WHO or Not WHO – Insights for the Future of CCP-19

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Alt Title: *The Who Said What?*

World Health Organization

WHO recommends against the use of convalescent plasma to treat COVID-19

7 December 2021 | News release | Reading time: Less than a minute (172 words)

Trials for severe and critical patients should continue

Narrative

- How I stumbled into this
- Big picture of the last 2 years.
- ~400 studies in PubMed or Preprints
    1. Early tx
    2. High Titer
    3. Replacement TX
- 100s of thousands treated
- The Next Variant – ***The Next Pandemic***

WSJ February 27, 2020

OPINION | COMMENTARY

How a Boy's Blood Stopped an Outbreak

A school physician's approach to measles in 1934 has lessons for the coronavirus.

By Arturo Casadevall

Feb. 27, 2020 6:48 pm ET

It isn't every day that a school physician's work gets published in a medical journal. But it happened in 1934, and the story contains a lesson for the coronavirus epidemic.

1930s Early Treatment Essential

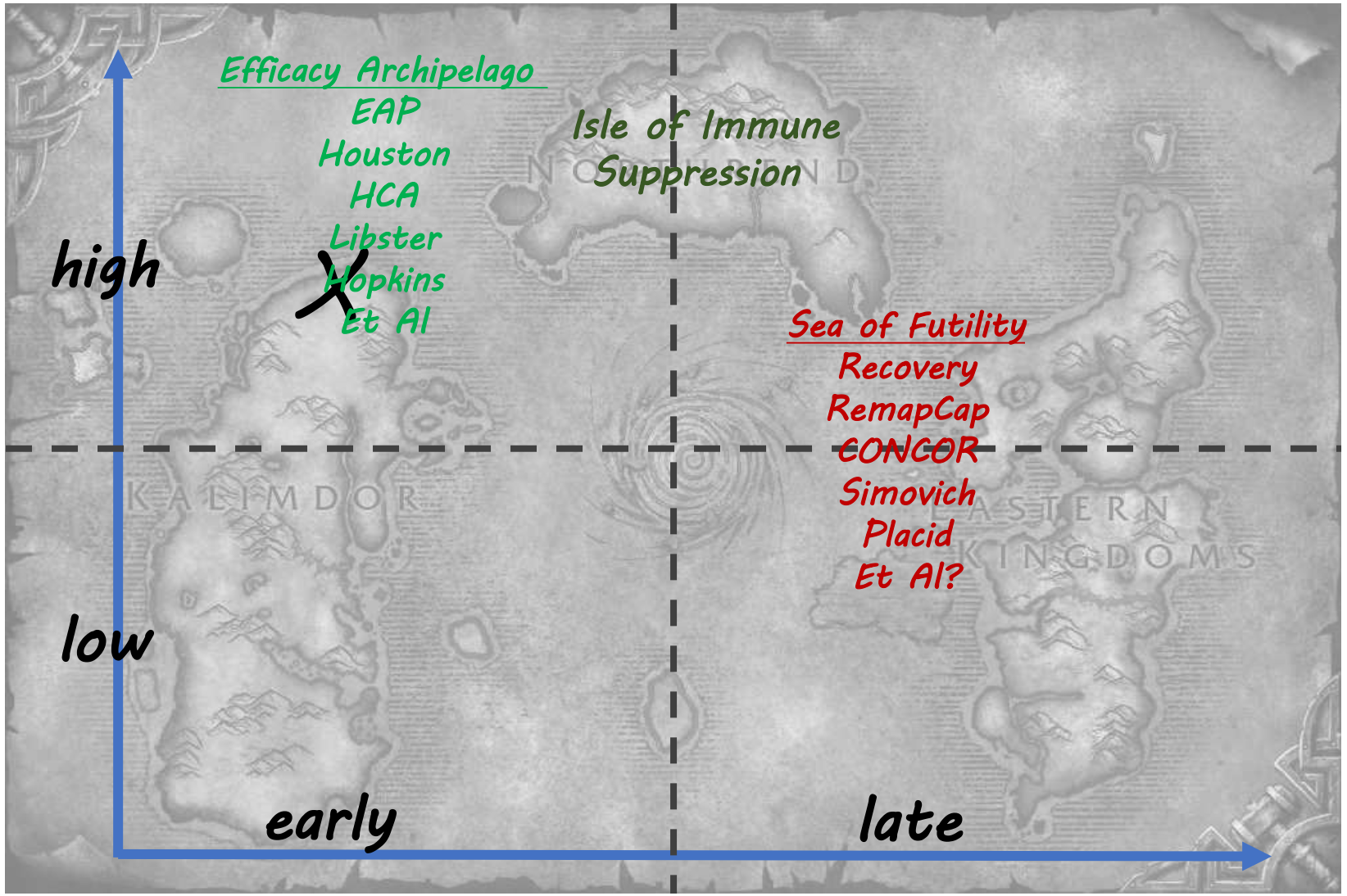
EFFECTS OF VERY EARLY SERUM TREATMENT IN PNEUMOCOCCUS TYPE I PNEUMONIA

RUSSELL L. CECIL, M.D.
NEW YORK

It is a fundamental principle in all serum therapy that to obtain the best results the serum must be given early in the disease. This statement holds true regardless of whether one is using antitoxic or antibacterial serum.

Cecil JAMA 1937

Convalescent Plasma: Where's The Buried Treasure?



