Convalescent plasma for treatment of respiratory viruses

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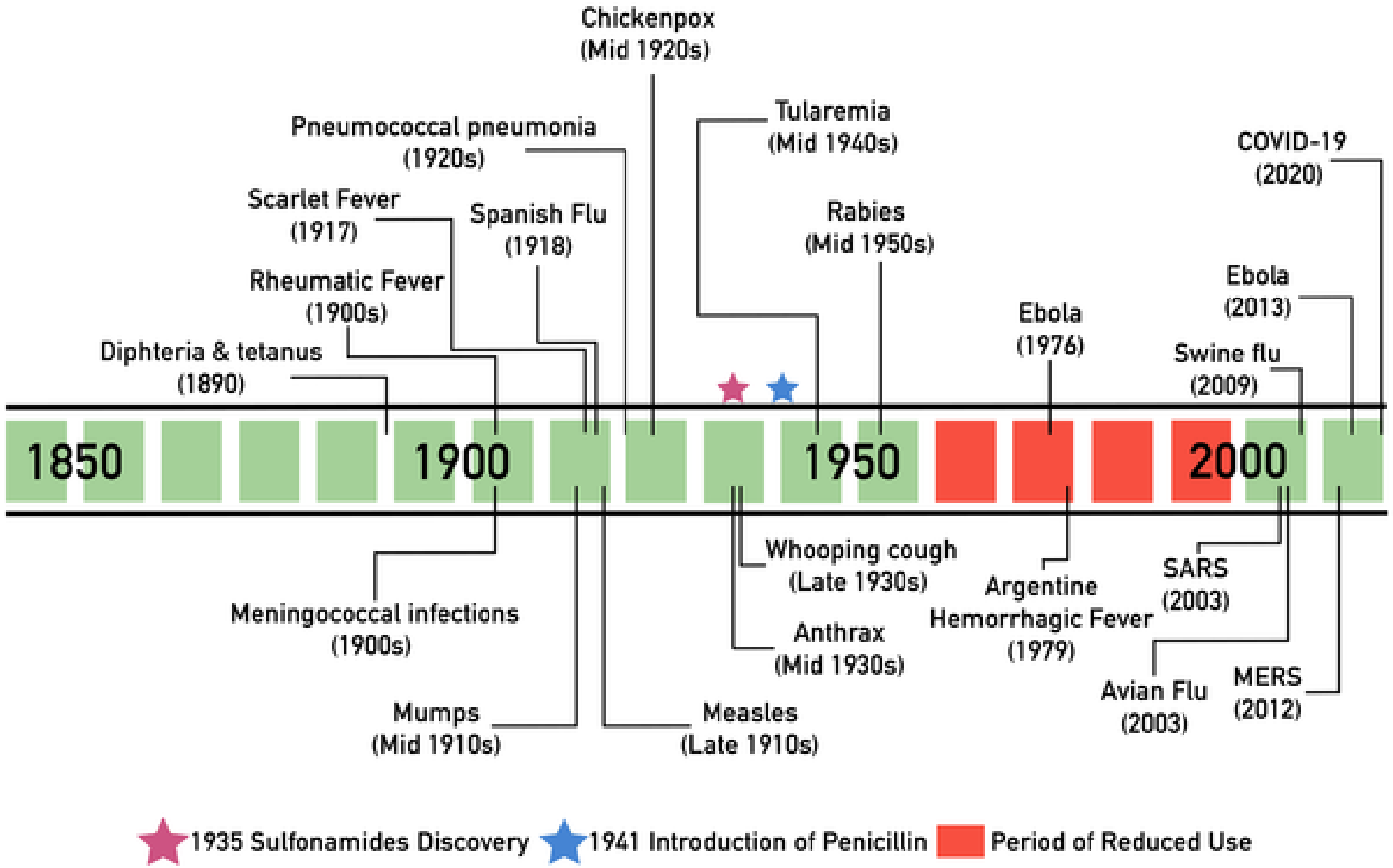
Pisa University Hospital

EMA workshop on primary efficacy endpoints for antivirals and monoclonal antibodies intended to treat COVID-19 and Influenza

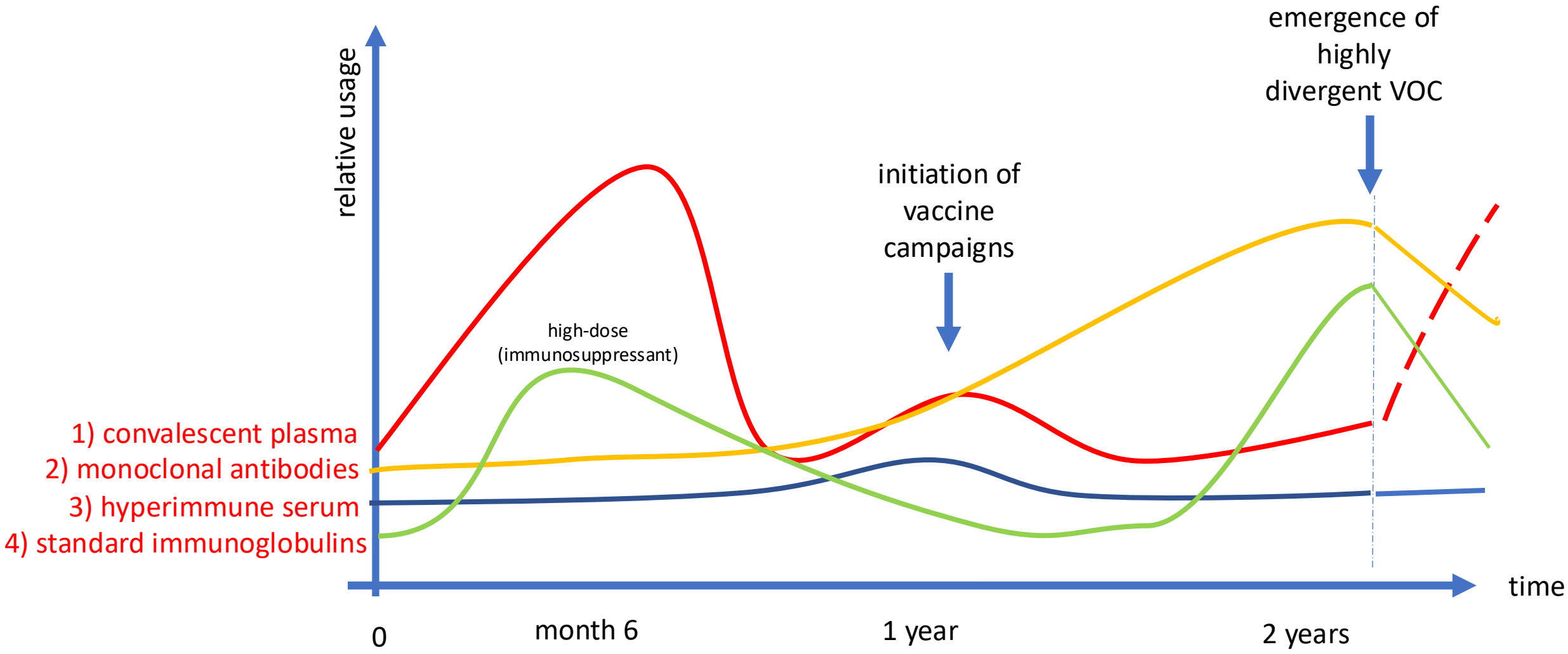
June 5-6, 2025

Notable historic uses of antibody therapy against infectious diseases



Montelongo-Jauregui *et al*, *PLoS Pathogens*, 2020
https://en.wikipedia.org/wiki/Convalescent_plasma

