19 are not getting the message about use of face masks to mitigate risk. In addition, younger people who are not experiencing such severe illness and elevated mortality yet have the ability to spread the virus, are not heeding the guidance to wear masks. Research is needed to understand possible barriers to using cloth face coverings and ways to promote their use among those who have yet to adopt this behavior.

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Editor-in-Chief, *Morbidity and Mortality Weekly Report* (*MMWR*) Series
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Message

From: Alexander, Paul (HHS/ASPA) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 7/19/2020 1:05:16 PM
To: Stephen Hahn [redacted] Shah, Anand (FDA/OC) [redacted] Caputo, Michael (HHS/ASPA) [redacted]
Subject: FW: COVID-19 NMA manuscript resubmitted
Attachments: BMJ-2020-059724.R1_Proof_hi SUBMITTED 19Jul2020.pdf

Hi Dr. Hahn and Anand and Michael, I share this so confidentially. Yikes…and I thought of it long and hard as the group submitted last night to BMJ after revisions…so I am part of the large international research group and one of the senior researchers in this network meta-analysis as seen in the list of authors. You would know the one reason why I stand out among this group of some the world's top researchers which I am proud of and made the personal decision to reveal it. I was told that had I not played such a prominent role in this project started in Feb before I came on deck, that they would have not wanted me in it and I expected this since coming to DC and experiencing the push back which is so terrible. But a lot of the work I did so folk had no choice and some was my own work…anyway, I share this submission (embargoed) so highly confidentially, please share with no one not even in people who work or report to you…please. But I weighed the balance and this is so important and such an emergency and while I have not done this before and will not again, I share this embargoed so that you are primed of what we found if it could help your decision-making to help the USA and the globe as the US leads the world, rightly. You two are an example. So I trust you and Michael, I trust him as a brother. This is for your eyes only but can inform your decision-making behind the scenes as it will be in print maybe one week.

I draw your attention to "Time to symptom resolution"…we included 13 RCTs for that outcome enrolling 2,282 participants. Remember, with Network meta-analysis (NMA), the approach is not simple pair-wise modelling of a treatment to its comparator but we include the indirect evidence in the models (briefly, in NMA we may have evidence of A vs C and B vs C where C is the common comparator e.g. placebo, but not A vs B (head to head) that we are interested in and NMA allows us to speculate mathematically 'if' they were actually compared and we include the direct and that indirect evidence in the model)…anyway, we found that in patients who received remdesivir (MD -2.58 days CI -4.32 to -0.54, moderate certainty), hydroxychloroquine (MD -4.53 days CI -5.98 to -2.99, low certainty), and lopinavir-ritonavir (MD -1.22 days CI -2.00 to -0.37, low certainty) had a shorter symptom duration than standard care. For hydroxy there was no other benefit and there was apparent risk of adverse events.

Again, I would never do this but do it here for we have lives on the line and we are searching for a treatment or combination and I want to help the administration and you two as the top regulators in this push. I am so confident in you and the team in beating this virus and the whole administration…yes, it is wearing on us for this is tough, and we are being fought by the other side and media which is horrendous for we have a very serious emergency and the people the public seek just simple, honest, direct guidance and allow them to be informed so they can make common sense 'best' decisions for themselves.

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Email: [redacted]

From: Paul Elias Alexander [redacted]
Sent: Sunday, July 19, 2020 8:35 AM
To: Alexander, Paul (HHS/ASPA) [redacted]
Subject: Fw: COVID-19 LNMA manuscript resubmitted

Time to symptom resolution Thirteen RCTs enrolling 2,282 participants31 34-39 41-43 45 46 50 53 55 64 reported time to symptom resolution. At least 100 patients received hydroxychloroquine, lopinavir-ritonavir, and remdesivir. Patients who received remdesivir (MD -2.58 days CI -4.32 to -0.54, moderate certainty), hydroxychloroquine (MD -4.53 days CI -5.98 to -2.99, low certainty), and lopinavir-ritonavir (MD -1.22 days CI -2.00 to -0.37, low certainty) had a shorter symptom duration than standard care.

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Pharmacologic treatment for COVID-19: living systematic review and network meta-analysis

Journal:	*BMJ*
Manuscript ID	BMJ-2020-059724.R1
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	n/a
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Keywords: COVID-19, Network Meta-analysis, Living Systematic Review, Glucocorticoids, Remdesivir, Hydroxychloroquine, SARS-CoV-2, severe acute respiratory syndrome

SCHOLARONE
Manuscripts

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Pharmacologic treatment for COVID-19: living systematic review and network meta-analysis

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RAS, JB, DZ, LG, and RBP were the core team leading the systematic review. JB, RC, SAF, RV, PA, SM, YW, ZY, IY, AD, TD, AI, AQ, CS, LY, FF, QL, XH, LLS, BF, and AV participated in study identification and selection. DZ, EK, NS, RV, AA, YW, KH, HPH, MH, CF, SM, QL, AQ, LY, and FF participated in data collection. LG, BS, LH, QI, DHA, GG, GT, and LT participated in data analysis. RBP, HPH, AI, RM, TD, NS, and DC participated in assessment of the certainty of the evidence. SM, EL, BR, TA, PV, GG, MM, JN, ML, TT, BT, FF, and GR provided advice at different stages. RAS, RBP and GHG drafted the manuscript. All authors approved the final version of the manuscript. RAC is the guarantor of this article.

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Competing interests declaration
All authors will complete the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and will declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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Transparency declaration

RS affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Patient involvement

Patients were involved in the interpretation of results and the generation of parallel recommendations, as part of the BMJ Rapid Recommendations initiative.

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What is already known/ what this paper adds

Despite huge efforts to identify effective pharmacologic interventions for COVID-19 disease, evidence for effective treatment remains limited.

This living systematic review and network meta-analysis provides a comprehensive picture and assessment of the evidence published as of 8 July 2020 and will be updated periodically

The certainty of the evidence for most interventions tested thus far is low or very low.

In patients with severe COVID-19, glucocorticoids probably decrease mortality and mechanical ventilation. Hydroxychloroquine, lopinavir-ritonavir, and remdesivir may reduce time to symptom resolution.

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Abstract

Objectives: To compare the effects of therapies for treatment of COVID-19

Design: Living systematic review and network meta-analysis (NMA).

Data sources: U.S. Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database, which includes 25 electronic databases up to 8 July 2020

Study selection: We included randomized clinical trials (RCTs) in which persons with suspected, probable, or confirmed COVID-19 were randomized to pharmaceuticals or standard care/placebo for treatment. Pairs of reviewers independently screened titles and abstracts, and full texts, of potentially eligible articles.

Methods: After duplicate data abstraction, we conducted a Bayesian-random effects network meta-analysis for each outcome of interest. We assessed the risk of bias of the included studies using a modification of the Cochrane Risk of Bias 2.0 tool, and the certainty of the evidence using the GRADE approach for NMA. We classified interventions in groups from the most to the least effective/ harmful following GRADE guidance using a minimally contextualized approach.

Results: We included 25 RCTs. The certainty of the evidence for the majority of comparisons is very low because of risk of bias (lack of blinding) and very serious imprecision. Glucocorticoids were the only intervention with evidence for a reduction in death compared to standard care (37 fewer per 1000 patients, 95% credible interval [CI] 63 fewer to 11 fewer, moderate certainty) and mechanical ventilation (31 fewer per 1000, CI 47 fewer to 9 fewer, moderate certainty). Three drugs may reduce symptom duration compared to standard care: hydroxychloroquine (-4.5 days, low certainty), remdesivir (-2.6 days, moderate certainty), and lopinavir-ritonavir (-1.2 days, low certainty). Hydroxychloroquine may increase the risk of adverse events when compared to the other interventions and remdesivir probably does not substantially increase the risk of adverse effects. No other interventions included enough patients to meaningfully interpret adverse effects leading to drug discontinuation.

Conclusion: Glucocorticoids probably reduce mortality and mechanical ventilation compared to standard care. The effectiveness of most interventions is very uncertain because most of the RCTs so far have been small and have important study limitations.

Protocol: The protocol is included as a supplement.

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Background

As of 18 July 2020, over 14.1 million people have been infected with COVID-19; of these, 600,000 have died.[1] Despite huge efforts to identify effective interventions for its prevention and treatment- which have resulted in almost 1500 trials completed or under way-[2] evidence of effective treatment remains limited.

Faced with the pressures of a global pandemic, healthcare workers around the world are prescribing medications off-label for which there is only very low quality evidence. The result - this appears to be certainly the case for the very well-publicized example of hydroxychloroquine - may be no benefit and appreciable harm. Timely evidence summaries and associated guidelines may ameliorate the problem.[3] Clinicians, patients, guideline bodies, and government agencies are also facing the challenges of interpreting the results from trials that are being published at a rate never seen before. This environment makes it necessary to produce well-developed summaries that distinguish more from less trustworthy evidence.

Living systematic reviews (SRs) and network meta-analyses (NMAs) address the main limitation of traditional reviews, that of providing a picture of the relevant evidence only at a specific timepoint.[4] This is crucial in the context of COVID-19, in which the picture is constantly changing. The ability of living NMA to present a complete, broad, and updated view of the evidence makes it ideal to inform the development of practice recommendations. NMA, rather than pairwise meta-analysis provides useful information about the comparative effectiveness of treatments that were not tested head-to-head. The lack of such direct comparisons is certain to limit inferences in the COVID-19 setting. Moreover, the incorporation of indirect evidence can strengthen evidence in comparisons that were tested head-to-head.[5]

The objective of this living SR and NMA is to compare the effects of pharmacologic therapies for treatment of COVID-19. This SR is part of the *BMJ Rapid Recommendations* project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and *The BMJ*. Our living NMA will directly inform *BMJ Rapid Recommendations*[6] on COVID-19 treatments, triggered to provide trustworthy, actionable, and living guidance to clinicians and patients soon after new and potentially practice-changing evidence becomes available.

Methods

A protocol provides the detailed methods of this SR, including all updates (available as supplementary material). We report this living SR following the guidelines of the PRISMA checklist for NMA.[7] A living systematic review is a cumulative synthesis that is updated regularly as new evidence becomes available.[8] The linked BMJ *Rapid Recommendations* the guideline panels approved all decisions relevant to data synthesis.

Eligibility criteria

We included randomized clinical trials (RCT) in persons exposed to COVID-19 or with suspected, probable or confirmed COVID-19 that compared pharmaceuticals for treatment against one another or against no intervention, placebo, or standard care. We included trials regardless of publication status (peer-reviewed, in press, or pre-print) or language. We applied no restriction based on severity of illness or setting and included trials of Chinese medicines if the drug was one or more specific molecules with a defined molecular weight dosing.

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We excluded RCTs evaluating vaccination, blood products, nutrition, traditional Chinese herbal medicines that include more than one molecule or a molecule without specific molecular weighted dosing and non-drug supportive care interventions. RCTs including patients with COVID-19 that evaluated these interventions were identified and categorized separately.

Information sources

We perform daily searches Monday to Friday in the U.S. Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database for eligible studies—the most comprehensive database of COVID-19 research articles[9]. The database includes 25 bibliographic and grey literature sources: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO COVID-19 website, CDC COVID-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).

The daily searches are designed to match the update schedule of the database and to capture eligible studies the day of or day after their publication. We filtered the results from the CDC's database through a validated and highly sensitive machine learning model to identify RCTs.[10] We tracked preprints of RCTs until publication and updated data to match that in the peer-reviewed publication when discrepant and reconciled corrections and retractions.

In addition, we searched six Chinese databases on a biweekly basis: Wanfang, CBM, CNKI, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). We adapted the search terms for COVID-19 developed by the CDC to the Chinese language. For the Chinese literature search, we also included search terms for randomized trials. The Supplementary Material includes the Chinese literature search strategy.

We monitor living evidence retrieval services on an ongoing basis. These included the Living Overview of the Evidence (L-OVE) COVID-19 Repository by the Epistemonikos Foundation and the Systematic and Living Map on COVID-19 Evidence by the Norwegian Institute of Public Health, in collaboration with the Cochrane Canada Centre at McMaster University.[11]

We searched all English information sources from 1 December 2019 and until 8 July 2020 and Chinese literature from the conception of the databases to 26 June 2020.

Study selection

Using a SR software, Covidence,[12] pairs of trained and calibrated reviewers independently screened all titles and abstracts followed by full texts of trials that were identified as potentially eligible. A third reviewer adjudicated conflicts.

Data collection

For each eligible trial, pairs of reviewers, following training and calibration exercises, extracted data independently using a standardised, pilot-tested data extraction form. Reviewers collected information on trial characteristics (trial registration, publication status, study status, design), patient characteristics (country, age, sex, smoking habits, comorbidities,

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setting and type of care, and severity of COVID-19 symptoms for studies of treatment), and outcomes of interest (means or medians and measures of variability for continuous outcomes and the number of participants analyzed and the number of participants that experienced an event for dichotomous outcomes).