Early Tx/High Titer

- Historical Precedent
- EAP August 2020
- Why did they persist?

https://www.planetminecraft.com/project/world-of-warcraft-wow-map-of-azeroth/

Used “Right” CP Works

Mortality rates among randomized clinical trials of optimal use convalescent plasma therapy for COVID-19

	Convalescent Plasma			Control					
Study	Survivor	Non-Survivor	Mortality	Survivor	Non-Survivor	Mortality	Mechanical ventilation (%)	Titer	Time to transfusion (days)
Avendaño-Solà et al.	172	7	4%	157	14	8%	0%	High titer	1 (admission)
Bar et al.	38	2	5%	29	10	26%	0%	High titer	1 (admission)
Bennett-Guerrero et al.	43	16	27%	10	5	33%	19%	High titer	4 (admission)
Devos et al.	310	10	3%	155	8	5%	0%	High titer	7 (symptoms)
Gharbharan et al.	37	6	14%	32	11	26%	12%	High titer	2 (admission)
Korper et al.	42	11	21%	35	17	33%	30%	High titer	2 (admission)
Libster et al.	78	2	3%	76	4	5%	0%	High titer	3 (symptoms)
Menichetti F et al.	217	14	6%	221	19	8%	0%	High titer	7 (symptoms)
O'Donnell et al.	131	19	13%	55	18	25%	11%	High titer	9 (symptoms)
Ortigoza et al. (No corticosteroids subgroup)	85	9	10%	69	18	21%	0%	High titer	1 (admission)
Simonovich et al.	197	25	11%	93	12	11%	0%	High titer	8 (symptoms)
Sullivan et al.	592	0	0%	289	3	1%	0%	High titer	6 (symptoms)
The CONCOR-1 Study Group (high titer subgroup)	268	75	22%	133	40	23%	0%	High titer	5 (diagnosis)
The RECOVERY Collaborative Group (No corticosteroids subgroup)	317	74	19%	313	100	24%	5%	High Titer	2 (admission)
The REMAP-CAP Investigators (Moderate state subgroup)	54	8	13%	17	7	29%	0%	High titer	2 (admission)
The SIREN-C3PO Investigators	256	5	2%	253	1	0%	0%	High titer	4 (symptoms)
Overall	**2837**	**283**	**9.1%**	**1937**	**287**	**12.9%**			

χ^2 = 20.13, *P* < 0.001; 41.7% relative mortality reduction associated with convalescent plasma therapy

Klassen & Senefeld Unpublished

Used Late - Not So Much

Mortality rates among randomized clinical trials of non-optimal use convalescent plasma therapy for COVID-19

	Convalescent Plasma			Control					
Study	Survivor	Non-Survivor	Mortality	Survivor	Non-Survivor	Mortality	Mechanical ventilation (%)	Titer	Time to transfusion (days)
Agarwal et al.	201	34	14%	198	31	14%	8%	Not high titer	4 (admission)
Ali Shaukat et al.	30	10	25%	4	6	60%	3%	Not high titer	8 (symptoms)
AlQahtani et al.	19	1	5%	18	2	10%	0%	-	-
Bajpai et al.	11	3	21%	14	1	7%	0%	Not high titer	3 (symptoms)
Bandopadhyay et al.	30	10	25%	26	14	35%	-	Not high titer	-
Gonzalez et al.	60	70	54%	28	32	53%	85%	-	-
Kirenga B et al.	59	10	14%	59	8	12%	0%	-	7 (symptoms)
Li et al.	43	8	16%	38	12	24%	30%	Not high titer	33 (symptoms)
Ortigoza et al. (Corticosteroids subgroup)	334	17	5%	333	24	7%	0%	High titer	1 (admission)
Pouladzadeh et al.	27	3	10%	25	5	17%	10%	Not high titer	0 (admission)
Rasheed et al.	20	1	5%	20	8	29%	81%	Not high titer	4+ (admission)
The CONCOR-1 Study Group (not high titer subgroup)	205	66	24%	101	23	19%	0%	Not high titer	5 (diagnosis)
The RECOVERY Collaborative Group (Corticosteroids subgroup)	4056	1314	24%	4012	1299	24%	5%	High titer	2 (admission)
The REMAP-CAP Investigators (Severe state subgroup)	679	407	37%	557	347	38%	0%	High titer	2 (admission)
Sekine et al.	62	18	23%	67	13	16%	30%	Not high titer	10 (symptoms)
Overall	**5836**	**1972**	**25.3%**	**5500**	**1825**	**24.9%**			

$\chi^2 = 0.23$, $P = 0.63$; - indicates data not available

Klassen & Senefeld Unpublished

Patients With Deficient Antibody Responses:
Experiments of Nature

- Heme Malignancy
- Patients who don't make endogenous antibodies
- Prolonged disease course
- Rapid improvement seen post CP administration in many
- Low mortality reported in these high-risk patients

