Convalescent Plasma: Therapeutic Clarity, Efficacy & Lessons Learned During the SARS-CoV-Pandemic.

Michael J. Joyner, MD

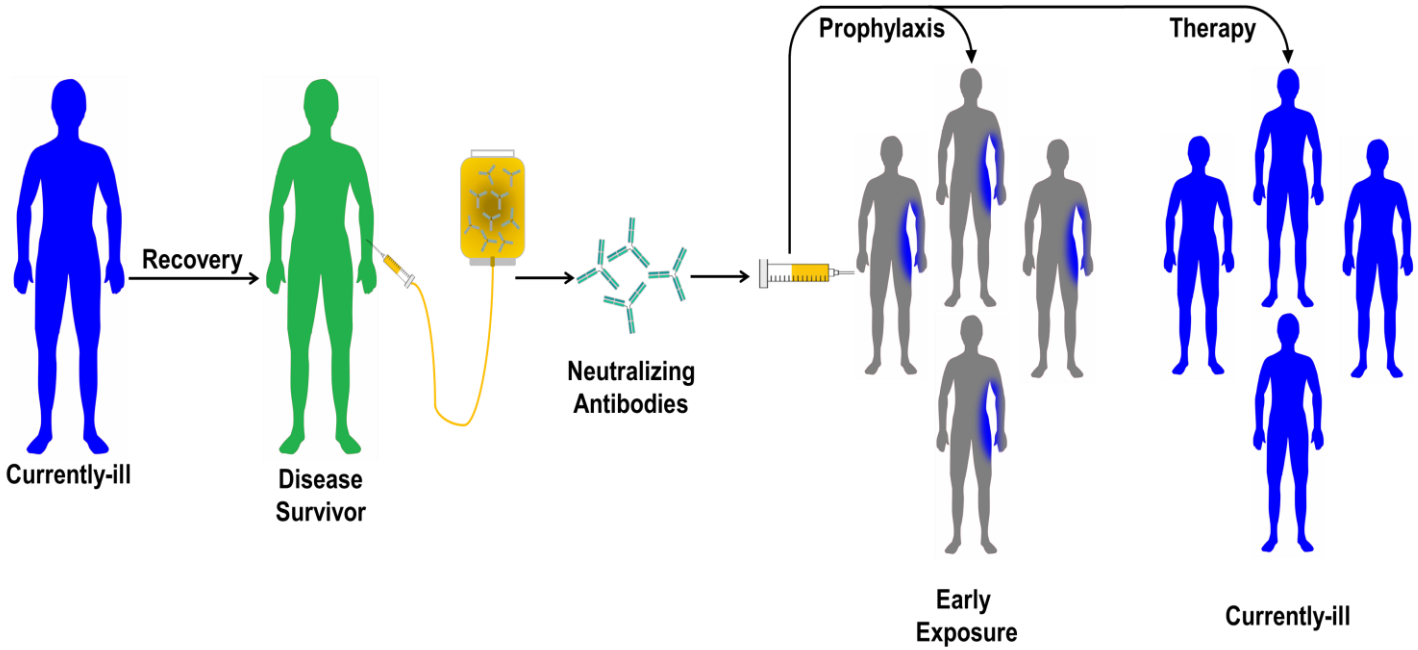
Dept. of Anesthesiology & Perioperative Medicine