Outcomes of interest were selected based on their importance to patients and were informed by clinical expertise in the SR team and in the linked guideline panel responsible for the BMJ Rapid Recommendations. The panel includes unconflicted clinical experts, recruited to ensure global representation, and patient-partners. Outcomes were rated from 1-9 based on importance to individual patients (9 being most important) and any outcome rated 7 or higher by any panel member was included. Selected outcomes included mortality (closest to 90 days), mechanical ventilation (total number of patients, over 90 days), adverse events leading to discontinuation (within 28 days), viral clearance (closest to 7 days +/- 3 days), duration of hospitalization, ICU length of stay, time to symptom resolution or clinical improvement, and time to viral clearance. Outcomes of interest for prophylaxis of COVID-19 include mortality, infection with COVID-19, hospitalization, adverse events leading to discontinuation, and time to symptom resolution or clinical improvement. Time to viral clearance was included because it may be a surrogate for transmissibility, although this is uncertain.[13]

Because of the inconsistent reporting observed across trials, in the updates we will use a hierarchy for the outcome mechanical ventilation in which we will include information from the total number of patients who received ventilation over a time period if available (as done for this analysis), but we will also include the number at the time point in which most of the patients were mechanically ventilated if that is the only way in which this outcome is reported.

Reviewers resolved discrepancies by discussion and, when necessary, by adjudication by a third party.

We update the data collected from included studies when they were published as preprint and as soon as the peer-review publication becomes available in studies initially included as preprints.

Risk of bias within individual studies

For each eligible trial, reviewers, following training and calibration exercises, used a revision of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2.0)[14] to rate trials as either 'low risk of bias', 'some concerns - probably low risk of bias', 'some concerns - probably high risk of bias' and 'high risk of bias', across the following domains: bias arising from the randomization process, bias due to departures from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported results including deviations from the registered protocol, and bias arising from early termination for benefit. We rated trials at high risk of bias overall if one or more domains were rated at 'some concerns - probably high risk of bias' or 'high risk of bias' and at low risk of bias if all domains were rated at 'some concerns - probably low risk of bias' or 'low risk of bias'. Reviewers resolved discrepancies by discussion and, when not possible, by adjudication by a third party.

Data synthesis

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We conducted NMA using a Bayesian framework.[15] In this report, we conducted an NMA for pharmacological treatments of COVID-19 that included all patients, regardless of severity of disease.

a. Summary measures

We summarized the effect of interventions on dichotomous outcomes using the odds ratio (OR) and its 95% credible intervals (CI). For continuous outcomes, we used the mean difference (MD) and its 95% CI in days for ICU length of stay and duration of mechanical ventilation because we expected similar durations across RCTs. For time to symptom resolution and length of hospital stay, we first performed the analyses using the relative effect measure ratio of means (RoM) and its 95% CI before calculating MD in days because we expected substantial variation between studies.[16]

b. Treatment nodes

Treatments were grouped into common nodes based on molecule but not dose or duration. For intervention arms with more than one medication, we created a separate node and included drugs from the same class within the same node. Chloroquine and hydroxychloroquine were included in the same node for COVID-19 specific effects and separated for disease-independent adverse effects. We drew network plots using the *networkplot* command of Stata version 15.1 (StataCorp, College Station, Texas, USA) with thickness of edges of the nodes based on the number of studies.[17]

c. Statistical analysis

For most outcomes, we conducted random-effects NMAs using a Bayesian framework with the same priors for the variance and effect parameters.[15] For networks where the outcome were particularly sparse, we conducted fixed-effect NMA.[18] We will use a plausible prior for variance parameter, and uniform prior for the effect parameter suggested by Turner *et al* based on empiric data.[19] For all analyses, we used three Markov-chains with 100,000 iterations after an initial burn-in of 10,000 and a thinning of 10. We used node-splitting models to assess local incoherence and to obtain indirect estimates.[20] All NMAs were performed using the *gemtc* package of R version 4.0.0 (RStudio, Boston, MA).[21]

Some treatment nodes with very few total participants and very few total events resulted in highly implausible and extremely imprecise effect estimates. We therefore decided to include only treatments that enrolled a total of at least 100 patients or had at least 20 events. For this iteration, the analyses included treatment nodes with fewer than 100 patients and 20 events, but the results are not reported.

Certainty of the evidence

We assessed the certainty of evidence using the GRADE approach for NMA.[5 22] Two people with GRADE experience rated each domain for each comparison separately and resolved discrepancies by consensus. We rated the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence (difference between direct and indirect effects), and imprecision.[23] Judgments of imprecision for this SR were made using a minimally contextualized approach, with a null effect as the threshold of importance.[24] The minimally contextualized approach considers only whether credible intervals include the null effect and thus does not consider whether plausible effects, captured by credible intervals, include both important and trivial effects.[25] We created GRADE evidence summaries (Summary of Findings tables) in the MAGIC Authoring and

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publication platform (www.magicapp.org) to provide user-friendly formats for clinicians and patients, and allow re-use in the context of clinical practice guidelines for COVID-19.

Interpretation of results

To facilitate interpretation of the results, we calculated absolute effects for outcomes in which the summary measure was OR or RoM. For the outcomes mortality and mechanical ventilation, we used baseline risks from the International Severe Acute Respiratory and Emerging Infection COVID-19 database.[26] For all other outcomes, we used the mean or median from all studies in which participants received standard of care for each outcome. We calculated absolute effects using the transitive risks model[27] using *R2jags* package in R.[28]

For each outcome, we classified treatments in groups from the most to the least effective using the minimally contextualized framework that focuses on the treatment effect estimates and the certainty of the evidence.[29]

Subgroup and sensitivity analysis

When a comparison was dominated by a single study (defined as >90% contribution in fixed effects), we conducted our primary analysis with a fixed effects model for that comparison.[18] We planned to perform subgroup analyses of preprints vs. peer reviewed studies and high vs. low risk of bias. We will perform additional subgroup analyses in the future if directed by the linked independent Rapid Recommendation guideline panels; in this case there was no such direction.

Results

Following screening of 6,516 titles and abstracts, and 109 full-texts, we identified 25 unique RCTs that evaluated pharmacological treatments as of 8 July 2020 (**Figure 1**).[30-54] Searches of living evidence retrieval services identified one additional eligible RCT.[55] Fifteen RCTs have been published in peer-reviewed journals; and ten only as preprints. Most trials were registered (23/25; 92%), published in English (23/25; 92%) and evaluated treatment in hospitalized patients with COVID-19 (24/25; 96%). Nearly two-thirds were conducted in China (16/25; 64%). Of the 25 included pharmacological trials, 6 evaluated treatment against active comparator(s), 12 evaluated treatment against standard care or placebo and 2 evaluated different durations/doses of the same treatment. Our NMA was performed on 26 June 2020 and includes 19 RCTs.[31 32 34-39 41 43-44 53] Table 1 presents the characteristics of the included studies. Additional study characteristics, outcome data, and risk of bias assessments for each study are available in the Supplementary Material.

The RCTs not included in the analysis are: 1) two RCTs evaluating different durations of the same drug because both arms would have been classified within the same treatment node;[32 40] 2) one RCT evaluating lincomycin vs azithromycin,[56] which was excluded because neither arm was connected to the network; 3) three RCTs, evaluating colchicine,[57] febuxostat,[58] and methylprednisolone[52] all versus standard care were excluded because they were identified after, or the data was available after the analysis was completed.

Two trials did not have publicly accessible protocols or registrations.[56 59] Of the trials with publicly accessible protocols or registrations, 16 reported results for one or more of our outcomes of interest that were not prespecified in protocols/registrations. No other discrepancies

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between the reporting of our outcomes of interest in trial reports and protocols/registrations were noted.

Three studies were initially posted as preprints and subsequently published after peer review.[32 45 54 60-62] In one study, mortality was not reported in the preprint but was reported in the peer reviewed paper.[45 61] There were no substantive differences between the preprint and peer reviewed publications for the other two studies. One RCT did not report outcomes in the groups as randomized; the authors shared outcome data with us in the groups as randomized.[52]

All analyses reached convergence based on trace plots and Brooks-Gelman-Rubin statistic <1.05. For glucocorticoids, there were two RCTs with substantial differences in size (RECOVERY enrolled 6425 patients[51] and GLUCOCOVID 63[52]), thus we performed a fixed effects analysis for the direct pairwise analysis for this the outcomes that were reported in both RCTs (mortality and mechanical ventilation). This analysis was separate from the network meta-analyses, which were all random effects. Due to the lack of sufficient data, we did not conduct any of the subgroup or sensitivity analyses specified in the protocol (see Supplementary Material).

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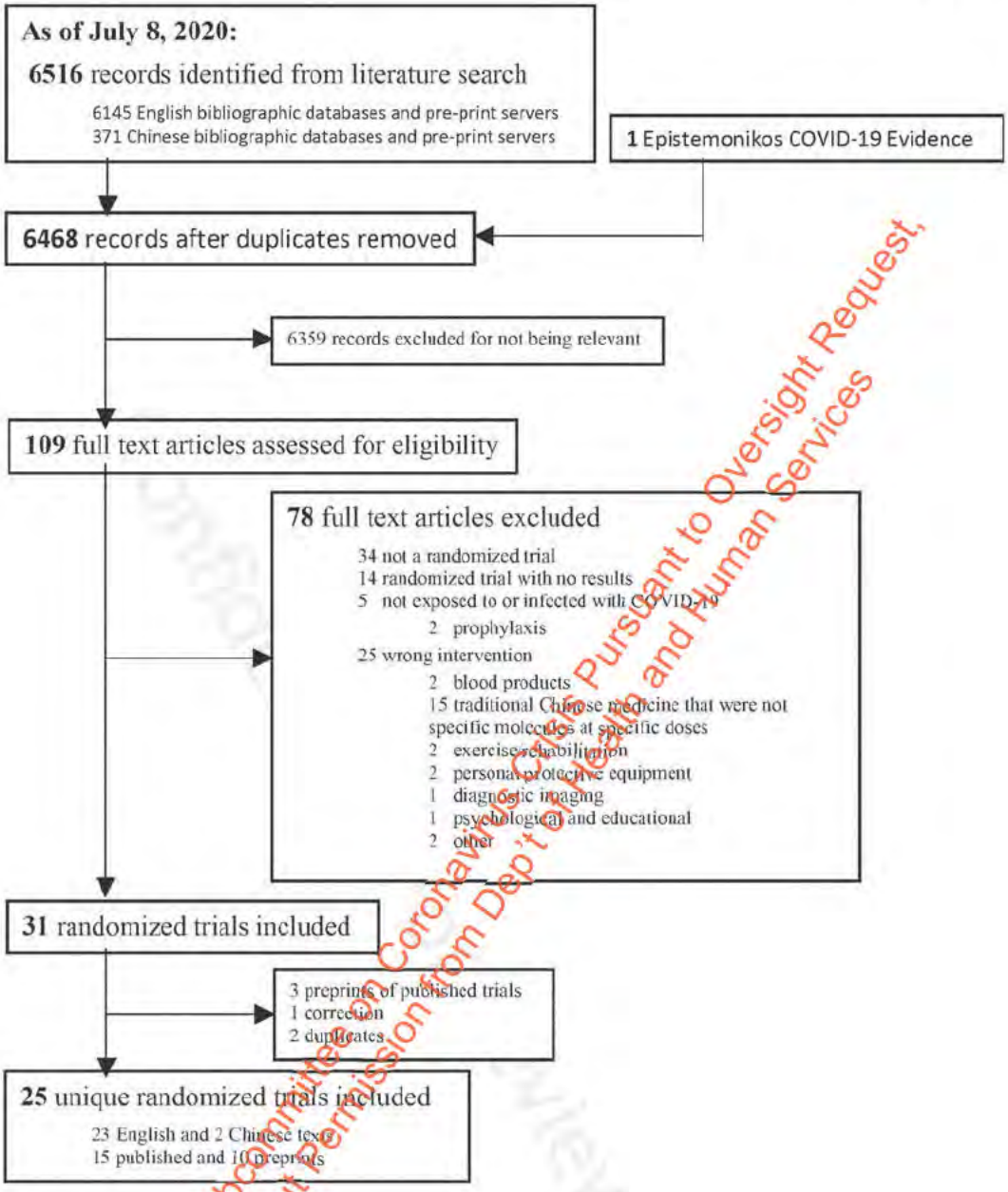

Figure 1: Study Selection

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Risk of bias in included studies

The supplementary material presents the assessment of risk of bias of the included studies per outcome. Two studies were judged at low risk of bias in all domains.[31 46] All other studies had probably high or high risk of bias in the domains of randomization or deviation from the intended interventions.

