COVID-19 Therapeutics in 2022: Advances and Controversies in Evidence, Oversight, Accessibility, and Utility of Therapy

COVID-19 Convalescent Plasma – Early 2022 Update

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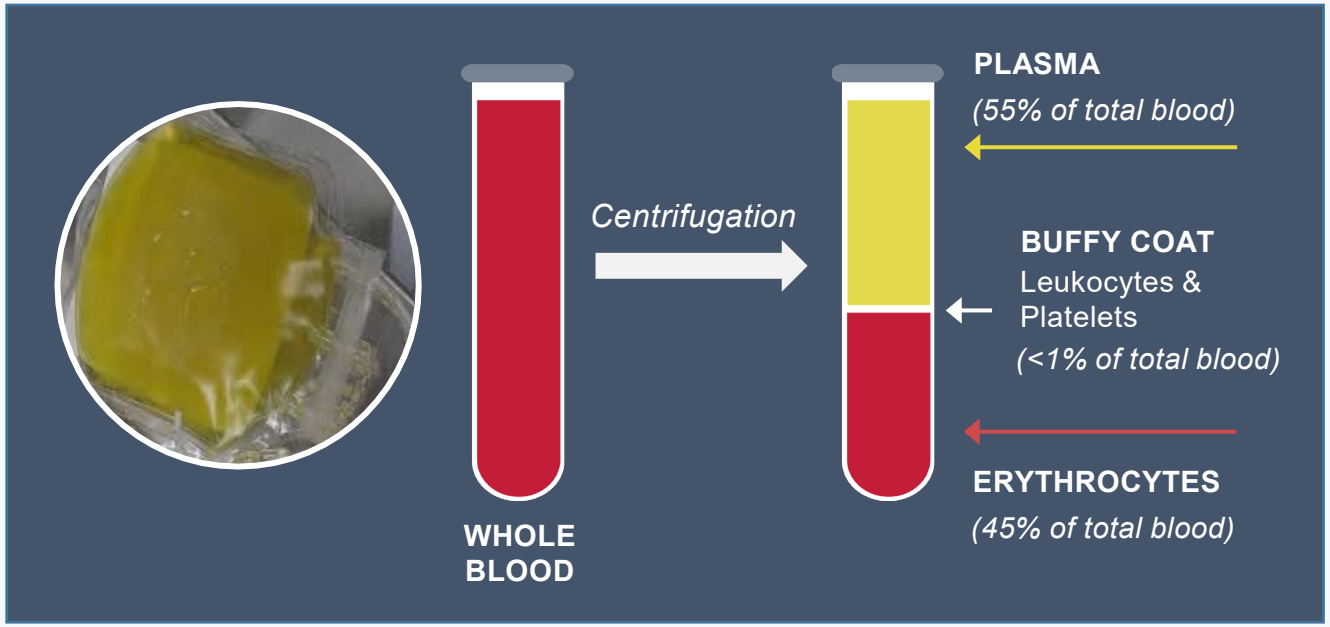
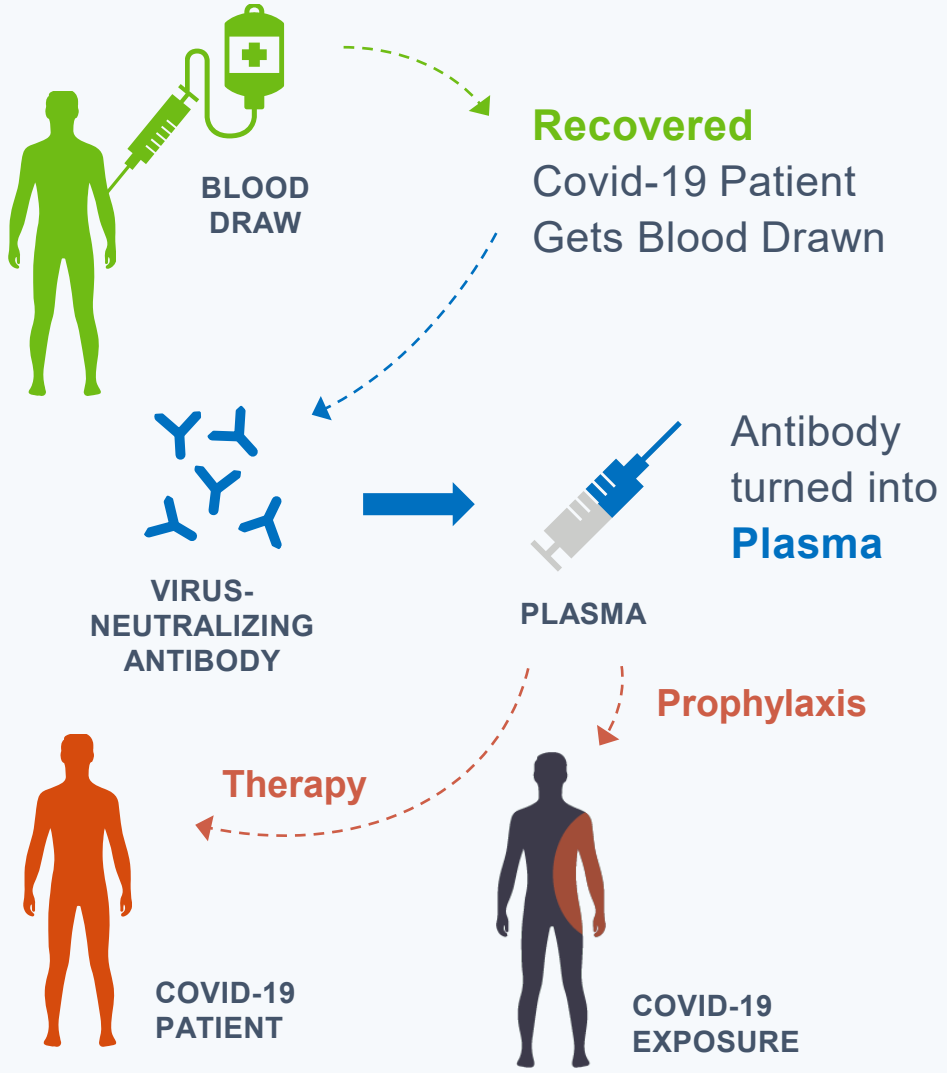
What is Convalescent Plasma?