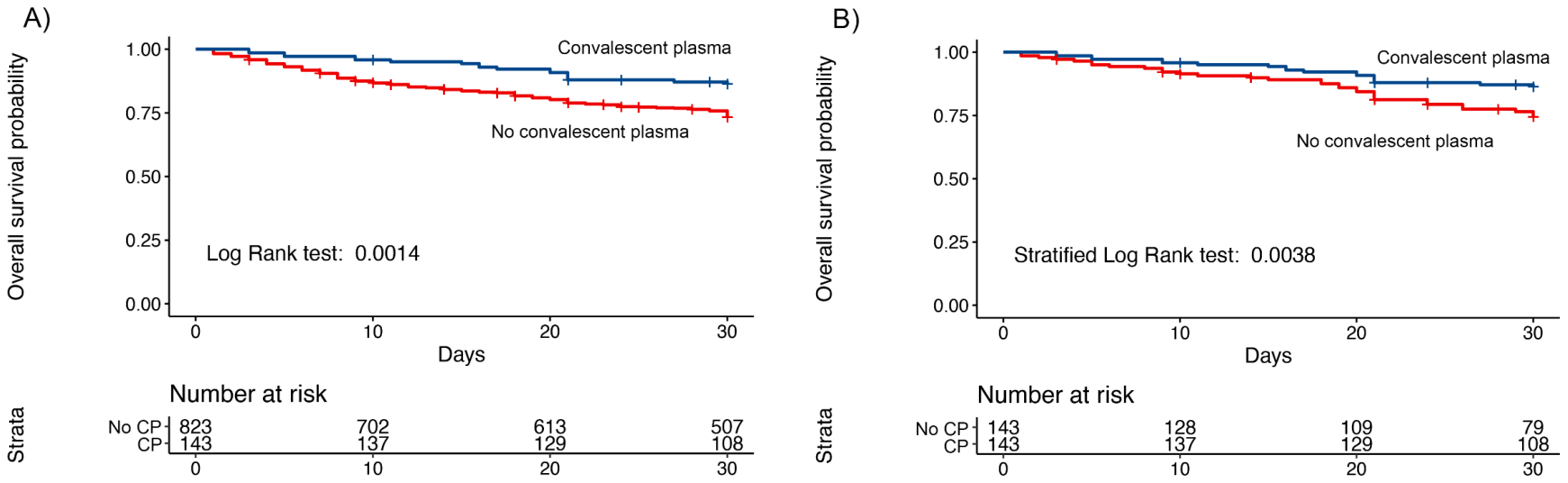


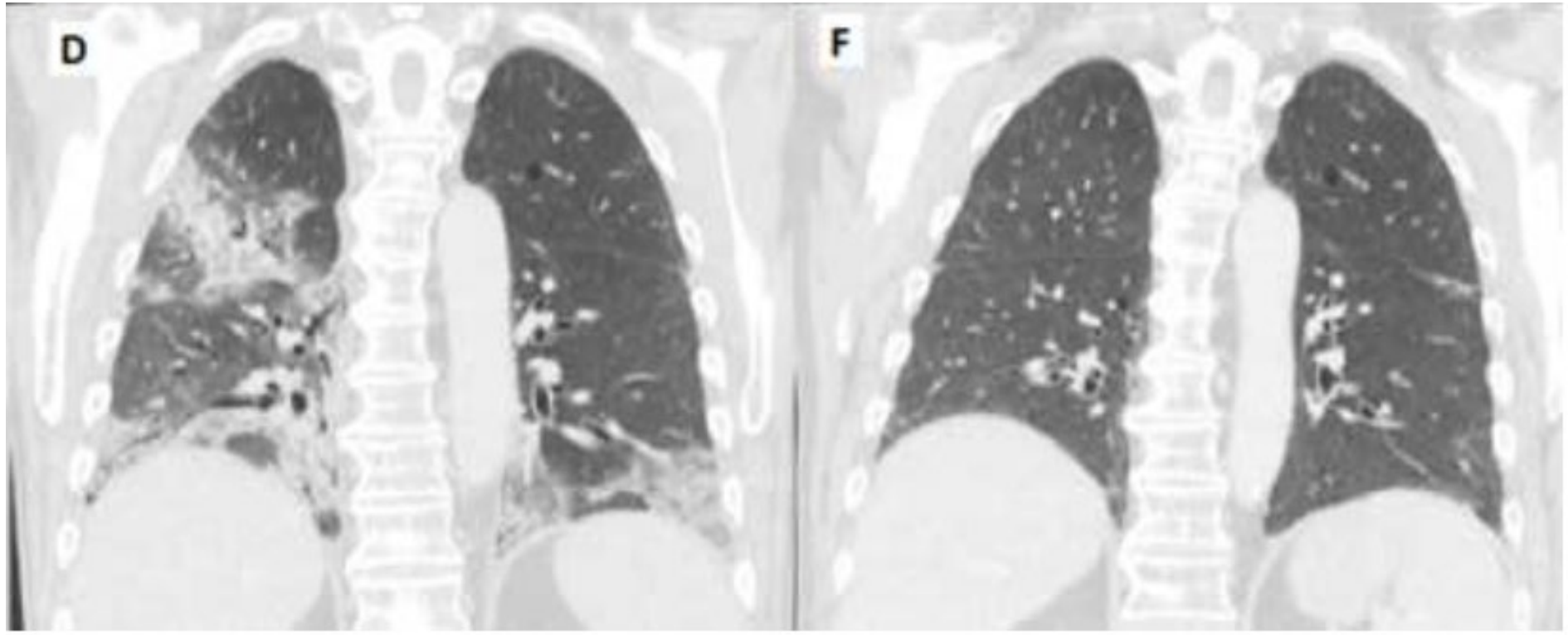
Figure 1: Primary Outcome in the A) Overall Population and B) Propensity-Score Matched Population