Mayo Clinic

@DrMJoyner

https://www.uscovidplasma.org/

Convalescent Plasma (CP): *Conceptual Model & Principles*



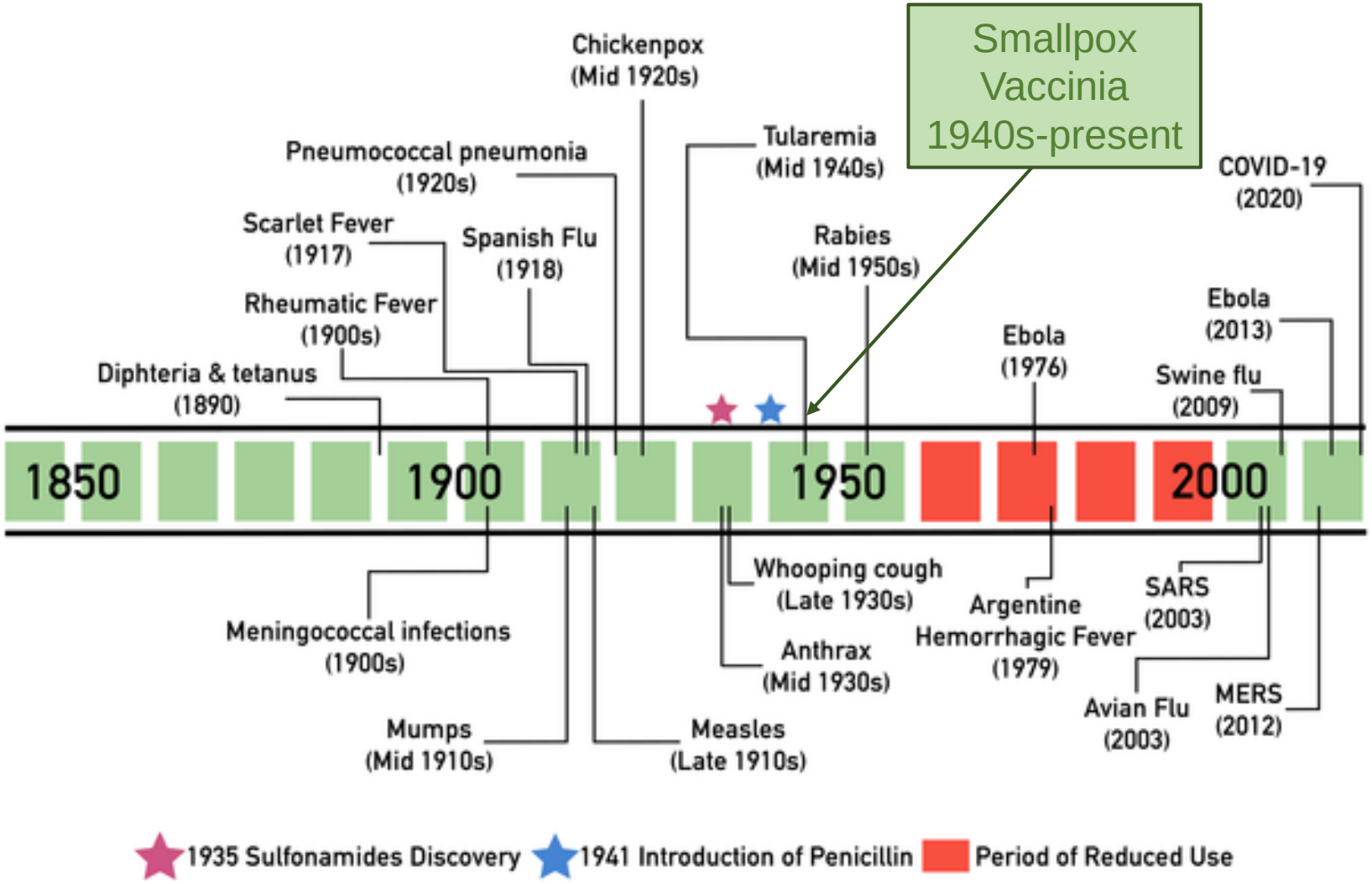
Principles of Antibody Therapy

- Specificity
- Early Timing
- High Dose

Give enough of the right stuff early

Adapted from Casavedall & Pirofski 2020

Notable Historic Uses of Antibody TX Against Infectious Diseases



Montelongo-Jauregui et al PlOS Path 2020

CP Pandemic Timeline – *Highlights 2020-2022*

2/20 use in China
2/20 Casadevall WSJ
3/20 FDE eINDs
3/20 FDA/Mayo EAP

8/20 FDA EUA
NY Sinai
Houston Methodist
+Immunosuppressed

Recovery is "negative" but late use

US Clinicians = high titer early

Libster NEJM & ++ Matched control studies

Thompson et al
Huseo et al
Bcell Depleted

More "negative" late use trials with signals of efficacy

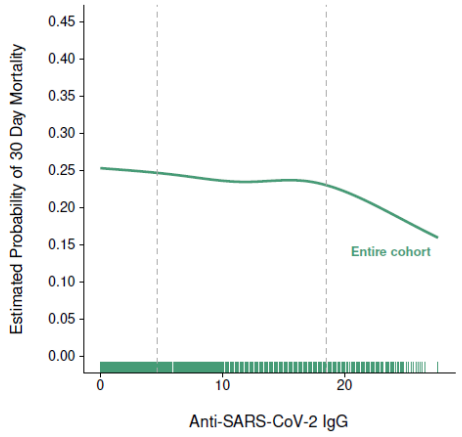
++ RCTS - Sullivan, Bar, O'Donnell, Korper, TBI etc.