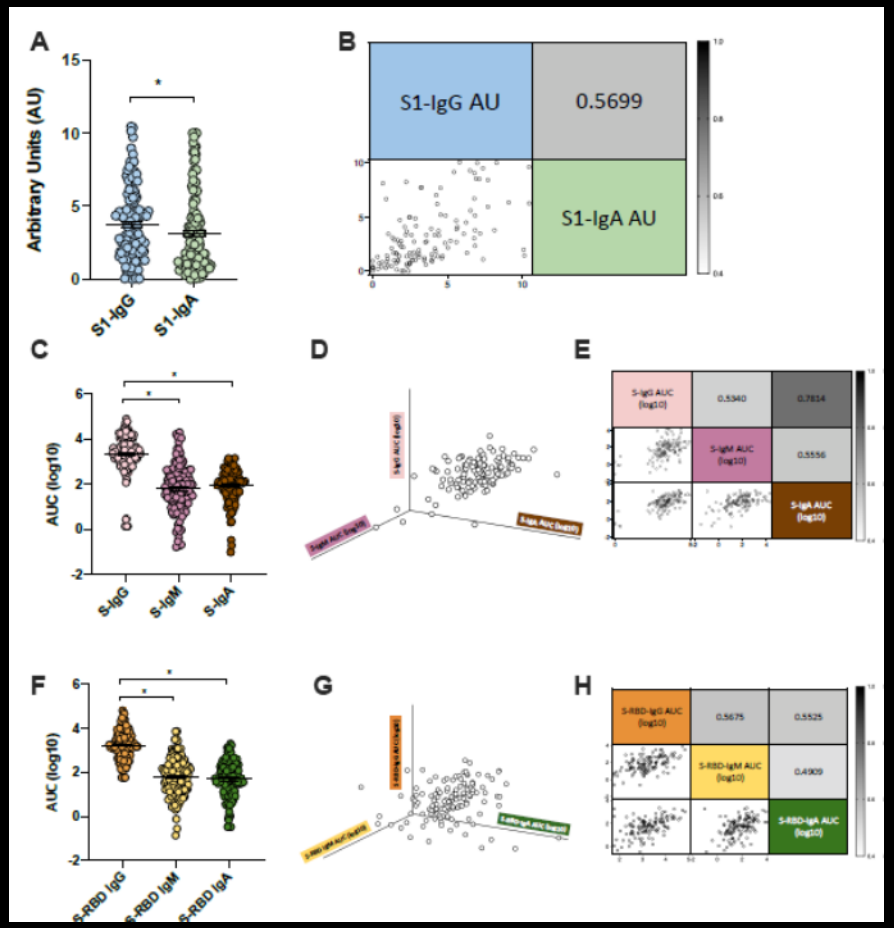
- The **liquid in the blood** that holds the blood cells
- Obtained from donors through **standard transfusion practices**
- Plasma contains an **antibody that neutralizes virus**
- Differs from vaccine in that **antibodies are already present**