Different types of passive immunotherapies against a novel pandemic microbe



Focosi *et al*, *Rev Med Virol*, 2022

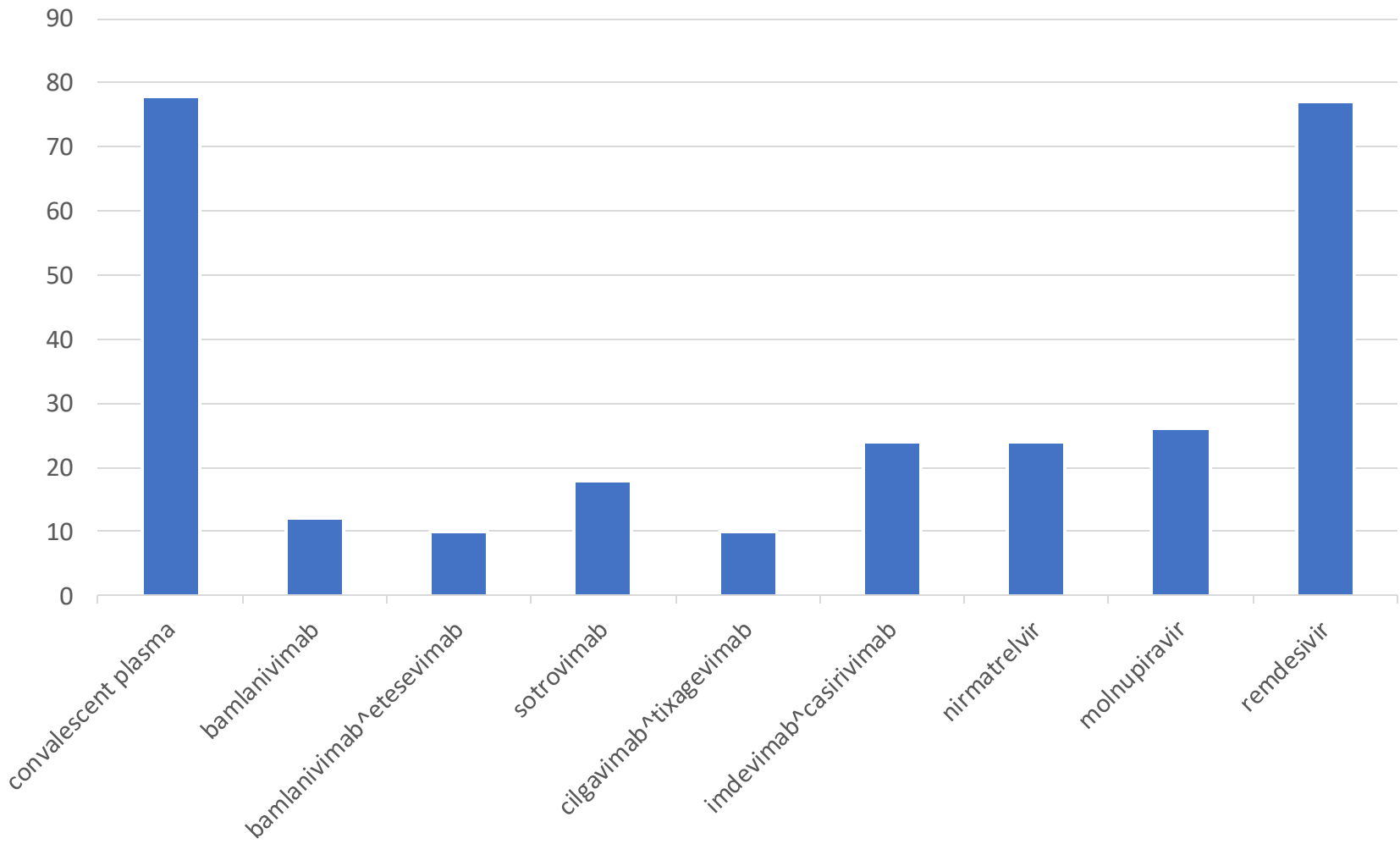
Fresh-frozen CCP is a heterogenous and hard-to-standardize product

- *Antiviral*
  - *$ACE2^+$ EV*
  - *FXa*
  - *neutralizing antibodies*
    - *from SARS-CoV-2 infection*
    - *from heterologous infection*
    - *from heterologous vaccine*
- *Antithrombotic*
  - *AT-III*
  - *albumin*
- *Antiinflammatory*
  - *dilution of proinflammatory cytokines*
  - *nonspecific Ig*
  - *A_1AT*

- *Proviral*
  - *Spike-activating endoproteases*
  - *virus-carrying EVs*
- *Prothrombotic*
  - *TF-expressing EV*
  - *autoantibodies (ADAMTS13, aPL, β_2G1, LAC, annexin A2)*
  - *α_2AP*
  - *sUPAR*
- *Proinflammatory*
  - *afucosylated IgG*
  - *autoantibodies (IFN, MDA5, ANA, , ANCA, ACE2, AT1R, MDA, AD, Yo, NMDAR)*

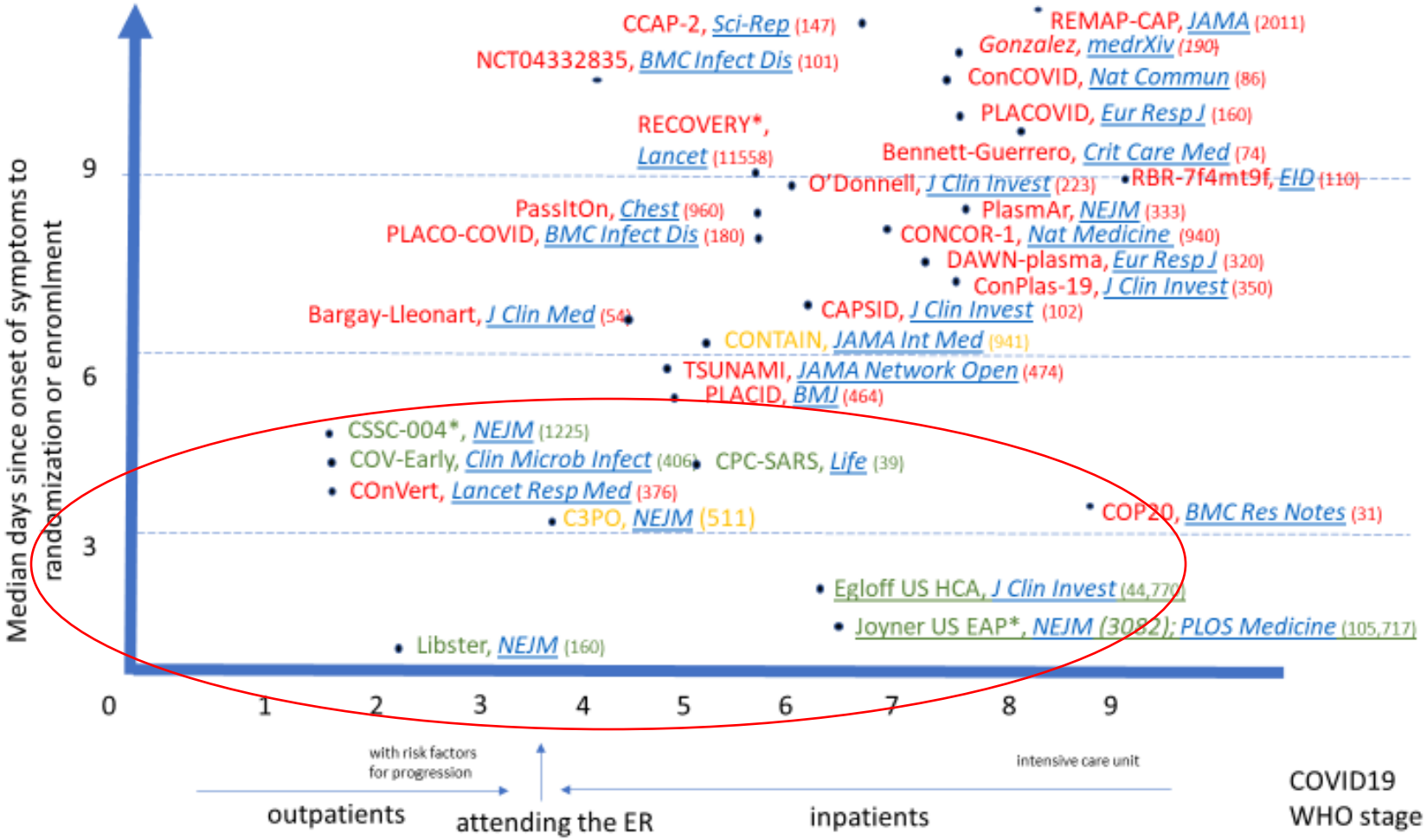
Focosi *et al*, *Viruses*, 2021

During the COVID-19 pandemic, COVID-19 convalescent plasma (CCP) was the most investigated antiviral in RCTs



Source: PubMed query with “Randomized Clinical Trials” filter

CCP in immunocompetent patients : summary of RCTs.
A few successes in early usage submerged by a plethora of failures in late stages



Focosi *et al*, *Clin Microb Rev* (2021), updated

Is CCP safe? Yes, it is.

Study or Subgroup	CP Events	CP Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
1.5.1 hospitalized pts						
Beltran Gonzalez	0	130	2	60	0.2%	−0.03 [−0.08, 0.02]
CCAP-2	1	98	0	46	0.3%	0.01 [−0.03, 0.05]
Holm	0	17	0	14	0.0%	0.00 [−0.12, 0.12]
O'Donnell	3	147	2	72	0.2%	−0.01 [−0.05, 0.04]
PassITON	1	487	0	487	14.4%	0.00 [−0.00, 0.01]
PLACO COVID	0	60	1	60	0.2%	−0.02 [−0.06, 0.03]
PLACOVID	0	80	0	80	0.8%	0.00 [−0.02, 0.02]
PlasmAr	0	228	0	105	2.2%	0.00 [−0.01, 0.01]
PROTECT	0	52	0	51	0.3%	0.00 [−0.04, 0.04]
REMAP-CAP	1	1075	0	905	63.5%	0.00 [−0.00, 0.00]
Subtotal (95% CI)		**2374**		**1880**	**82.3%**	**0.00 [−0.00, 0.00]**
Total events	6		5			
Heterogeneity: Tau² = 0.00; Chi² = 5.32, df = 9 (*p* = 0.81); I² = 0%						
Test for overall effect: Z = 0.81 (*p* = 0.42)						
1.5.2 outpatients						
CONV-ERT	1	188	0	188	2.2%	0.01 [−0.01, 0.02]
Libster	0	80	0	80	0.8%	0.00 [−0.02, 0.02]
Shoham	0	87	1	93	0.5%	−0.01 [−0.04, 0.02]
Sullivan	2	592	0	589	14.2%	0.00 [−0.00, 0.01]
Subtotal (95% CI)		**947**		**950**	**17.7%**	**0.00 [−0.00, 0.01]**
Total events	3		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 3 (*p* = 0.77); I² = 0%						
Test for overall effect: Z = 1.17 (*p* = 0.24)						
Total (95% CI)		**3321**		**2830**	**100.0%**	**0.00 [−0.00, 0.00]**
Total events	9		6			
Heterogeneity: Tau² = 0.00; Chi² = 5.77, df = 13 (*p* = 0.95); I² = 0%						
Test for overall effect: Z = 1.22 (*p* = 0.22)						
Test for subgroup differences: Chi² = 0.52, df = 1 (*p* = 0.47), I² = 0%						