Effects of the interventions

The supplementary material presents the network plots depicting the interventions included in the NMA of each outcome. Table 2 presents a summary of the effects of the interventions on the outcomes. The supplementary material presents detailed relative and absolute effect estimates and certainty of the evidence for all comparisons and outcomes. We did not detect statistical incoherence in any of the NMAs.

a. Mortality

The 15 RCTs including 8,654 participants[31 34-37 39 41 43-47 50-53 63 64] addressed mortality. The treatment nodes included in the NMA were glucocorticoids, hydroxychloroquine, lopinavir-ritonavir, remdesivir, umifenovir, and standard care. The network estimates did not reveal a convincing reduction for any of these interventions compared to standard care. The certainty of the evidence was low for the comparison between remdesivir and standard of care, and very low for all other comparisons (Table 2). For glucocorticoids, the direct estimate was more credible than the network estimate (moderate certainty vs. very low certainty) because the direct estimate was more precise. The network estimate, which considers heterogeneity of the entire network, was RR 0.84 CI 0.52 to 1.36. The direct meta-analysis of two RCTs for glucocorticoids versus standard care[31 52] suggested a probable mortality reduction with glucocorticoids: RR 0.88 CI 0.80 to 0.97, RD 37 fewer per 1000 CI 63 fewer to 11 fewer, moderate certainty for risk of bias.

b. Mechanical ventilation

Eight RCTs that enrolled 6,953 participants[31 34 35 39 41 43 46 51 52 63 64] reported mechanical ventilation in patients who were not receiving mechanical ventilation at baseline. The treatment nodes included in the NMA were glucocorticoids, remdesivir, and standard care (Table 2). The network estimate for glucocorticoids was very low certainty because of very serious imprecision RR 0.71 CI 0.29 to 1.73. The direct pairwise direct meta-analysis for glucocorticoids versus standard care[31 52] resulted in higher certainty and suggested a probable reduction with glucocorticoids versus standard care: RR 0.74 CI 0.59 to 0.93, RD 30 fewer per 1000 CI 48 fewer to 8 fewer, moderate certainty for risk of bias.

c. Adverse events leading to discontinuation

Eleven RCTs that enrolled 1,875 participants [31 38 39 41 44-50 53 64] reported adverse effects leading to discontinuing the study drug. The treatment nodes included in the NMA were hydroxychloroquine, remdesivir, and standard care. There was moderate certainty evidence that remdesivir did not incur any additional harm beyond standard care and low certainty evidence that hydroxychloroquine increased the risk of adverse events compared with standard care (Table 2).

d. Viral clearance at 7 days (+/- 3 days)

All ten RCTs that cumulatively enrolled 856 participants [34 37 43 45-48 50 53 55 64] measured viral clearance with PCR cutoff points. The treatment nodes included in the NMA were hydroxychloroquine, lopinavir-ritonavir, remdesivir, and standard care. There was no

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convincing evidence that any of the interventions increased the rate of viral clearance (Table 2). The certainty of the evidence was low for the comparison between remdesivir and standard care, and very low for all other comparisons.

e. Duration of hospitalization

Eight RCTs enrolling 855 participants[34 35 37 39 41 46 51 53 55 64] reported duration of hospitalization. The treatment nodes included in the NMA were lopinavir-ritonavir, remdesivir, and standard care. Patients who received lopinavir-ritonavir had fewer days of hospitalization than patients who received standard care but the effect estimate included no difference: RD -1.42 days CI -3.03 to 0.02 (low certainty; Table 2). Remdesivir did not appear to reduce duration of hospitalization (low certainty).

f. ICU length of stay

Two RCTs enrolling 280 participants studied lopinavir-ritonavir (99 patients) and interferon beta 1 (42 patients) versus standard care (139 patients) reported length of ICU stay.[35 39] Standard care was the only treatment node with at least 100 patients and therefore no analyses were performed for this outcome.

g. Duration of mechanical ventilation

Three RCTs and enrolling 557 participants[35 39 46] reported duration of mechanical ventilation. The treatment nodes included in the meta-analysis were remdesivir and standard care. Moderate certainty evidence that remdesivir reduces the duration of mechanical ventilation compared to standard care, MD-5.15 days CI -8.28 to -2.02 (Table 2).

h. Time to symptom resolution

Thirteen RCTs enrolling 2,282 participants[31 34-39 41 43 45 46 50 53 55 64] reported time to symptom resolution. At least 100 patients received hydroxychloroquine, lopinavir-ritonavir, and remdesivir. Patients who received remdesivir (MD -2.58 days CI -4.32 to -0.54, moderate certainty), hydroxychloroquine (MD -4.53 days CI -5.98 to -2.99, low certainty), and lopinavir-ritonavir (MD -1.22 days CI -2.00 to -0.37, low certainty) had a shorter symptom duration than standard care.

i. Time to viral clearance

Ten RCTs enrolling 684 participants[35 37 41 43 45 47 48 50 53 55 64] revealed no convincing evidence that any of the interventions reduced the time to viral clearance; at least 100 patients received hydroxychloroquine, lopinavir-ritonavir, and remdesivir. The certainty of the evidence was very low for all comparisons (Table 2).

Discussion

This living SR and NMA provides a comprehensive picture of the evidence for pharmacologic treatments of COVID-19 up to 8 July 2020. The certainty of the evidence for the majority of the comparisons is very low. The only intervention that probably reduces mortality and mechanical ventilation is glucocorticoids, a result driven entirely by the RECOVERY trial.[51] Remdesivir is the only intervention in which moderate certainty exists supporting benefits for both time to symptom resolution and duration of mechanical ventilation, but it remains uncertain whether remdesivir has any impact on mortality and other outcomes important to patients. Remdesivir was the only intervention where all of the data came from RCTs sponsored by a pharmaceutical company. Direct evidence from RCTs in patients with COVID-19 has so far provided

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little definitive evidence about adverse effects for most interventions.

Hydroxychloroquine may increase the risk of adverse events leading to drug discontinuation when compared to the other interventions. Notably, this iteration of the living NMA did not include three recently published large RCTs on hydroxychloroquine versus standard care.[65-67] RECOVERY, the largest hydroxychloroquine RCT, suggests that hydroxychloroquine may not reduce mortality and may increase length of hospital stay.[65] These data will be included in the next update. There was no convincing evidence that the other interventions resulted in benefits or harms when compared to standard of care.

Stengths and limitations of our review

Our search strategy and eligibility criteria were comprehensive, without restrictions of language of publication, and provide a full picture of the current evidence. To ensure expertise in all areas, our team is composed of clinical and methods experts trained and calibrated for all stages of the review process. In order to minimize problems with counterintuitive results, the data analysis plan anticipated challenges that arise in NMA when data is sparse.[18] We assessed the certainty of the evidence using the GRADE approach and interpreted the results considering absolute effects. Many of the results for comparisons with sparse data were uninformative and were sometimes implausible. For that reason, we decided to report evidence on treatments that randomized at least 100 patients. In the future, when more data from more treatments are available, our classification of interventions from the most to the least effective will facilitate clear interpretation of results.

The main limitation of the systematic review is the very low quality of the evidence as a result of the current sparse data available. As the many ongoing trials are completed, we anticipate that the effect estimates will quickly become both plausible and informative as the quality of the evidence rises. Only two studies were judged to be at low risk of bias.[31 32 60] The most common limitation was lack of blinding, including the largest trials.

Another limitation of this SR is the limited quality of reporting. For some outcomes, the method in which the researchers measured and reported outcomes proved inconsistent across studies did not match across studies and thus such studies could not be included in the NMAs. This led the team to propose a hierarchy for the outcome mechanical ventilation as described in the methods. We expect that the relative effect will not vary importantly across methods of measurements.

The living nature of our NMA could conceivably (at least temporarily) amplify publication bias because studies with promising results are more likely to be published and are published sooner than studies with negative results. The inclusion of preprints, many of which have negative results might mediate this risk. Industry-sponsored trials such as those for remdesivir and other patented medications may be particularly at risk for publication bias and positive results for these medications may require more cautious interpretation than generic medications tested in RCTs independent of industry influence. However, the inclusion of preprints in our NMA may introduce bias from simple errors and reporting limitations of preprints. We include preprints because of the urgent need for information and because so many of the studies on COVID-19 are published first as preprints.

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For comparisons with sufficient data, the primary limitation of the evidence is lack of blinding, which may introduce bias through differences in co-interventions between randomization groups. We chose to consider the treatment arms that did not receive an active experimental drug (i.e., placebo or standard care) within the same node: it is possible that the unblinded standard care groups received systematically different co-interventions than in studies that were blinded.

It is also possible that study-level meta-analysis may not detect important subgroup modification that would otherwise be detected within trial comparisons.[68] Direct comparisons in which the evidence is dominated by unblinded studies were rated down, consistent with GRADE, for risk of bias and that is reflected in the rating of the quality of evidence from the network estimate.[69] For example, the RECOVERY trial suggested that patients with more severe disease may obtain a greater benefit from dexamethasone than patients with less severe disease.[51]

Our living NMA is informing the development of the *BMJ Rapid Recommendations*. There is, however, an important difference in the methods for assessing the certainty of the evidence between the two. In this SR and living NMA, we are using a minimally contextualized approach for rating the certainty of the evidence, whereas the *BMJ Rapid Recommendations* are using a fully contextualized approach in which the thresholds of importance of magnitudes of effects depend on all other outcomes and factors involved in the decision.[24] The contextualization explains potential differences in the certainty of the evidence between the two. The limitations of potentially misleading results when the network is sparse, and the desirability of focusing on direct estimates from larger studies when this is the case, explain differences in the details of the estimates of effect in this NMA and in the associated remdesivir guidelines.

To date, we are aware of two other efforts similar to ours.[68 70] We decided to proceed independently to ensure that the results fully inform clinical decision making for the associated living guidance in BMJ Rapid Recommendations. We are also including a more comprehensive search for the evidence, and several differences in analytic methods which we believe are best suited for this process. It is also important to evaluate the reproducibility and replicability of results from different scientific approaches.

We will periodically update this SR and living NMA. The changes from each version will be highlighted for readers and the most updated version will be the one available in the publication platform. Previous versions will be archived in the supplementary material. This SR and living NMA will also be accompanied by interactive infographics and a website for users to access the most updated results in a user-friendly format.

Conclusions

The evidence suggests that glucocorticoids probably reduce mortality and mechanical ventilation in patients with severe COVID-19. Remdesivir probably reduces length of hospital stay. The effects of most pharmacologic interventions is currently highly uncertain, and no definitive evidence exists that other interventions result in important benefits and harms for any outcomes.

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Table 1. Study characteristics

Study	Publication status/ Registration	Number of participants	Country	Mean age	% Male	Comorbidities	Type of care	Severity	% Mechanical ventilation (at baseline)	Treatments (dose and duration)	Outcomes
Siegel, 2020 ACTT-1[9]	Published NCT04280705	1063	United States, Denmark, United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	58.9	64.3	Coronary artery disease (11.6%) Congestive heart failure (5.0%) Diabetes (29.7%) Hypertension (49.6%) Asthma (11.4%) Chronic oxygen requirement (2.2%) Chronic respiratory disease (7.6%)	Inpatient	Mild/Moderate (11.1%) Severe (88.7%)	44.3	remdesivir (200 mg/day for 10 days) placebo	Mortality Mechanical ventilation Adverse effects leading to discontinuation Time to symptom/clinical improvement
Cao_1, 2020 (OTLPS China)[10]	Published ChiCTR2000029308	199	China	58.0	40.3	Cerebrovascular disease (6.5%) Diabetes (11.6%)	Inpatient	Severe (100%)	16.1	lopinavir-ritonavir (400 mg BID-800 mg BID for 14 days) standard care	Mortality Mechanical ventilation Viral clearance Duration of hospitalization ICU length of stay Duration of ventilation Time to symptom/clinical improvement
Cao_2, 2020[11]	Published ChiCTR-OPN-2000029580	43	China	63.0	58.5	Coronary artery disease (7.3%) Diabetes (19.5%) Hypertension (30.0%)	Inpatient	Severe (100%)	12.2	ribavirin (500 mg BID) placebo	Mortality Mechanical ventilation Duration of hospitalization Duration of ventilation Time to symptom/clinical improvement Time to viral clearance
Chen_1, 2020[12]	Preprint ChiCTR2000029559	62	China	44.7	50.8	NR	Inpatient	Mild/Moderate (100%)	NR	hydroxychloroquine (200 mg BID for 5 days) standard care	Adverse effects leading to discontinuation Time to symptom/clinical improvement
Chen_2, 2020[13]	Preprint ChiCTR2000030254	240	China	NR	46.6	Diabetes (11.4%) Hypertension (28.0%)	NR	Mild/Moderate (88.6%) Severe (10.2%) Critical (1.2%)	NR	favipiravir (600 mg BID for 7 days) umifenovir (200 mg TID for 7 days)	Mortality Time to symptom/clinical improvement
Chen_3, 2020[14]	Published ChiCTR2000029387	101	China	42.5	45.5	Severe heart disease (0%) Severe lung disease (0%)	NR	Mild/Moderate (100%)	NR	ribavirin (400-600 mg BID for 14 days), interferon-α (2 mg BID for 14 days), lopinavir-ritonavir (400 mg and 100 mg BID for 14 days), interferon-α (2 mg BID for 14 days), ribavirin (400-600 mg BID for 14 days), lopinavir-ritonavir (400 mg and 100 mg BID for 14 days)	Mortality Duration of hospitalization Time to symptom/clinical improvement Time to viral clearance
Chen_4, 2020[15]	Published NCT04261517	30	China	48.6	70.0	Severe heart disease (0%) Diabetes (6.7%) Hypertension (26.7%) Chronic obstructive pulmonary disease (3.3%) Severe lung disease (0%)	Inpatient Intensive care (0%)	Mild/Moderate (100%)	NR	hydroxychloroquine (400 mg/day for 5 days) standard care	Mortality Adverse events leading to discontinuation Viral clearance Time to symptom/clinical improvement Time to viral clearance
Chen_5, 2020[16]	Preprint ChiCTR2000030054	48	China	46.5	45.8	Diabetes (18.8%) Hypertension (16.7%)	Inpatient	Mild/Moderate (100%)	NR	chloroquine (500 mg/day for 10 days) hydroxychloroquine (200 mg BID for 10 days) standard care	Mortality Adverse events leading to discontinuation Viral clearance Duration of hospitalization Time to symptom/clinical improvement Time to viral clearance
Corral-Gudino, 2020 BLOCKCOVID[17] †	Preprint 2020-001534-37	63	Spain	69.8	61.9	Arrhythmia (0%) Heart disease (12.7%) Diabetes (37.5%) Hypertension (47.6%) Respiratory condition (7.9%)	Inpatient Intensive care (0%)	Critical (0%)	0	methylprednisolone (48 mg BID for 3 days, then 20 mg BID for 3 standard care	Mortality Mechanical ventilation
Davoudi-Monfared, 2020[18]	Preprint IRCT20100228003449N28	92	Iran	57.8	73.1	Cardiovascular disease (28.4%) Diabetes (27.2%) Hypertension (38.3%) Asthma (1.2%) Chronic obstructive pulmonary disease (1.2%)	Inpatient	Severe (100%)	29.6	interferon β-1a (44 μg/ml TIW for 14 days) standard care	Mortality Mechanical ventilation Adverse events leading to discontinuation Duration of hospitalization ICU length of stay Duration of ventilation Time to symptom/clinical improvement
Goldman, 2020[19]	Published NCT04292899	402	United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan	61.5	63.7	Diabetes (22.7%) Hypertension (49.5%) Asthma (12.34%)	Inpatient	Severe (100%)	30.7	remdesivir (100 mg/day for 5 days) remdesivir (100 mg/day for 10 days)	Mortality Mechanical ventilation Adverse events leading to discontinuation Duration of hospitalization Time to symptom/clinical improvement