Hybrid VaxPlasma
++ Titer covers VOCs

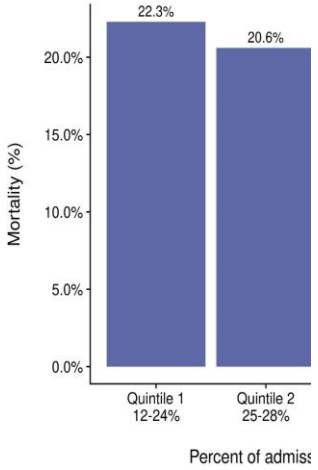
Rigid Application of EBM vs nuanced epistemology?

Guidelines start to catch up with +data

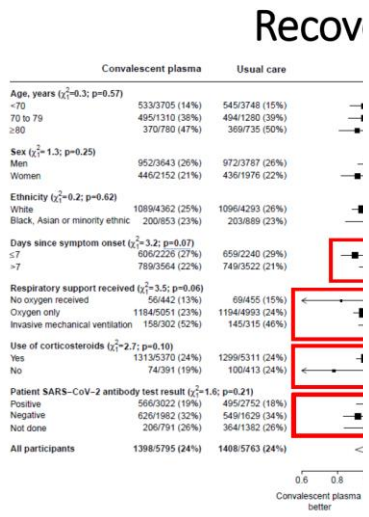
12/19 1/20 | 4/20 | 8/20 | **12/20 1/21** | 4/21 | 8/21 | **12/21 1/22** | 4/22 | 8/22