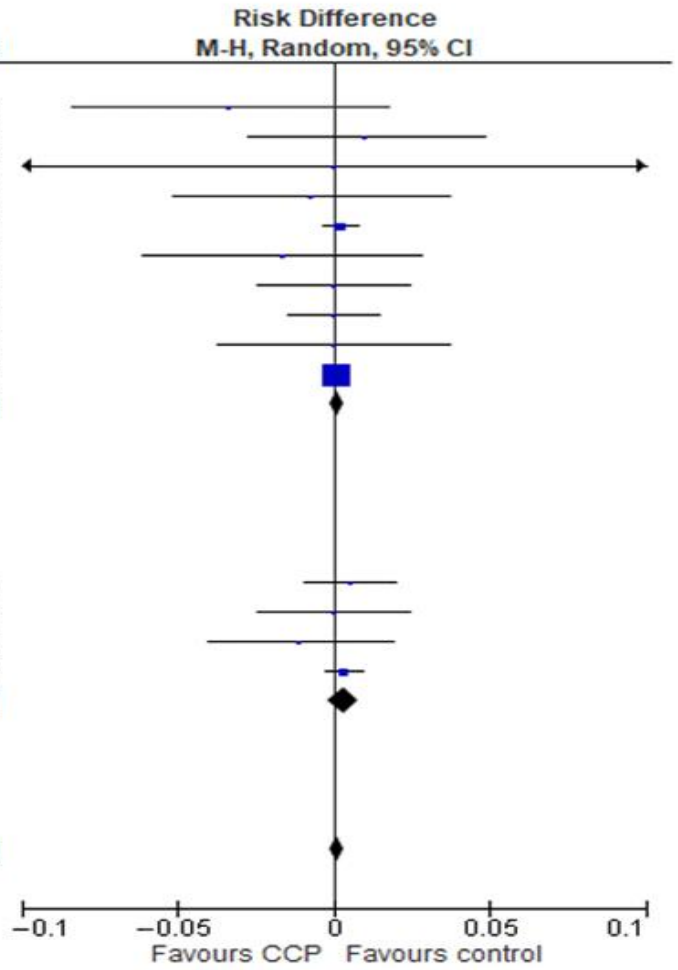
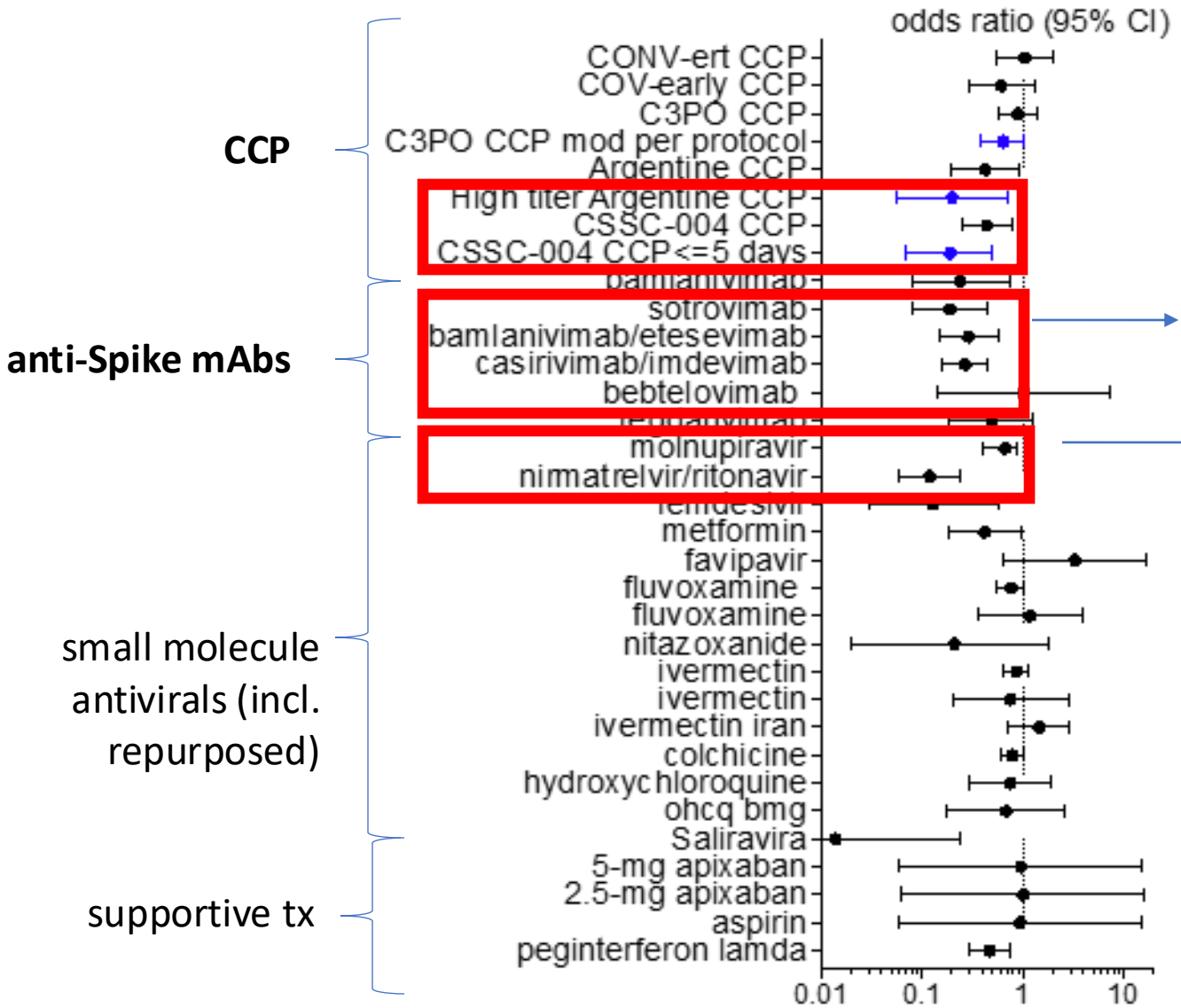


FIGURE 4 Forest plot of comparison: Convalescent plasma versus control, outcome: 1.5 Treatment-related adverse reactions (serious).

Franchini *et al*, *Transfusion*, 2023

Can CCP reduce hospitalizations in outpatients? Yes, it can, at the same level as with anti-Spike mAbs.

