Le plasma convalescent COVID-19: une immunothérapie efficace?

Pierre Tiberghien
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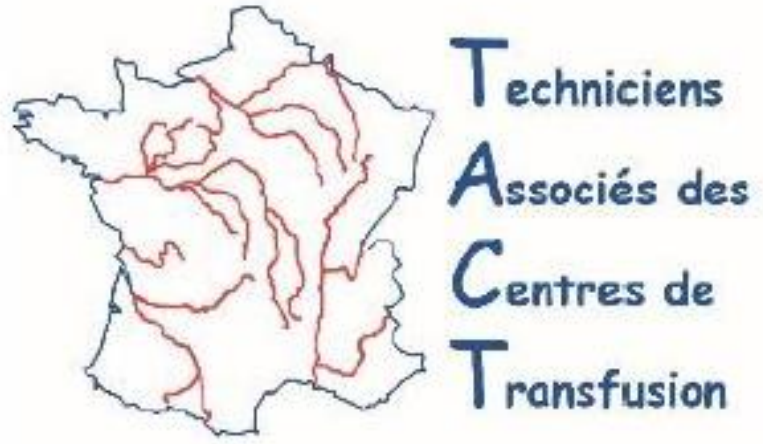
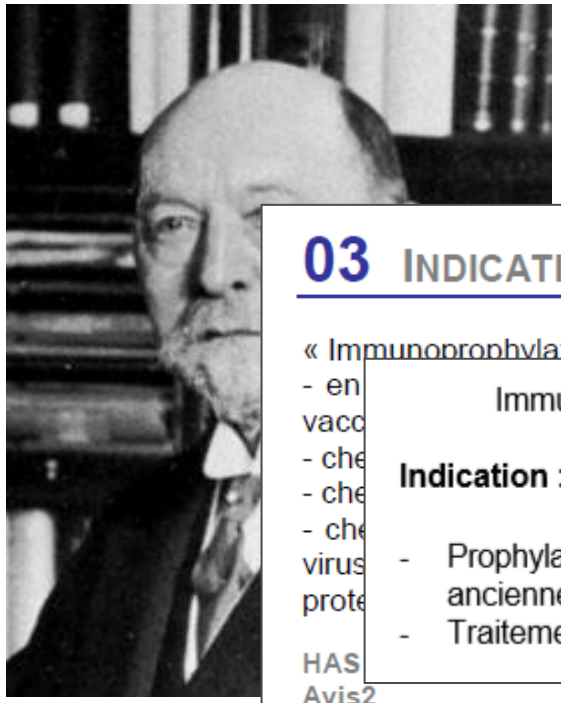


Rencontres TACT
14/10/22

Utiliser le plasma ou sérum de patients convalescents pour guérir ou prévenir une maladie
A propos du 1er prix Nobel de Médecine en 1901



Adolf von Behring médecin allemand et premier lauréat du prix Nobel de physiologie ou de médecine en 1901 pour avoir découvert le sérum* de l'antitoxine de la diphtérie (1890) et du tétanos (1890) et démontré un transfert de l'immunité (avec Kitasato Shibasaburō, médecin japonais).

03 INDICATIONS THERAPEUTIQUES — HAS

« Immunoprophylaxie de l'hépatite B :
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- che
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virus
prote

HAS
Avis2

Immunoglobuline humaine tétanique

Indication :

- Prophylaxie du tétanos en cas de plaie souillée chez les sujets dont la vaccination est incomplète, trop ancienne ou inconnue.
- Traitement du tétanos déclarée.

** Le sérum: surnageant obtenu après coagulation et centrifugation*

Plasma convalescent pour traiter / prévenir des maladies infectieuses

- **Affections respiratoires d'étiologie virale** : preuves d'efficacités limitées (Mair-Jenkins J et al, J Infect Dis. 2015).
- **Fiévres hémorragiques:** peu ou pas efficace dans la **maladie d'Ebola** (Van Griesven et al, NEJM, 2014), mais efficace dans la **fièvre hémorragique d'Argentine** (AHF, zoonose provoquée le virus Junin (Arenovirus), son vecteur et hôte réservoir étant un rongeur, la souris du maïs.

TABLE I—MORTALITY IN PATIENTS WITH AHF TREATED WITH IMMUNE OR NORMAL PLASMA

Treatment	Total cases	Improved	Died	Mortality (%)
Immune plasma	91	90	1	1·1
Normal plasma	97	81	16	16·5
Total	188	17		

χ_1=13·53; p<0·01

Dose of neutralizing antibodies in treatment of AHF with immune plasma prospective study (1982–92)

Outcome	TU/kg		
	1000–1999	2000–2999	3000–3999
Died	2	3	5
Improved			
Total			
Mortality			