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Gueverez, 2020[Ref]	Published	24	Turkey	58.8	62.5	NR	Inpatient	NR	0	Azithromycin (600 mg BID for 5 days) azithromycin (250 mg/day for 5 days)	Viral clearance	
Horby, 2020 RECOVERY[Ref]	Preprint NCT04381936	6425	United Kingdom	66.1	64.6	Heart disease (27.0%) Diabetes (24.1%) Chronic lung disease (20.9%) Tuberculosis (0.4%)	Inpatient	NR	15.2	dexamethasone (6 mg/day for 10 days) standard care	Mortality Mechanical ventilation Duration of hospitalization	
Huang, 2020[Ref]	Published ChiCTR2000030543	33	China	44.0	55.1	Cerebrovascular disease (4.5%) Diabetes (9.1%) Hypertension (18.2%)	Inpatient	Mild/Moderate (63.6%) Severe (36.4%)	NR	chloroquine (500 mg BID for 10 days) lopinavir-ritonavir (400 mg and 100 mg BID for 10 days)	Viral clearance Duration of hospitalization Time to symptom/clinical improvement Time to viral clearance	
Hung, 2020[Ref]	Published NCT04276688	127	China	57.3	53.5	Coronary artery disease (7.9%) Cerebrovascular disease (1.6%) Diabetes (13.4%) Hypertension (28.4%) Obstructive sleep apnea (1.6%) Tuberculosis (1.6%)	Inpatient	Mild/Moderate (100%)	0	lopinavir-ritonavir (400 mg and 100 mg BID for 14 days), ribavirin lopinavir-ritonavir (400 mg and 100 mg BID for 14 days)	Mortality Mechanical ventilation Adverse effects leading to discontinuation Duration of hospitalization Time to symptom/clinical improvement Time to viral clearance	
Li, 2020 LLACOVID19[Ref]	Preprint NCT04252885	86	China	49.4	46.5	Cardiovascular disease (2.3%) Diabetes (2.3%) Hypertension (10.5%) Respiratory condition (9%)	Inpatient	Mild/Moderate (100%)	0	lopinavir-ritonavir (400 mg and 100 mg BID for 7 to 14 days) umifenovir (200 mg TID for 7 to 14 days) standard care	Mortality Adverse effects leading to discontinuation Viral clearance Time to viral clearance	
Liu, 2020[Ref]	Preprint ChiCTR2000029544	30	China	52.5	72.4	Cardiovascular disease (13.8%) Diabetes (6.9%) Hypertension (20.7%) Chronic obstructive pulmonary disease (0%)	Inpatient Intensive care (0%)	Critical (0%)	0	[illegible] (200 mg/day for up to 3 doses on days 1, 4, or [illegible] (600 mg BID for 14 days) [illegible]	Mortality Mechanical ventilation Viral clearance Time to symptom/clinical improvement Time to viral clearance	
Silva Borba, 2020 [illegible][Ref]	Published NCT04321522	81	Brazil	51.1	15.3	Cardiovascular disease (9.1%) Diabetes (25.5%) Hypertension (45.5%) Asthma (7.4%) Tuberculosis (5.6%)	Inpatient Intensive care (45.7%)	Severe (100%)	NR	chloroquine (600 mg BID for 10 days) chloroquine (450 mg/day for 5 days)	Mortality	
Tang, 2020[Ref]	Published ChiCTR2000029866	150	China	46.1	15.0	Cardiovascular disease (0%) Diabetes (14.0%) Hypertension (6.0%)	Inpatient	Mild/Moderate (99.3%) Severe (1.0%)	NR	hydroxychloroquine (800 mg/day for 31 to 21 days) standard care	Mortality Adverse effects leading to discontinuation Viral clearance Time to symptom/clinical improvement Time to viral clearance	
Wang, 2020[Ref]	Published NCT04257656	237	China	65.0	39.3	Cardiovascular disease (7.2%) Diabetes (23.7%) Hypertension (41.2%)	Inpatient	Severe (100%)	16.1	remdesivir (100 mg/day for 10 days) placebo	Mortality Mechanical ventilation Adverse events leading to discontinuation Viral clearance Duration of hospitalization Duration of ventilation Time to symptom/clinical improvement	
Zheng, 2020[Ref]	Preprint ChiCTR2000029496	89	China	46.7	47.2	Severe heart disease (0%) Severe lung disease (0%)	Inpatient	Mild/Moderate (54.4%) Severe (45.6%)	NR	novaferon (20 μg BID for 7 to 10 days) Novaferon, lopinavir-ritonavir (200 mg and 50 mg BID for 7 to 10 lopinavir-ritonavir (200 mg and 50 mg BID for 7 to 10 days)	Adverse events leading to discontinuation Viral clearance Time to viral clearance	
Zheng, 2020[Ref]	Preprint ChiCTR2000029851	37	China	63.0	76.0	Cardiovascular disease (5.5%) Diabetes (24.5%) Hypertension (37.1%)	Inpatient	Severe (100%)	54.1	arbidol mesylate (1200 mg/day for 7 days) placebo	Mortality Adverse events leading to discontinuation	
Zhou, 2020[Ref]	Published	104	China	52.1	57.7	Severe heart disease (0%) Hypertension (0%) Interstitial pneumonia (0%)	Inpatient Intensive care (0%)	Mild/Moderate (100%)	NR	Glycyrrhizin glycyrrhizinate (150 mg BID for 14 days), lopinavir- lopinavir-ritonavir (500 mg BID for 14 days)	Adverse events leading to discontinuation	

NR: not reported
[illegible] included in network meta-analysis
[illegible] included in the current iteration of the network meta-analysis but will be included in the next iteration. Corrales-Guerrero et al. 2020 was included in the pairwise meta-analysis of glucocorticoids.

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Message

From: Alexander, Paul (HHS/ASPA) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 8/2/2020 9:30:40 PM
To: Robinson, Michael J (HHS/ASPA) [redacted]
Subject: RE: H1N1 vs COVID; A TALE OF 2 PANDEMICS

Ah models, I can manipulate models to make it what I want...we all do and this is the issue with models.

Point is there is no need to test the way we are for covid..we test symptomatic, higher risk, suspect cases...we do not go about testing testing for it is true we limit resources...we could never contact trace positive cases correctly. So the response to H1N1 was actually more close to correct, what is being done for covid or done is wrong...just wrong...politics.

We focus on our higher risk people, we lock them down, message to all to safeguard older folk in your homes and old aged homes, message proper mitigation actions, and go on...we ensure hospitals have the infrastructure in place and we go on...it settles out in time.

Dr. Paul E. Alexander, PhD
Senior Advisor to the Assistant Secretary
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Office of the Assistant Secretary of Public Affairs (ASPA)
US Department of Health and Human Services (HHS)
Washington, DC
Tel: [redacted] (Office)
Tel: [redacted] (Cellular)

Email: [redacted]

From: Robinson, Michael J (HHS/ASPA) [redacted]
Sent: Sunday, August 2, 2020 2:27 PM
To: Alexander, Paul (HHS/ASPA) [redacted]
Subject: Re: H1N1 vs COVID; A TALE OF 2 PANDEMICS

And

#6, but think that was due to modeling that showed low death rate

---

On: 02 August 2020 14:24,
"Robinson, Michael J (HHS/ASPA)" [redacted] wrote:

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Hi

#4?

Some would also say it's and election year and many more people have iPhones w/ curated feeds and great virtual reach; see this:

"In 2009, the number of smartphones sold worldwide added up to 170 million. By 2015, this figure stood at more than 1.4 billion"

https://www.statista.com/statistics/266219/global-smartphone-sales-since-1st-quarter-2009-by-operating-system

I believe we're now at 3.8B users worldwide -to me, our pandemic response plans need to better account for people driving news more than agencies like HHS managing news; we also always assume in our planning that expert leadership has clear and unchain messages -it's good that SMEs say response will change with emerging data, but laypeople don't understand that (or do and can't keep up with the changes). They would like to hear it (once, maybe twice), pack it and live life as normal with fewer disruptions and with little change.

Another critical point, is that there were significantly fewer deaths w/ H1N1 -even over a full year:

"From April 12, 2009 to April 10, 2010, CDC estimated there were 60.8 million cases (range: 43.3-89.3 million), 274,304 hospitalizations (range: 195,086-402,719), and **12,469 deaths** (range: 8868-18,306) in the United States due to the (H1N1)pdm09 virus."

https://www.cdc.gov/flu/pandemic-resources/2009-h1n1-pandemic.html

H1N1, pneumonia and influenza deaths in the US, for 2009 came in just under, 67,000 total.

The latest CDC forecast predicts 168,000 to 182,000 total COVID-19 deaths will be reported by August 22.

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/forecasting-us.html

V/r,
Mike

On: 02 August 2020 12:52
"Alexander, Paul (HHS/ASPA)" [redacted] wrote:

On: 02 August 2020 12:52 "Alexander, Paul (HHS/ASPA)" [redacted] wrote:

1. For H1N1 pandemic in 2009, they came out, said it once or twice, take precautions and that was it, society was left to go on
2. No Fab 4 or Fab 5
3. No shut down for H1N1 or any school closure; NONE
4. Children were at great risk but no focus on H1N1 for that
5. No testing Czar, no daily reporting of cases, deaths, NONE

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6. Administration ordered CDC to stop testing after 4 months, ALL states stopped testing; for COVID testing and results each day
7. No issue about websites and where data came from etc.
8. No Dr. Fauci making statements that confuses even me; no need for googles, thank god
9. No media focus or obsessions; no 24/7 news
10. Children many times more at risk of infection and illness and death form H1N1; but no focus by the media or obsession; H1N1 was even more difficult than seasonal influenza
11. Both seasonal influenza and H1N1 had more deaths for children and infection and illness, but no focus by the media etc.

What is the difference? I have looked at all the data, all aspects, only one issue, I think I can see what it is; do you?

Dr. Paul E. Alexander, PhD
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Message

From: Alexander, Paul (HHS/ASPA) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 8/18/2020 8:02:07 PM
To: Lemar, Naweed (OS/ASPA) [redacted]; Caputo, Michael (HHS/ASPA) [redacted]
Subject: RE: Interview request: Hydroxychloroquine fact-check

I struggle with this. Why? Because the evidence on remdesivir is actually similar to HCQ and remdesivir has adverse events. Some anecdotal is suggesting severe ones. The RCT evidence was weak on remdesivir, small sample sizes, questionable methods, the Lancet study said don't touch it, harmful, then NIH reported it did not reduce mortality or adverse events, but there was something (some signal) on time to symptom resolution. That's it. It failed as an ebola virus drug. It was experimental. The evidence on remdesivir is very weak. Similar to HCQ. And yes, CQ was very attractive in 2005 and yes, in vitro but that's decent evidence too...

All these people talking about the science and they have no clue the garbage they are saying on the television and media. With credentials etc. It is so dismaying.