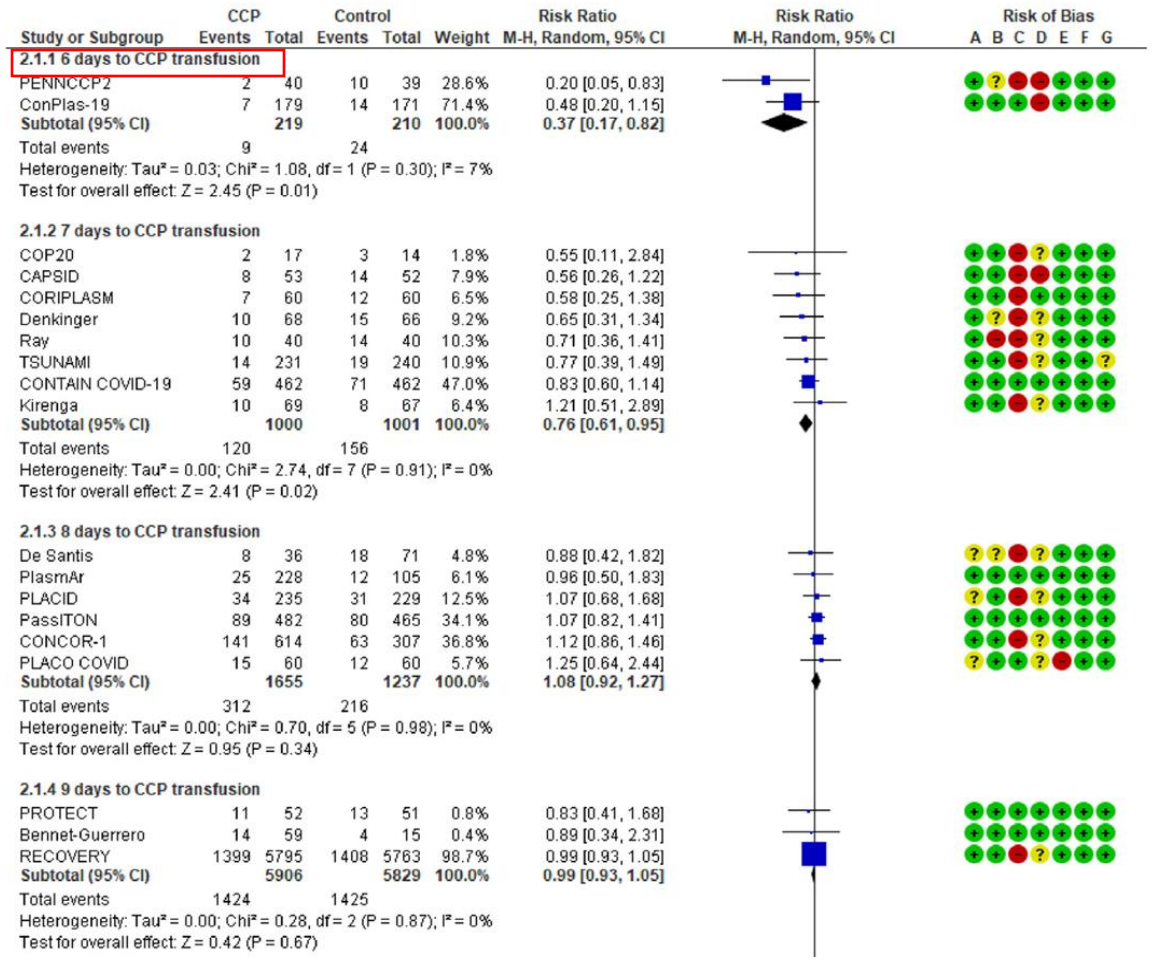


EUA withdrawn by FDA for all 4 mAbs

PANORAMIC RCT : no reduction in hospitalizations at the time of Omicron. Mutagenicity concerns

Sullivan *et al*, *J Med Virol*, 2023

Can CCP reduce mortality in hospitalized patients? Yes, only if administered within 5 days



Study or Subgroup	CCP Events	CCP Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 6 days to CCP transfusion						
PENNCCP2	2	40	10	39	28.6%	0.20 [0.05, 0.83]
ConPlas-19	7	179	14	171	71.4%	0.48 [0.20, 1.15]
Subtotal (95% CI)		**219**		**210**	**100.0%**	**0.37 [0.17, 0.82]**
Total events	9		24			
Heterogeneity: Tau² = 0.03; Chi² = 1.08, df = 1 (P = 0.30); I² = 7%						
Test for overall effect: Z = 2.45 (P = 0.01)						
2.1.2 7 days to CCP transfusion						
COP20	2	17	3	14	1.8%	0.55 [0.11, 2.84]
CAPSID	8	53	14	52	7.9%	0.56 [0.26, 1.22]
CORIPLASM	7	60	12	60	6.5%	0.58 [0.25, 1.38]
Denkinger	10	68	15	66	9.2%	0.65 [0.31, 1.34]
Ray	10	40	14	40	10.3%	0.71 [0.36, 1.41]
TSUNAMI	14	231	19	240	10.9%	0.77 [0.39, 1.49]
CONTAIN COVID-19	59	462	71	462	47.0%	0.83 [0.60, 1.14]
Kirenga	10	69	8	67	6.4%	1.21 [0.51, 2.89]
Subtotal (95% CI)		**1000**		**1001**	**100.0%**	**0.76 [0.61, 0.95]**
Total events	120		156			
Heterogeneity: Tau² = 0.00; Chi² = 2.74, df = 7 (P = 0.91); I² = 0%						
Test for overall effect: Z = 2.41 (P = 0.02)						
2.1.3 8 days to CCP transfusion						
De Santis	8	36	18	71	4.8%	0.88 [0.42, 1.82]
PlasmAr	25	228	12	105	6.1%	0.96 [0.50, 1.83]
PLACID	34	235	31	229	12.5%	1.07 [0.68, 1.68]
PassITON	89	482	80	465	34.1%	1.07 [0.82, 1.41]
CONCOR-1	141	614	63	307	36.8%	1.12 [0.86, 1.46]
PLACO COVID	15	60	12	60	5.7%	1.25 [0.64, 2.44]
Subtotal (95% CI)		**1655**		**1237**	**100.0%**	**1.08 [0.92, 1.27]**
Total events	312		216			
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 5 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
2.1.4 9 days to CCP transfusion						
PROTECT	11	52	13	51	0.8%	0.83 [0.41, 1.68]
Bennet-Guerrero	14	59	4	15	0.4%	0.89 [0.34, 2.31]
RECOVERY	1399	5795	1408	5763	98.7%	0.99 [0.93, 1.05]
Subtotal (95% CI)		**5906**		**5829**	**100.0%**	**0.99 [0.93, 1.05]**
Total events	1424		1425			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 2 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						

Risk Ratio M-H, Random, 95% CI

Risk of Bias A B C D E F G

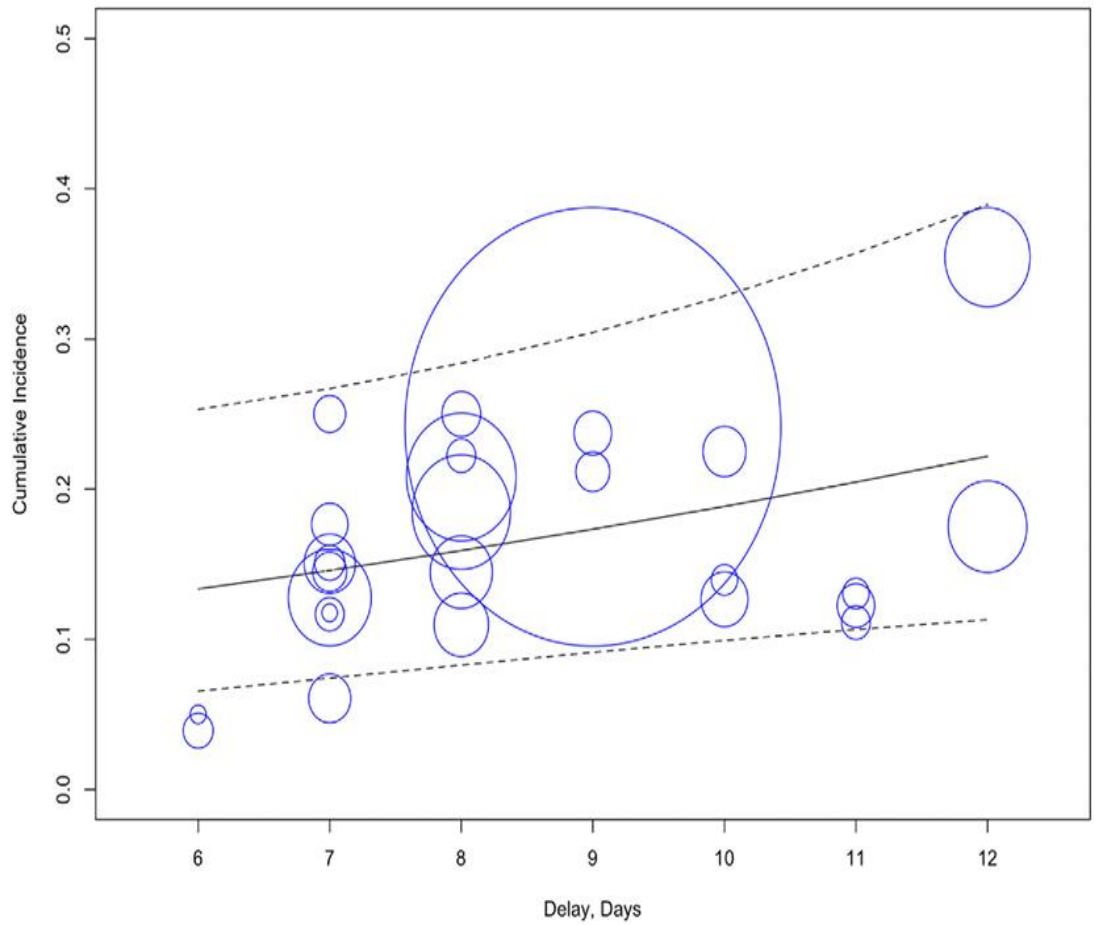
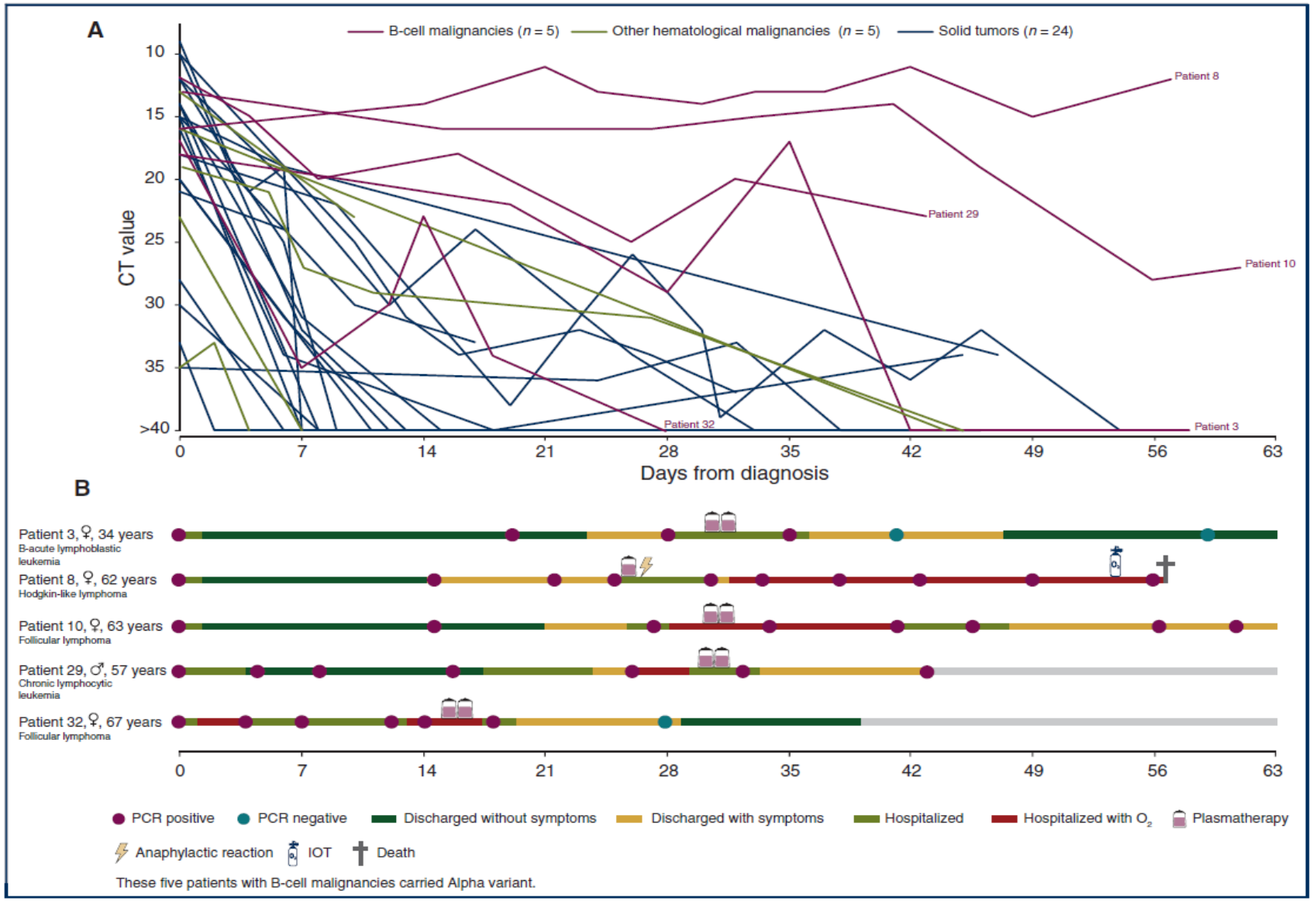