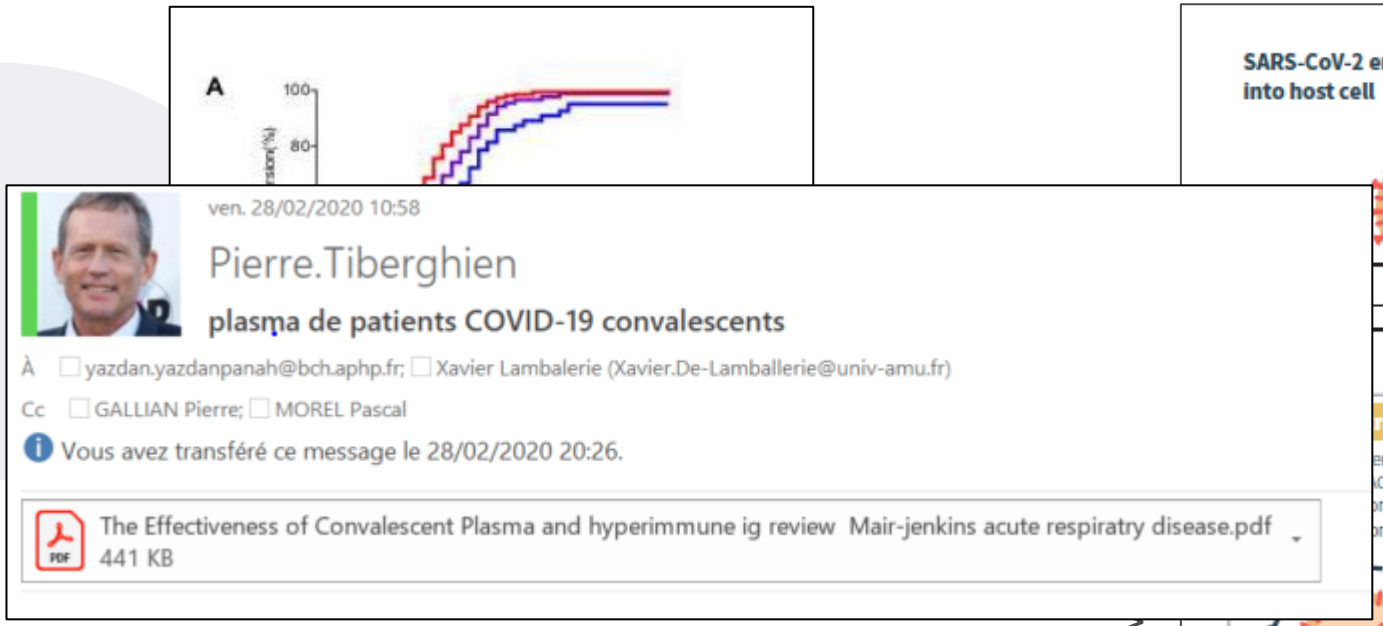
X^2: 26.32; P =

Mortality in AHF patients-treated with immune plasma after 8 days of illness

Outcome	Immune plasma	
	yes	no
Improved	40	74
Died	21	31
Total	61	105
Mortality	34%	30%

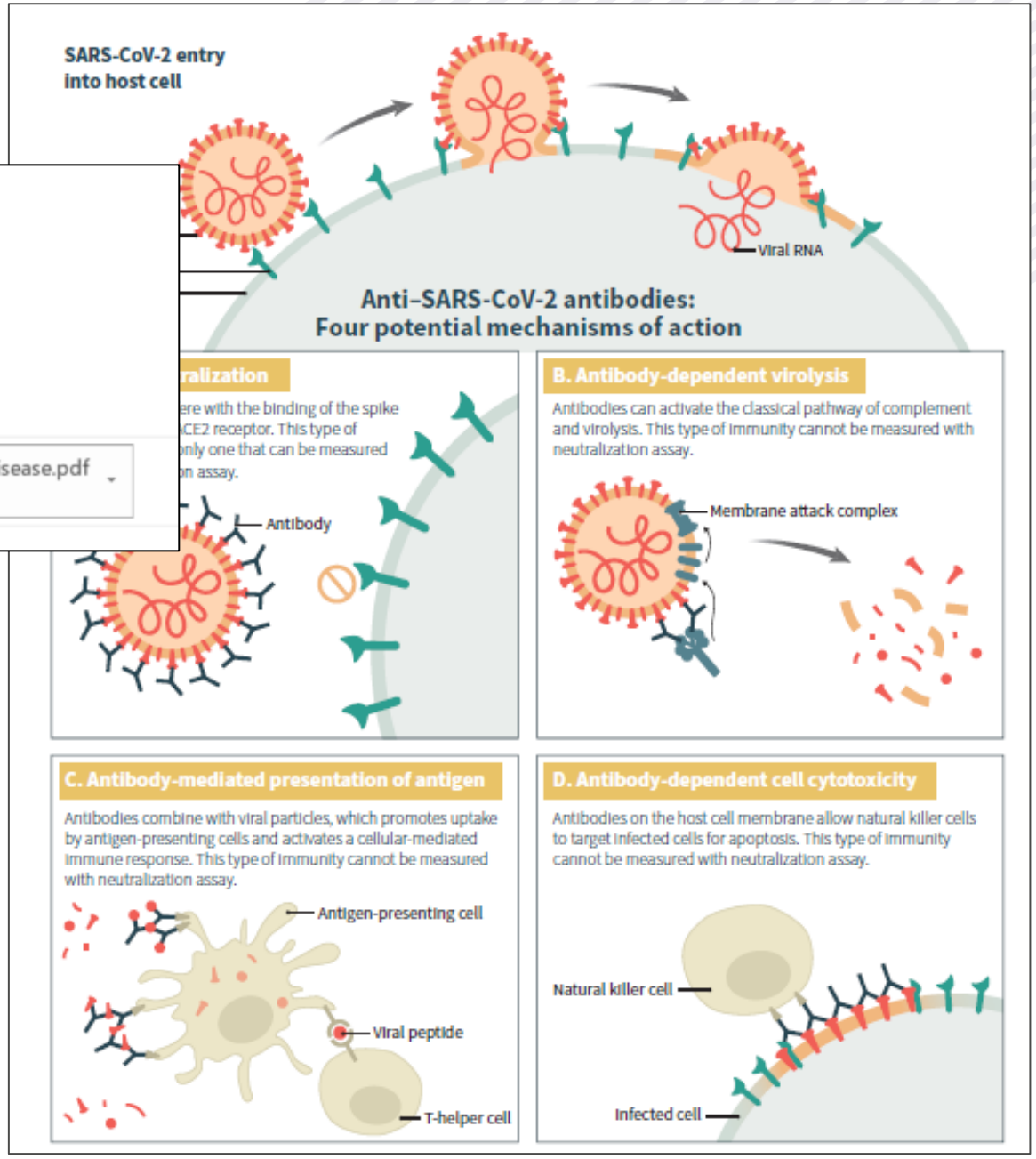
X^2: 0.23; P = 0.63.