Thompson et al. 2021, JAMA ONC

VaxPlasma In A B-Cell Depleted Patient: Covid Positive ~270 days

Pre VaxPlasma

3 days post VaxPlasma



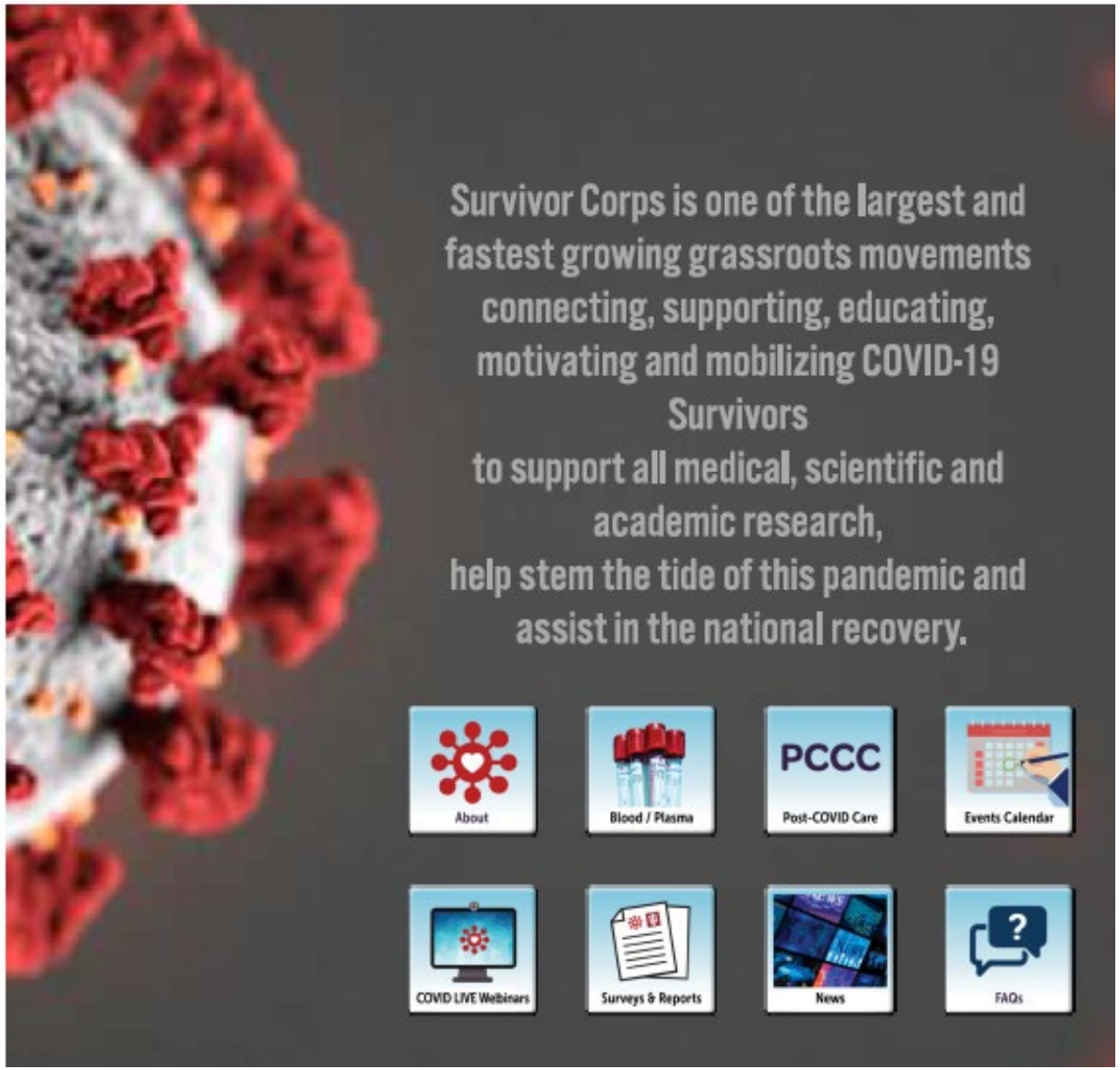
Espinosa et al MCP 2021

SURVIVOR CORPS

Empathize • Organize • Mobilize

About
Donate Plasma / Research