Dr. Fauci was wrong in what he stated below. Evidence can come from nonrandomized studies if they are well conducted. So much so that we will take a well conducted nonrandomized study with large magnitudes of effect and dose response and plausible confounding dealt with, and appropriate statistical adjustment etc. over a poorly conducted RCT...so he is very wrong. He misspoke. He knows it. The HF study on HCQ was a good study in that regard. As far as I know, research is ongoing on HCQ and trials.

This is not a medical or public health issue but now a political issue because the President said good things about it...had he not, this HCQ would be standard of care. I wrote in the past on the shabby methods in the area but as a scientist, clearly said it may work but the science is not yet done to prove it. But I am open to this.

Go ahead with your response and I am not weighing in on the record but the folk at NIH know that remdesivir is shaky and they do not have the conclusive evidence to make that claims on HCQ. But its politics. They all know it and they know the evidence on their study on remdesivir is very questionable.

I wanted to go on record to get it out of my system. I am so upset how much all is done against the administration when lives are at stake and all we are trying to do is help people and save lives.

I will keep quiet in this issue but wanted you Lemar to understand.

Dr. Paul E. Alexander, PhD
Senior Advisor to the Assistant Secretary
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Office of the Assistant Secretary of Public Affairs (ASPA)
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From: Akinso, Woleola (NIH/OD) [E] [redacted]
Sent: Tuesday, August 18, 2020 3:41 PM
To: Lemar, Naweed (OS/ASPA) [redacted]
Cc: OS - Interviews [redacted] Burklow, John (NIH/OD) [E] [redacted] Prince, Scott (NIH/OD) [E] [redacted] OCPLPressTeam [redacted] ODOCPL Interviews (NIH/OD OCPL) [redacted] NIAID COGCORE [redacted] NIAID Media Inquiries [redacted] Deatrick, Elizabeth (NIH/NIAID) [C] [redacted]
Subject: RE: Interview request: Hydroxychloroquine fact-check

ADD:

Reporter: Gustavo Queiroz
Organization: Agência Lupa
Phone #(s): [redacted]
Subject: hydroxychloroquine fact-check
Deadline: 8/19
Spokesperson: Emailed statement attributed to NIAID
Expected place of publication: print, web
Expected date of publication/airing: unknown
Expected prominence: fact check

Key message/talking points: Reporter is fact-checking claims trending in Brazil saying that "an in vitro study published in Virology Journal in 2005 would prove that the medicine chloroquine would be effective against Covid-19. Besides that, the article also says that this journal is the official NIH research journal and, because of that, Mr. Fauci would already know that chloroquine cures coronavirus since 2005." Reporter asks: Can you help us with these demands? Does the Virology Journal, owned by Springer Nature, have any relation with the NIH?

We would send the same response we've provided previously, attributable to NIAID:
"Dr. Fauci has previously stated that there is a lack of good evidence from randomized placebo-controlled trials to indicate that hydroxychloroquine is an effective therapeutic for COVID-19. The 2005 paper you are referring to was a cell-culture experiment with a different virus than SARS-CoV-2, and the study was conducted by CDC investigators. Virology Journal is published by BMC, part of Springer-Nature."

From: Lemar, Naweed (OS/ASPA) [redacted]
Sent: Wednesday, August 5, 2020 3:47 PM
To: Akinso, Woleola (NIH/OD) [E] [redacted]
Cc: HHS/OS Interviews [redacted] Burklow, John (NIH/OD) [E] [redacted] Prince, Scott (NIH/OD) [E] [redacted] OCPLPressTeam [redacted] ODOCPL Interviews (NIH/OD OCPL) [redacted] NIAID COGCORE [redacted] NIAID Media Inquiries [redacted] Deatrick, Elizabeth (NIH/NIAID) [C] [redacted]
Subject: Re: Interview request: Hydroxychloroquine fact-check

Ok

V/R,

Naweed Lemar
U.S. Department of Health & Human Services
Direct: [redacted]
Mobile: [redacted]
Email: [redacted]

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On Aug 5, 2020, at 3:31 PM, Akinso, Woleola (NIH/OD) [E] [redacted] wrote:

Reporter: Esther Chan
Organization: Agence France-Presse (AFP)
Phone #(s): [redacted]
Subject: Hydroxychloroquine fact-check
Deadline: 8/6
Spokesperson: Emailed statement attributed to NIAID
Expected place of publication: print, web
Expected date of publication/airing: unknown
Expected prominence: news story/Fact Check
Key message/talking points: AFP is fact-checking an online claim that Dr. Fauci has known of hydroxychloroquine (HCQ) as a "cure and vaccine" for coronavirus for years: https://www.instagram.com/p/CDYdiRzp3VD/ The claim cited a paper published on the Virology Journal, which was described as "the official publication of Dr. Fauci's National Institute of Health". https://virologyj.biomedcentral.com/articles/10.1186/1743-422X-2-69 . They would like to know the following:

1. What is Dr. Fauci's stance on HCQ and its effect on coronavirus?
2. Is Dr. Fauci associated with said academic paper, any of the authors, or the Virology Journal?
3. Is NIAID/BIH associated with the Virology Journal?

We would like to send back the following response, attributable to NIAID:
"Dr. Fauci has previously stated that there is a lack of good evidence from randomized placebo-controlled trials to indicate that hydroxychloroquine is an effective therapeutic for COVID-19. The 2005 paper you are referring to was a cell-culture experiment with a different virus than SARS-CoV-2, and the study was conducted by CDC investigators. Virology Journal is published by BMC, part of Springer-Nature."

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Message

From: Alexander, Paul (HHS/ASPA) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 8/19/2020 6:35:23 PM
To: Stephen Hahn [redacted] Shah, Anand (FDA/OC) [redacted] Caputo, Michael (HHS/ASPA) [redacted] Wagner, John (FDA/OC) [redacted]
Subject: All existing Convalescent plasma studies (2 reviews, 2 RCTs, 14 non randomized)
Attachments: Convalescent plasma summary table of existing studies as of August 19.doc

Hi Dr. Hahn and Anand, see this table as per our discussion today.

Michael and Wolf, this was the evidence I was referring to, it's the current 18 studies on Convalescent.

I wrote up a summary now quickly and my views...I did a risk of bias...as you see even the 2 RCTs have high risk of bias due to open label, underpower etc.

I share this to help give us cover in our decisions. It to me is well positioned. My view is that CP should be used and is showing to be safe, and an EUA as an example, if one is ever contemplated, is well credible and has merit. NIH has stepped out of their lane based on what I am reading now and I will tell you this, that nonrandomized evidence will shortly be mainstreamed alongside RCT evidence once it is high quality evidence.

Not because it is a RCT means it is optimal. Evidence based medicine is changing and I am part of the GRADE working group writing guidance on this. A well conducted nonrandomzied observational study (ideally prospective) that has large sample size, and has good multivariate adjustments, large magnitude of effect, a dose response relationship, and control for confounding etc. will TRUMP a poorly conducted RCT...pardon the pun.

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Email: [redacted]

From: Paul Elias Alexander [redacted]
Sent: Wednesday, August 19, 2020 2:25 PM
To: Alexander, Paul (HHS/ASPA) [redacted]
Subject:

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Best,

Paul E. Alexander, PhD
Health Research Methodologist
Evidence-Based-Medicine
Department of Health Research
Methods, Evidence and Impact
McMaster University
Assistant Professor
http://hei.mcmaster.ca/
GUIDE Research Methods Group
https://protect2.fireeye.com/url?k=9425937a-c871ba51-9425a245-0cc47a6d17cc-ee8018f6f5f7d76a&u=http://guidecanada.org/

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Dr. Paul Alexander
August 19th 2020

Convalescent Plasma (review of 18 studies; 2 reviews, 2 RCTs, 14 nonrandomized studies):

- At this time, the research on convalescent plasma (CP) is underpinned by largely small-sample size observational studies with small event number, and they are confounded mainly because of the lack of prognostic balance.
- One very large convenience sample (observational design) of 20,000 patients on adverse events adds important information to the possible use of CP in COVID-19 patients. The convenience sample appears to indicate that CP is generally safe and well tolerated in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.
- A Cochrane systematic-review found 20 studies (1 RCT, 3 controlled NRSIs, 16 non-controlled NRSIs) with 5443 participants, of whom 5211 received convalescent plasma. Researchers concluded there is great uncertainty on whether convalescent plasma is beneficial for people admitted to hospital with COVID-19.
- The RCT looked at CP (n=52 patients) vs standard treatment alone (n=51) with a median age of 70 and 58.3% of patients being male. Hypertension, cardiovascular disease, diabetes, kidney disease, and liver disease were the principle types of co-morbidities.
- The trial was stopped early before arriving at its targeting sample size of 200 suggestive that it was underpowered.
- Among those with severe disease, the primary outcome occurred in 91.3% (21/23) of the CP group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; $p = 0.03$); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the CP group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; $p = .83$) (P for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; $p = .30$) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; $p = .12$). CP treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; $p < .001$). Two patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care.
- The RCT was open-label, randomization and concealment appeared reasonably well done. Methodologically an improvement from among the COVID-19 research published to date but not optimal methods wise.
- Larger sample sized RCTs are needed urgently to establish the benefit (or harm) of CP, and whether this treatment option will be stand-alone or work optimally in combination with other therapeutics.
- On balance, the preponderance of nonrandomized studies were small in size and methods not optimal but collectively, suggest that there is benefit and that CP is not harmful. The limited RCT evidence was not optimal methodologically and very small sample size. While evidence accumulates, CP should be used within ethically approved RCTs and off-label, as well as some form of EUA.

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CONVALESCENT PLASMA (CP)

There is insufficient evidence to draw a conclusion on benefits and harms.
The effectiveness is being evaluated in various randomized clinical trials.

OBSERVATIONAL (clinical)

[HYPERLINK "https:/doi.org/10.1001/jama.2020.4783"][25]; case-series; 2020	Convalescent plasma (CP) to all; 5; age range 36-73 years; 60% Note: CP administered to all between 10 and 22 days after admission	1 has hypertension and mitral insufficiency; antivirals (lopinavir/ritonavir; interferon alfa-1b; favipiravir; arbidol; darunavir) and corticosteroid methylprednisolone	Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PAO2/FIO2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Did not apply GRADE
[HYPERLINK "https://doi.org/10.1073/pnas.2004168117"][26]; case-series; 2020	CP to all; 10; median age was 52.5 years (IQR, 45.0–59.5); 60%	Hypertension 30%, cardiovascular and cerebrovascular disease 10%; arbidol, ribavirin, remdesivir, Interferon-α, oseltamivir, peramivir and corticosteroid methylprednisolone	Following transfusion, the level of neutralizing antibody quickly increased to 1:640 in five cases, and maintained at a high level (1:640) in remaining of cases. Researchers reported that the clinical symptoms were substantially improved. They also found an increase in oxyhemoglobin saturation within 3 days. Several parameters tended to improve as compared to pre-transfusion. Improved parameters included "increased lymphocyte counts and decreased C-reactive protein. Radiological examinations showed varying degrees of absorption of lung lesions within 7 days. The viral load was undetectable after transfusion in seven patients who had previous viremia". No severe adverse effects. Note: case-series, nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, not optimally comparative, sub-optimal reporting of methods and outcomes.	High; Did not apply GRADE
[HYPERLINK "https://doi.org/10.1016/j.chest.2020.03.039"][27]; case-series; 2020	CP to all; 4; 31, 55, 69, 73 years old and F, M, M, and pregnant F respectively	None reported; arbidol, lopinavir-ritonavir, ribavirin, interferon alpha inhalation, oseltamivir, albumin, zadaxin and immunoglobulin, antibacterial and antifungal drugs	Researchers reported no serious adverse reactions and all 4 patients recovered from COVID-19. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Did not apply GRADE
[HYPERLINK "https://doi.org/10.1101/2020.04.07.20056440"][29]; case-series; 2020	CP to all three; 3; not reported; not reported	Not reported; not reported	There were 2 patients with negative conversions and 1 failure due to anaphylaxis shock (discontinued); 1st patient treated on 12th day admission, turned severe, 2nd treatment, then significantly improved (nucleic acid test became negative and symptoms improved) and met discharge criteria on 26th day, 2nd patient, treatment on 27th day, the nucleic acid test became negative 4 days later, 3rd patient was a 51-year old pregnant woman who suffered anaphylaxis shock and CP was discontinued).	High; Did not apply GRADE