Maiztegui et al, Lancet, 1979
Enria et al, Lancet, 1984
Enria an Maitzegui, Antivir Res, 1994



Anticorps anti-SARS-CoV-2: mécanismes d'action

- Neutralisation virale
- Lyse virale
- Présentation de l'Ag au système immunitaire
- Cytotoxicité



Devasenapathy et al, CN

Centres 06,09 et 19 Mise en place – 15/04/2020

Etude **CORIMUNO19-CORIPLASM**

Evaluation de l'efficacité du plasma de convalescents pour le traitement de patients COVID-19, essai niché dans la cohorte CORIMUNO-19

Investigateur coordonnateur : Pr Karine LACOMBE
Responsable scientifique : Pierre TIBERGHIEN

Promoteur : APHP / DRCI Ile de France,
Chefs de projet DRCI-Siege: Emmanuelle LIEGEY/ Riad BAAMEUR
Chefs de projet DRCI-URC : Nora Soussi-SEMAI
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Méthodologie : Pr T. SIMON, Dr L. BERARD, A. ROUSSEAU

Data management : Claire Pacheco
Analyses statistiques : Dr Raphael PORCHER

Coriplasm_diapo-mep_v1

Essai clinique CORIPLASM

- **Covid-19 convalescent plasma (PlasmaCoV2) and standard of care vs standard of care only**
- **Plasma administration:** Two units of plasma (400-440 ml/day) as soon as possible, 2 days in a row (4 units total), at the latest on day 10 and 11 after onset of symptoms.
- **Primary endpoints:**
    1. Survival without needs of ventilator utilization (including non- invasive ventilation) or of other immunomodulatory agents at day 14
    2. Early end point : WHO progression scale >=7 at day 4 after plasma transfusion
- **Inclusion Criteria:** Patients included in the CORIMUNO-19 cohort* with the specific following criteria:
    - Mild severity (grade 4 or 5) as described in the WHO scale
    - Hospitalized and less than 10 days after onset of symptoms
- **15 clinical sites**
- **First patient included on April 15th, 2020, target of 120 included patients reached on April 24th**

***CORIMUNO-19 eligibility criteria's:**

- Confirmed COVID-19 infection
- Illness of any duration and severity, with symptoms, AND at least one of the following:
    - Radiographic infiltrates by imaging (CT scan), and clinical assessment (evidence of rales/crackles on exam) OR SpO2 ≤ 94% on room air, or oxygen saturation ≤97 % with O2 > 5L/min.
    - Requiring mechanical ventilation and/or supplemental oxygen
    - With any comorbidities.
- Male or female adult ≥ 18 years of age at time of enrolment

Ten-points WHO ordinal clinical progression scale

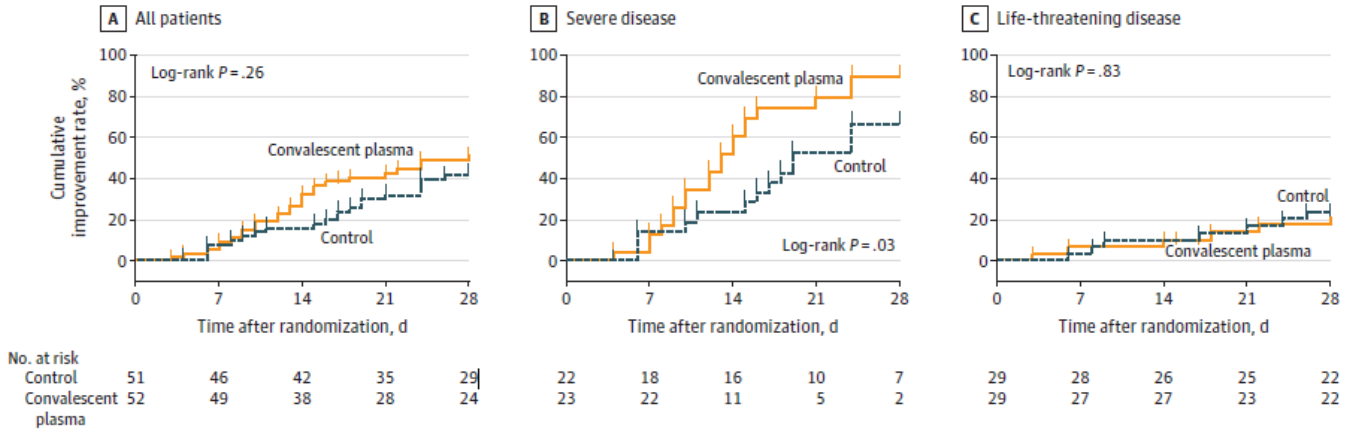
Score	Descriptor
0	Uninfected; non viral RNA detected
1	Asymptomatic; viral RNA detected
2	Symptomatic; Independent
3	Symptomatic; Assistance needed
4	Hospitalized; No oxygen therapy
5	Hospitalized; oxygen by mask or nasal prongs
6	Hospitalized; oxygen by NIV or High flow
7	Intubation and Mechanical ventilation, pO2/FIO2 ≥ 150 OR SpO2/FIO2 ≥ 200
8	Mechanical ventilation, (pO2/FIO2 < 150 OR pO2/FIO2 < 200), OR vasopressors (norepinephrine > 0.3 µg/kg/min)
9	Mechanical ventilation, pO2/FIO2 < 150 AND vasopressors (norepinephrine > 0.3 µg/kg/min), OR Dialysis, OR ECMO
10	Dead

Plasma convalescent pour le traitement de la COVID-19: 1er résultats

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19
A Randomized Clinical Trial

Li et al, JAMA, 2020)

Figure 2. Time to Clinical Improvement in Patients With COVID-19



The cumulative improvement rate is the percentage of patients who experienced a 2-point improvement or were discharged alive from the hospital. Ticks on the curves indicate censored events. All patients who did not reach clinical improvement were observed for the full 28-day period or until death. COVID-19 indicates coronavirus disease 2019.