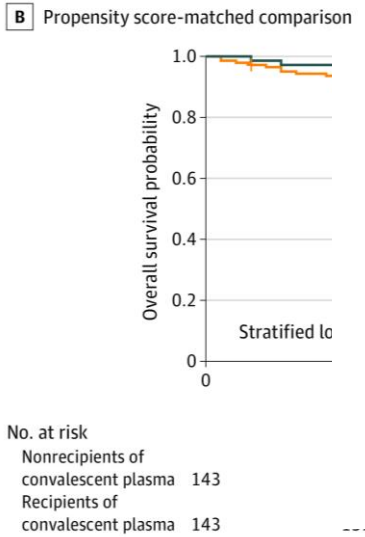
Joyner et al NEJM



Casadevall et al eLife



Landray et al Lancet



Thompson et al JAMA Onc

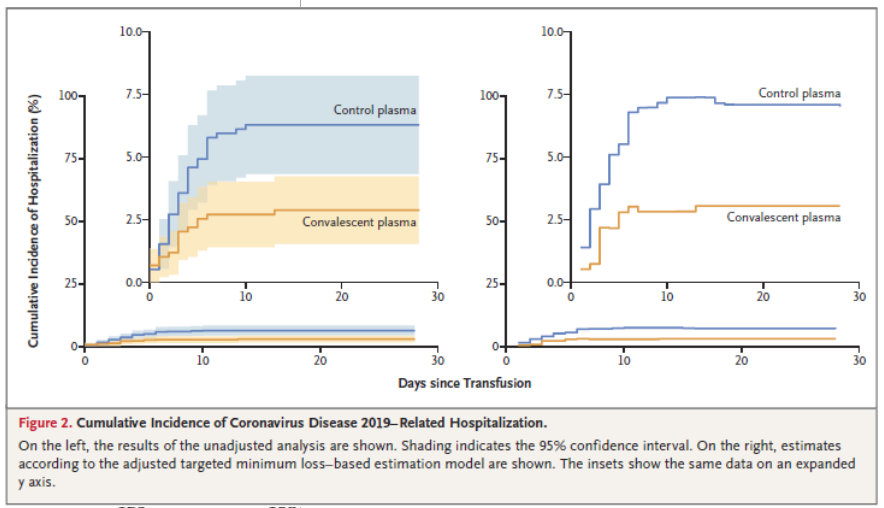
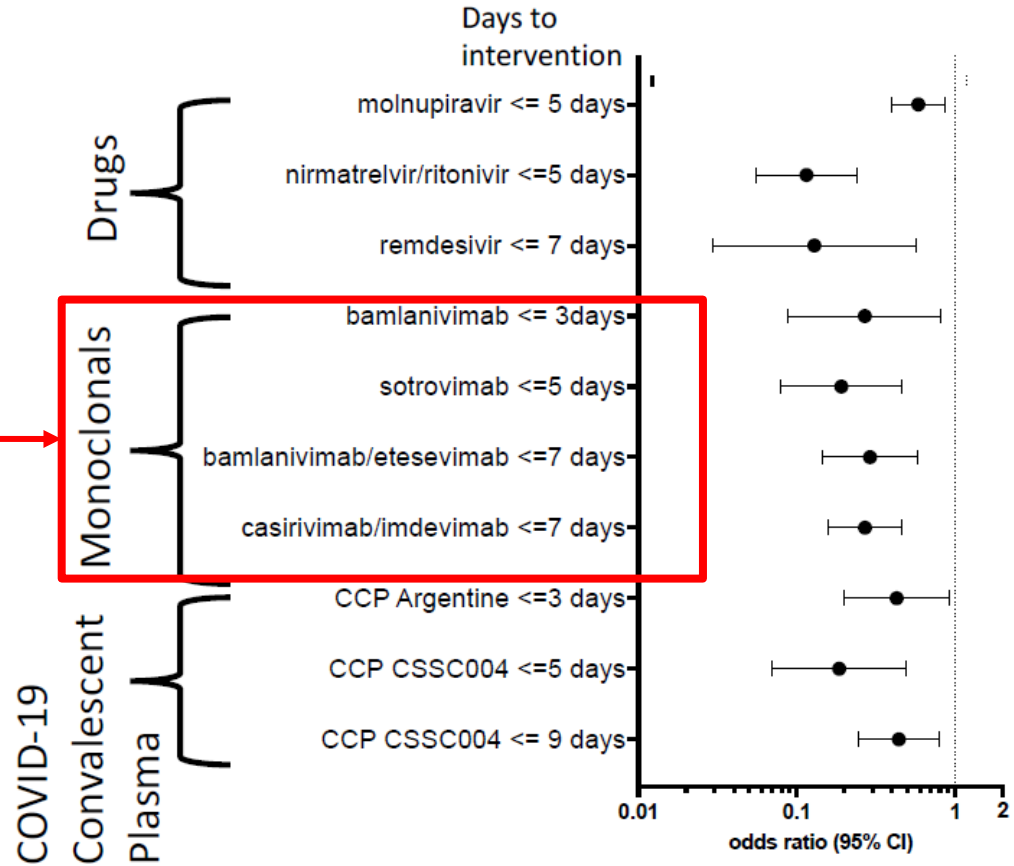


Figure 2. Cumulative Incidence of Coronavirus Disease 2019–Related Hospitalization.
On the left, the results of the unadjusted analysis are shown. Shading indicates the 95% confidence interval. On the right, estimates according to the adjusted targeted minimum loss–based estimation model are shown. The insets show the same data on an expanded y axis.