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			Note: pre-print, small, only 3 patients, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes.	
[HYPERLINK "https://www.sciencedirect.com/science/article/pii/S0924857920301 31X?via%3Dihub"][48]; case-series; 2020	1 patient, 50-year old female	Antiviral therapy plus interferon-α2b, followed by lopinavir and ritonavir and empiric ceftriaxone	IVIG (20g) and thymalfasin were initiated, corticosteroid (intravenous 80 mg methylprednisolone) was also commenced and halved to 40mg two days later, symptoms deteriorated and ceftriaxone was replaced with piperacillin-tazobactam; initiated the administration of three consecutive sessions of PE with 6000ml plasma (frozen plasma served as the sole replacement solution) followed by 20g IVIG from DOI 14 to DOI 17; symptoms were almost all rapidly relieved, with three consecutive sessions of PE treatment; no adverse events or complications were seen during PE treatment; oxygenation index increased with oxygen saturation of 96%; patient was breathing ambient air oxygen and the blood pressure was re-established. Note: small case-series of n=1	High; Did not apply GRADE
[HYPERLINK "https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa228/5826985"][91]; retrospective observational; 2020	CP (n=6) vs no CP (15); 21; CP median 61.5 (31.5-77.8) vs control median 73 (60-79); 76%	Hypertension 19%, diabetes 28.5%, liver disease 9.5%, cardiovascular 4.7%, kidney 4.7%; antiviral treatment 76%, IVIG 90%, glucocorticoid pulse 76%. There was fever 85.7%, cough 90.5%, fatigue 67%, dyspnea 76%, bilateral pneumonia in 95%	There was respiratory failure in 100%, ARDS 85%, septic shock 52%, secondary infection 76%; 5 deaths in treatment (83%) vs 14 (93%) in control group, 100% SARS-CoV-2 clearance in treatment group vs in 4 patients (26.7%) in the control group and there was SARS-CoV-2 clearance before death in 5/5 fatal patients in treatment group vs 3/14 (21%) in control; the 6 treatment patients with respiratory failure received convalescent plasma at a median of 21.5 days after first detection of viral shedding; overall, it appears that CP treatment may halt SARS-CoV-2 shedding but failed in reducing mortality in critically end-stage COVID-19 patients; researchers suggested that treatment should be stated earlier. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, a small number of events, sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]
[HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/?term=Use+of+Convalescent+Plasma+Therapy+in+Two+COVID-19+Patients+with+Acute+Respiratory+Distress+Syndrome+in+Korea."][76]; observational case-series; 2020	CP; 2; ages 67 and 71; 1 males and 1 female	Both critical; a medical history of hypertension, previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): Concomitant therapy: 400 mg of hydroxychloroquine once daily and lopinavir/ritonavir 400 mg/100 mg twice daily, empirical antibiotics, intubation and mechanical ventilator care, IV methylprednisolone (0.5/1 mg/kg/day daily).	Both received lopinavir/ritonavir and hydroxychloroquine but showed persistent fever, rapidly aggravated hypoxemia and progressive bilateral infiltrations in accordance with the criteria of severe ARDS; following CP infusion, the patients showed improved oxygenation and chest X-rays with decreased inflammatory markers and viral loads; researchers reported that when used with systemic corticosteroids, there is the possibility of reducing excessive inflammatory response by corticosteroids as well as promoting the reduction of viral loads by convalescent plasma simultaneously. Note: small case series of 2 patients, not blinded for outcome detectors, not adjusted for confounding.	High; Did not apply GRADE
[HYPERLINK "https://www.medrxiv.org/c	5000[a] patients (of 8,932 enrolled patients with COVID-19) received CP; 5000; median age 62.3 (18.5,	72% respiratory failure, 63% dyspnea, 62% blood oxygen saturation ≤	81% patients had severe or life-threatening COVID-19 and 949 (19%) were judged to have a high risk of progressing to severe or life-threatening COVID-19; prior to COVID-19 convalescent plasma transfusion, a total of 3,316 patients (66%)	High; Did not apply GRADE

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ontent/10.1101/2020.05.12.20099879v1.full.pdf"] [78]; observational (retrospective case-series); 2020	97.8); 63.1% male	93%, 43% had lung infiltrates >50% within 24-28 hours of enrollment, 38% had a respiratory frequency ≥ 30 breaths·minute-1 , 34% had partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, 18% had multiple organ dysfunction or failure, and 15% had septic shock.	were admitted to the ICU; incidence of all serious adverse events (SAEs) in the first four hours after transfusion was <1%, Of the 36 reported SAEs, there were 25 reported incidences of related SAEs, including mortality (n=4), transfusion-associated circulatory overload (TACO; n=7), transfusion-related acute lung injury (TRALI; n=11), and severe allergic transfusion reactions (n=3); 2 (of 36) SAEs were judged as definitely related to the convalescent plasma transfusion by the treating physician. The seven-day mortality rate was 14.9%. Researchers suggested the CP is safe in a hospital setting, to be used in COVID-19 and warrants further study. Note: large case-series, nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, not optimally comparative, sub-optimal reporting of methods and outcomes.	
[HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.05.20.20102236v1"] [88]; prospective case-control; 2020	CP transfused patients; 39; 55 ± 13; 64% males Note 1:4 matching 156; 1:2 matching 74	Asthma 8%, cancer 5%, CKD 3%, COPD 3%, diabetes 21%, obesity 54%; not reported	CP patients were more likely than control patients to remain the same or have improvements in their supplemental oxygen requirements by post-transfusion day 14, with an odds ratio of 0.86 (95% CI: 0.75~0.98; p=0.026). Plasma recipients also demonstrated improved survival, compared to control patients (log-rank test: p=0.032). In covariates-adjusted Cox model, convalescent plasma transfusion improved survival for non-intubated patients (hazard ratio 0.19 (95% CI: 0.05 ~0.72); p=0.015), but not for intubated patients (1.24 (0.33~4.67); p=0.752).	High; Very low certainty[1]
[HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/32473109/"] [93]; observational case-series; 2020	CP in patients with severe and/or life-threatening COVID-19 disease; 25; ages ranged from 19 to 77 years (median 51, interquartile range [IQR] 42.5 to 60); 44% male	40% diabetes, hypertension 32%, CKD 4%, hyperlipidemia 20%; hydroxychloroquine 100%, tocilizumab 56%, corticosteroids 36%, remdesivir 8%	At day 7 post-transfusion with CP, 9 (36%) patients had at least a 1-point improvement in clinical scale, and seven of those were discharged. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged. No adverse events as a result of plasma transfusion were observed. Whole genome sequencing data did not identify a strain genotype-disease severity correlation. The data indicate that administration of convalescent plasma is a safe treatment option for those with severe COVID-19 disease. Note: small case series of 25 patients, not adjusted for confounding.	High; Did not apply GRADE
[HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.05.26.20113373v1.full.pdf"] [95]; one-arm multicenter interventional study; 2020	Hyperimmune plasma (CP); 46; mean age 63 years (SD 12); 61% male	Hypertension 46%, diabetes 17%, cardiovascular disease 14%, COPD 5%, CKD 9%, dyslipidemia 21%; antiviral 42%, antibiotics 84%, HCQ 86%, anticoagulant 98%	Twenty-four patients received one unit of plasma, 21 received two units and one patient received 3 units. Three patients (6.5%) died within 7 days (at 1, 4 and 6 days); two had important comorbidities, such as diabetes, hypertension and cancer, while the third had an extremely low PaO2/FiO2 level of 67 at the time of plasma infusion; among survivors, the severity of the condition at baseline was confirmed by the low oxygen saturation (mean 94%) and PaO2/FiO2 (mean 131); > than 89% of patients showed bilateral multilobe infiltrates at chest radiogram and all laboratory biomarkers were markedly elevated; at 7 days after plasma infusion PaO2/FiO2 increased by 112 units in survivors, the chest radiogram severity decreased in 23% of patients; CRP, Ferritin and LDH all decreased by 60, 36 and 20%, respectively; no or little improvement was present in the three deceased patients; five serious adverse events occurred in 4 patients. Note: nonrandomized, confounded, small case series of 46 patients, not optimally adjusted for confounding.	High; Very low certainty[1]
[HYPERLINK "https://mayoclinicproceedings.org/pb/as	Data from 28,000 patients including the initial 5,000[78] and subsequent 15,000 transfused patients. By June 2, 2020, a total of 20,000	NR clearly; NR clearly	The incidence of all serious adverse events was quite low; including transfusion reactions (n=89, <1%), thromboembolic or thrombotic events (n=87,1%); cardiac events (n=680, ~3%), notably, the vast majority of the thromboembolic or thrombotic events (n=55) and cardiac events (n=562) were	High; Very low certainty[1]

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sets/raw/Health%20Advance/journals/jmcp/jmcp_ft95_6_8.pdf"] [118]; observational convenience sample; 2020	patients had been transfused with COVID-19 convalescent plasma, thus, 7-day mortality data is presented for all 20,000 patients; 20,000; 7.6% 18-39 years, 31.8% 40-59 years, 27.1% 60-69%, 20.6% 70-79, 12.8% 80 and over; 60.8% males		judged to be unrelated to the plasma transfusion per se; the seven-day mortality rate was 8.6% (8.2%, 9.0%), and was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%).	
[HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/32694043/"] [161]; observational; 2020	189 patients, 115 plasma, 74 control; mean age 56; 55.6% male	Hypertension 21.9%, diabetes 22.9%	Comparison of outcomes including all-cause mortality, total hospitalization days and patients' need for intubation between the two patient groups shows that total of 98 (98.2 %) of patients who received convalescent plasma were discharged from hospital which is substantially higher compared to 56 (78.7 %) patients in control group. Length of hospitalization days was significantly lower (9.54 days) in convalescent plasma group compared with that of control group (12.88 days). Only 8 patients (7%) in convalescent plasma group required intubation while that was 20 % in control group. Note: nonrandomized, selection bias is an issue and confounding bias, small sample size and events; control group comprised of mainly milder patients and also co-interventions with antivirals etc.	High; Very low certainty[1]
[HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.08.02.20166710v1.full.pdf"] [166]; observational case series; 2020	16 patients, case-series, all administered CP; age range 30-90; 68.7% males	Hypertension 25%, diabetes 19%, CHD 19%; NR	Among the 16 patients, 10 of them had a consistently positive result of viral NAA test before convalescent plasma transfusion. Eight patients (8/10) became negative from day 2 to day 8 after transfusion. Severe patients showed a shorter time for NAA test turning negative after transfusion (mean rank 2.17 vs 5.90, P = 0.036). Two critically ill patients transfused plasma with lower antibody level remained a positive result of NAA test. CRP level demonstrated a decline 1 day after convalescent plasma treatment, compared with the baseline (P = 0.017). No adverse events were observed during convalescent plasma transfusion. Note: case-series, small sample size, very provocative findings.	High; Very low certainty[1]
RCT (clinical)				
[HYPERLINK "https://jamanetwork.com/journals/jama/article-abstract/2766943?utm_campaign=articlePDF&utm_medium=articlePDF link&utm_source=articlePDF&utm_content=jama.2020.10218"] [97]; RCT; 2020	CP added to standard treatment (n=52) vs standard treatment alone (n=51); 103; median age, 70 years s (IQR, 62-78 years); 58.3% male	Hypertension 54.3%, cardiovascular disease 25%, cerebrovascular 15.5%, diabetes 10.6%, kidney disease 5.8%, liver disease 10.7%	Among those with severe disease, the primary outcome occurred in 91.3% (21/23) of the convalescent plasma group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; *P* = .03); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the CP group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; *P* = .83) (*P* for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; *P* = .30) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; *P* = .12). CP treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; *P* < .001). Two patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care. Researchers concluded that CP did not result in a statistically significant improvement in time to clinical improvement within 28 days, and no improvement in the risk of death. Note: the trial was terminated before it reached its targeted original sample size of 200 patients; only 103 were enrolled (for whom randomization was stratified by disease severity); the	High; Very low certainty[1]