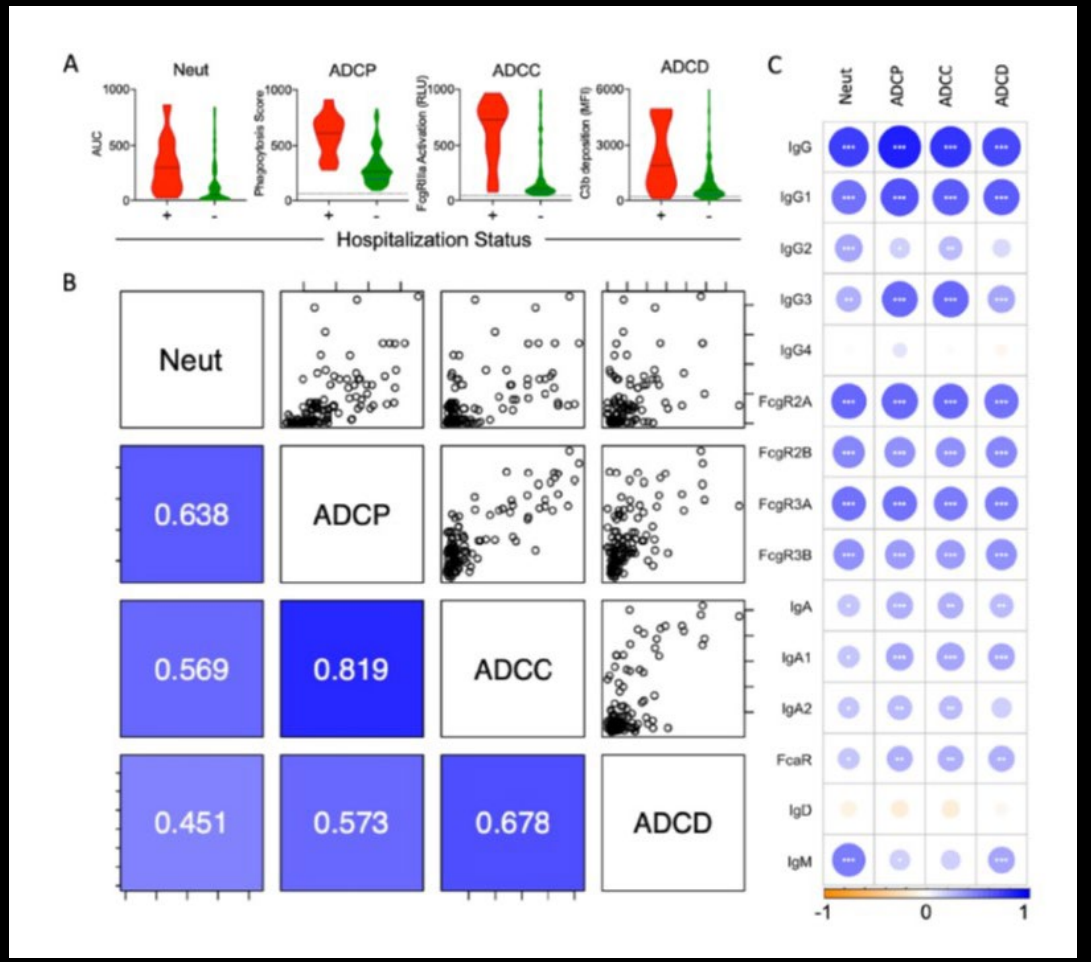
How it Works



Convalescent Plasma is a highly heterogenous product with at least four antiviral activities



Klein et al. JCI 2020



Natarajan et al. mBio 2021

Serum therapy experience establish the three principles of antibody therapy for Infectious Diseases

1. **The Specificity Principle** - ***effective antibody preparations for the prevention and therapy of infectious diseases must contain antibody specific to the microbe targeted***
2. **The Quantitative Principle** – ***effective antibody preparations for the prevention and therapy of infectious diseases must contain sufficient antibody to microbe targeted to mediate protection.***
3. **The Temporal Principle** - ***antibody preparations are most effective when given prophylactically or early in the course of disease.***

Mortality according to the Period of Injection of the Serum.

Period of injection.	No. of cases.	Recovered.	Died.	Per cent. recovered.	Per cent. died.
1st to 3d day	199	163	36	81.9	18.1
4th to 7th day	346	252	94	72.8	27.2
Later than 7th day	666	423	243	63.5	36.5
Totals	1,211	838	373	69.2	30.8

Flexner, JEM 1913

The Principles of Antibody Therapy for Infectious Diseases with Relevance for COVID-19

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Casadevall et al. mBio 2021

The Convalescent Plasma Rollercoaster

2020 (CP is UP)

- CP is rapidly deployed in United States
- Usage goes from 0 to >20,000 doses in months
- By October 2020, 40% of all hospitalized patients treated; > 500,000 people treated in USA alone
- Mayo Clinic Expanded Access Program produces clear evidence of efficacy

2021 (CP is down)

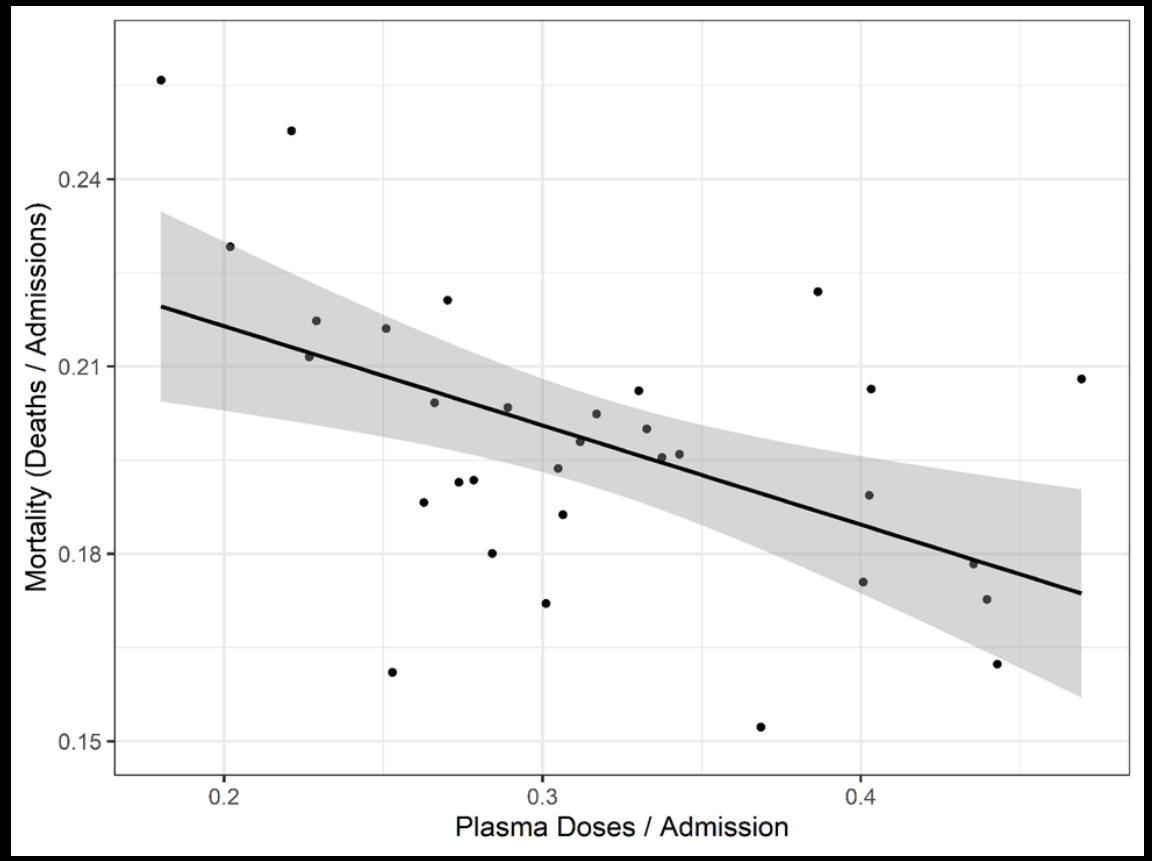
- Dozens of Randomized Controlled Trials Completed – results mixed
- Negative evidence favored over positive evidence
- Plasma falls out of favor; use falls markedly
- NIH, WHO, and IDSA recommend against plasma