Sullivan et al NEJM

Outpatient RCTs To Prevent Hospitalization
Antivirals, mAbs & CP Comparison

No longer in use due to escape



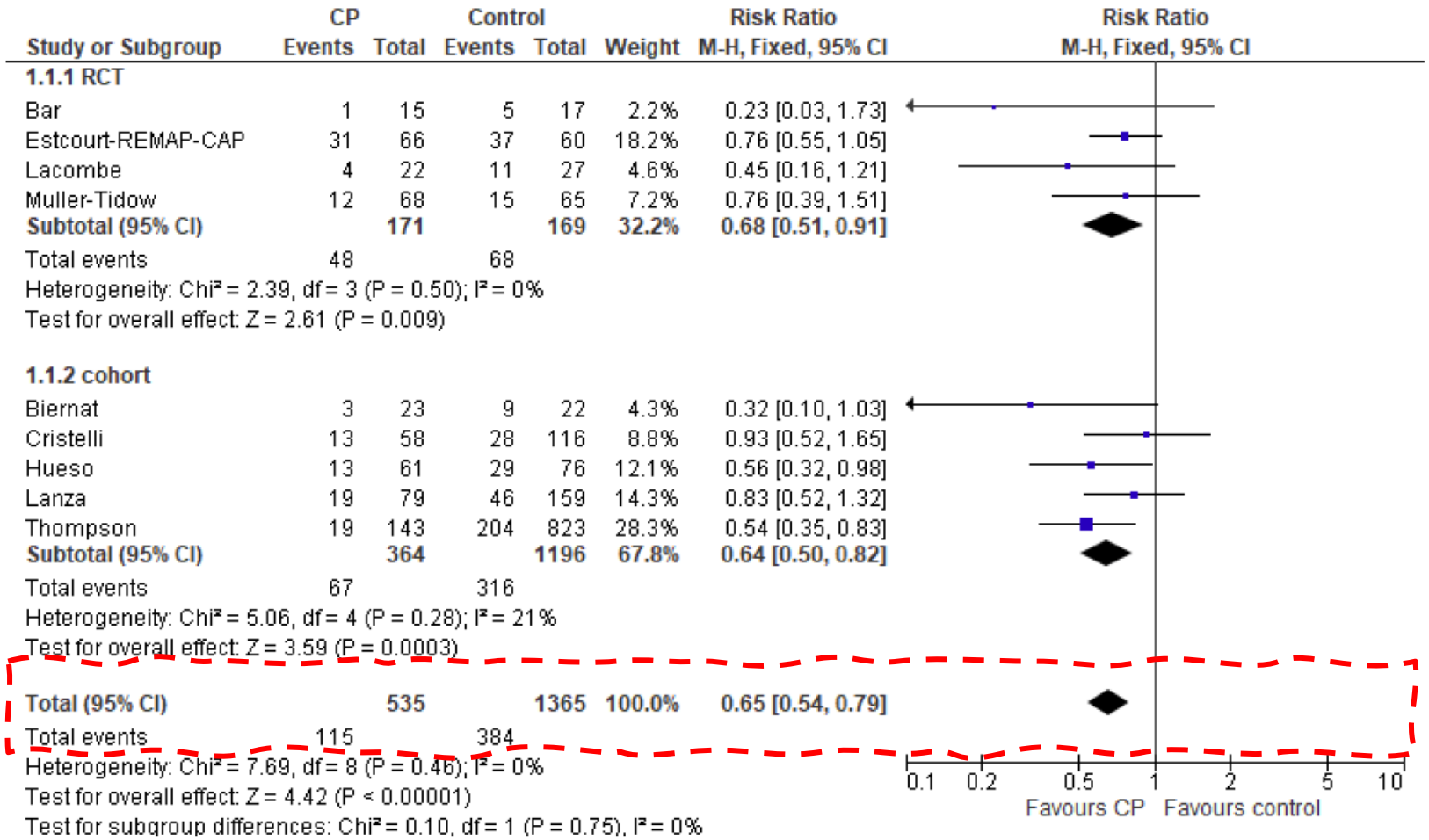
Control hospital	Control No hospital	Intervention hospital	Intervention No hospital	odds ratio	(95% CI)	Control h	Rel Rate
68	699	48	709	0.5853	(0.3986 to 0.8595)	9.7%	29%
66	1046	8	1039	0.1152	(0.0550 to 0.2412)	6.3%	88%
15	283	2	279	0.1290	(0.0292 to 0.5695)	5.3%	87%
9	156	5	309	0.2686	(0.0885 to 0.8158)	5.7%	44%
30	529	6	528	0.1912	(0.0789 to 0.4633)	5.6%	80%
36	517	11	518	0.2899	(0.1459 to 0.5760)	6.9%	69%
62	1341	18	1355	0.2697	(0.1587 to 0.4583)	4.6%	71%
25	80	13	80	0.4269	(0.1998 to 0.9120)	31%	48%
Argentine only-hypoxemia or tachypnea = hospital.							
25	259	5	258	0.1850	(0.0697 to 0.4912)	9.6%	80%
37	589	17	592	0.4411	(0.2455 to 0.7926)	6.3%	54%