Support SC Resources
SC News Contact

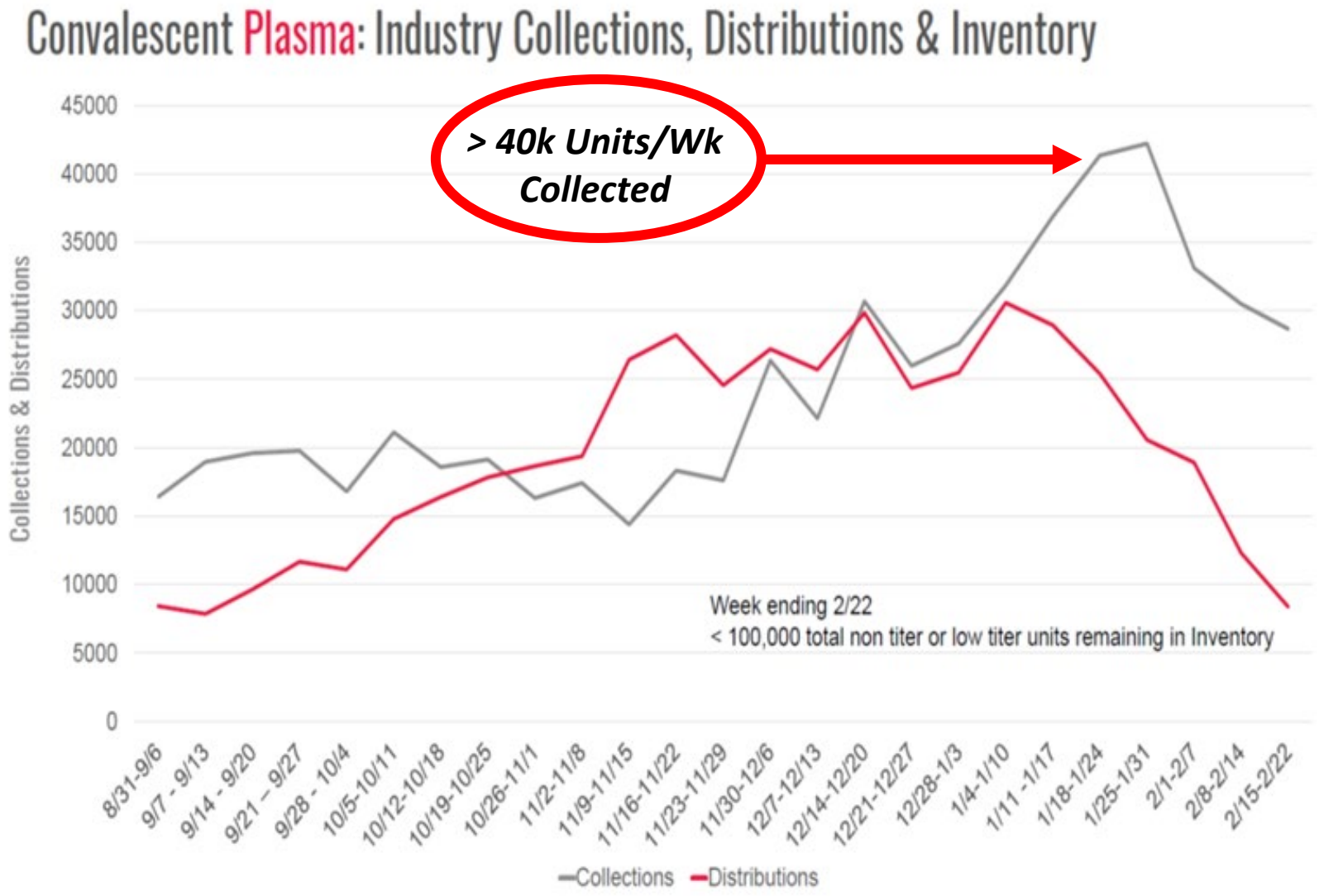
Donate $



Access & Next Level Community Engagement

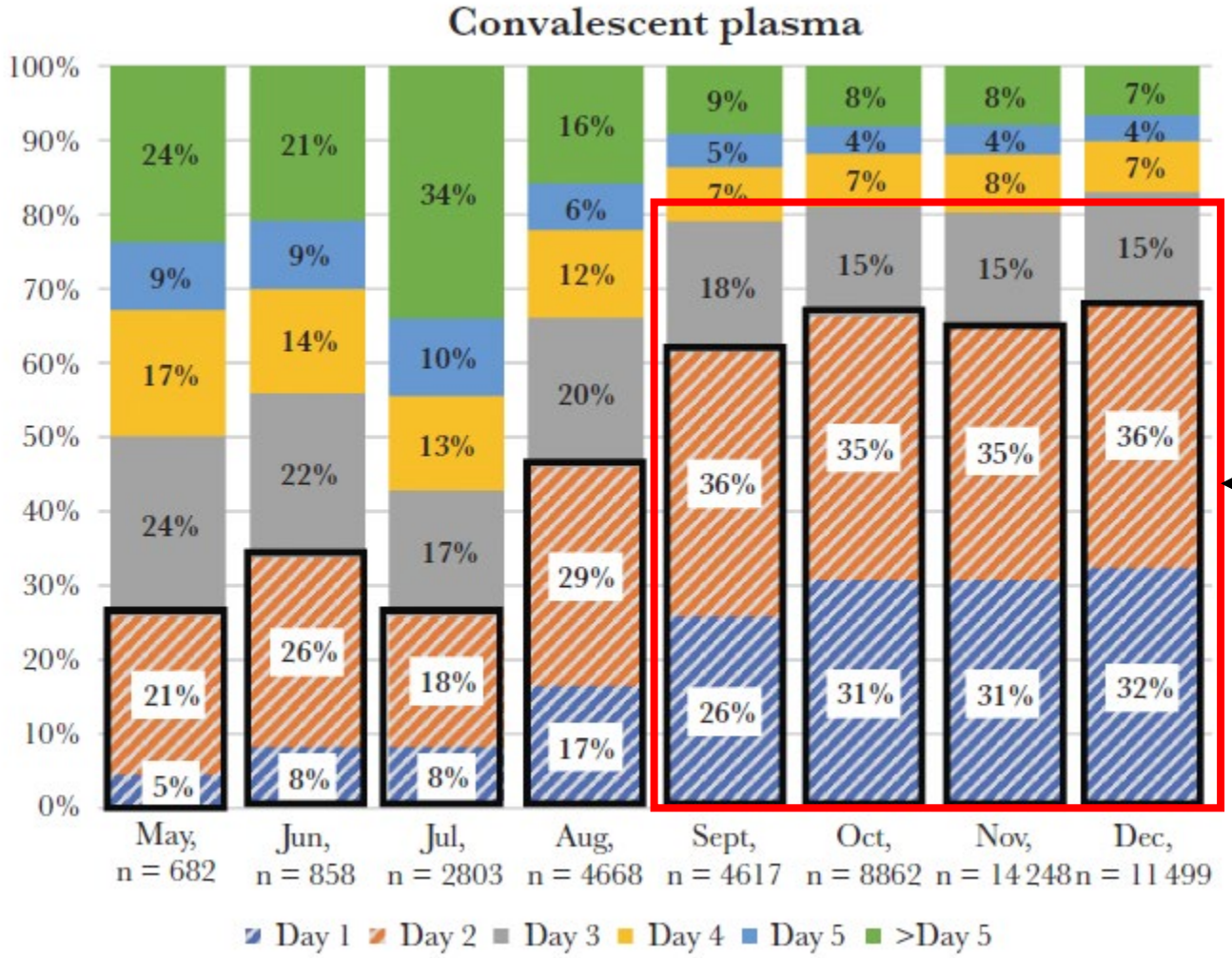
CP Used at Scale in the US

Sept 2020 – Feb 2021 CP Collections & Distributions



Real World Clinicians Get It!