2022 (CP is UP)

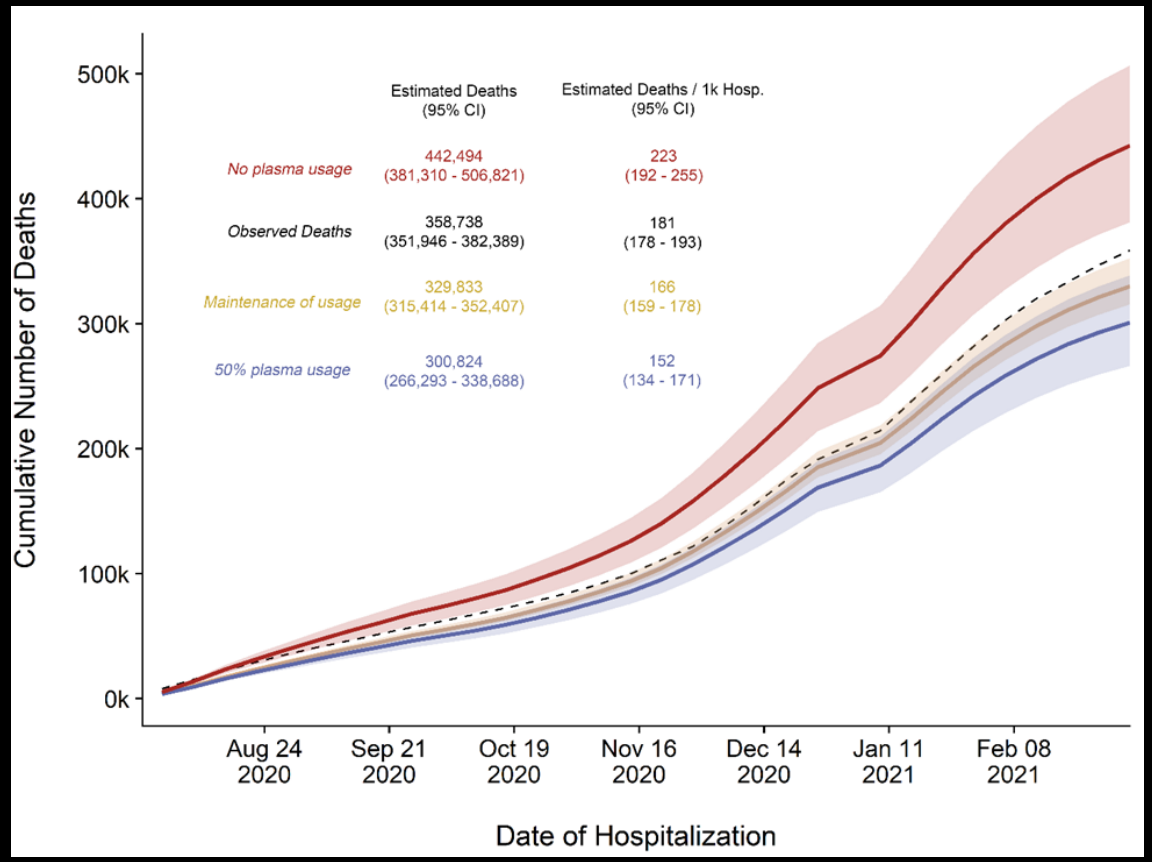
- Hopkins Outpatient trial (early & high titer) shows CP to be effective
- Omicron defeats most monoclonal antibody therapies but not CP
- FDA modifies EUA to allow outpatient usage
- IDSA recommends CP in outpatients when no other therapies available
- CP is scarce – supply problems
- A niche emerges for CP in immunocompromised populations