Courtesy D Sullivan

CP & Antibody Therapy for COVID-19 After Two Years: *Take Home Messages*

- Convalescent Plasma (CP) safety profile similar to FFP
- No evidence of ADE
- High titer CP is effective if used early and *especially* in patients who don't make endogenous antibodies
- mAbs are safe and effective in preventing hospitalization and in patients who don't make endogenous antibodies – *however, mAbs are subject to escape by novel variants*
- Very high titer VaxPlasma from donors who have been both vaccinated and infected *adapts to and retains efficacy against variants*
- High titer CP including VaxPlasma is available worldwide at relatively low cost

CP & The Immune Suppressed:
RCT and Cohort Data 0.65 (0.54-0.79)



Study or Subgroup	CP Events	CP Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 RCT						
Bar	1	15	5	17	2.2%	0.23 [0.03, 1.73]
Estcourt-REMAP-CAP	31	66	37	60	18.2%	0.76 [0.55, 1.05]
Lacombe	4	22	11	27	4.6%	0.45 [0.16, 1.21]
Muller-Tidow	12	68	15	65	7.2%	0.76 [0.39, 1.51]
Subtotal (95% CI)		**171**		**169**	**32.2%**	**0.68 [0.51, 0.91]**
Total events	48		68			
Heterogeneity: Chi² = 2.39, df = 3 (P = 0.50); I² = 0%						
Test for overall effect: Z = 2.61 (P = 0.009)						
1.1.2 cohort						
Biernat	3	23	9	22	4.3%	0.32 [0.10, 1.03]
Cristelli	13	58	28	116	8.8%	0.93 [0.52, 1.65]
Hueso	13	61	29	76	12.1%	0.56 [0.32, 0.98]
Lanza	19	79	46	159	14.3%	0.83 [0.52, 1.32]
Thompson	19	143	204	823	28.3%	0.54 [0.35, 0.83]
Subtotal (95% CI)		**364**		**1196**	**67.8%**	**0.64 [0.50, 0.82]**
Total events	67		316			
Heterogeneity: Chi² = 5.06, df = 4 (P = 0.28); I² = 21%						
Test for overall effect: Z = 3.59 (P = 0.0003)						
Total (95% CI)		**535**		**1365**	**100.0%**	**0.65 [0.54, 0.79]**
Total events	115		384			
Heterogeneity: Chi² = 7.69, df = 8 (P = 0.46); I² = 0%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						

Senefeld et al preprint

Hybrid VaxPlasma & Commercial Assays (Roche)