Fig. 3. Results of the meta-regression analysis. (a) Cumulative incidence of death (mortality) as a function of the delay in the start of the convalescent plasma treatment. The prediction line of the mean after the regression on the treated arm is depicted as a solid line, the confidence area is delimited by the dashed curves. The size of the original studies is indicated by the area of the circles. (b) Meta-regression on 28-day mortality, table of coefficients (estimate). The coefficients of predictors "WHO" and "Days", expressed in logit

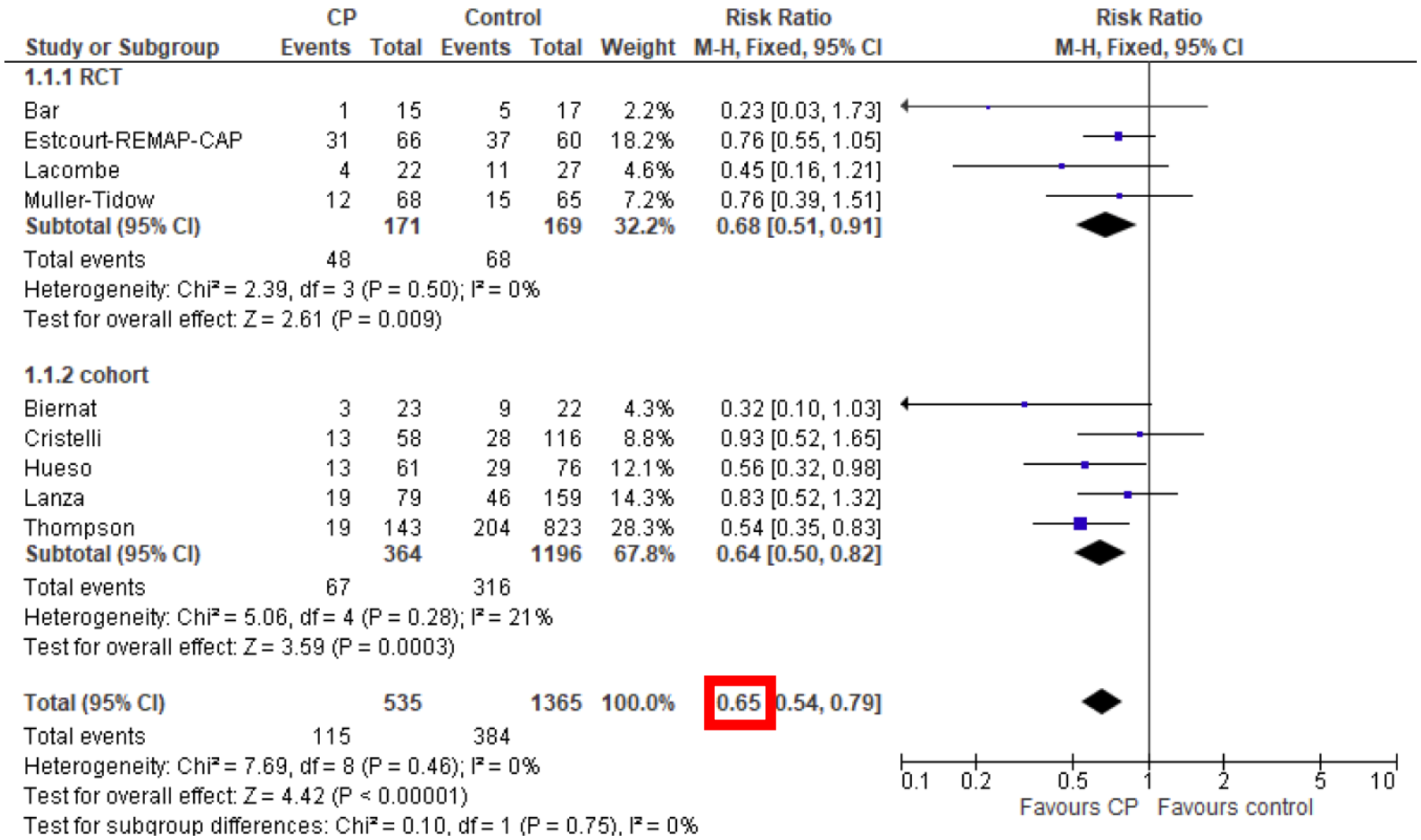
Franchini *et al*, *Clin Microbiol Infect*, 2024

Can CCP rescue anti-Spike mAb treatment failures? Yes, it can.



Pommeret *et al*, *Ann Oncol,* 2021

Can CCP reduce mortality in immunocompromised patients? Yes, it can (1/2).



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*, *JAMA Network Open*, 2024

Can CCP reduce 60-day mortality in B-cell depleted patients? Yes, it can

Table 3. Conditional logistic regression results.

Characteristic	OR	95% CI	p
Patient type			0.013
Autoimmune disorder	6.88	(1.50, 31.63)	
Hematologic cancer/disorder	1.00	(reference)	
Days since the last anti-CD20 dose†	1.16	(1.04, 1.29)	0.007
Number of COVID-19 vaccine doses†	0.92	(0.69, 1.22)	0.566
Anti-spike Ab status			0.929
Negative	1.00	(reference)	
Positive	0.95	(0.31, 2.88)	
Treatment of underlying condition			
BTK inhibitors	1.12	(0.21, 6.11)	0.984
Anti-CD19 CAR T-cell therapy	0.10	(0.02, 0.66)	0.016
Bendamustine	0.94	(0.44, 2.05)	0.884
Venetoclax	3.65	(0.46, 29.23)	0.223
CCP treatment			
Type of plasma transfused			0.005
CCP or Vaccine-only plasma	1.00	(reference)	
Vaccine-boosted CCP	9.49	(2.01, 44.82)	
Total units transfused, units	0.93	(0.78, 1.11)	0.426
Total volume transfused, mL	0.98	(0.81, 1.19)	0.827
Days from first symptoms	1.01	(1.00, 1.02)	0.179
Days from hospital admission	1.00	(0.99, 1.02)	0.575
Concomitant COVID-19 therapy			
Non-specific IVIG	1.82	(0.48, 6.88)	0.377
Steroids	0.95	(0.45, 1.97)	0.879
Remdesivir	1.31	(0.66, 2.61)	0.440
Nirmatrelvir/ritonavir	2.76	(0.32, 23.74)	0.354
Hydroxychloroquine	1.61	(0.34, 7.76)	0.550
Anti-spike mAb	2.17	(0.66, 7.10)	0.202

