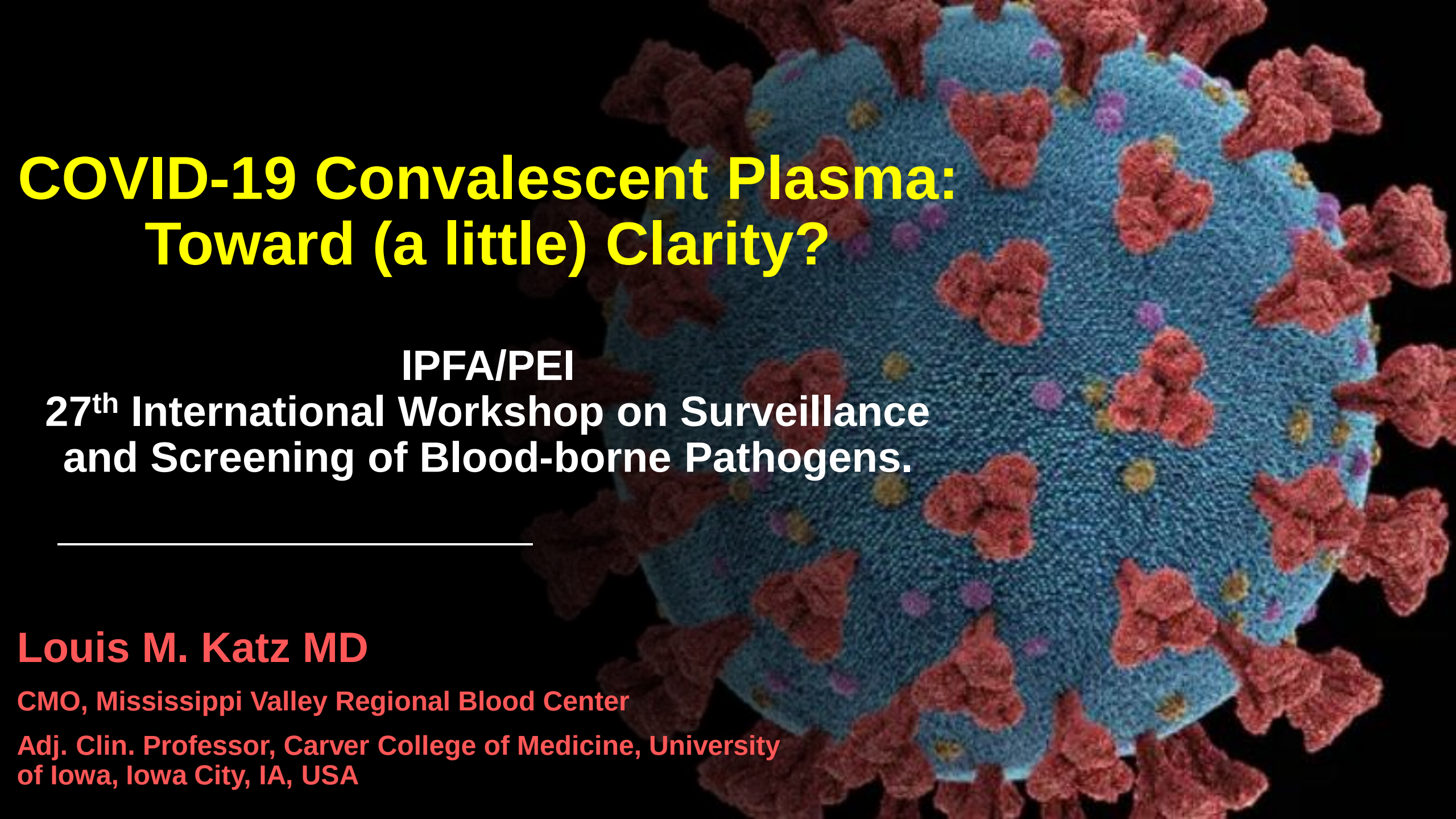

COVID-19 Convalescent Plasma: Toward (a little) Clarity?

IPFA/PEI
27th International Workshop on Surveillance and Screening of Blood-borne Pathogens.

Louis M. Katz MD

CMO, Mississippi Valley Regional Blood Center

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Disclosures

- No relevant conflicts of interest
- Paid consultant (past 12 months)
  - TerumoBCT (Mirasol)
  - Cellphire (Thrombosomes)
  - Ortho Clinical Diagnostics (COVID)
  - Roche Molecular Systems (MPX)

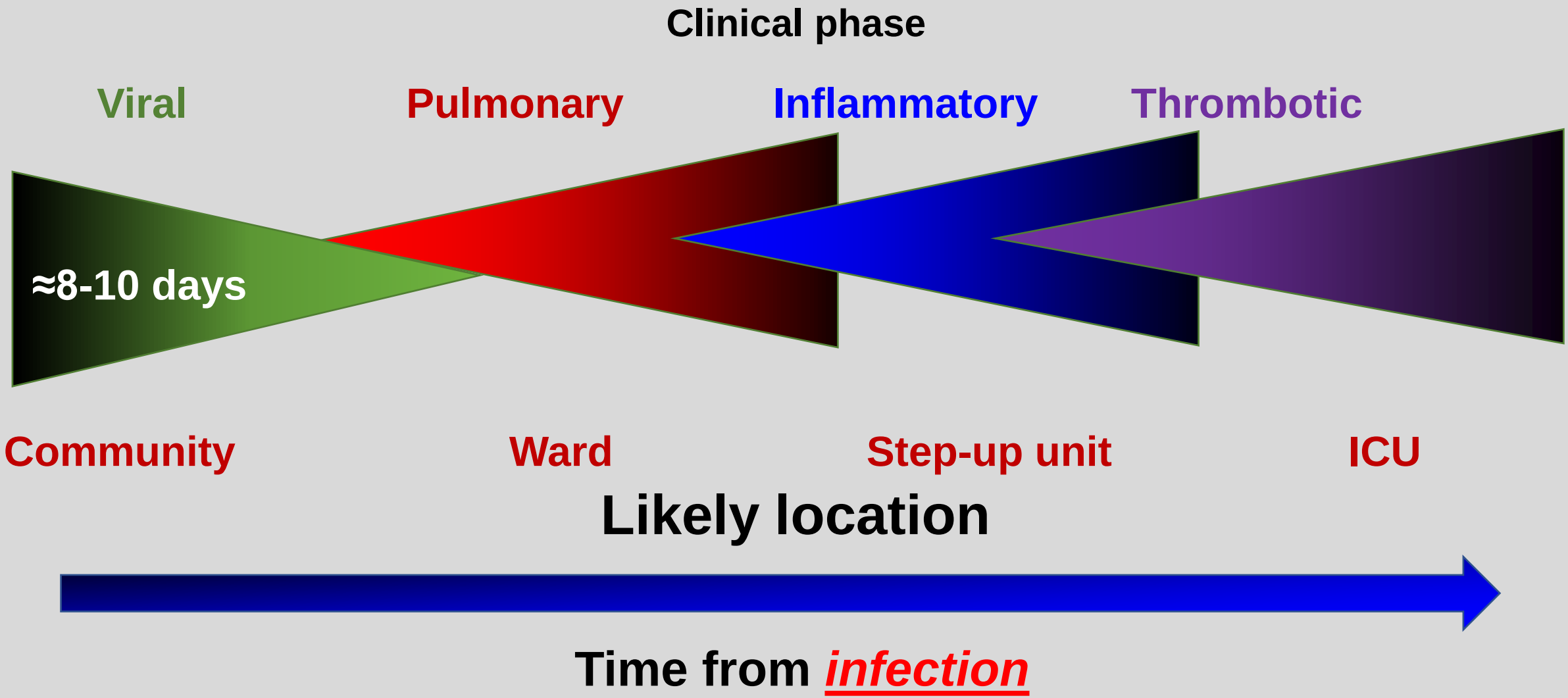
Objectives:

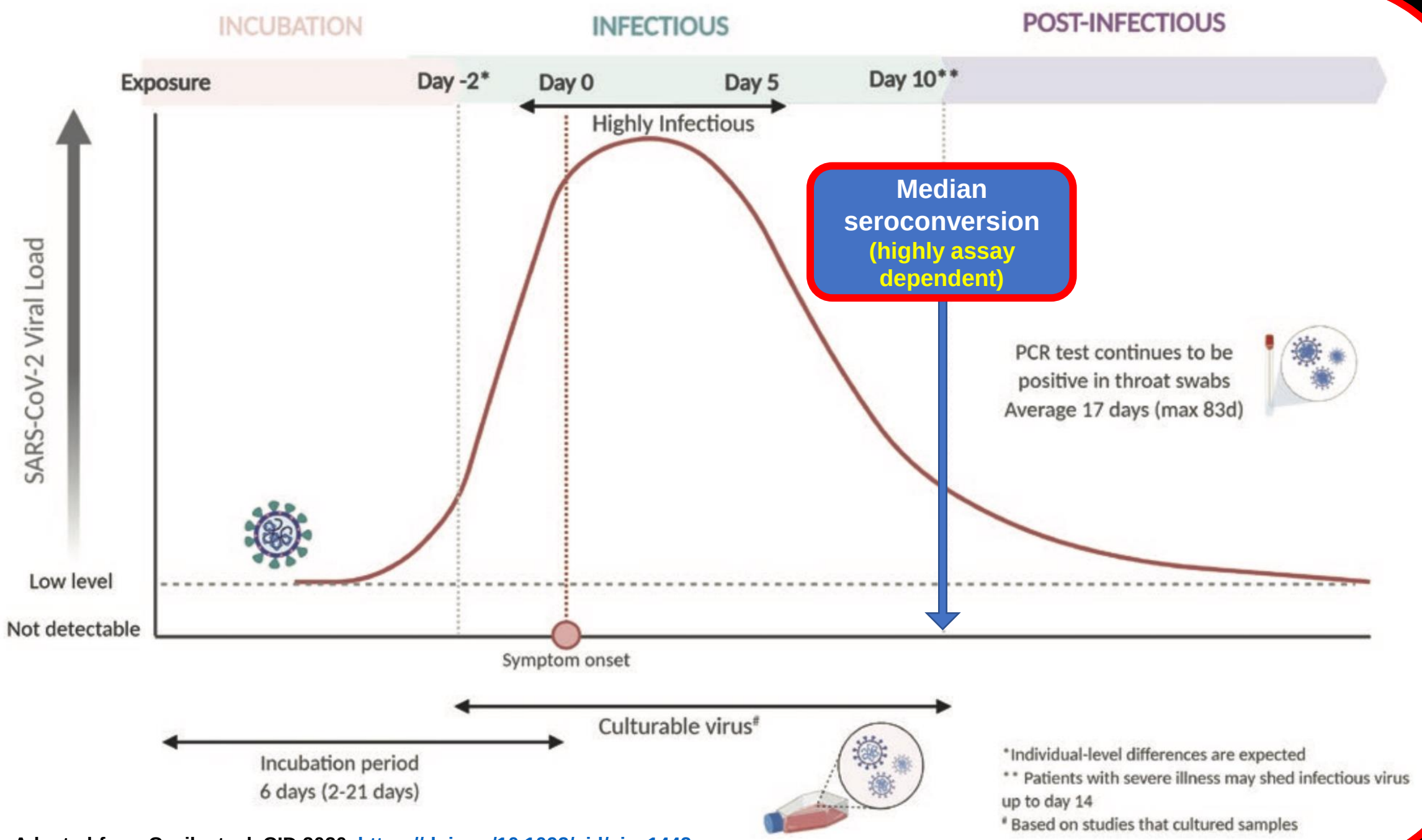
COVID-19 Convalescent Plasma (CCP)

1. Who
2. What
3. Where
4. Whither CCP?

CCP is an ***antiviral*** preparation

It is likely to work best if there is virus around!!





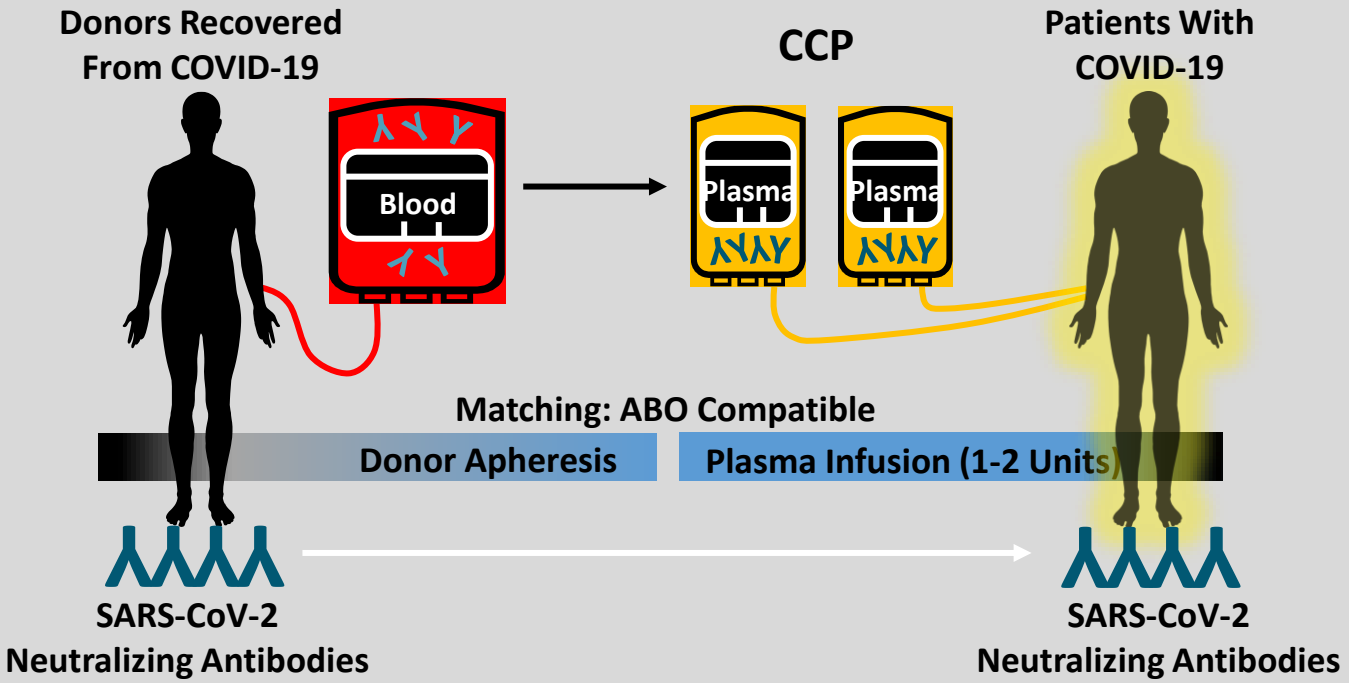
Adapted from Cevik et. al. CID 2020. https://doi.org/10.1093/cid/ciaa1442