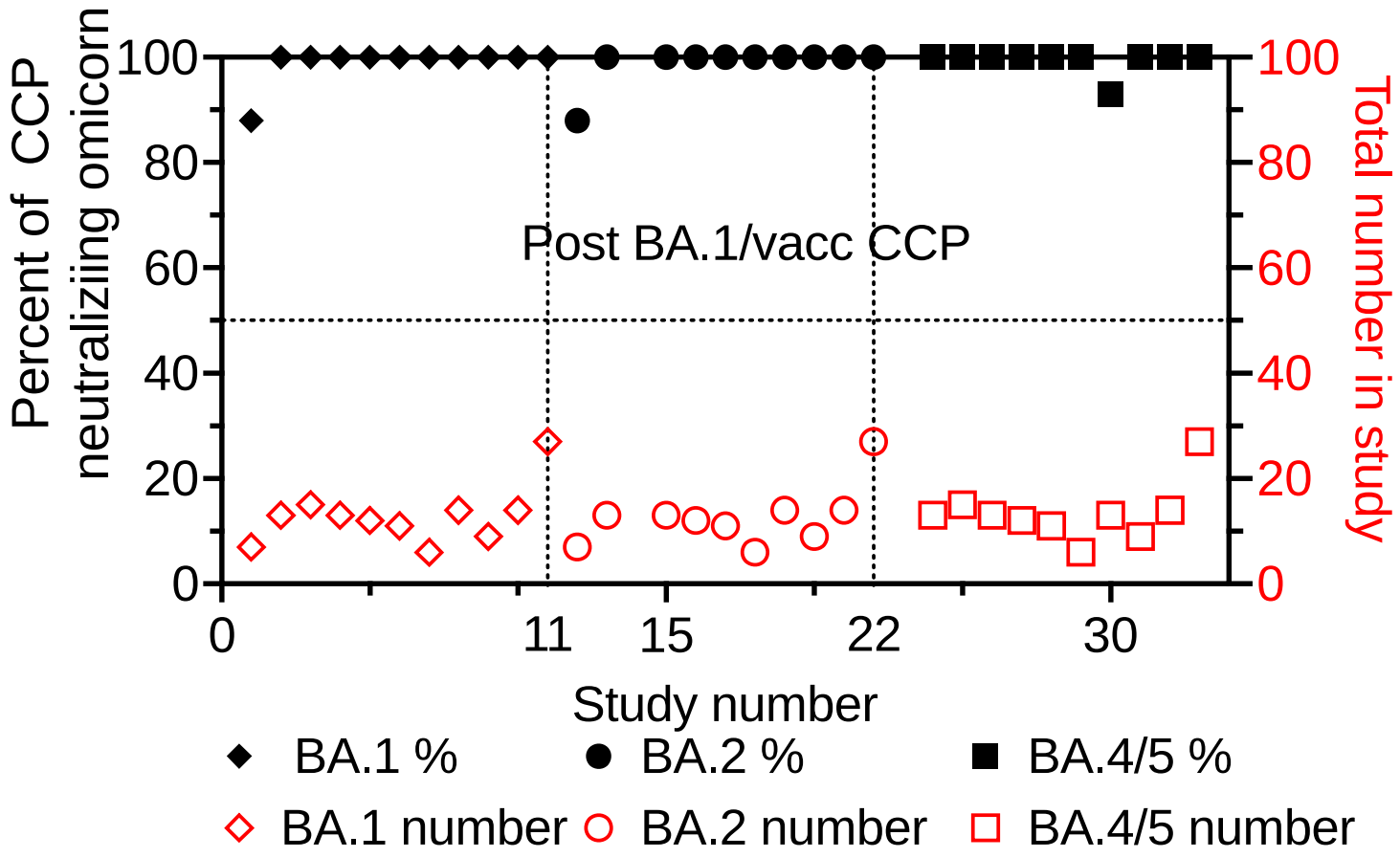
- Triple vaxed donor
- Omicron breakthrough May 2022
- Assay maxes out at 250
- Serial dilutions ~ 25,000
- 100x compared to summer 2020
- Seems to cover/keep up with variants

The results (U/mL) were as follows:
Neat = >250
On board X10 = >2500
X10 = 10*>250= >2500
X100 = 231*100= 23,100
X500 = 56.8*500 = 28,400
X1000 = 29.4*1000 = 29,400

The following comment with the result will be as follows:

"A x10 dilution was performed and the result was >2500 U/mL. The laboratory is unable to perform additional dilutions to achieve an absolute concentration. No minimum antibody level or threshold has been established to indicate long-term protective immunity against re-infection."

Hybrid (BA1 Breakthrough) VaxPlasma *Neutralizes BA4/5*



Sullivan et al in revision

Thinking About Year 3 & *Next Time*

- VaxPlasma for smoldering cases in the immune suppressed – ***DO NOW***
- Readiness for Next Time
  - CP will always be the 1st Ab available
  - Bioplausible & *totality of data perspective needed*
  - Blood banking preparedness
  - Community engagement & motivated donors
  - Adaptable assay system for model organisms that can be scaled quickly for a specific pathogen
  - Worldwide access!
- High Titer (*locally sourced ?*) - *Early Use, Early Use, Early Use plus High Risk*
- Expanded access plus pre-designed adaptive trials
- Templates for trials, compliance & funding
- Integrated approach to data/evidence - EBM and related methodology can be hammers and pandemics are not always nails….

Backup

High Titer CP Used Early "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.	258	20	7%	138	7	4%	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.	203	25	11%	93	12	11%	0%	High titer	8 (symptoms)
Sullivan et al.	592	0	0%	586	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	252	5	2%	253	1	0%	0%	High titer	4 (symptoms)
Overall	**2787**	**293**	**9.5%**	**2217**	**286**	**11.4%**			

$\chi^2 = 5.44$, $P = 0.019$; 16.7% relative mortality reduction associated with convalescent plasma therapy