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			study was underpowered and many comparisons between the CP group and the control group were not statistically significant; open-label, randomization and concealment appeared reasonably well done. Methodologically an improvement from among the COVID-19 research published to date.	
[HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1"] [138]; RCT; 2020	CP (ConvP); 85 enrolled when trial halted; median age 63 (IQR 56 – 74) years; 72% male	Diabetes 25.5%, hypertension 31.3%, cardiac 24.4%, pulmonary 33.7%, cancer 9.3%, kidney disease 8.7%; NR	The adjusted OR for overall mortality for patients treated with ConvP was 0.95 (CI 0.20 – 4.67., p=0.95). Of the 45 patients randomized to ConvP 6 (14%) had died while 11 of the 43 (26%) control patients had died. At that time, all 86 patients had been followed for at least 15 days after inclusion, and 75 and 32 for at least 30 and 60 days respectively. The trial was halted prematurely after 86 patients were enrolled. Although symptomatic for only 10 days (IQR 6-15) at the time of inclusion, 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline. A SARS-CoV-2 plaque reduction neutralization test showed neutralizing antibodies in 44 of the 56 (79%) patients tested with median titers comparable to the 115 donors (1:160 vs 1:160, p=0.40). These observations caused concerns about the potential benefit of convalescent plasma in the study population and after discussion with the data safety monitoring board the study was discontinued. No difference in mortality (p=0.95), hospital stay (p=0.68) or day-15 disease severity (p=0.78) was observed between plasma treated patients and patients on standard of care. Note: stopped early and unclear; randomization and concealment, blinding not optimally reported. Small sample size and events.	High; Very low certainty[1]
Systematic review				
[HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/32648959/"] [149]; systematic-review; 2020	20 studies (1 RCT, 3 controlled NRSIs, 16 non-controlled NRSIs) with 5443 participants, of whom 5211 received convalescent plasma, and identified a further 98 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin, of which 50 are randomised; hyperimmune immunoglobulin studies were found.	Not reported clearly; not reported clearly	4 controlled studies (1 RCT (stopped early) with 103 participants, of whom 52 received convalescent plasma; and 3 controlled NRSIs with 236 participants, of whom 55 received convalescent plasma) to assess effectiveness of convalescent plasma. Control groups received standard care at time of treatment without convalescent plasma. *All-cause mortality at hospital discharge (1 controlled NRSI, 21 participants);* very uncertain whether convalescent plasma has any effect on all-cause mortality at hospital discharge (risk ratio (RR) 0.89, 95% confidence interval (CI) 0.61 to 1.31; very low-certainty evidence). *Time to death (1 RCT, 103 participants; 1 controlled NRSI, 195 participants);* very uncertain whether convalescent plasma prolongs time to death (RCT: hazard ratio (HR) 0.74, 95% CI 0.30 to 1.82; controlled NRSI: HR 0.46, 95% CI 0.22 to 0.96; very low-certainty evidence). *Improvement of clinical symptoms, assessed by need for respiratory support (1 RCT, 103 participants; 1 controlled NRSI, 195 participants);* very uncertain whether convalescent plasma has any effect on improvement of clinical symptoms at seven days (RCT: RR 0.98, 95% CI 0.30 to 3.19), 14 days (RCT: RR 1.85, 95% CI 0.91 to 3.77; controlled NRSI: RR 1.08, 95% CI 0.91 to 1.29), and 28 days (RCT: RR 1.20, 95% CI 0.80 to 1.81; very low-certainty evidence). *Quality of life* No studies reported this outcome. Safety of convalescent plasma for people with COVID-19; 1 RCT, 3 controlled NRSIs and 10 non-controlled NRSIs assessing safety of convalescent plasma. Reporting of adverse events and serious adverse events was variable. The controlled studies reported on adverse events and serious adverse events only in participants receiving convalescent	AMSTAR II[7] critical appraisal of the review: high-quality

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			plasma. The duration of follow-up varied. Some, but not all, studies included death as a serious adverse event. *Grade 3 or 4 adverse events (13 studies, 201 participants)* The studies did not report the grade of adverse events. Thirteen studies (201 participants) reported on adverse events of possible grade 3 or 4 severity. The majority of these adverse events were allergic or respiratory events; very uncertain whether or not convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence). *Serious adverse events (14 studies, 5201 participants)* Fourteen studies (5201 participants) reported on serious adverse events. The majority of participants were from one non-controlled NRSI (5000 participants), which reported only on serious adverse events limited to the first four hours after convalescent plasma transfusion. This study included death as a serious adverse event; they reported 15 deaths, four of which they classified as potentially, probably or definitely related to transfusion. Other serious adverse events reported in all studies were predominantly allergic or respiratory in nature, including anaphylaxis, transfusion-associated dyspnoea, and transfusion-related acute lung injury (TRALI); very uncertain whether or not convalescent plasma affects the number of serious adverse events. Researchers concluded there is great uncertainty on whether convalescent plasma is beneficial for people admitted to hospital with COVID-19.	
[HYPERLINK "url:%20https://www.medrxiv.org/content/10.1101/2020.07.29.20162917v1.full.pdf"] [165]; review; 2020	12 studies including three RCTs, five matched control studies, and four case series studies containing 804 COVID-19 patient outcomes; 804; mean or median age of patients enrolled in these studies ranged from 48 to 70 years, with a greater proportion of men than women in most studies (proportion of women: 25% to 56%).	NR; NR	All case series studies demonstrated relatively low mortality rates for COVID-19 patients transfused with convalescent plasma (0% to 13%). Among RCTs, patients transfused with convalescent plasma exhibited a reduced mortality rate (13%) compared to non-transfused COVID-19 patients (26%; OR: 0.46, P = 0.03). Among matched control studies, patients transfused with convalescent plasma exhibited a reduced mortality rate (12%) compared to non-transfused COVID-19 patients (25%; OR: 0.41, P = 0.001). When patient outcomes from controlled studies were aggregated, patients transfused with convalescent plasma exhibited a reduced mortality rate (13%) compared to non-transfused COVID-19 patients (25%; OR: 0.43, P < 0.001). Meta-regression analysis indicated that mean or median cohort age, proportion of cohort receiving mechanical ventilation, and duration of study follow up did not affect the aggregate OR computed for all controlled studies (all coefficients P > 0.22). The fixed effect OR (OR: 0.44, P<0.001)	AMSTAR II [7] critical appraisal of the review: high-quality

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Message

From: Alexander, Paul (HHS/ASPA) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 8/21/2020 4:17:45 PM
To: Wagner, John (FDA/OC) [redacted]; Stephen Hahn [redacted]
Subject: FW: Interview request: Hydroxychloroquine fact-check randomized versus nonrandomized trials

Dr. Paul E. Alexander, PhD
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From: Alexander, Paul (HHS/ASPA) [redacted]
Sent: Friday, August 21, 2020 12:17 PM
To: Routh, Jennifer (NIH/NIAID) [E] [redacted] Folkers, Greg (NIH/NIAID) [E] [redacted]
Cc: Lemar, Naweed (OS/ASPA) [redacted]; Akinso, Woleola (NIH/OD) [E] [redacted]; OS - Interviews [redacted] Burklow, John (NIH/OD) [E] [redacted] Prince, Scott (NIH/OD) [E] [redacted]; OCPLPressTeam [redacted]; ODOCPL Interviews (NIH/OD OCPL) [redacted] NIAID COGCORE [redacted] NIAID Media Inquiries [redacted]; Deatrick, Elizabeth (NIH/NIAID) [C] [redacted]
Subject: RE: Interview request: Hydroxychloroquine fact-check randomized versus nonrandomized trials

Hi, I have been giving this much more thought and decided to give my view on the issue of randomized vs nonrandomized study.

I think over time as I examine the good nonrandomized research, well conducted, strong methods, then I am saying that RCT evidence should not be considered the gold standard. There are instances when nonrandomized evidence must be taken above RCT or to supplement RCT or compliment it. My appreciation of evidence today that comes from nonrandomized research, especially a well conducted large sample size prospective observational study, with a large magnitude of effect, dose response, adequate statistical adjustment of confounders...a well done nonrandomized to me trumps a poorly conducted RCT, with a small sample size, small events, poor randomization, poor allocation concealment, poor blinding, stopping for benefit, data loss etc. So I recalled in this piece the exchange below and the issue of RCT evidence. We are having this debate again over convalescent plasma and I think it is incorrect. Overall, to me, when I look at the 2 small problematic RCTs, the 2 reviews, and the 14 or so nonrandomized studies, I conclude that convalescent plasma is potentially useful now as we await more evidence. I think based on what I am seeing, that it has a role in COVID treatment now.

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Consider this as a philosophical sharing and debate to spurn discussion. All this to say that if the NIH's position is that RCT evidence is your standard, then this must change. I am part of global research groups now writing guidance to argue for a more prominent role for nonrandomized evidence, especially when it is in an emergency and lives are at stake. Once it is good quality nonrandomized evidence, then it should not be sidelined. Once we are showing no significant harms, then we should give weight to nonrandomized evidence.

My opinion. I wanted to share.

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From: Routh, Jennifer (NIH/NIAID) [E] [redacted]
Sent: Wednesday, August 5, 2020 8:00 PM
To: Folkers, Greg (NIH/NIAID) [E] [redacted]
Cc: Alexander, Paul (HHS/ASPA) [redacted]; Lemar, Naweed (OS/ASPA) [redacted] Akinso, Woleola (NIH/OD) [E] [redacted]; OS - Interviews [redacted]; Burklow, John (NIH/OD) [E] [redacted]; Prince, Scott (NIH/OD) [E] [redacted] OCPLPressTeam [redacted] ODOCPL Interviews (NIH/OD OCPL) [redacted] NIAID COGCORE [redacted] NIAID Media Inquiries [redacted]; Deatrick, Elizabeth (NIH/NIAID) [C] [redacted]
Subject: Re: Interview request: Hydroxychloroquine fact-check

Per the earlier OK, we have provided the responses to the reporter.

On Aug 5, 2020, at 7:36 PM, Folkers, Greg (NIH/NIAID) [E] [redacted] wrote:

There are three simple questions from AFP on the table, and three succinct answers.

1. What is Dr. Fauci's stance on HCQ and its effect on coronavirus?
2. Is Dr. Fauci associated with said academic paper, any of the authors, or the Virology Journal?
3. Is NIAID/BIH associated with the Virology Journal?

- Dr. Fauci has previously stated that there is a lack of good evidence from randomized placebo-controlled trials to indicate that hydroxychloroquine is an effective therapeutic for COVID-19.
- The 2005 paper you are referring to was a cell-culture experiment with a different virus than SARS-CoV-2, and the study was conducted by CDC investigators.
- Virology Journal is published by BMC, part of Springer-Nature."

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Can we provide these answers and move on?

Greg
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Message

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Sent: 8/27/2020 4:25:49 PM
To: Hubbard, Madeleine (OS/ASPA) [redacted] Gordon Hensley [redacted] McKeogh, Katherine (OS/ASPA) [redacted] Oakley, Caitlin B. (OS/ASPA) [redacted] Caputo, Michael (HHS/ASPA) [redacted] Murphy, Ryan (OS/ASPA) [redacted]
Subject: Paul's thoughts for testing op-ed DRAFT 1

CDC has updated the guidance on testing for SARS-CoV-2 virus as one tool along with mitigation steps, in stopping the spread. This comes on the heels of a noticeable decline in the number of active cases, hospitalizations, and deaths, and the updated guidance is driven by informed policy making that included testing and was not only because of testing. A compendium of mitigation augmented testing and with these remaining in place as we work to slow the spread, we anticipate that the updated guidance should lead to even fewer cases, hospitalizations, and deaths. Overall, with extensive debate amongst the White House Task Force members, the decision was to update the guidance given the changing data and effectiveness of wearing masks and other mitigation measures. There has also been acute focus on the need to shield the vulnerable as well the ability to shield the vulnerable has increased significantly. We were also driven by the high levels of false negative tests that pervade testing as no testing is perfect (the ideal is a perfect test with no false positives or false negatives). False negatives gives a false sense of security and drives complacency whereby a possibly infected person takes the virus into high-risk settings. We also know that people can become symptomatic well over 14 days post exposure. We also estimated that at least 40% are symptomatic, pre-symptomatic, or mildly symptomatic. Given all we now know, we felt the guidance needed a bit of updated and why we specifically note the need to test asymptomatic persons but not carte blanch, and rather via a rational thought out plan. We thus decided to remove the randomness of testing any and all asymptomatic persons.

An emerging contention surrounds the statement "If you have been in close contact (within 6 feet) of a person with a COVID-19 infection for at least 15 minutes, but do not have symptoms, you do not necessarily need a test". Note that we sought to clarify this in the guidance by stating "*the decision to be tested should be one made in collaboration with public health officials or your health care provider based on individual circumstances and the status of community spread.*" And more importantly, a single negative test does not relieve one of being disciplined about all acts of mitigation, including wearing a mask and protecting the vulnerable".

We seek to add some more clarity here to help explain our thinking in this update. The purpose of diagnostic testing is to protect high risk people. These people we seek to protect are persons who are at higher risk of severe illness or death once infected e.g. the elderly who often have co-morbid underlying medical conditions. So we focus on testing symptomatic persons, persons who are exposed for an extended period and are at risk of spread to high-risk persons, nursing home staff, vulnerable populations and persons (including asymptomatic persons) who have been prioritized (flagged) for testing by their health care practitioner/provider. Thus we would take the situation of the asymptomatic person into account, the prevalence of pathogen in the setting e.g. is it less than 1% positivity? And the prevailing epidemiology/spread in the setting. Testing is not to find asymptomatic infections in low risk people. It is highly reasonable that in high risk settings such as nursing homes and long term care facilities, more stringent and frequent testing of all who enter is in order - asymptomatic – and is part of the CDC guideline. Testing asymptomatic people to seek asymptomatic cases is not the point of testing, for in the end, all this accomplishes is we end up quarantining asymptomatic, low risk people and preventing the workforce from working. In this light, it would be unreasonable based on the prevailing data to have widespread testing of schools and colleges/universities. This will not allow them to optimally re-open. These are very low risk environments, and as such very low risk students. Moreover, we have data to show the risk of children spreading pathogen is very low if at all, as well as going onto to severe illness or death if indeed infected. Older students who can be classed as young adults and are in university, if you widespread tested them and repeatedly, you will force the college to close and inadvertently, be sending low risk carriers into high risk communities and high risk homes – their homes and nursing homes when they visit or their parents visit. This lacks common sense.

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To close, the purpose of testing is NOT to detect low risk and asymptomatic people. We have to use the CDC guidance on the mitigation for high risk teachers and students and importantly, sick kids need to stay home and consult with their doctors.