Passive Immunotherapy

Administration of immune plasma, immunoglobulins (IM/SC/IV) from pooled plasma, or MoAbs to prevent/treat infections

- **Specific**
- **Early**
- **Enough**

- **Passive PEP works for multiple pathogens**
  - **HBIG**
  - **VZIG**
  - **ISG or IgIV for HAV**
  - **TIG**
  - **RIG**
  - **ISG for measles, rubella, mumps….**
- **Successful for Argentine Hemorrhagic Fever in RCT Every pandemic in 20th century, pneumococcal disease**
- **In use &/or tried for RSV, Ebola, SARS, MERS, flu A, CMV, botulism, anthrax, vaccinia, varicella….**



“Convalescent plasma strikes out as COVID-19 treatment”

Richard Harris

10 March 2021, Morning Edition

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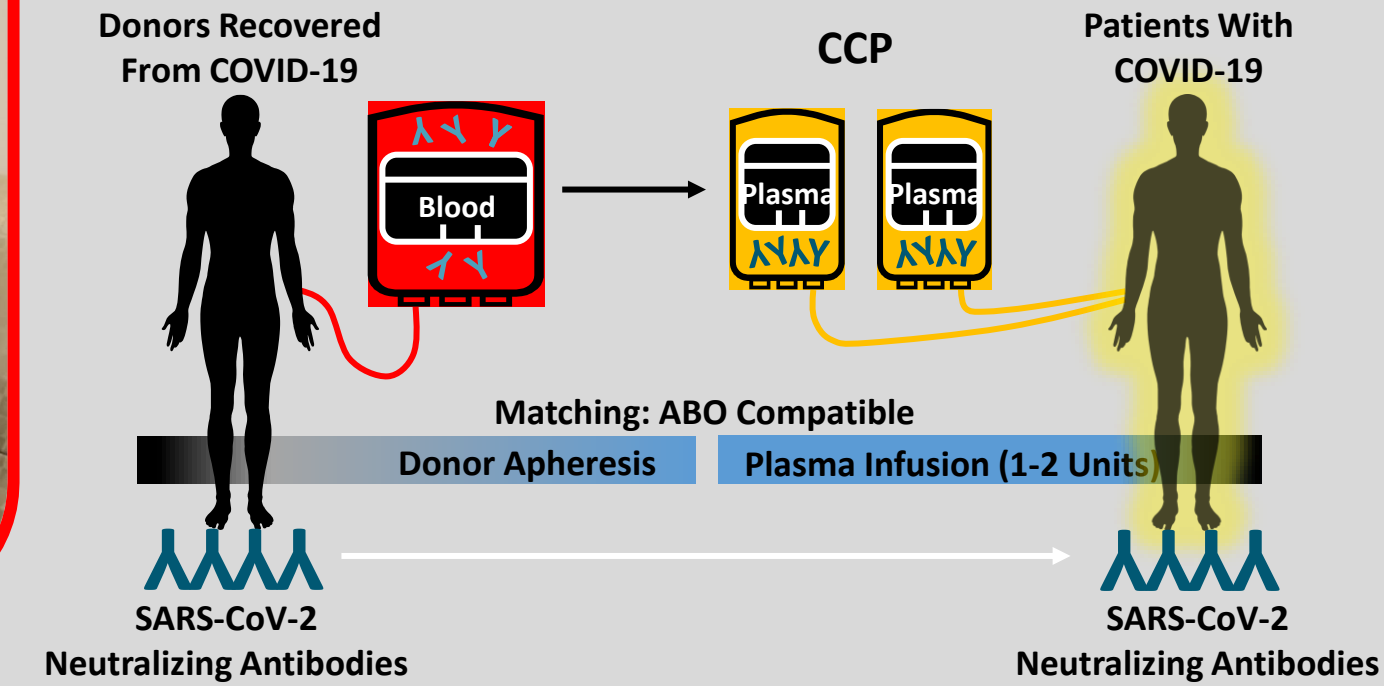