The median (IQR) follow-up times for the convalescent plasma group and control group, respectively, were 15 (10-28) days and 24 (13-28) days overall; 13 (10-16) and 18.5 (11-26) days among those with severe COVID-19; and 28 (12-28) and 26 (15-28) days among those with life-threatening COVID-19.

Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study

Liu et al, Nature Medicine

Figure 2. Survival Probability

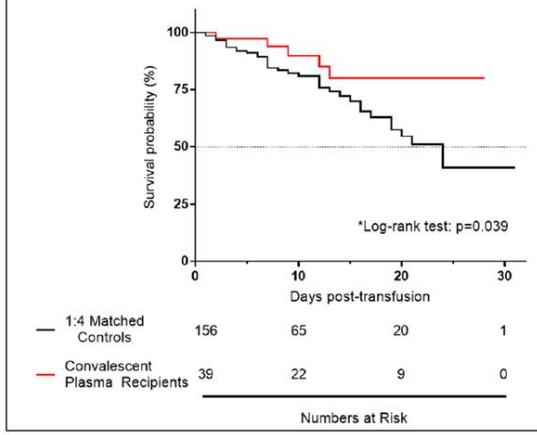
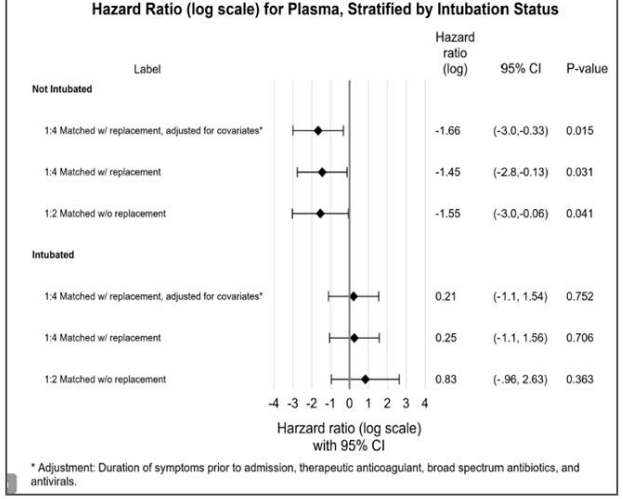


Figure 3. Hazard ratios for in-hospital mortality



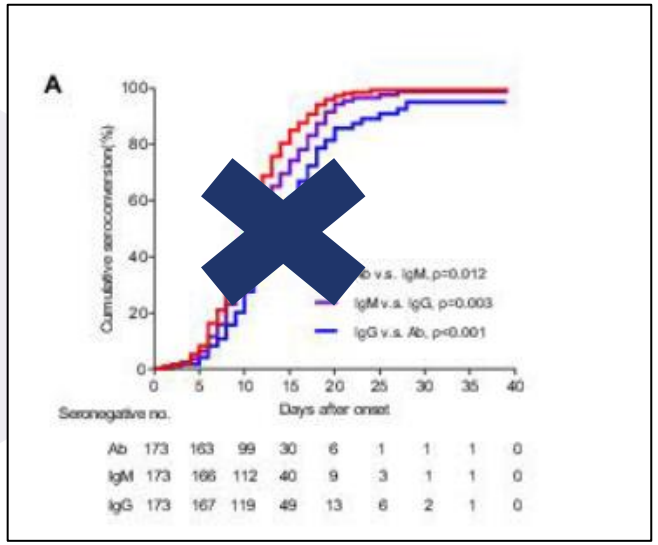
Agence nationale de sécurité du médicament et des produits de santé

PROTOCOLE D'UTILISATION THERAPEUTIQUE

24 avril 2020

Plasma convalescent COVID-19

Infection par le coronavirus SARS-CoV-2 (maladie COVID-19)

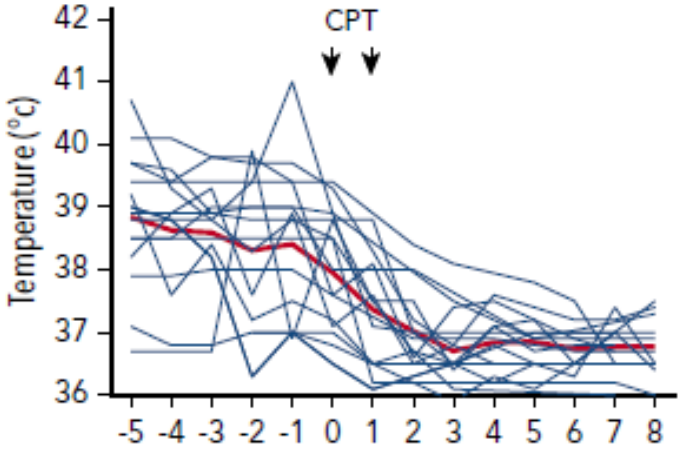


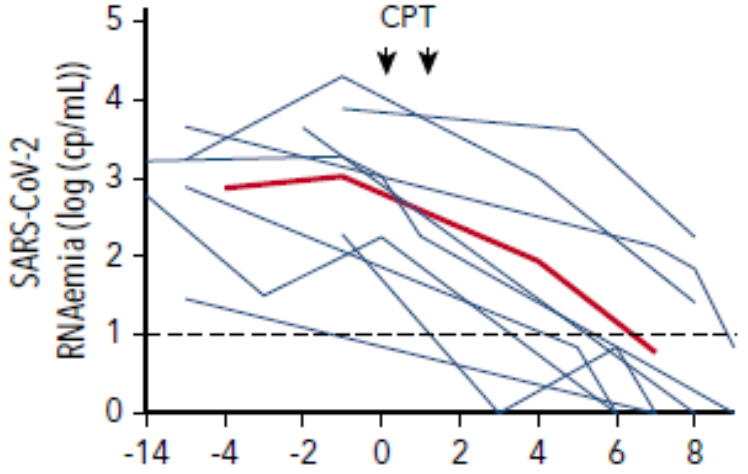
Intérêt du PCC chez les patients immunosupprimés?