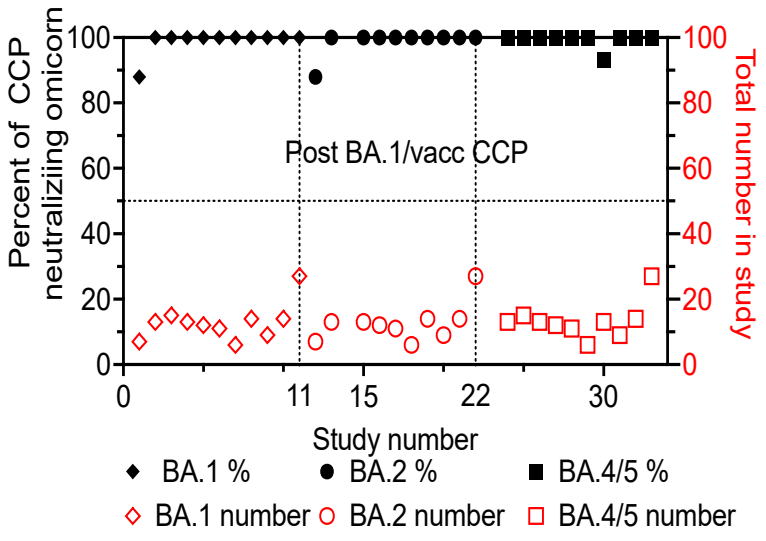
Individual patient data metanalysis
570 B-cell depleted patients

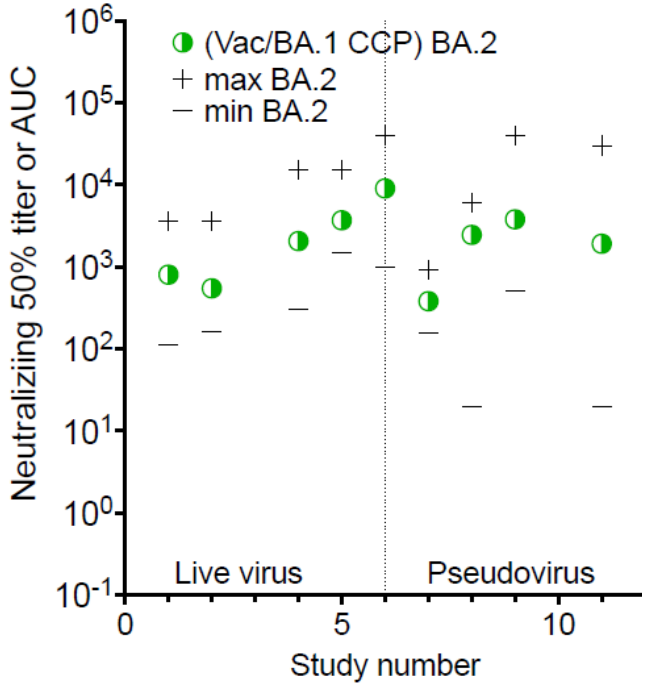
- 64% clinical improvement within 5 days
- 70.1% SARS-CoV-2 clearance
- 86.5% 60-day survival

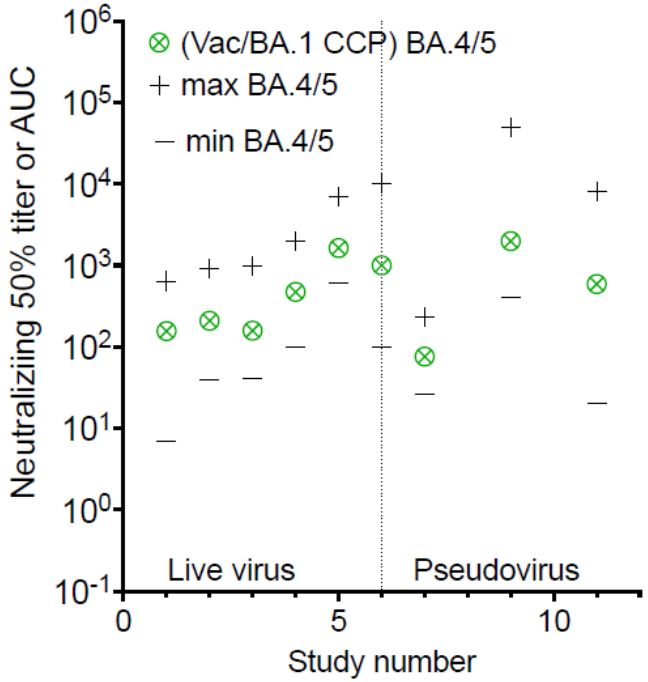
Zaremba *et al*, submitted to Blood
Available at https://www.medrxiv.org/content/10.1101/2025.05.15.25327576v1

Why is VaxCCP superior to CCP? Hybrid immunity is heterologous

BA.1 breakthrough (hybrid) VaxPlasma neutralizes BA.2 and BA.4/5 with high titers and 100% prevalence