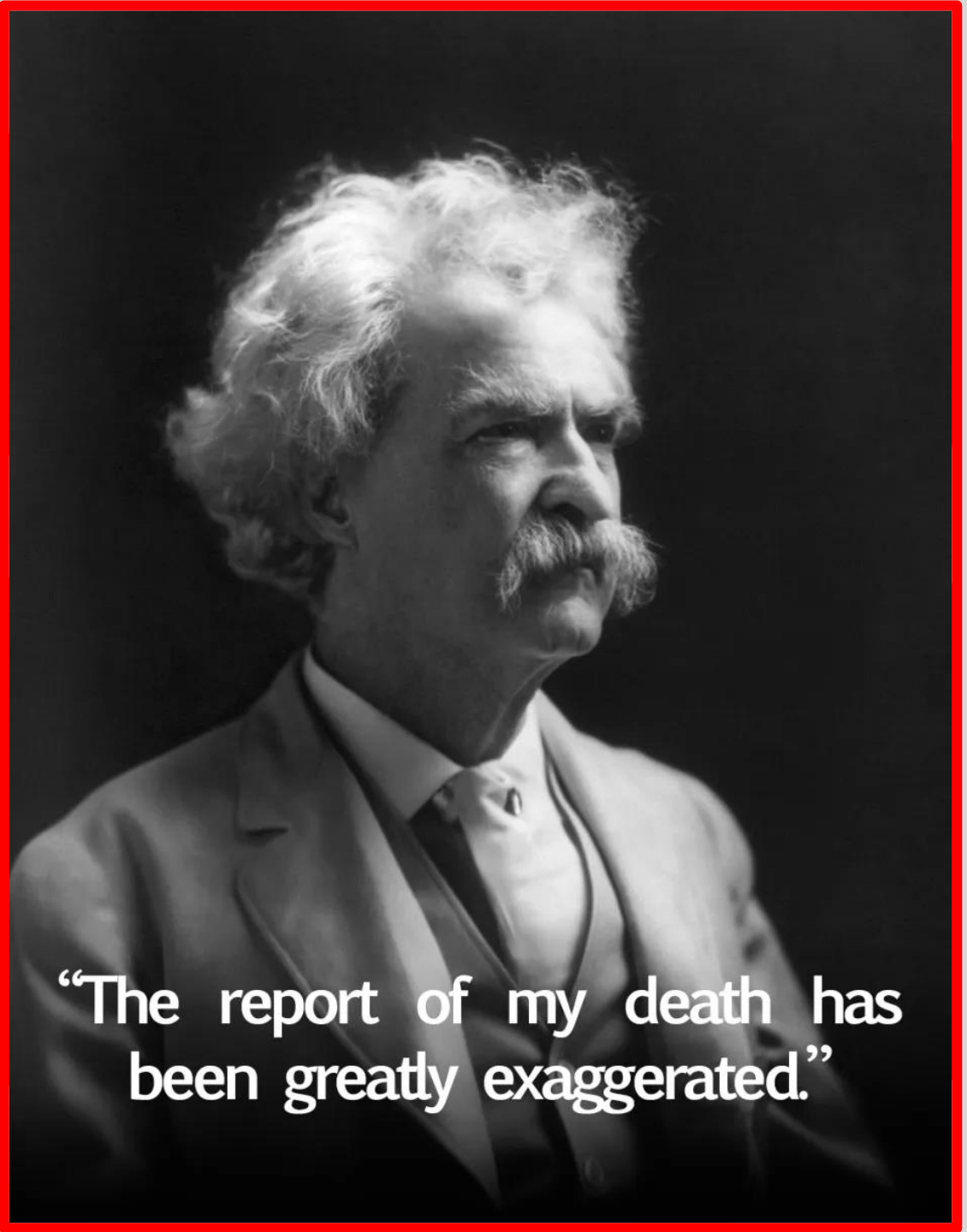

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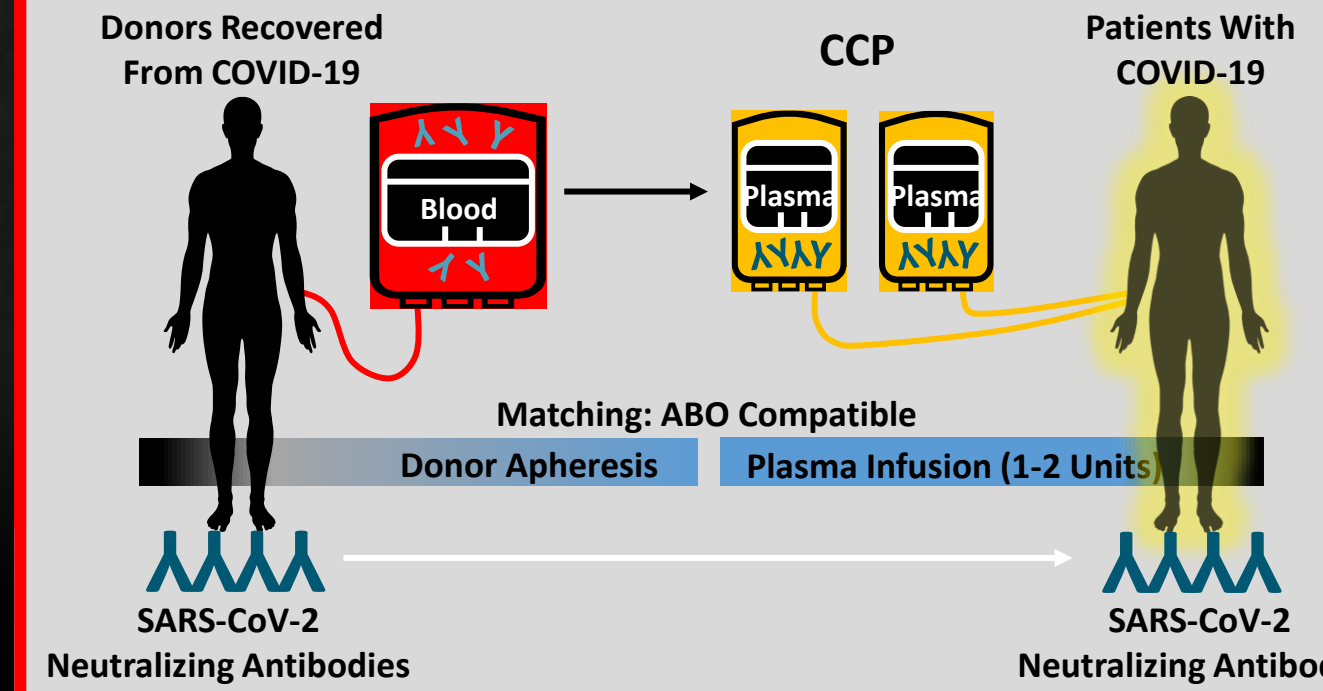


So, what's happened?


The Washington Post
Democracy Dies in Darkness

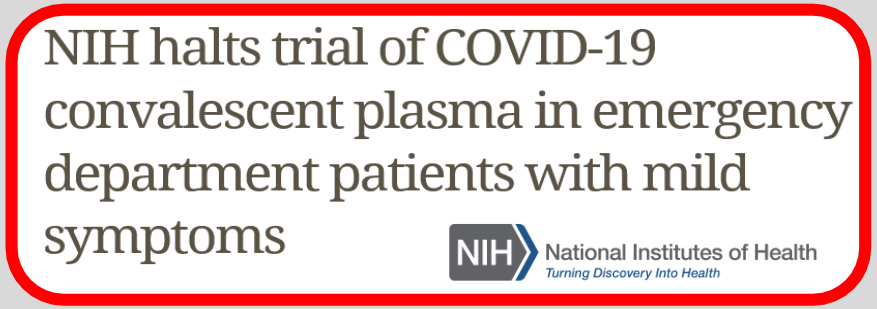
Coronavirus U.S. map World map Vaccine tracker Vaccine FAQ Variants FAQ A pandemi

The Fix • Analysis

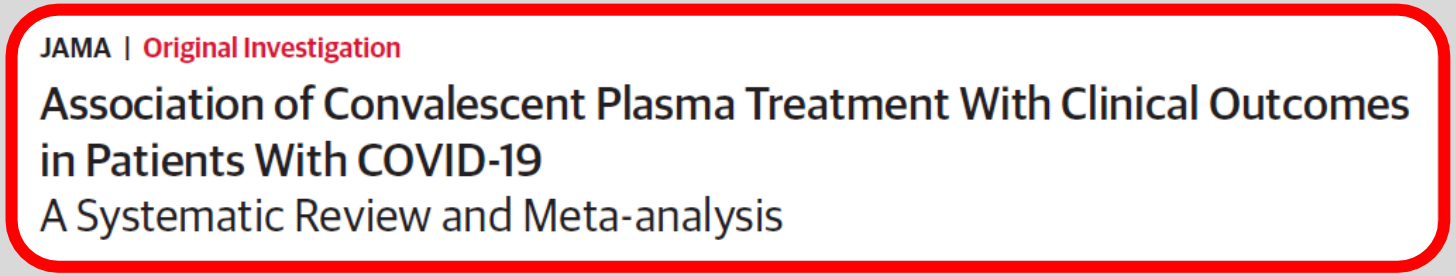
The FDA offers a big correction after helping hype Trump's coronavirus announcement


Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES


NIH halts trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms

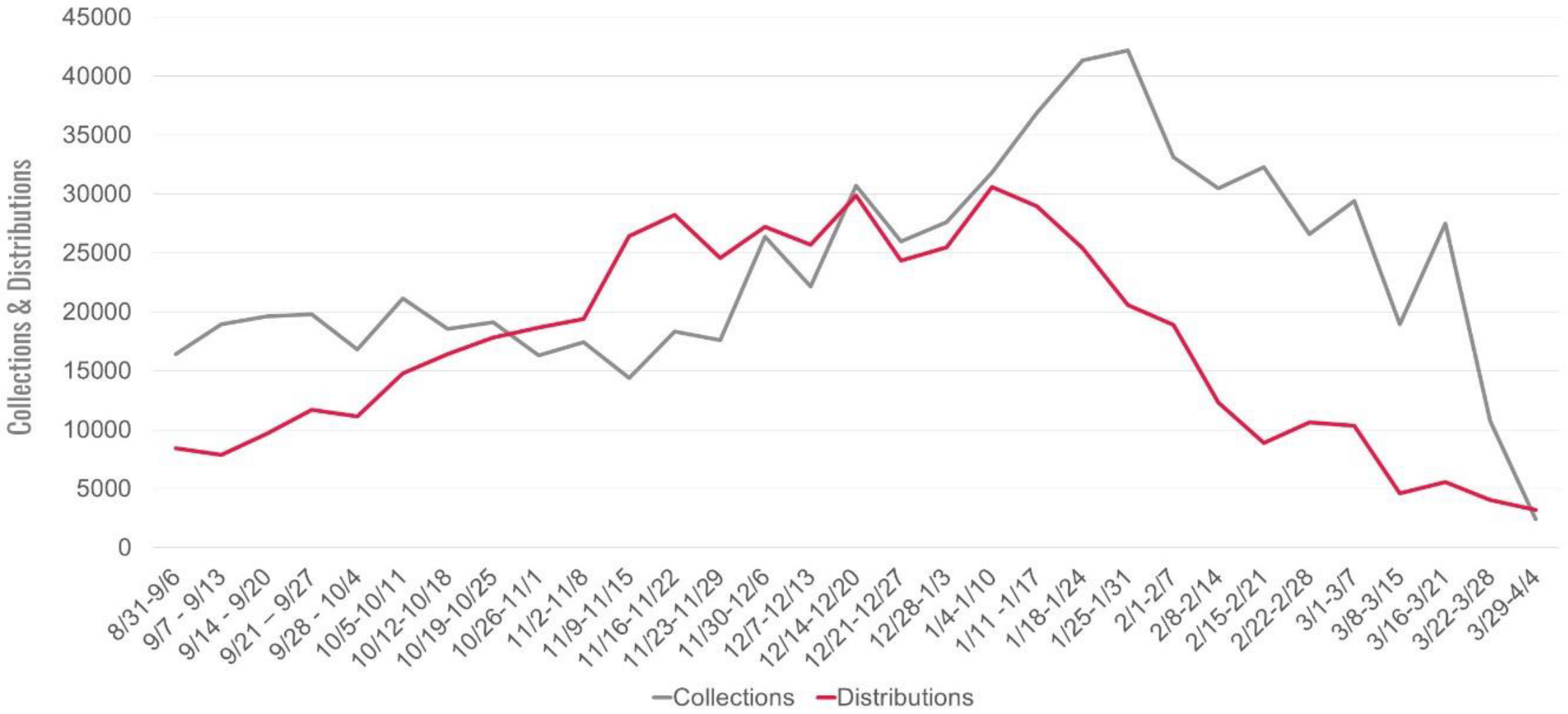
NIH National Institutes of Health
Turning Discovery Into Health


JAMA | Original Investigation

Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19
A Systematic Review and Meta-analysis

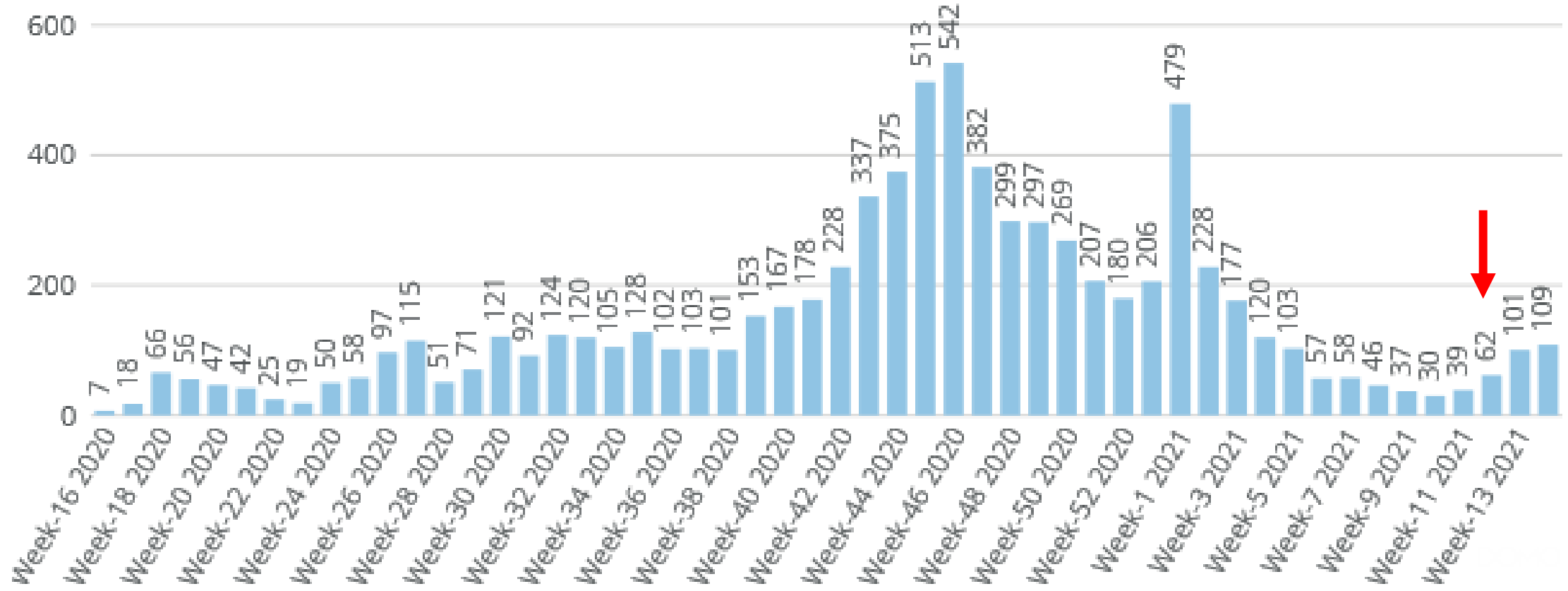
- 08/20: **EAP CCP data "misrepresented" by White House/FDA**
- 01/21: **RECOVERY RCT suspended for futility**
- 03/21: **C3PO RCT suspended for futility**
- 03/21: **Meta-analysis of "good studies"**

Convalescent Plasma: Industry Collections and Distributions



Convalescent Plasma- Distribution Totals

MVRBC suspends CCP collections epi-week 12, and mothballs SOPs



CCP: systematic review & meta-analysis

	All cause mortality		Length of stay		Mechanical ventilation	
	Risk ratio	95% CI	Risk ratio	95% CI	Risk ratio	95% CI
Peer reviewed (n=4)	0.93	0.63-1.38	1.17	0.07-20.34	0.76	0.2-2.87
All (n=10)	1.02	0.92-1.12	1.07	0.79-1.45	0.81	0.42-1.58

CONCLUSIONS AND RELEVANCE Treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes. The certainty of the evidence was low to moderate for all-cause mortality and low for other outcomes.