Convalescent plasma therapy for B-cell–depleted patients with protracted COVID-19

Hueso et al, Blood, 2020

- 17 patients COVID-19 avec lymphopénie B: pour la plupart suite à un traitement par anticorps anti-CD20 (Rituximab) pour hémopathie sous-jacente
- Résolution rapide des signes cliniques chez 16 patients / 17
- Un décès (pneumopathie bactérienne)





Le PCC chez les patients (non immunosupprimés) hospitalisés pour COVID-19: pas d'efficacité?

COVID-19 convalescent plasma in hospitalized COVID-19 patients

The RECOVERY Collaborative Group, Lancet, 2021

	Deaths/patients randomised (%)		Observed minus expected deaths*		Ratio of death rates, RR (95% CI)
	Convalescent plasma group	Usual care group	(O–E)	Var (O–E)	
AlQahtani et al (2020)[16]	1/20 (5%)	2/20 (10%)	−0·5	0·7	0·50 (0·05–5·06)
Bajpai et al (2020)[15]	3/14 (21%)	1/15 (7%)	1·1	0·9	3·32 (0·42–26·4)
Avendaño-Solà et al (2020)[19]	0/38	4/43 (9%)	−1·9	1·0	0·14 (0·02–1·05)
Balcells et al (2020)[17]	5/28 (18%)	2/30 (7%)	1·6	1·6	2·82 (0·59–13·5)
Gharbharan et al (2020)[14]	6/43 (14%)	11/43 (26%)	−2·5	3·5	0·48 (0·17–1·39)
Li et al (2020)[11]	8/51 (16%)	12/50 (24%)	−2·1	4·0	0·60 (0·22–1·58)
Ray et al (2020)[18]	10/40 (25%)	14/40 (35%)	−2·0	4·3	0·62 (0·24–1·62)
O'Donnell et al (2021)[20]	19/150 (13%)	(18/73) ×2† (25%)	−5·9	6·8	0·42 (0·20–0·89)
Simonovich et al (2021)[13]	25/228 (11%)	(12/105) ×2† (11%)	−0·3	7·1	0·95 (0·46–1·99)
Agarwal et al (2020)[12]	34/235 (14%)	31/229 (14%)	1·1	14·0	1·08 (0·64–1·82)
Subtotal: 10 trials	**111/847 (13%)**	**137/826 (17%)**	**−11·4**	**43·8**	**0·77 (0·57–1·04)**
RECOVERY	1399/5795 (24%)	1408/5763 (24%)	−1·8	692·7	1·00 (0·93–1·07)
All trials	**1510/6642 (23%)**	**1545/6589 (23%)**	**−13·2**	**736·5**	**0·98 (0·91–1·06)**
					p=0·63

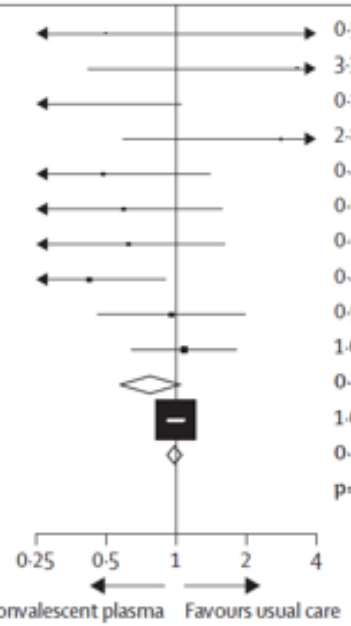


Figure 4: **Meta-analysis of mortality in RECOVERY and other trials**

O–E=observed–expected. Var=variance. RR=rate ratio.*Log–rank O–E for RECOVERY, O–E from 2 × 2 contingency tables for the other trials. RR is calculated by taking ln rate ratio to be (O–E)/V with normal variance 1/V, where V=Var (O–E). Subtotals or totals of (O–E) and of V yield inverse-variance weighted averages of the ln rate ratio values. †For balance, controls in the 2:1 studies count twice in the control totals and subtotals, but do not count twice when calculating their O–E or V values. Heterogeneity between RECOVERY and ten previous trials combined, χ_1^2=2·7 (p=0·10).

Efficacité des anticorps monoclonaux anti-SARS-CoV-2 en administration précoce en ambulatoire

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Chen et al, NEJM, 2020

- Ongoing randomized phase 2 (Blaze) trial
- Outpatients with recently diagnosed mild or moderate Covid-19 (less than 3 days since positive SARS-CoV-2 testing),
- Single iv infusion of of LY-CoV555 (anti-spike, derived from a human convalescent plasma) in one of three doses (n=309) or placebo (n=153)
- No reported serious adverse events

Primary outcome			
Mean change from baseline in viral load at day 11		−3.47	
	700 mg, −3.67		−0.20 (−0.66 to 0.25)
	2800 mg, −4.00		−0.53 (−0.98 to −0.08)
	7000 mg, −3.38		0.09 (−0.37 to 0.55)
	Pooled doses, −3.70		−0.22 (−0.60 to 0.15)