Klassen & Senefeld Unpublished

CP Pandemic Timeline – *Highlights 2020-2022*

2/20 use in China
2/20 Casadevall WSJ
3/20 FDE eINDs
3/20 FDA/Mayo EAP

8/20 FDA EUA
NY Sinai
Houston Methodist
+Immunosuppressed

Recovery is "negative" but late use

US Clinicians = high titer early

Libster NEJM & ++ Matched control studies

Thompson et al
Huseo et al
Bcell Depleted

More "negative" late use trials with signals of efficacy

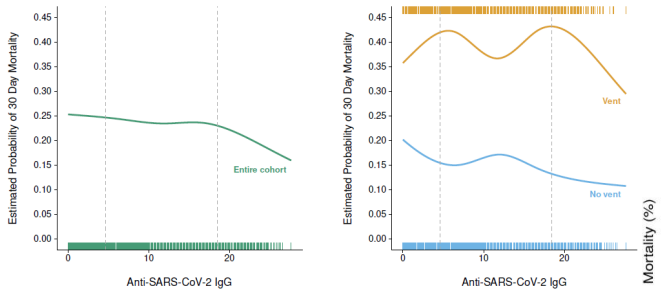
++ RCTS - Sullivan, Bar, O'Donnell, Korper, TBI etc.

Hybrid VaxPlasma
++ Titer covers VOCs

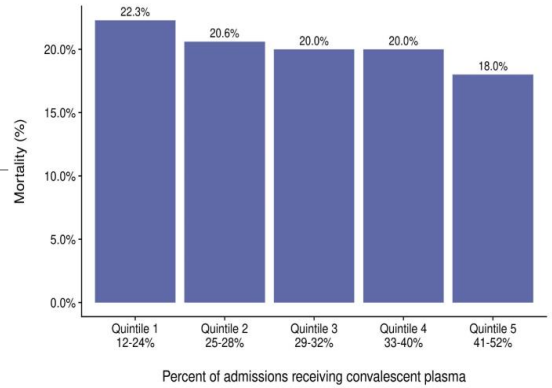
Rigid Application of EBM vs nuanced epistemology?

Guidelines start to catch up with +data

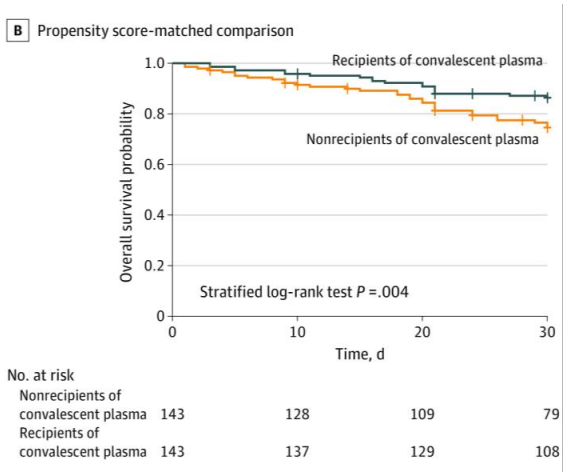
12/19 1/20 | 4/20 | 8/20 | **12/20 1/21** | 4/21 | 8/21 | **12/21 1/22** | 4/22 | 8/22



Joyner et al NEJM



Casadevall et al eLife



Thompson et al JAMA Onc

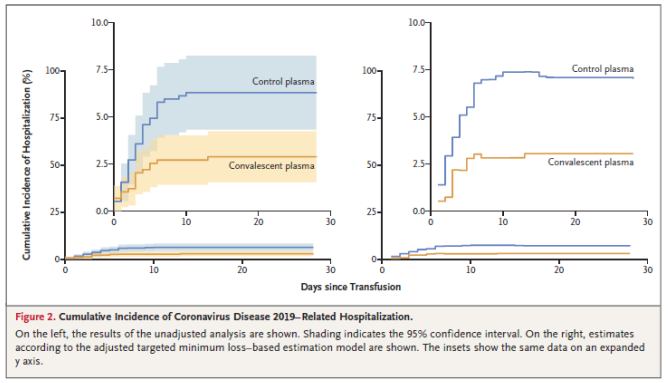


Figure 2. Cumulative Incidence of Coronavirus Disease 2019–Related Hospitalization.
On the left, the results of the unadjusted analysis are shown. Shading indicates the 95% confidence interval. On the right, estimates according to the adjusted targeted minimum loss–based estimation model are shown. The insets show the same data on an expanded y axis.

Sullivan et al NEJM