March 2020 to March 2021
CP use inversely Related to Mortality

Inverse Correlation between use and mortality in USA

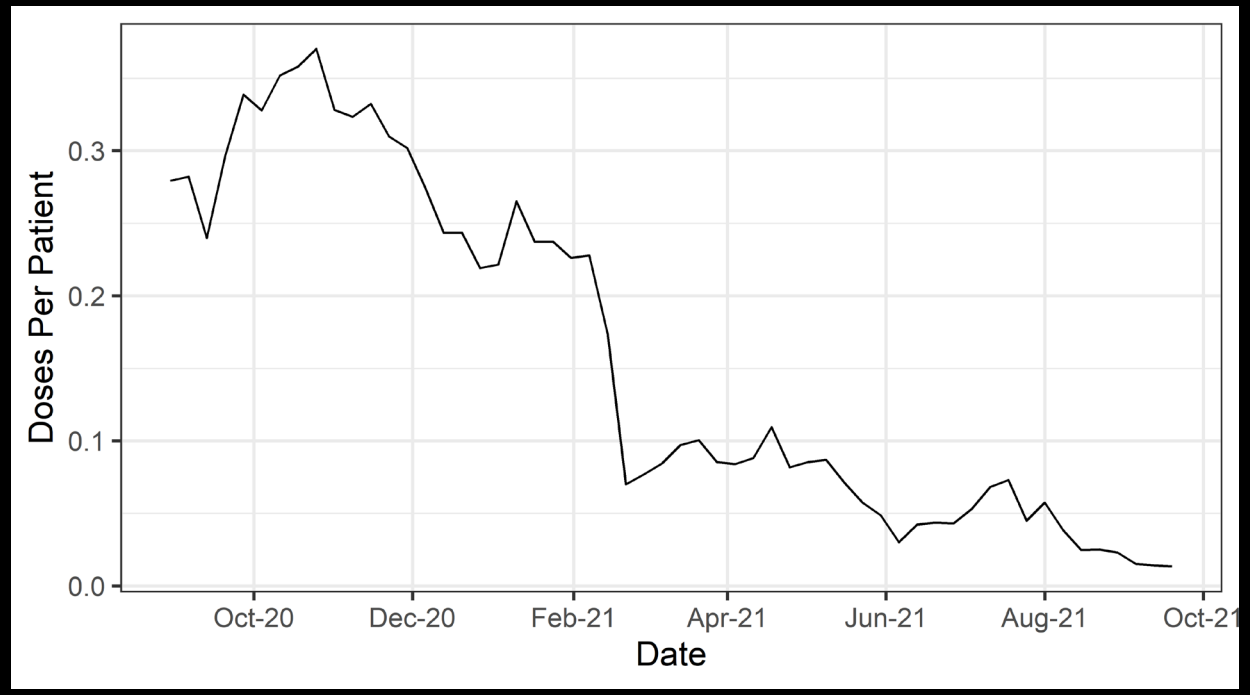


Deployment of CP in USA saves ~100,000 lives



Casadevall et al. eLife 2021

CP Use in USA Falls Precipitously in 2021 just as physicians are using it properly



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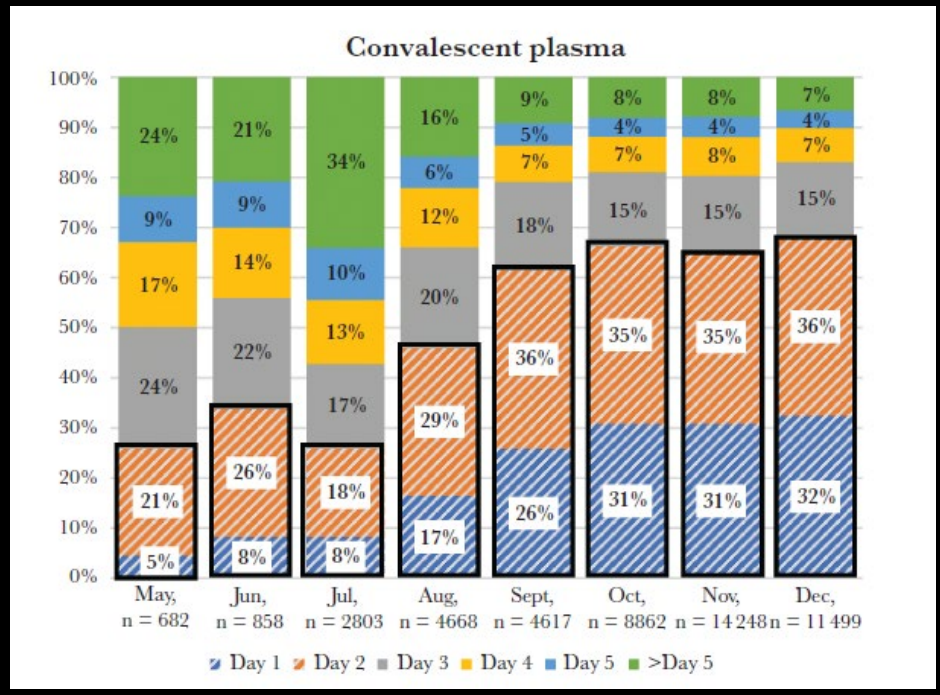
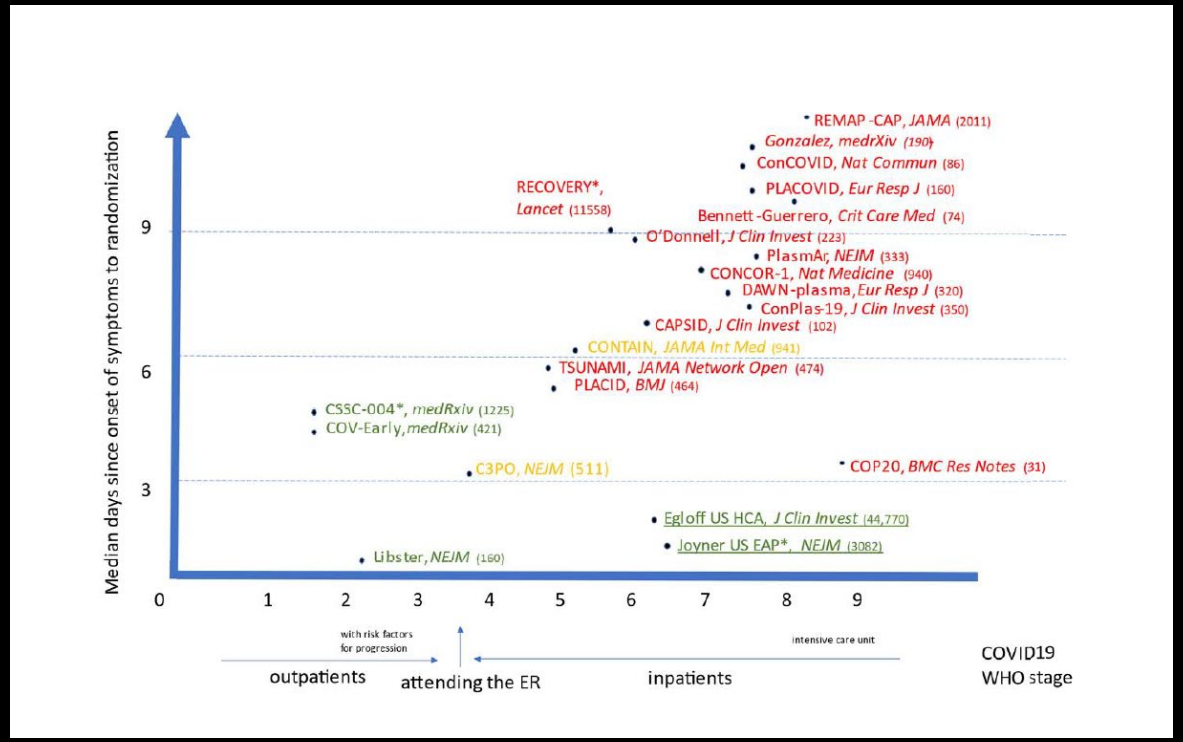