Table 3. Hospitalization.*

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

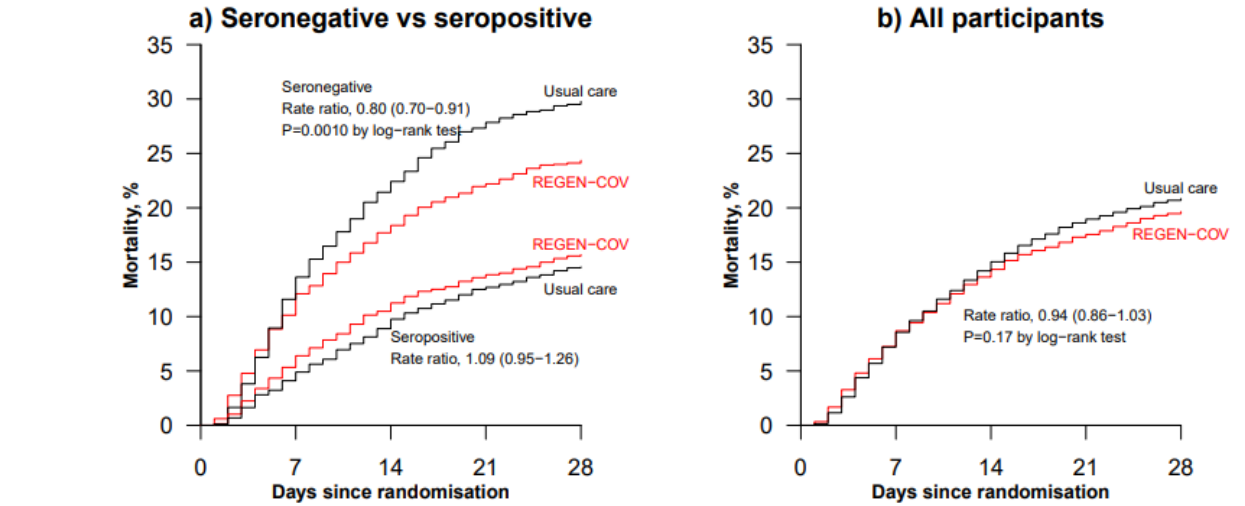
* Data for patients who presented to the emergency department are included in this category.

Inefficacité des anticorps monoclonaux anti-SARS-CoV-2 chez des patients COVID-19 séropositifs hospitalisés

Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Recovery, Horby et al, MedRxiv

Figure 2: Effect of allocation to REGEN−COV on 28−day mortality in: a) seronegative vs seropositive participants; and b) all participants



No. at risk, Seronegative					
REGEN−COV	1633	1429	1325	1260	1224
Usual Care	1520	1308	1173	1088	1059

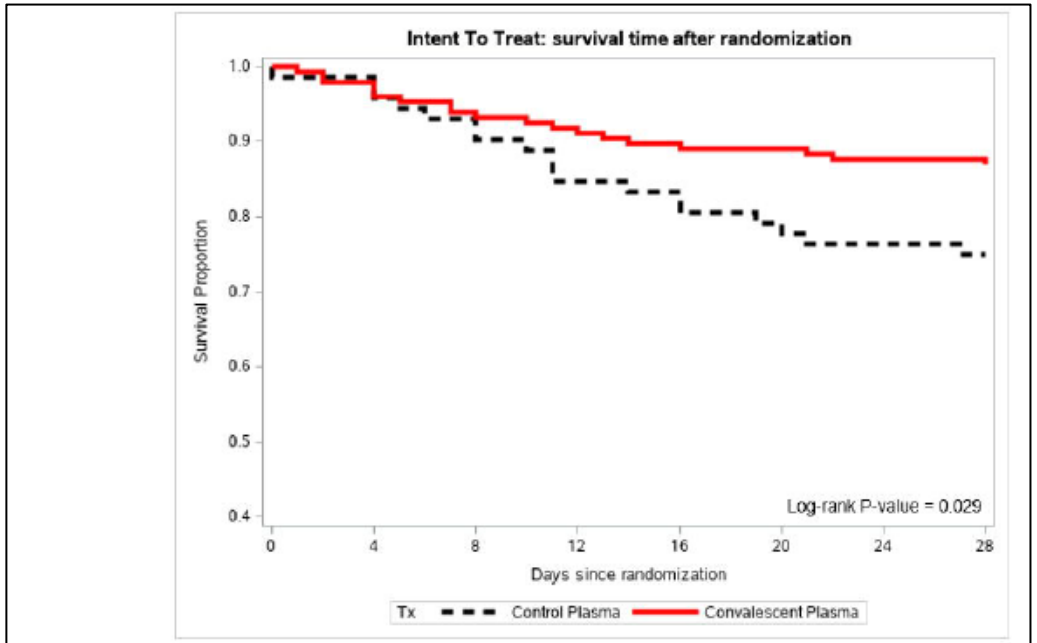
No. at risk, Seropositive					
REGEN−COV	2636	2452	2322	2252	2201
Usual Care	2636	2503	2375	2292	2243

No. at risk					
REGEN−COV	4839	4388	4112	3952	3848
Usual Care	4946	4504	4182	3980	3888

Une minorité d'essais PCC positifs chez des patients COVID-19 hospitalisés

A randomized, double-blind, controlled trial of convalescent plasma in adults with severe COVID-19

O'Donnell et al, JCI



Time since randomization (days)		0	4	8	12	16	20	24	28
Control plasma	At risk	73	71	67	61	60	57	55	50
	Died	1	3	7	11	14	16	17	18
Convalescent Plasma	At risk	150	144	137	134	131	130	128	122
	Died	0	6	10	13	16	16	18	19

La nécessité d'utiliser des PCC à haut titre d'anticorps?

Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19

Joyner et al, NEJM, 2021

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

Libster et al, NEJM, 2021

Table 3. Primary End Point, According to Donor SARS-CoV-2 S IgG Titer.