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Message

From: Alexander, Paul (HHS/ASPA) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 8/30/2020 6:47:01 PM
To: Caputo, Michael (HHS/ASPA) [redacted]; Pratt, Michael (OS/ASPA) [redacted]; Traverse, Brad (HHS/ASPA) [redacted]; Hubbard, Madeleine (OS/ASPA) [redacted]; McKeogh, Katherine (OS/ASPA) [redacted]; Oakley, Caitlin B. (OS/ASPA) [redacted]; gordon hensley [redacted] Wagner, John (FDA/OC) [redacted] Witkofsky, Nina (CDC/OD/OCS) [redacted] Baldassarre, Natalie (OS/ASPA) [redacted] Murphy, Ryan (OS/ASPA) [redacted]
Subject: Atlas says the medical studies are 'garbage'; I have been saying this 6 months now, as to COVID, pure garbage research

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What a refreshing article. I am a scientist and I can second what Atlas states here, that the research community, and ONLY to hurt the administration, has been and is producing garbage research and their conclusions and statements are pure politics and not the truth. I also believe strongly that the administration is not pushing snake oil, the administration has been doing all it could to save lives. As Atlas states, the system has 'gone mad'…Not only as it relates to HCQ which really cannot anymore be looked at unbiasedly, but generally all COVID research and I know the research in depth, across all drugs. I can state here that every study to date since February on COVID, I have read and studied. No data or evidence, the talking head researchers and doctors and the like just rattle off their political opinion. Their own political agenda is driving their thinking and statements. But they are hurting the nation and it is distressing and disturbing. I am glad Atlas stated it for it is so, pure garbage medical studies with extremely deficient methodologies that should not even be published. He is maybe one of the most unbiased critical thinkers I know. And the loser is the American people and parents who simply want the truth for their informed decision making. COVID has revealed the tragedy with the medical and research community today which seems to be guided principally by politics…I thought it was 'Primum non nocere", first, do no harm. We do not know what to believe anymore and to me, as I have seen, this administration seeks to help save lives and try everything that may hold benefit. For example, the 'Right to Try' that the administration has championed in COVID is so exceptional for it has translated into saving lives. I am very proud of the robust sustained response by this administration in dealing with this difficult disease situation. Especially ASPA.

Hydroxychloroquine 'Very Safe,' Says Dr. Scott Atlas; Blasts 'Garbage' Medical Studies

Washington Times (8/29, Valerie Richardson)

The Washington Times reports "hydroxychloroquine has gotten a bad rap thanks to a politics, media hype, and some 'garbage' medical research, according to Dr. Scott Atlas, a member of the White House coronavirus task force." While at the Steamboat Institute Freedom Conference, Atlas on Friday said, "What's happened with hydroxychloroquine is that the system has gone mad," adding, "I sort of make the analogy that we all know objective journalism is basically dead in this country, I'm very cynical about that, and now what we're seeing is that objective science is nearly dead." Atlas "emphasized that the drug has not been proven as a treatment for the novel coronavirus – 'I'm not going to say it's proven to work because it's not' – but challenged those who have accused President Trump of pushing snake oil." He added that the drug "is super safe."

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Message

From: Alexander, Paul (HHS/ASPA) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 9/2/2020 1:16:18 AM
To: Stephen Hahn [redacted] Shah, Anand (FDA/OC) [redacted]
Subject: FW: [EXTERNAL] NIH panel contradicts plasma claims in new recommendations

fyi as to my defense of the FDA...I could go deep into methods but my boss would slap me for writing too much...;-)

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Email: [redacted]

From: Alexander, Paul (HHS/ASPA)
Sent: Tuesday, September 1, 2020 9:12 PM
To: Brennan, Patrick (OS/ASPA) [redacted] Oakley, Caitlin B. (OS/ASPA) [redacted] ASPA-Deputies [redacted]
Subject: RE: [EXTERNAL] NIH panel contradicts plasma claims in new recommendations

These NIH researchers are very wrong and clearly not updated on the current shift in research methods thinking (guidance is coming) whereby non-randomized evidence can trump randomized evidence. Completely if there are large magnitudes of effect, a dose response relationship, and plausible residual confounding adjusted for. RCT evidence is not the gold standard as proclaimed especially if there are serious limitations in those randomized studies, as we often see in COVID-19 research. A well conducted nonrandomized study is a gold standard relative to a poorly conducted RCT. Period.

Moreover, I am puzzled why this would be put out when NIAID decided to stop its trial on remdesivir early for benefit and give remdesivir to patients in the placebo, preventing researchers from collecting additional data on if the drug does save lives. It suggests this, but does not prove this (8% getting remdesiver died, and 11.6% in the placebo died, and not statistically significant). We have closed and shut down the society and the reason for the research was to see if the drug saves lives, not if its prevents patients from spending a few more days in hospital. Having it now as SoC prevents any further research on this drug as to if it saves lives and so the opportunity is gone. Stopping the trial early for benefit flags it also as a high risk of bias study as it did not run to its sample size.

I would caution NIH in making this assertion on CP because FDA issued a EUA contingent on more accumulating evidence. FDA did not carte blanche recommend using it, and FDA suggested potential benefits and will continue looking at the accumulating evidence. FDA also did not report that the CP evidence they used came from RCTs. I have seen all the nonrandomized observational evidence in CP and it is reasonable and solid and yes, the ideal is randomized findings

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from large sample sized studies. We await. Like how we await the accumulating remdesivir evidence and the EUA may well be reversed for remdesivir. We do not know. This is how an EUA works or am I missing something? Read attached to understand how the NIH remdesivir study has its own methods implications.

https://www.statnews.com/2020/05/11/inside-the-nihs-controversial-decision-to-stop-its-big-remdesivir-study/

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From: Brennan, Patrick (OS/ASPA) [redacted]
Sent: Tuesday, September 1, 2020 4:46 PM
To: Oakley, Caitlin B. (OS/ASPA) [redacted]; ASPA-Deputies [redacted]
Subject: RE: [EXTERNAL] NIH panel contradicts plasma claims in new recommendations

Neither Hahn nor the Secretary ever said there was data from "well-controlled, adequately powered randomized clinical trials that demonstrate the efficacy and safety of convalescent plasma."

From: Oakley, Caitlin B. (OS/ASPA) [redacted]
Sent: Tuesday, September 1, 2020 4:44 PM
To: ASPA-Deputies [redacted]
Subject: FW: [EXTERNAL] NIH panel contradicts plasma claims in new recommendations

From: POLITICO Pro Health Care <politicoemail@politicopro.com>
Sent: Tuesday, September 1, 2020 4:43 PM
To: Oakley, Caitlin B. (OS/ASPA) [redacted]
Subject: [EXTERNAL] NIH panel contradicts plasma claims in new recommendations

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NIH panel contradicts plasma claims in new recommendations

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By Sarah Owermohle

09/01/2020 04:41 PM EDT

There are not enough data yet to recommend using convalescent plasma as a coronavirus treatment, an expert panel convened by the National Institutes of Health wrote in an update published to the agency's treatment advisory page Tuesday.

"There are currently no data from well-controlled, adequately powered randomized clinical trials that demonstrate the efficacy and safety of convalescent plasma for the treatment of COVID-19," read an update posted to the Covid-19 Treatment Guidelines page. The website shares regular recommendations from a panel of physicians, statisticians and other experts both in and outside of government agencies as Covid-19 research evolves.

Background: FDA authorized convalescent plasma for emergency use a little over a week ago amid reports that top NIH officials Francis Collins and Anthony Fauci voiced concerns that there is not enough data to show plasma's benefit against the virus.

FDA did not recommend plasma as a new standard of care — as it did when it authorized Gilead's experimental infusion, remdesivir — but pointed to potential benefits in a 70,000-person expanded access program run by Mayo Clinic.

FDA Commissioner Stephen Hahn overstated plasma therapy's benefits during a press briefing with President Donald Trump and later apologized for mischaracterizing the available research.

"I have been criticized for remarks I made Sunday night about the benefits of convalescent plasma. The criticism is entirely justified," Hahn wrote on Twitter. "What I should have said better is that the data show a relative risk reduction not an absolute risk reduction."

While plasma is considered safe, it is still unclear whether it can effectively fight a Covid-19 infection.

What's next: Scientists at both agencies still await results from randomized controlled clinical trials for plasma, which could take months. The panel encouraged more clinical trial participation.

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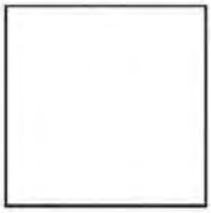

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Message

From: Alexander, Paul (HHS/ASPA) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 9/11/2020 6:04:48 PM
To: Atlas, Scott W. EOP/WHO [redacted]
Subject: FW: (CUI/SBU) One MMWR COVID-19 Response Early Release Scheduled for Tuesday, September 15

Heads up, CDC is asking clearance of this and as usual, sent only a few lines and not the full report. Then they send the full report and give us (me) 2 hours or so to respond with edits, with 5 other reports accompanying. I don't understand the 121 descendants number. It is ludicrous to lump 10-20 as a child. Note they did not indicate that the deaths were mostly in 18 and above. Note they did not talk about the 21 year olds.

Know this is coming out in the next couple days if not this weekend and CNN and Fox will be running the CDC indicated caption of "deaths in children elevated due to COVID" etc. This is very duplicitous to damage the administration. Can you help me craft an op-ed and I will ask to put out disputing the reporting for on face value, it is meant to mislead. E.g. I have a real problem with the lumping of 0-21 years as pediatric deaths. Its misleading, when I hear 'children' I think of 2, 4, 7, 9 , 10 maybe 12 years old, even 13. A 20 year old is an adult, albeit young. Age bands should be <1, 1-5, 6-10, 11-15, and 16 to 20, and 21>. Its very misleading and I will guarantee you all the deaths (most) will clump near 20. By saying the pediatric population makes up 26% of the US population is very misleading as children as we know it do not make up 26%. That is comprised of adolescents and young adults. This is timed for the election and the push to re-open schools safely and rationally and with needed mitigations using CDC sensible guidance. The timing of this is meant to interfere with school re-opening and we need to get something out fast to pre-empt this in the next day or so and I can work with you on it. Please advise.

This is your heads up as sent to me internally. Let us advise the President and get permission to pre-empt this please for it will run for the weekend so we need to blunt the edge as it is misleading. I seek for this administration, any administration, that simply we follow the data and not mislead so that the public is well informed for their decisions. The nation just wants the truth, that's all, not spin or deceit.

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From: Kent, Charlotte (CDC/DDPHSS/CSELS/OD) [redacted]
Sent: Friday, September 11, 2020 1:34 PM
To: Redfield, Robert R. (CDC/OD) [redacted]; Schuchat, Anne MD (CDC/OD) [redacted]; Galatas, Kate (CDC/OD/OADC) [redacted]; Bunnell, Rebecca (CDC/DDPHSS/OS/OD) [redacted]; Richards, Chesley MD (CDC/DDPHSS/OD) [redacted]; Iademarco, Michael (CDC/DDPHSS/CSELS/OD) [redacted]

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Subject: (CUI/SBU) One MMWR COVID-19 Response Early Release Scheduled for Tuesday, September 15

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Produced pursuant to House Oversight Committee Document Request, Do Not Sell or Distribute Without Permission of the Office of Congressman James Comer, Ranking Member, Committee on Oversight and Human Resources

One *MMWR* Early Release related to the COVID-19 Response is scheduled for Tuesday, September 15, with the planned embargo lifting at 1 pm. Please note that the title, content, and timing might change.

SARS-CoV-2–Associated Deaths Among Children, Adolescents, and Young Adults Aged <21 Years — United States, February 12–July 31, 2020

Since February 12, 2020, approximately 6 million cases of SARS-CoV-2 infection, the cause of coronavirus disease 2019 (COVID-19), and 189,000 SARS-CoV-2–associated deaths have been reported in the United States. SARS-CoV-2–associated illness in the pediatric population (persons aged <21 years) is usually mild. The pediatric population constitutes 26% of the U.S. population, and this report describes characteristics of U.S. persons in that population who died in association with SARS-CoV-2 infection. Among approximately 120 SARS-CoV-2–associated deaths reported to CDC among persons aged <21 years in the United States during February 12–July 31, 2020, 6 in 10 occurred in males, 1 in 10 of decedents were aged <1 year, 2 in 10 were aged 1–9 years, 7 in 10 were aged 10–20 years, 1 in 9 were Hispanic/Latinx (Hispanic) persons, 1 in 3 were non-Hispanic Black (Black) persons, and 1 in 20 were non-Hispanic American Indian or Alaska Native (AI/AN) persons. Among these 121 decedents, 3 in 4 had an underlying medical condition. These data show that nearly three quarters of pediatric SARS-CoV-2–associated deaths have occurred in persons aged 10 – 20 years, with a disproportionate percentage among among Hispanics, Blacks, AI/ANs, and children with underlying medical conditions. Careful monitoring of deaths and other severe outcomes associated with SARS-CoV-2 infection among children, adolescents, and young adults remains particularly important as schools reopen in the United States.

Charlotte Kent, PhD, MPH
Editor-in-Chief, *Morbidity and Mortality Weekly Report* (*MMWR*) Series
Center for Surveillance, Epidemiology, and Laboratory Services
Centers for Disease Control and Prevention

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