Janiaud *et al*. *JAMA*. 2021

CCP: Systematic review & meta-analysis

ble 1. Characteristics of the 10 Trials

	Trial registration No. (study acronym)[a]									
	ChiCTR 2000029757[19]	NCT 04479163[16]	NCT 04383535 (PlasmAr)[18]	CTRI /2020/04/ 024775 (PLACID)[17]	NCT 04345523 (ConPlas-19)[23]	NCT 04346446 (ILBS-COVID-02)[21]	NCT 04356534[20]	NCT 04342182 (ConCOVID)[22]	CTRI /2020/05/ 025209 (PICP19)[24]	NCT 04381936 (RECOVERY)[8]
Publication format	Journal	Journal	Journal	Journal	Preprint	Preprint	Preprint	Preprint	Preprint	Press release
Peer-reviewed	Yes	Yes	Yes	Yes	No	No	No	No	No	No
No. included	103	160	333	464	81	29	40	86	80	10 406
No. planned for inclusion	200	210	333	452	278	40	40	426	80	20 000
Setting	Hospitalized	Outpatient	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized
Oxygen supplementation	All patients	[illegible]	Some patients	All patients	Some patients	All patients	All patients	Some patients	All patients	Some patients
Plasma titer[b]	High	High: >1:1000	High: ≥1:800 (RBD)	No minimum	High: ≥1:80 neutralizing	No minimum	No minimum	Low: ≥1:400 RBD	Unclear	Unclear
Dose description	Single transfusion of 4-13 mL/kg	Single transfusion of 250 mL	Single transfusion of 5-10 mL/kg (minimum, 400 mL; maximum, 700 mL)	Two transfusions of 200 mL administered 24 h apart	Single transfusion of 250-300 mL	Two transfusions of 500 mL administered 24 h apart	Two transfusions of 200 mL administered 24 h apart	Single transfusion of 300 mL[c]	Two transfusions of 200 mL administered 24 h apart	Two transfusions of 275 mL (±75 mL) administered 24 h apart
Treatment since symptom onset	Any time	≤72 h	Any time	Any time	≤12 d	≤3 d	≤14 d	Any time	≤14 d	Any time
Type of control	Standard of care	Placebo and standard of care	Placebo and standard of care	Standard of care	Standard of care	Placebo and standard of care	Standard of care	Standard of care	Standard of care	Standard of care

Abbreviations: ConCOVID, Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease; ConPlas-19, Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients; PICP19, Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease; PlasmAr, Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia; RBD, receptor-binding domain; RECOVERY, Randomized Evaluation of COVID-19 Therapy.

[a] Three of the trials did not have study acronyms (only trial registration numbers) and ILBS-COVID-02 and PLACID did not have expansions in the original publications.

[b] High was defined in this meta-analysis as S-protein RBD–specific IgG antibody titer of 1:640 or higher or serum neutralization titer of 1:40 or higher.

[c] The COVIDAR IgG test was used to determine the dose.

Janiaud *et al*. *JAMA*. 2021

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

- 160 patient RCT with masked saline placebo infusion, June-October 2020
- ≥75 years or 65-74 & ≥1 comorbidity
- Symptomatic & positive PCR from in-home screening
- ***≤72 hours of symptoms at infusion***
- 250 mL high titer CCP outpatient
- No other experimental therapy
- 1º endpoint, progression to defined severe disease within 15 d. of CCP

Intention-to-treat population outcomes

	No./total no. (%)		
	CCP (n-80)	Placebo (n=80)	RR (95% CI)
1º endpoint	13/80 (16)	25/80 (31)	0.52 (0.29-0.94)
2º endpoints			
Life threatening	4/80 (5)	10/80 (12)	0.40 (0.13-1.22)
Ventilator	2/80 (2)	4/80 (5)	0.50 (0.09-2.65)
Critical illness	5/80 (6)	6/80 (8)	0.83 (0.27-2.62)
COVID death	2/80 (2)	4/80 (5)	0.50 (0.09-2.69)
Composite 2º	7/80 (9)	12/80 (15)	0.58 (0.24-1.41)

Libster *et al. NEJM. 2021*

Randomized, double-blind, controlled trial of CCP in adults with severe COVID-19 (Apr.-Nov. 2020)

CCP (median neutralization titer 1:160) vs. control plasma collected before pandemic.

Hospitalized at 5 facilities in NYC & Rio. Mean age 60 vs. 63. Mean symptoms 9 vs. 10 days. 94% vs. 93% on HFO_2 or more support.

Outcome	CCP (n=150)	Control (n=73)	Adjusted Odds ratio	95% CI
Primary (clinical status day 28)	**Improvement in WHO ordinal scale (modified)**		1.38	0.73-2.61
Secondary (28-day mortality)	19 (12.6)	18 (24.6)	0.47	0.21-1.06

"…use of convalescent plasma was not associated with significant improvement in 28 days clinical status. The "*significant" reduction in mortality* associated with convalescent plasma, however, may warrant further evaluation."

O'Donnell *et al. MedRxiv.* 2021.