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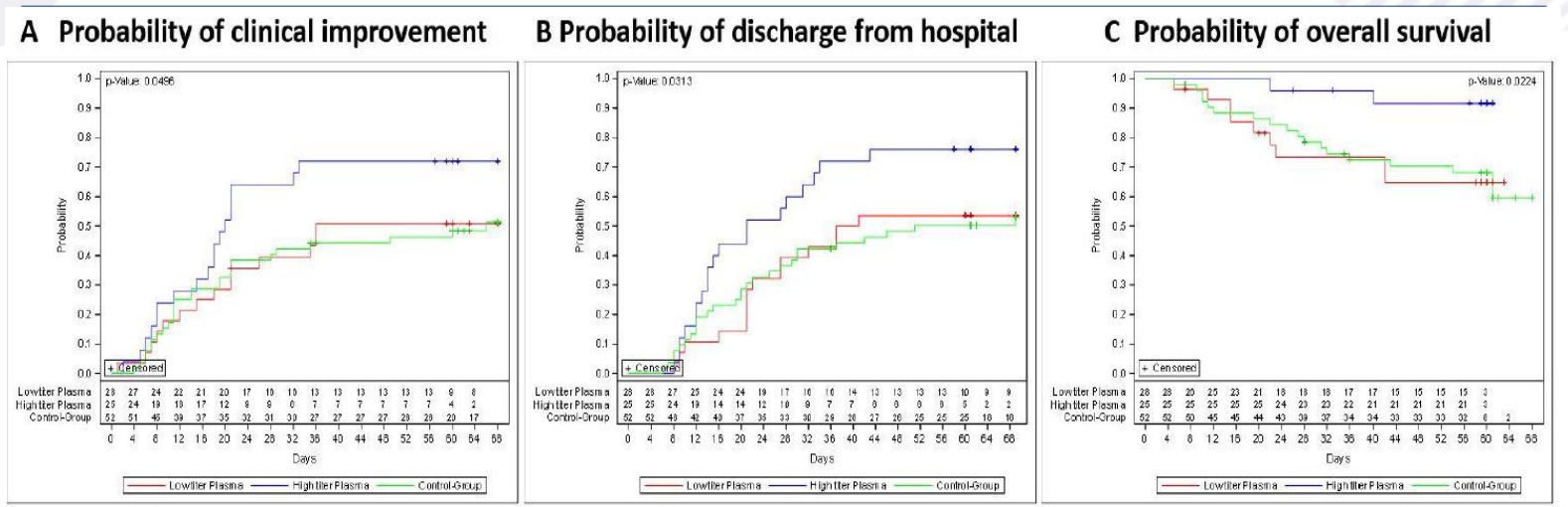
High dose convalescent plasma in COVID-19: results from the randomized trial CAPSID

Korper et al, MedRxiv



Utilisation précoce de PCC à haut titre d'anticorps

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

Libster et al, NEJM, 2021

Table 3. Primary End Point, According to Donor SARS-CoV-2 S IgG Titer.

Patient Group	Patients with Severe Respiratory Disease	Relative Risk (95% CI)	Relative Risk Reduction
	no./total no. (%)		*percent*
Placebo group	25/80 (31)	1.00	
Recipient of SARS-CoV-2 S IgG in donor plasma*			
At a titer at or above median concentration	3/36 (8)	0.27 (0.08–0.68)	73.3
At a titer below median concentration	9/42 (21)	0.69 (0.34–1.31)	31.4

* The median concentration is a SARS-CoV-2 S IgG titer of 1:3200.

Utilisation précoce de PCC à haut titre d'anticorps

Early Outpatient Treatment for Covid-19 with Convalescent Plasma

Sullivan et al, NEJM 2022

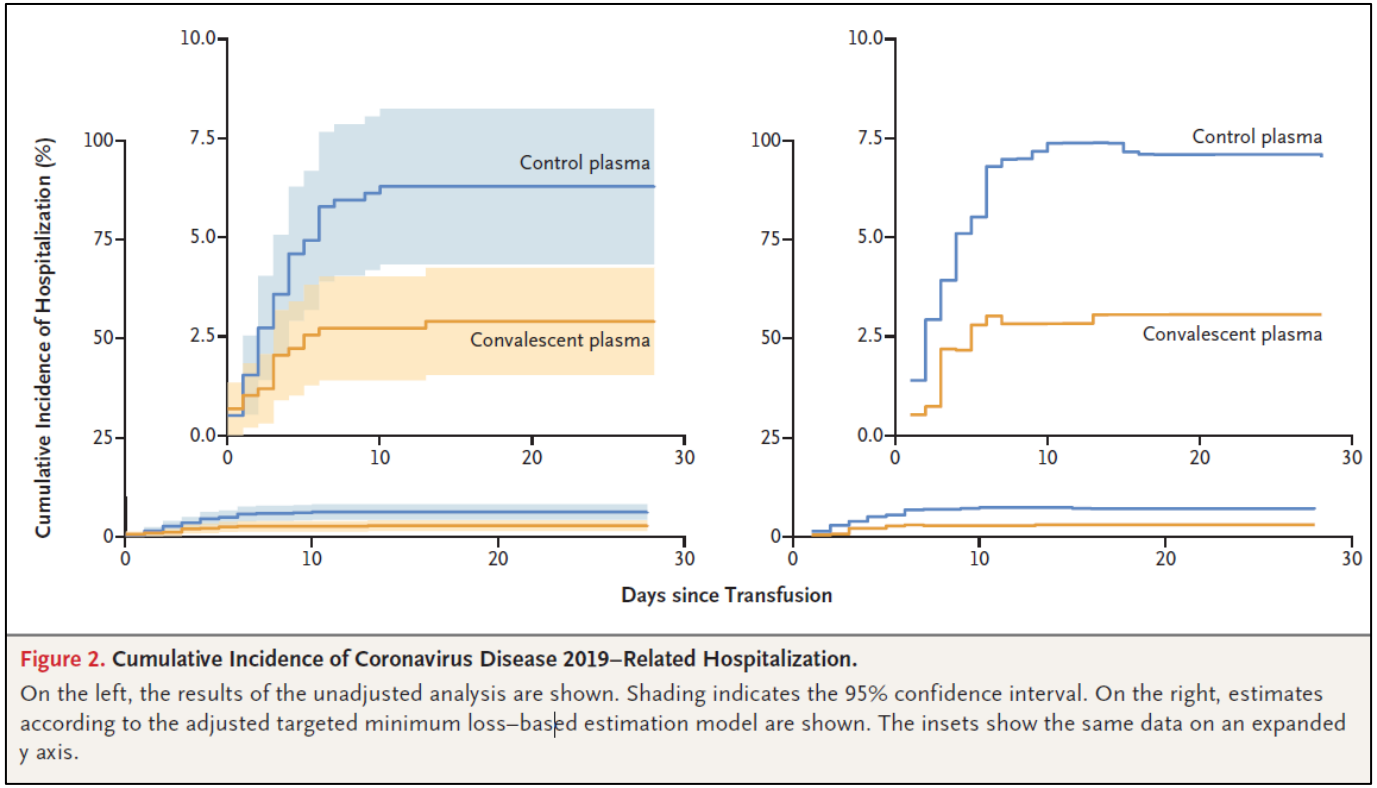
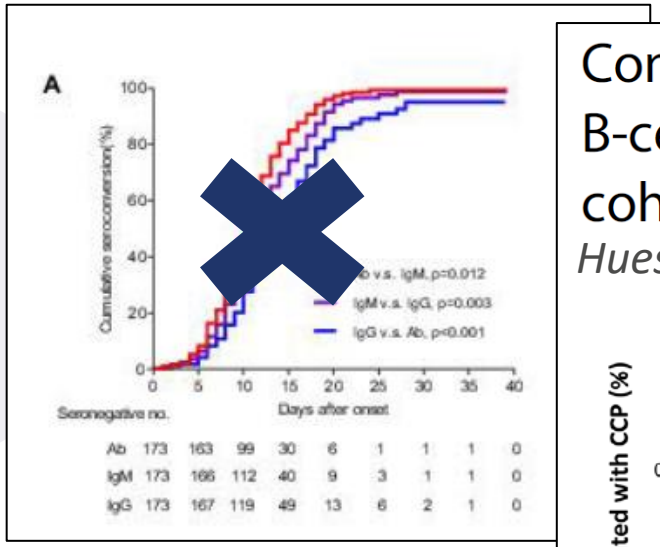