Mozzafari et al. CID 2021

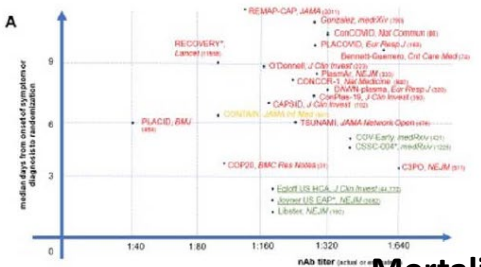
CP Efficacy Becomes an Epistemic Conundrum

- Spring-Summer 2020: dozens of RCTs are began to evaluate CP efficacy but the majority focus on hospitalized patients without much attention to the principles of antibody therapy.
- Some trials use inadequate amounts of antibodies; others treat too late.
- All RCTs focus on time to randomization but actual time to infusion is much later, handicapping the efficacy of time dependent therapy such as CP further
- By 2021 most RCTs are reporting that CP has no effect on mortality.
- One small RCT from Argentina reports large efficacy in outpatients at high risk but attracts little attention.
- None of the RCTs changes course and modifies their protocols despite the Mayo Clinic EAP study showing that you need high titer early in hospitalization

> 30 RCTs and Large Observational Studies Begin to Clarify who Benefits from CCP

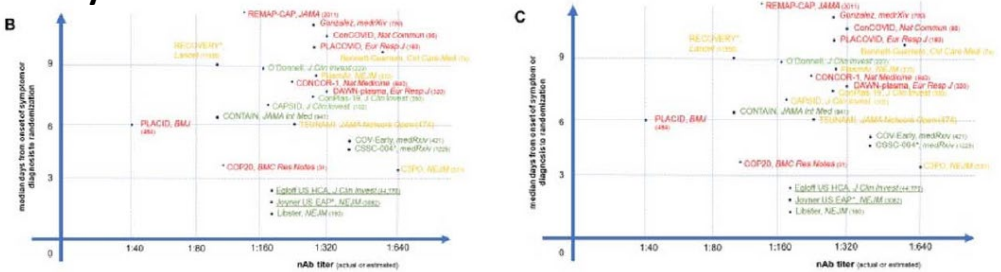


Primary Endpoint



Mortality Benefit

Mortality Benefit p < 0.05



Focosi et al. 2022 Clinical Microbiology Reviews (in press)