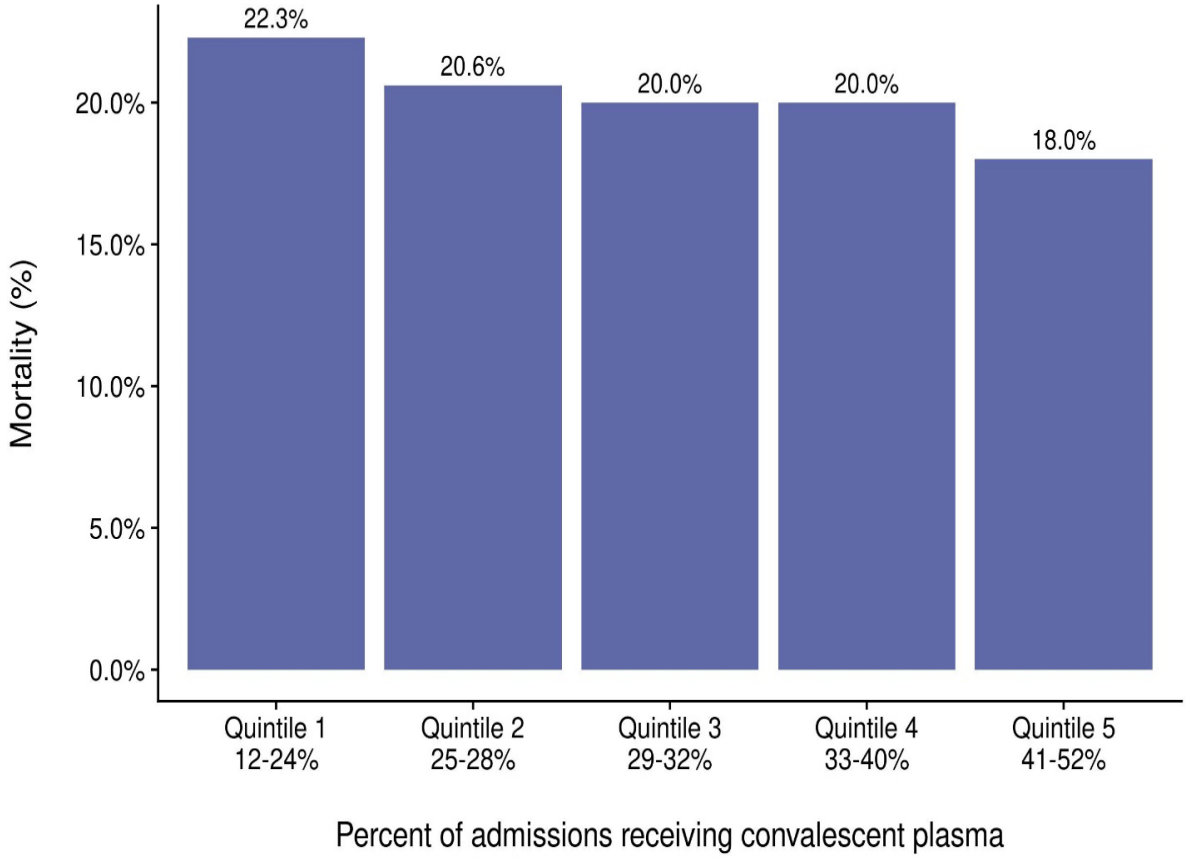
CP in 2020 ~50k Patients

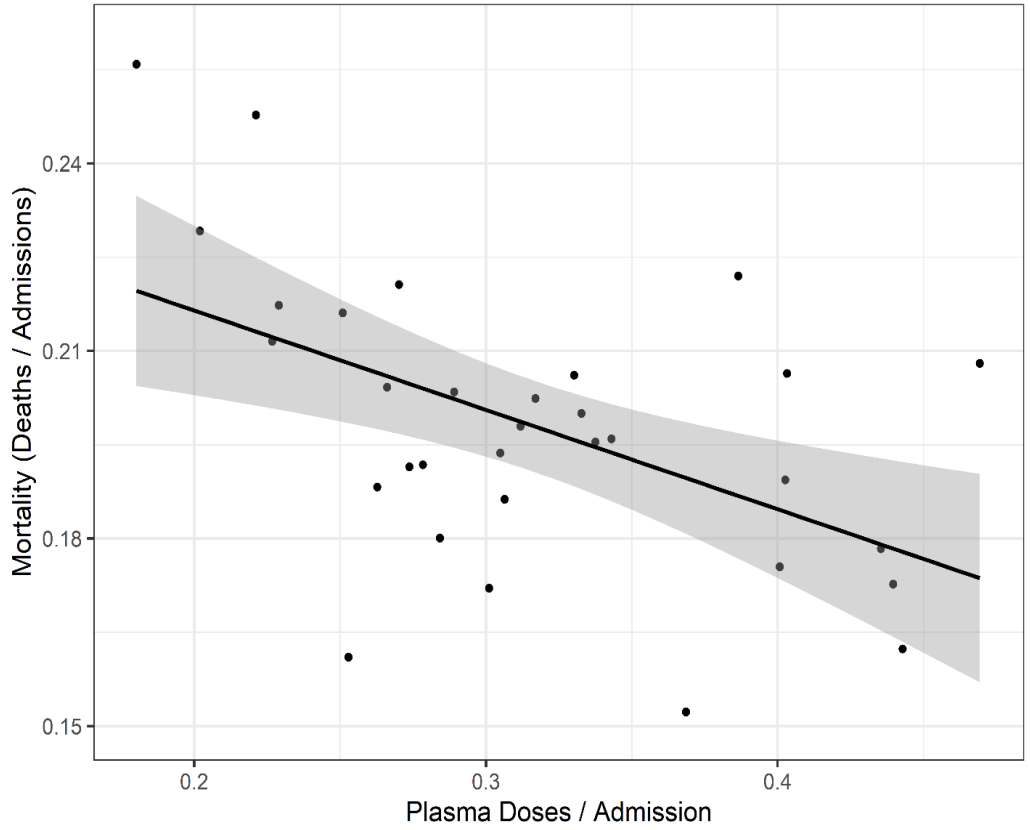


Early use of high titer plasma was happening!

Mozaffari et al 2021

The Population Data Shows An Inverse Relationship Between Plasma Use & Mortality





Casadevall et al eLife 2021

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- Big picture of the last 2 years.
- ~400 studies in PubMed or Preprints
    1. Early tx
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- 100s of thousands treated
- The Next Variant – ***The Next Pandemic***