RECOVERY: RCT of CCP in hospitalized patients vs. SOC

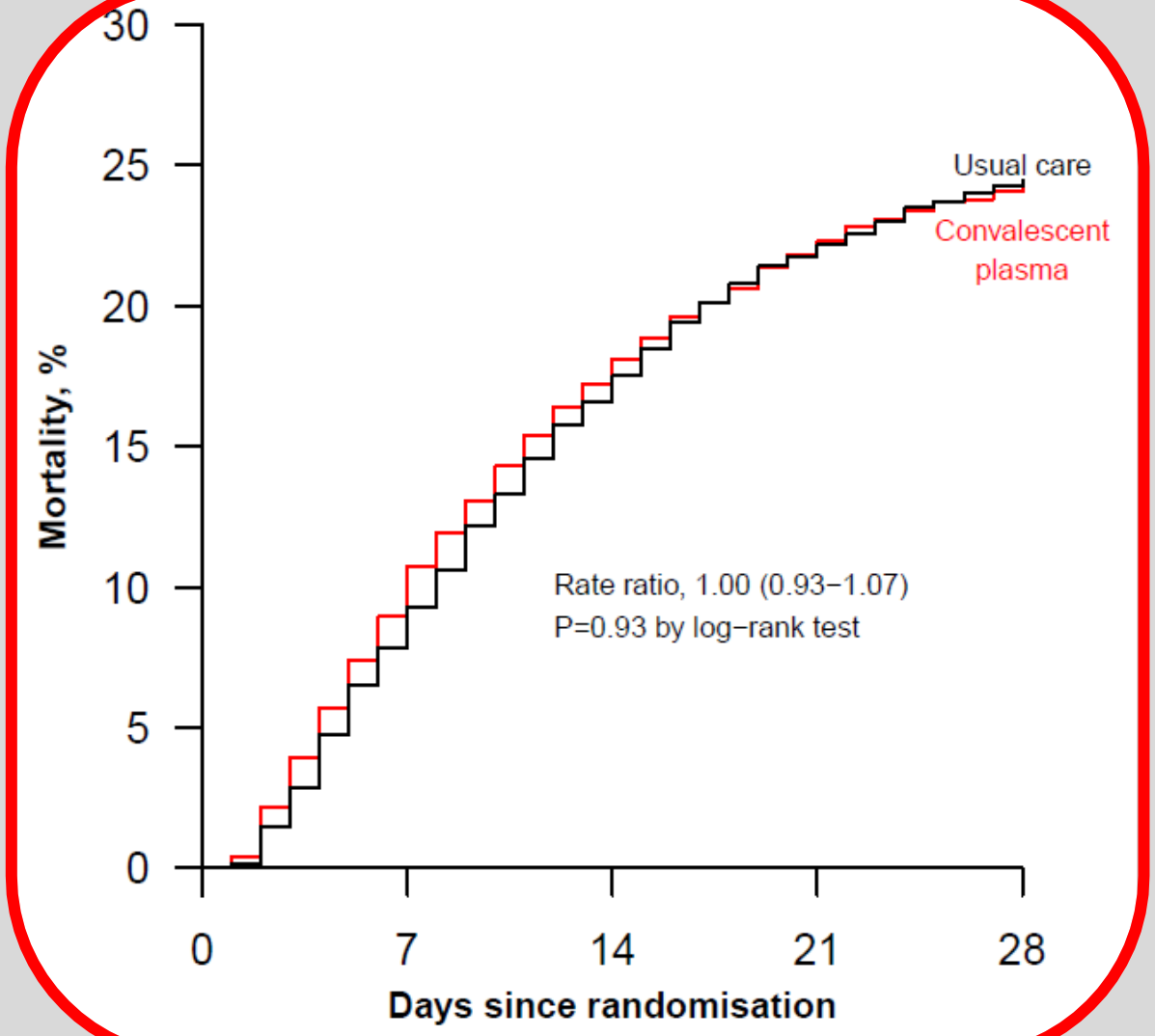
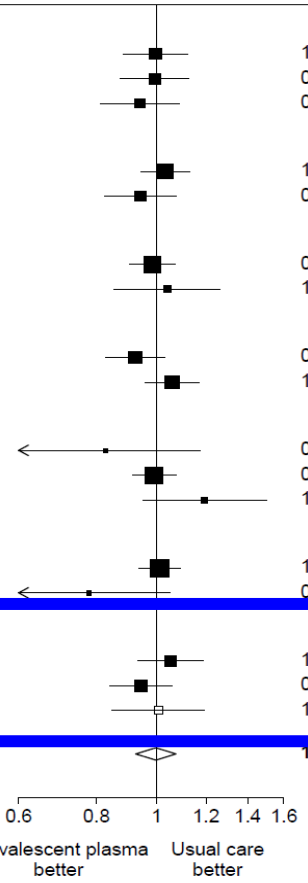


Figure 3: Effect of allocation to convalescent plasma on 28–day mortality by prespecified characteristics at randomisation

	Convalescent plasma	Usual care	RR (95% CI)
Age, years (χ^2_1=0.3; p=0.57)			
<70	533/3705 (14%)	545/3748 (15%)	1.00 (0.88–1.12)
70 to 79	495/1310 (38%)	494/1280 (39%)	0.99 (0.87–1.13)
≥80	370/780 (47%)	369/735 (50%)	0.94 (0.81–1.09)
Sex (χ^2_1= 1.3; p=0.25)			
Men	952/3643 (26%)	972/3787 (26%)	1.03 (0.94–1.13)
Women	446/2152 (21%)	436/1976 (22%)	0.94 (0.82–1.07)
Ethnicity (χ^2_1=0.2; p=0.62)			
White	1089/4362 (25%)	1096/4293 (26%)	0.98 (0.90–1.07)
Black, Asian or minority ethnic	200/853 (23%)	203/889 (23%)	1.04 (0.85–1.26)
Days since symptom onset (χ^2_1=3.2; p=0.07)			
≤7	606/2226 (27%)	659/2240 (29%)	0.92 (0.83–1.03)
>7	789/3564 (22%)	749/3522 (21%)	1.06 (0.96–1.17)
Respiratory support received (χ^2_1=3.5; p=0.06)			
No oxygen received	56/442 (13%)	69/455 (15%)	0.83 (0.58–1.18)
Oxygen only	1184/5051 (23%)	1194/4993 (24%)	0.99 (0.91–1.07)
Invasive mechanical ventilation	158/302 (52%)	145/315 (46%)	1.19 (0.95–1.50)
Use of corticosteroids (χ^2_1=2.7; p=0.10)			
Yes	1313/5370 (24%)	1299/5311 (24%)	1.01 (0.93–1.09)
No	74/391 (19%)	100/413 (24%)	0.78 (0.58–1.05)
Patient SARS–CoV–2 antibody test result (χ^2_1=1.6; p=0.21)			
Positive	566/3022 (19%)	495/2752 (18%)	1.05 (0.93–1.19)
Negative	626/1982 (32%)	549/1629 (34%)	0.94 (0.84–1.06)
Not done	206/791 (26%)	364/1382 (26%)	1.01 (0.85–1.19)
All participants	**1398/5795 (24%)**	**1408/5763 (24%)**	**1.00 (0.93–1.07) p=0.93**



The RECOVERY Collaborative Group. *MedRxiv.* 2021

Is convalescent plasma futile in COVID-19? A Bayesian re-analysis of the RECOVERY randomised controlled trial

Table 1: Estimated posterior probabilities of benefit for a variety of prior assumptions