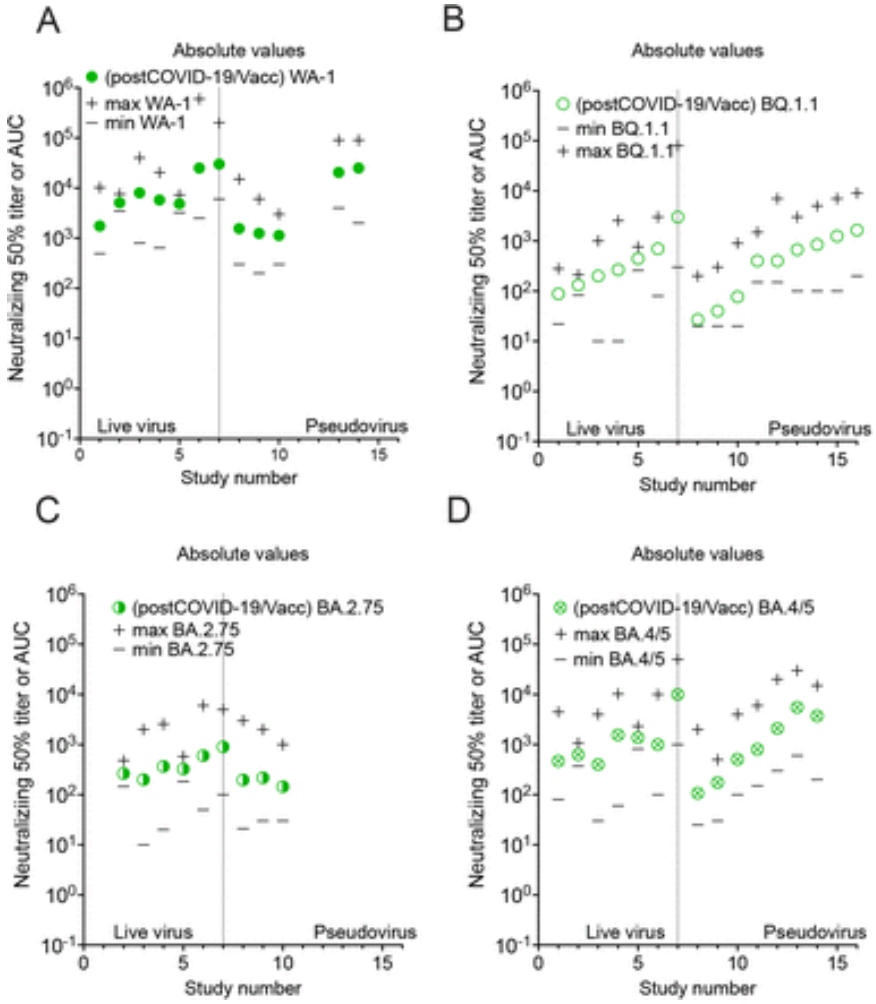


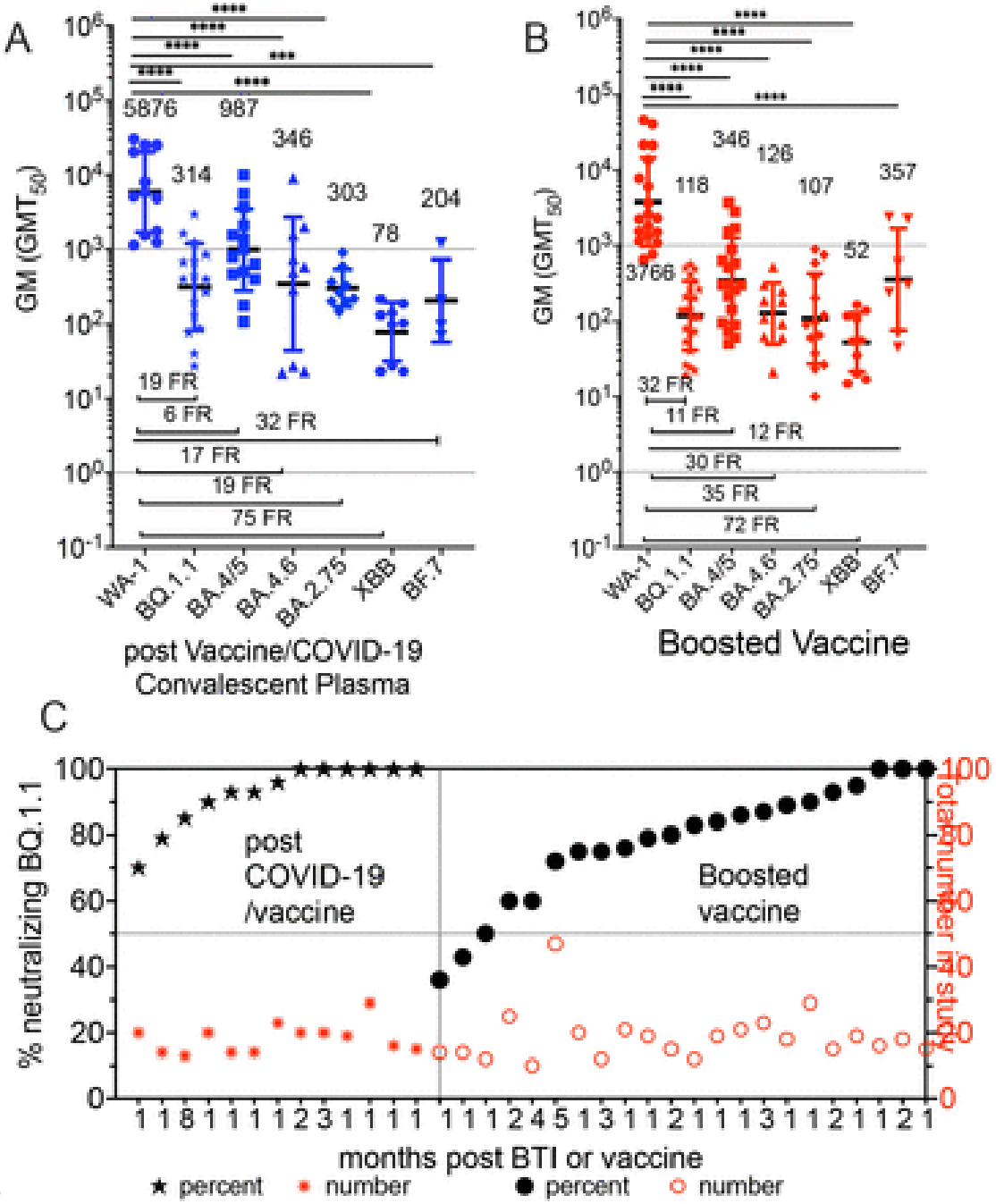
Sullivan *et al*, *Nat Comm*, 2021

Plasma after both SARS-CoV-2 boosted vaccination and COVID-19 potently neutralizes BQ.1.1 and XBB.1

David J Sullivan, Massimo Franchini, Jonathon W. Senefeld, Michael J. Joyner, Arturo Casadevall, Daniele Focosi

doi: https://doi.org/10.1101/2022.11.25.517977





What do scientific societies recommend about CCP ?

Guideline	Issuance	Indication	Strength of Recommendation	Certainty of Evidence
AABB	09/2022	Hospitalized: suggested use with standard care.	weak	low
		Outpatients (immunocompromised or not): suggested use with standard care.	weak	low
NIH	12/2022	There is insufficient evidence for the panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in hospitalized or nonhospitalized patients who are immunocompromised. o Some Panel members would use CCP to treat an immunocompromised patient with significant symptoms attributable to COVID-19 and with signs of active SARS-CoV-2 replication and who is having an inadequate response to available therapies. In these cases, clinicians should attempt to obtain high-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness.	-	-
FDA	12/2021	COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.	-	-
IDSA	3/2/2022	Recommendation 14: Among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests FDA-qualified high-titer CCP within 8 days of symptom onset.	weak	low
ECIL-9	9/17/2021	Mild COVID-19: high-titer CCP is recommended in hematological patients within 72 h from symptom onset and anti-SARS-CoV-2 monoclonal antibodies not available.	weak	moderate
		Moderate COVID-19: CCP is recommended in seronegative hematological patients.	moderate	low
NCCN (CCP obtained from subjects recovered from Omicron and previously vaccinated is preferred)	8/19/2022	Hospitalized COVID-19 cancer patients: consider high-titer CCP in immunocompromised patients, particularly those with B-cell impairment, and when anti-SARS-CoV-2 monoclonal antibodies are not available.	2A [1]	-
		COVID-19 cancer outpatients: high-titer CCP may be beneficial in immunocompromised patients, particularly those with B-cell impairment, with persistent SARS-CoV-2 infection.	2A [1]	-

[1] Category 2A: based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Focosi et al, Life, 2023

Group for the study of infection in transplantation and other immunocompromised host (GESITRA-IC) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)

https://www.sciencedirect.com/science/article/abs/pii/S0955470X23000423

What does WHO recommend about CCP ?

Cochrane Database of Systematic reviews | Review - Intervention

Free access

Convalescent plasma for people with COVID-19: a living systematic review

Claire Iannizzi, Khai Li Chai, Vanessa Piechotta, Sarah J Valk, Catherine Kimber, Ina Monsef, Erica M Wood, Abigail A Lamikanra, David J Roberts, Zoe McQuilten, Cynthia So-Osman, Aikaj Jindal, Lise J Estcourt, Nina Kreuzberger[a], Nicole Skoetz[a] Authors' declarations of interest

Version published: 10 May 2023 Version history

The Cochrane review is halted at March 2022 (published on May 2023), then includes only 21 out of 50 RCTs.

No subgroup analysis for immunocompromised patients

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

WHO has updated its living guideline on COVID-19 therapeutics to include convalescent plasma. For non-severe COVID-19 patients, WHO recommends against its use, while it should only be used within clinical trials for severe and critical COVID-19 patients.

Convalescent plasma is a transfusion of blood plasma from someone who has recovered from COVID-19.

Current evidence shows that convalescent plasma does not improve survival or reduce the need for mechanical ventilation, while it has significant costs.

Take-home messages

- CCP is safe

- CCP works until SARS-CoV-2 is there and neutralizing antibodies are not produced, which means …
  - 5 days in immunocompetent outpatients
  - much longer (until seronegative?) in immunocompromised patients

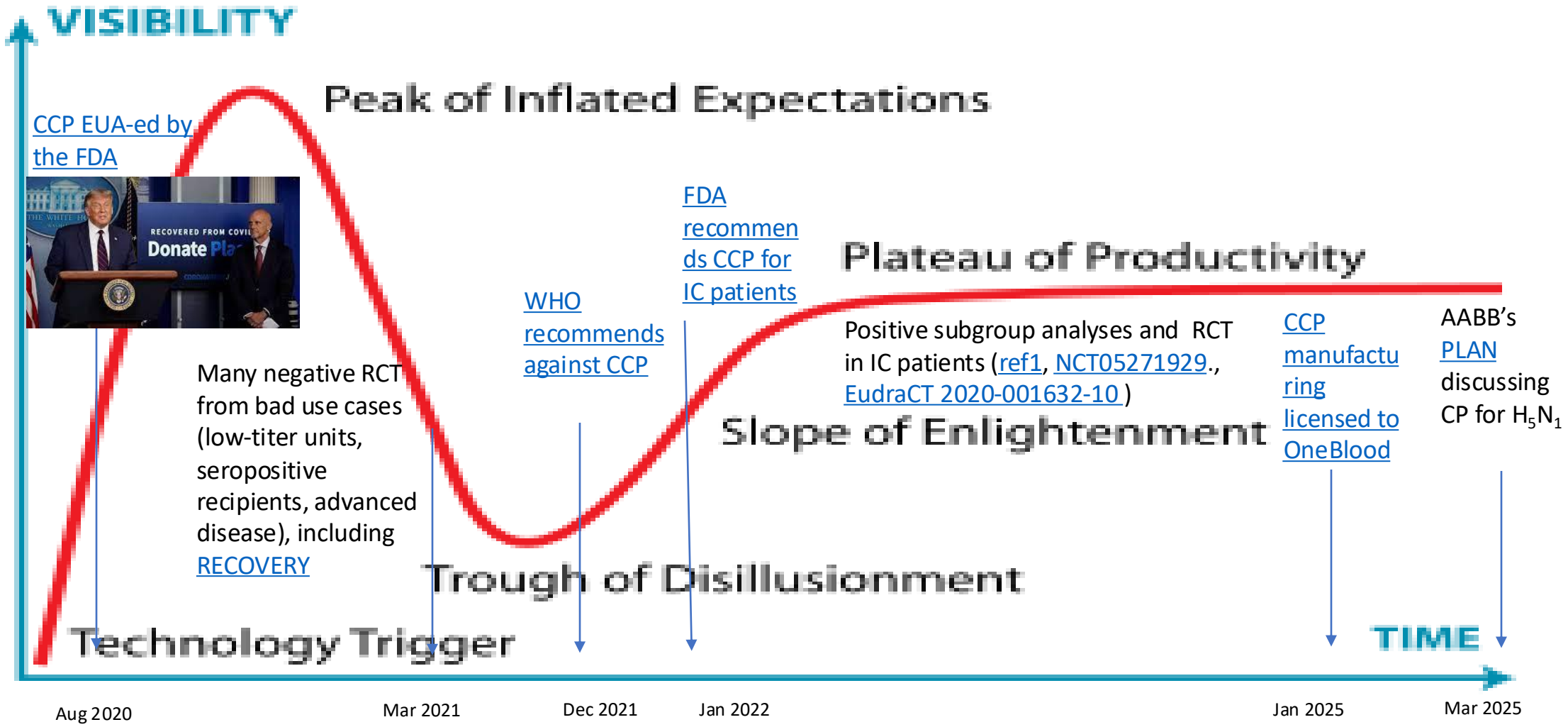
- High-titer CCP is essential: very high titer VaxCCP from donors who have been both vaccinated and infected *adapts to and retains efficacy against (future) variants.*

- ALL of the anti-Spike mAbs authorized so far have been escaped by novel variants, and anti-Spike mAb monotherapy is prone to treatment-emergent resistance

- VaxCCP is widely available worldwide at relatively low cost.