Winter 2021-2022: The World Changes

1. Omicron defeats Most mAbs

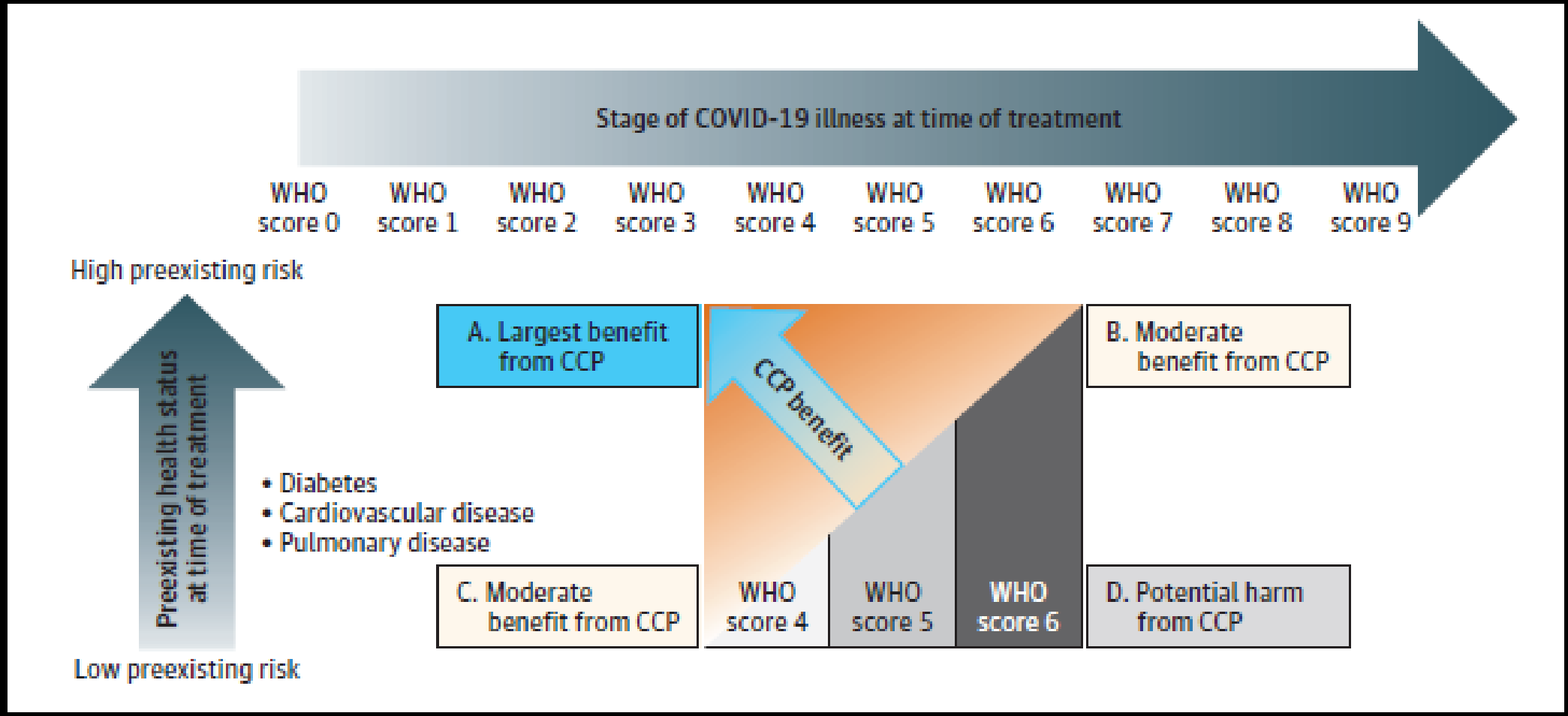
3. Immunosuppressed patients therapeutic issues

CP Remerges

2. Hopkins RCT shows efficacy in outpatients

4. FDA allows outpatient use and IDSA recommends outpatient CP

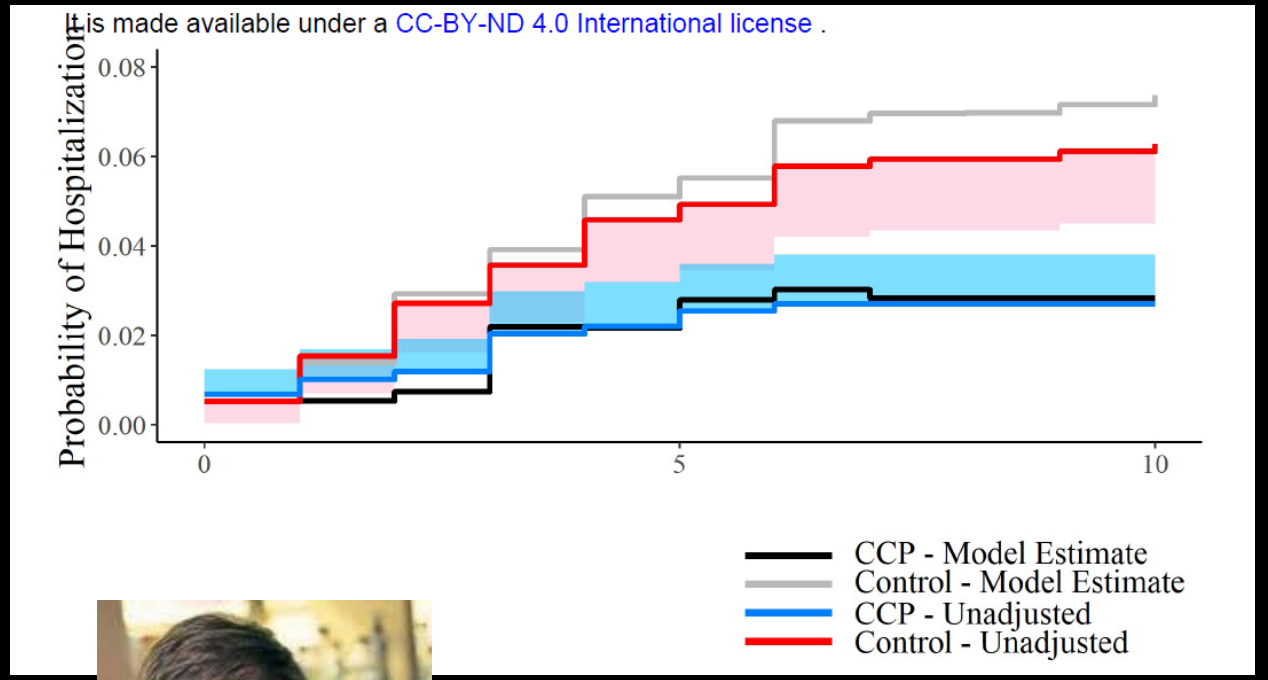
Individual Patient meta-analysis yields algorithm to identify those who benefit