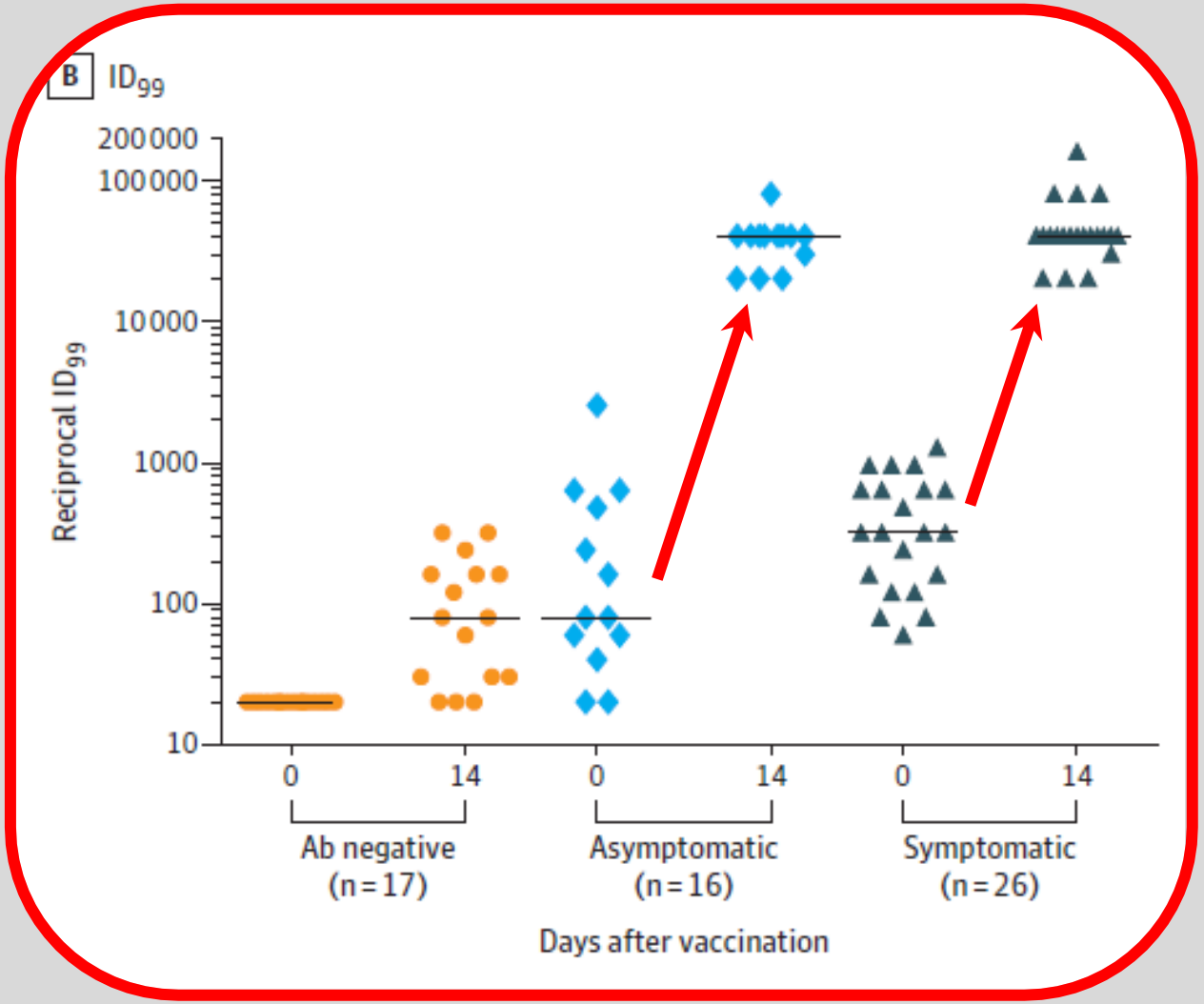
	Vague prior	Optimistic prior:	Skeptical prior	Pessimistic prior
Whole trial (n = 11,558)				
Any benefit:	64%	65%	64%	62%
Small benefit	43%	41%	40%	38%
Moderate benefit	20%	19%	19%	18%
Seronegative subgroup (n = 3,611)				
Any benefit	90%	91%	91%	91%
Small benefit	84%	85%	85%	84%
Moderate benefit	74%	76%	76%	73%

Vague prior: N(0, SD=10,000); Optimistic prior: N(0, SD=0.007); Skeptical prior: N(0,SD=0.007); Pessimistic prior N(0, SD=0.0036). Small benefit defined as a risk difference >0.5% (equivilanet to a NNT <=200); Moderate benefit defined as a risk difference >1% (equivilanet to a NNT <=100).

Hamilton FW. *MedRxiv*. 2021

Other issues arising

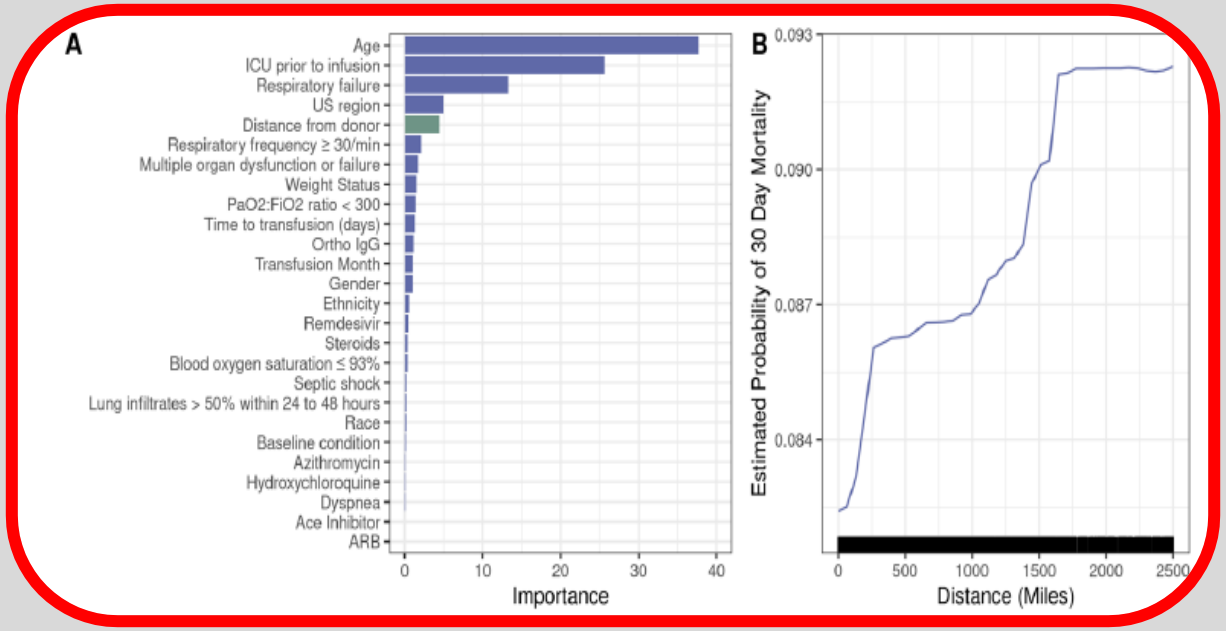
- **Making CCP after immunization of *recovered* patients**
  - **FDA allows this**
  - **If CCP works, can "super" donors after vaccine overcome immune escape by variants?**
  - **Stay tuned**
- **"New vs. old" & "local vs. imported" CCP for "variant" therapy**
  - **"Data-free zone"** (***almost—EAP preprint***)



Saadat *et al. JAMA.* 2021

Donor proximity vs. mortality (June-August 2020)
(US EAP COVID-19 plasma consortium)

	Estimated relative risk	95% CI	P value
Base model (n=27,952)	0.83	0.74-0.86	<.001
Model 2 (n=27899)*	0.83	0.78-0.90	<.001
Model 3 (n=9279)¶	0.77	0.68-0.87	<.001



* Adjusted for age, ICU, respiratory failure, region, gender, time to transfusion, donor distance

¶ Adjusted for age, ICU, respiratory failure, region, weight cohort, gender, infiltrates or hypoxia, Remdesivir, corticosteroids, time to transfusion, donor distance

A. Variable importance plot predicting 30-day mortality
B. Partial dependence plot of estimated mortality accounting for average effect of all other predictors

Kunze KL *et al. MedRxiv.* 2021

Whither CCP (very US-centric)?

FDA (EUA)…

- **High titer may work *in hospitalized* patients given early**
- **Early generally means *prior to respiratory failure.***

Houston, we have a problem!

- **"Hospitalized" is an issue regarding "early" use**
  - **(*N.B.* ER & infusion centers are often "in hospitals")**
- **Need more data on *very early* patients and *high risk exposed***
- **If time & place matter variants may extend the "life" of CCP *cf.* MoAbs and HIG**
- **Role of recipient antibody screening?**

Whither CCP?

1. CCP is an antiviral therapy
2. There must be antibody in the preparation
3. History tells us to use it early (see #1)
4. In the face of variants may be the “go to” passive immune therapy
5. “Off-the-shelf” protocols for production & use in the next pandemic?

Katz' Law of COVID-19

- This is what I think today
- Ask me again tomorrow
- I may change my opinion

Thanks for the invitation and stay safe

lkatz@mvrbc.org