The Next Variant – *The Next Pandemic*

Next Variant

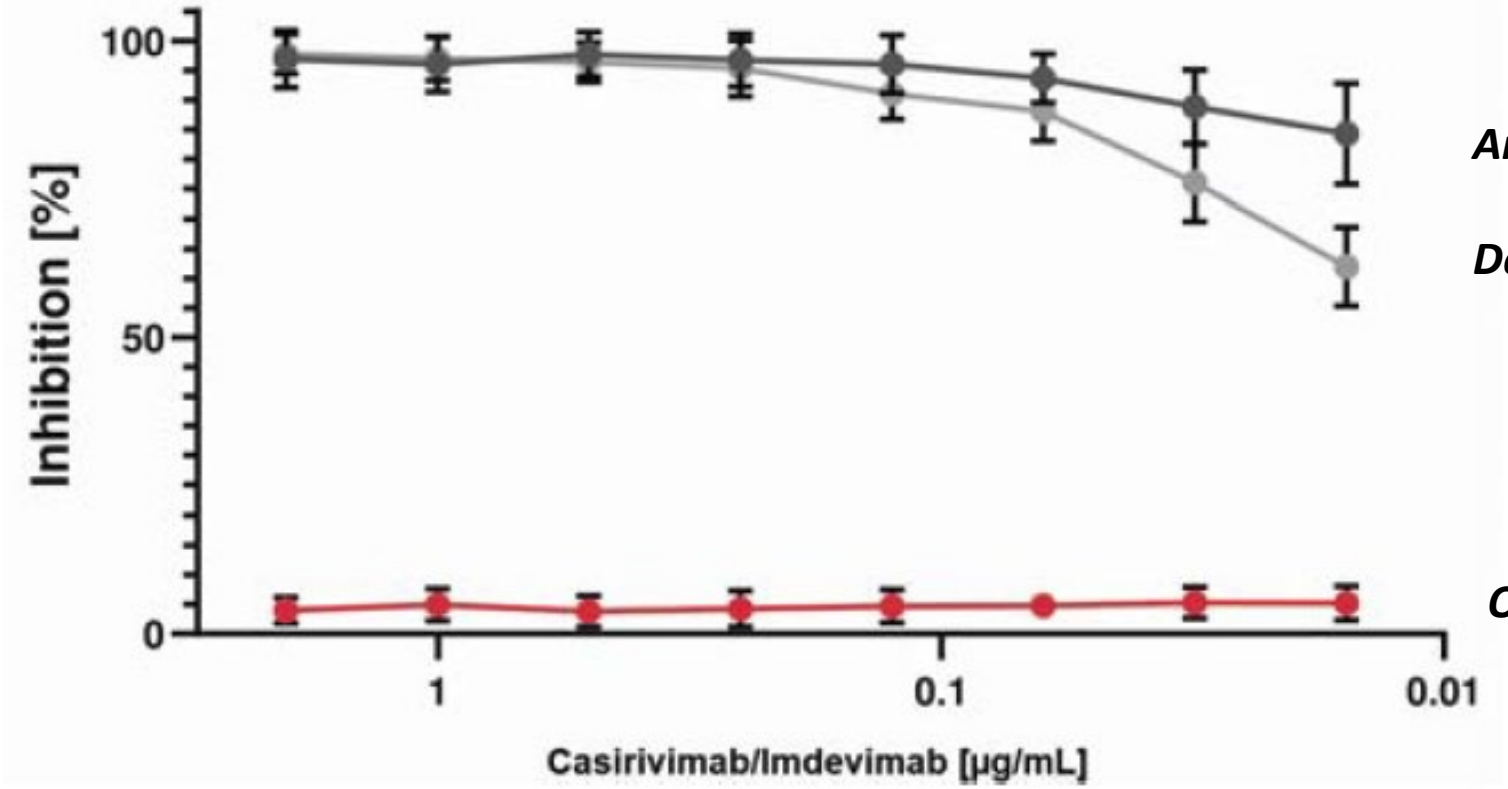
- mAb escape – need polyclonal solution
- Vaccine boosted CP or breakthrough CP

Next Pandemic

Warm infrastructure

- Site network
- Preplanned streamlined trials
- Coordination with Blood Banks
- Assay systems

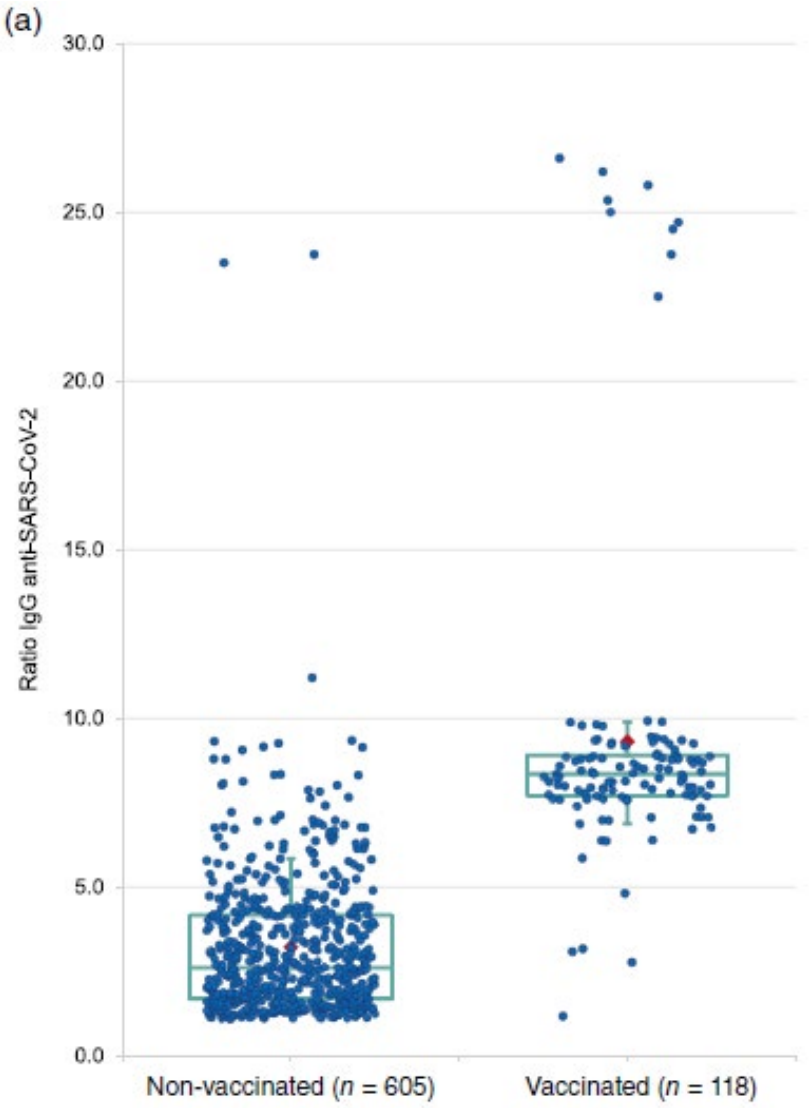
OMICRON Escapes Commonly Used mAbs



- ***Regeneron* = reduced efficacy**
- ***Lilly* = likely reduced efficacy**
- ***GSK* = seems OK but supply limited**