Park et al JAMA IM Open 2022

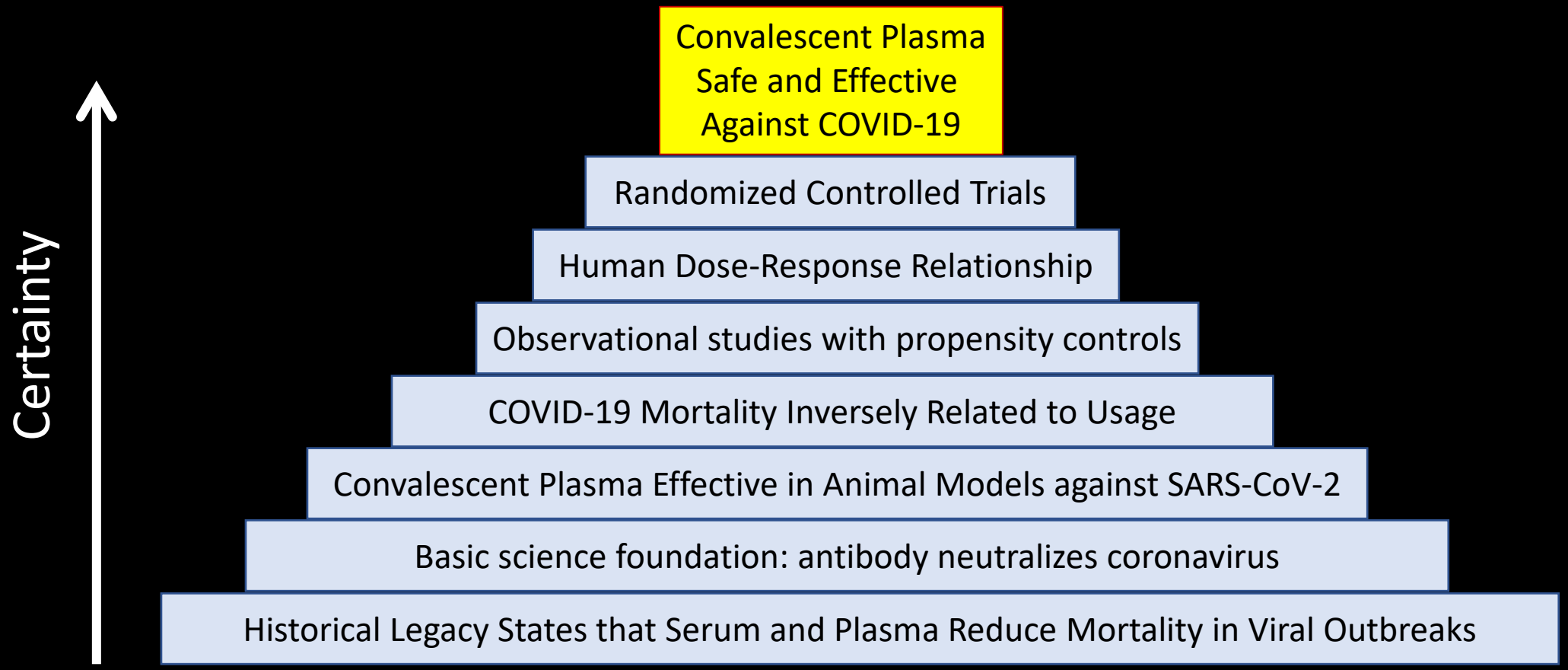
Hopkins Outpatient Trial Provides Definitive Evidence that Convalescent Plasma is Effective

- Unlike other RCTs we set out from the beginning study convalescent plasma early in disease with high titer units
- Difficult to do an outpatient trial that involve infusions to infected individuals
- Large – 1225 patients
- Randomized, Double blinded.
- Control – non-convalescent plasma
- Result – 54% reduction in progression of disease to hospitalization; safe!
- Within 6 days of public announcement FDA allows outpatient use on Dec 27, 2021



David Sullivan

CP for COVID-19 Climbs the Epistemic Pyramid



Variables that affect CP efficacy for COVID-1

- **Dose – need high titer units**
- **Time – the earlier the most effective**
- **WHO Score – disease state matters**
- **Geographic provenance – locally sourced better than distantly sourced**
- **Negative serology – particularly effective in B-cell deficiency**
- **Other drugs – effect lost with remdesivir…probably it means that both are doing the same thing as antivirals.**

Some special advantages of CP for COVID-19

- **Relatively inexpensive (cost of unit varies but < $1,000)**
- **One time usage**
- **Relatively safe and well tolerated**
- **Polyclonal nature means less likely to select for resistance**
- **Available in low- and middle-income countries**
- **Only therapy that keeps up with the variants**
- **Currently there are millions of potential donors in USA and worldwide**

CP for COVID-19 Current Status USA

- **CP for COVID-19 remains under EUA in USA.**
- **Use permitted for both outpatients and inpatients who are immunosuppressed or receiving immunosuppressive therapy.**
- **‘Immunosuppressed’ not defined in EUA, which gives physicians considerable latitude in determining usage.**
- **Consensus is emerging that it is effective if used early and with high titer units.**
- **A clear niche has emerged as preferred antibody therapy in immunosuppressed patients, who often have high viral loads.**
- **Major problem today is supply – scarcity from various causes.**

Some thoughts as we approach the 2-year anniversary of the deployment of CP for COVID-19

- **We have learned what we should have known all along from history, that antibody therapies work best when used early and with high titer**
- **The RCT instrument did not work well for CP – most RCTs tested CP in conditions where it could not work and then concluded that it did not work…creating a futile epistemic loop.**
- **A public good like CP, which has no patent or profit can be damaged by clinical research that tests it in conditions of biological implausibility.**
- **Convincing physicians and regulators requires high quality data.**
- **Although originally meant as 'stop gap' therapy, CP has found a niche in the immunosuppressed since its polyclonal nature gives it tremendous advantages relative to monoclonal antibody therapeutics.**
- **The experience with COVID-19 teaches us how to use it for the 'next one', when humanity inevitably turn to CP again during the early pandemic days.**