- In many high-income countries CCP prescription is hurdled by bureaucracy

COVID-19 convalescent plasma (CCP) has followed a Gartner hype cycle



Licensed High Titer COVID-19 Convalescent Plasma Order Form

Fill out the form below and a OneBlood representative will be in touch shortly!

*All fields are required

Contact First Name

Contact Last Name

Contact Phone Number

Contact Email Address

Hospital Name

Hospital Shipping Address

Is Billing the same as shipping?

Yes No

CCP usage in EU remains confined to scarce investigator-initiated clinical trials or compassionate usage. Trasfusion services have no regulatory framework. Then usage of fresh-frozen CCP remains minimized.

Actions to take in Europe to minimize bureaucratic hurdles:

1) updating regulatory frameworks : updating the EDQM's Blood Guide and European Pharmacopeia

2) partnership with plasma manufacturers interested at generating pharmaceutical-grade convalescent plasma (PG-CP) is what is needed to let EMA take control of convalescent plasma

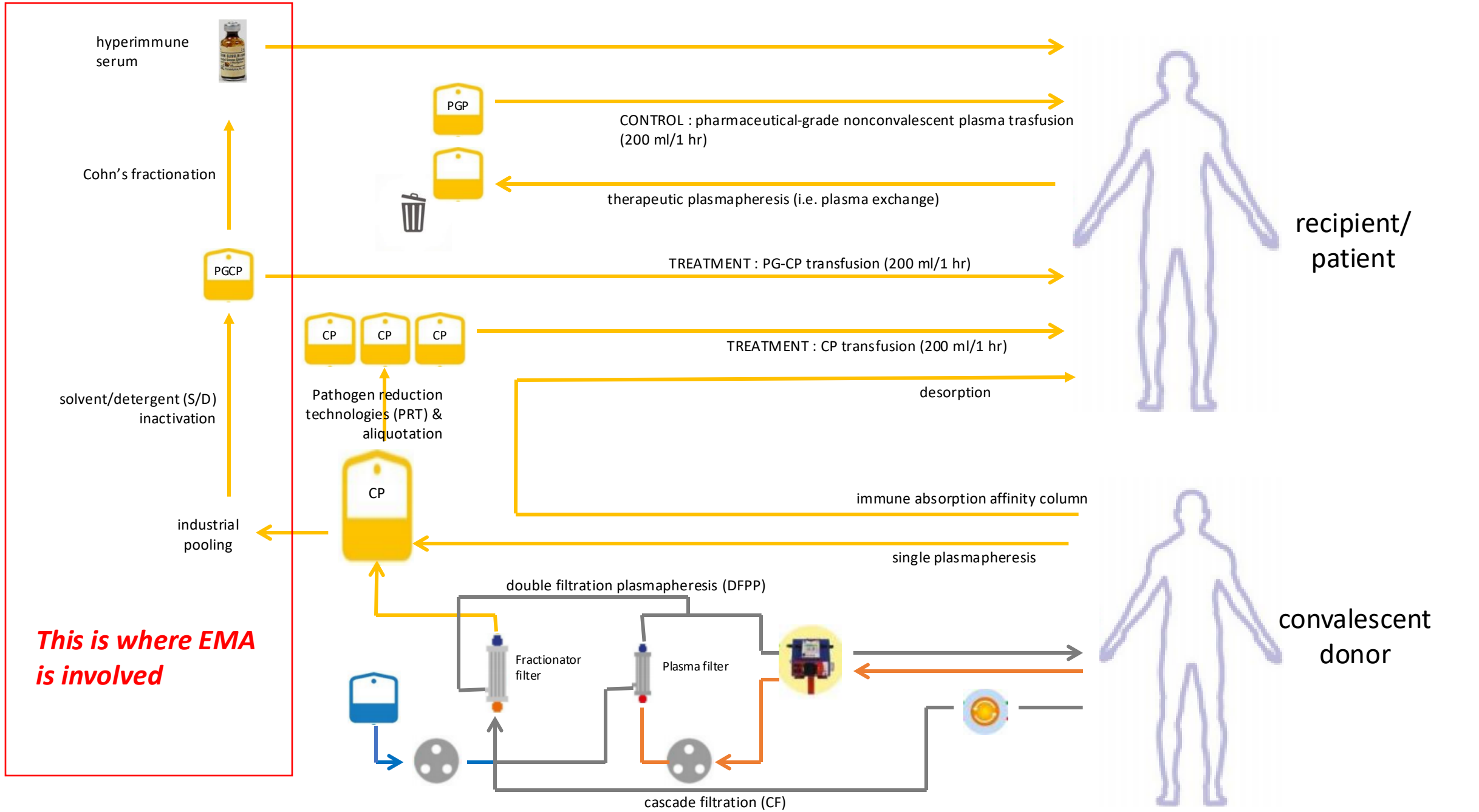
PLASMA PROTEIN THERAPEUTICS ASSOCIATION

https://www.pptaglobal.org
(stuck at Feb 2021 on CCP)

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE
edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

https://pheur.edqm.eu/home
(no CCP monography at all ever despite May 2025 update)

https://www.edqm.eu/en/blood-guide
(no CCP monography at all ever despite Apr 2023 update)



Focosi et al, *Clin Microb Infect*, 2020

Polyclonal antibody preparations in clinical trials for the treatment of influenza.

Product	Specificity	NCT	Study design	N	outcome
equine F(ab')2 (FBF00, Fab'entech)	H_5N_1	NCT02295813	double-blind, placebo-controlled phase I	16	safe
convalescent plasma (CP)	seasonal flu	NCT01306773	nonrandomized, parallel assignment	80	n/a
		NCT01052480	phase II	98	Statistically nonsignificant trends towards normalized respiratory functions, day in hospital, days on mechanical ventilation, and mortality with CP
		NCT02572817	phase III	140	83% under oxygen, underpowered to detect benefits, terminated for futility
	H_1N_1pdm09	PMID 21248066	non-randomized, matched corhort study	93	Treatment of severe infection reduced respiratory tract viral load, serum cytokine response, and mortality (20 vs. 54.8%).
hyperimmune immunoglobulins (0.25 g/kg) (HIG)	H_1N_1pdm09 (CSL Biotherapies)	NCT01617317	double-blind, IVIG-controlled phase III	35	mortality benefit if < 5 days (0/12 vs. 4/10)
	2013-2019 seasonal flu (Emergent Biosolutions)	NCT02008578	double-blind phase II	31	safe
		NCT02287467	double-blind, placebo-controlled phase III FLU-IVIG	347	no benefit compared to placebo
		NCT03315104	double-blind, placebo-controlled phase II	65	n/a

WHO has secured access to 11% of pandemic influenza vaccine production for allocation and distribution to "developing countries" via SMTA2s, but what about therapeutics ? With such a low vaccine coverage, therapeutics will invariably be required there. Convalescent plasma will likely represent the only antiviral therapy affordable in low-and-middle income countries along a future pandemic.

MAJOR ARTICLE

CID 2011:52 (15 February) • 447

Convalescent Plasma Treatment Reduced Mortality in Patients With Severe Pandemic Influenza A (H1N1) 2009 Virus Infection

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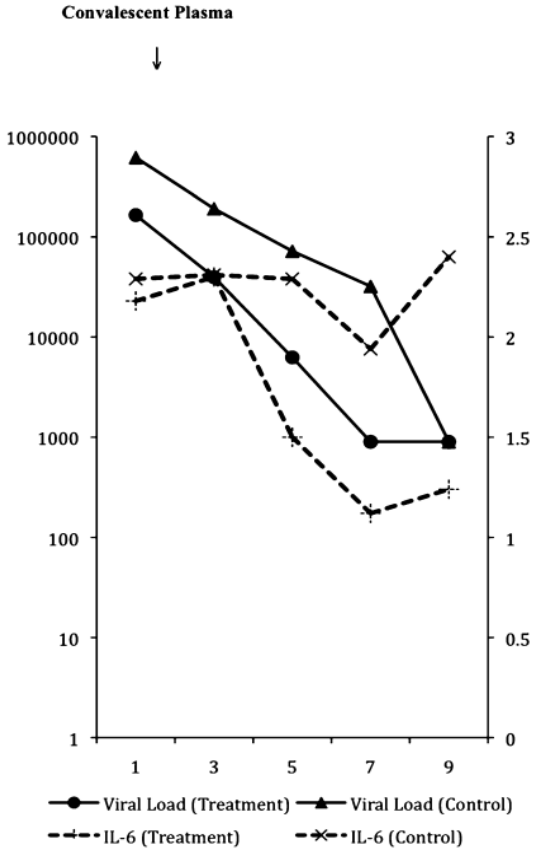

Results. Ninety-three patients with severe H1N1 2009 infection requiring intensive care were recruited. Twenty patients (21.5%) received plasma treatment. The treatment and control groups were matched by age, sex, and disease severity scores. Mortality in the treatment group was significantly lower than in the nontreatment group (20.0% vs 54.8%; $P = .01$). Multivariate analysis showed that plasma treatment reduced mortality (odds ratio [OR], .20; 95% confidence interval [CI], .06-.69; $P = .011$)