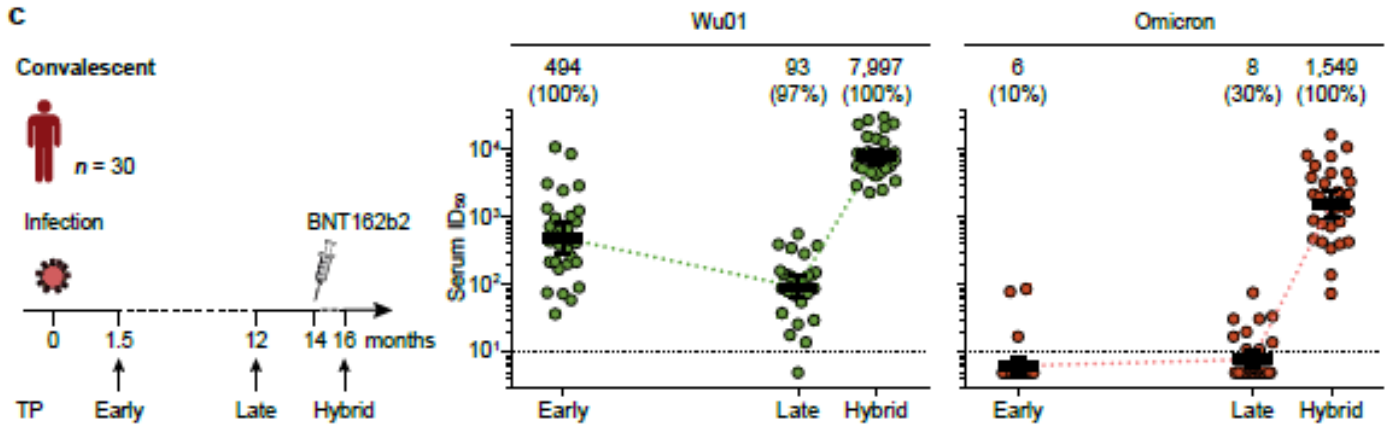
Wilhelm et al preprint

VaxPlasma – Ultra High Titer

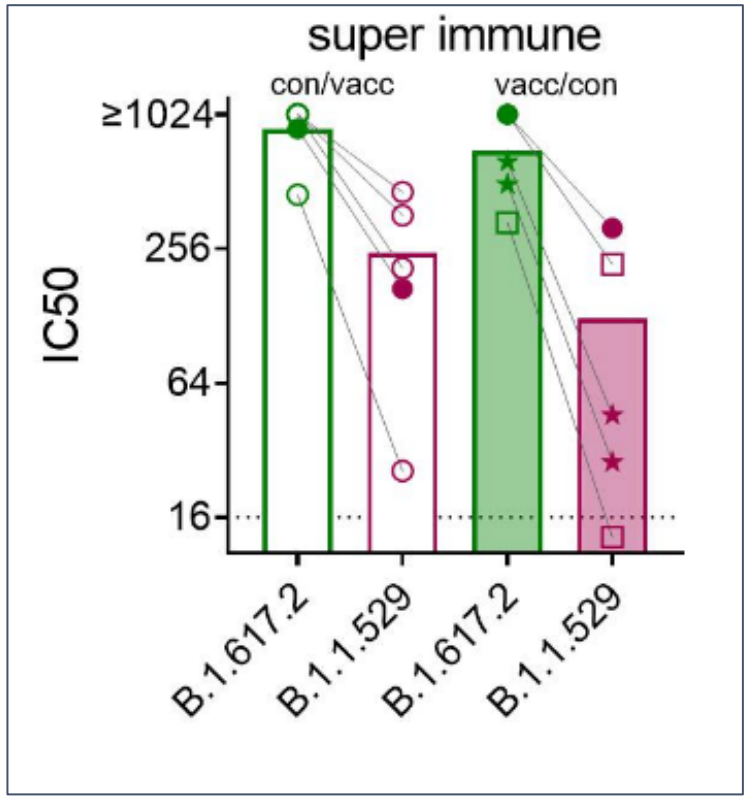


Gallian Vox et al Sang 2021

Vaccine Boosted Plasma *Covers* OMICRON



Cologne group preprint



Austrian group preprint

The Next Variant – *The Next Pandemic*

Next Variant

- mAb escape – need polyclonal solution
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Next Pandemic

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Discussion

UK RECOVERY CP "Negative" Trial:
But - Signals of Efficacy Seen In Low-Risk Subsets

LOW RISK CONDITION	CONVALESCENT PLASMA ARM	CONTROL ARM	ODDS RATIO (95% CONFIDENCE INTERVAL)
< 7 days since symptom onset	690/2149 = 32.1%	741/2156 = 34.4%	0.93 (0.86 – 1.02)
No oxygen received	60/442 = 13.7%	75/455 = 16.5%	0.82 (0.60 – 1.13)
Not receiving corticosteroids	66/360 = 18.3%	90/375 = 24%	0.76 (0.58 - 1.01)
Negative antibody test result	709/1935 = 36.7%	649/1586 = 40.9%	0.90 (0.82 – 0.97)

Paneth Analysis: Recovery Supplement