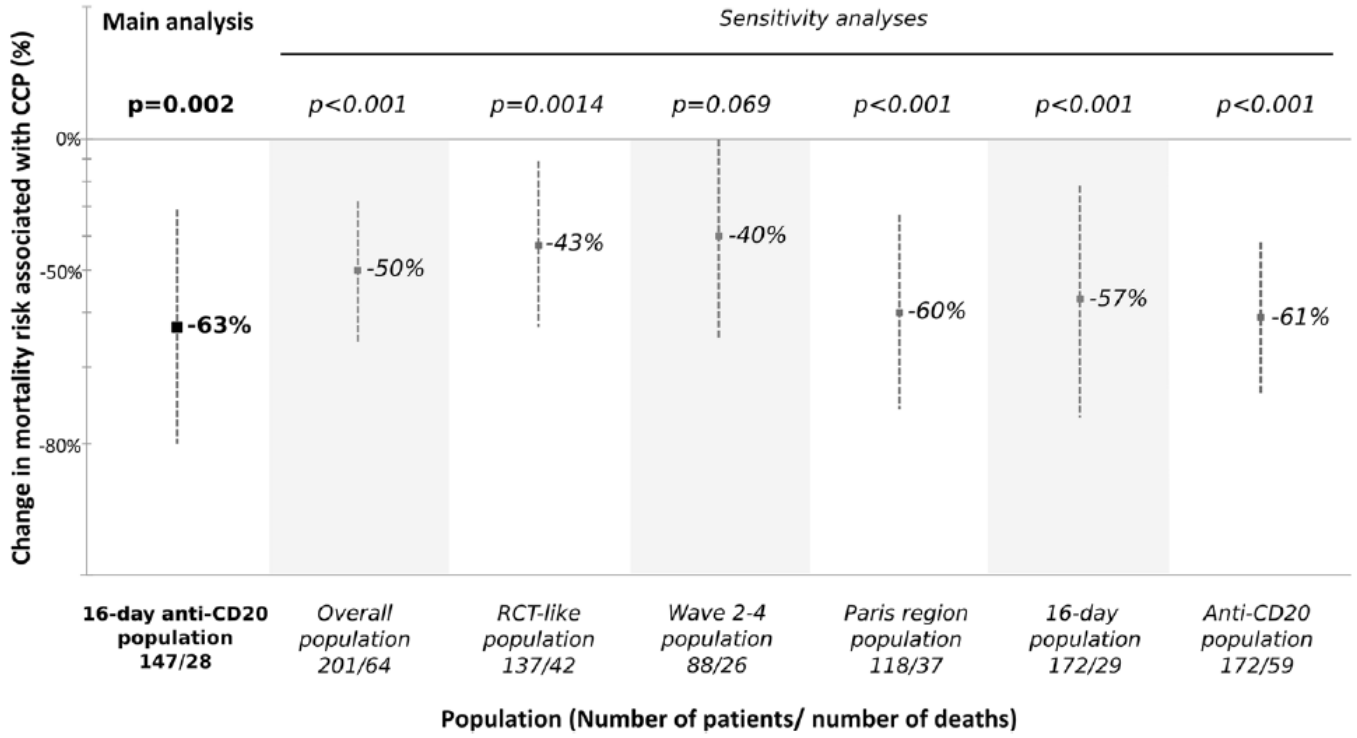
Figure 2. Cumulative Incidence of Coronavirus Disease 2019–Related Hospitalization.

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.



Convalescent plasma improves overall survival in patients with B-cell lymphoid malignancy and COVID-19: a longitudinal cohort and propensity score analysis

Hueso et al, Leukemia



Propensity score analysis: decreased mortality of 63% (95% CI=31%–80%) in patients pre-exposed to anti-CD20 and 50% (95% CI=28%–66%) in the overall population of the CCP-treated group compared to the CCP-untreated group

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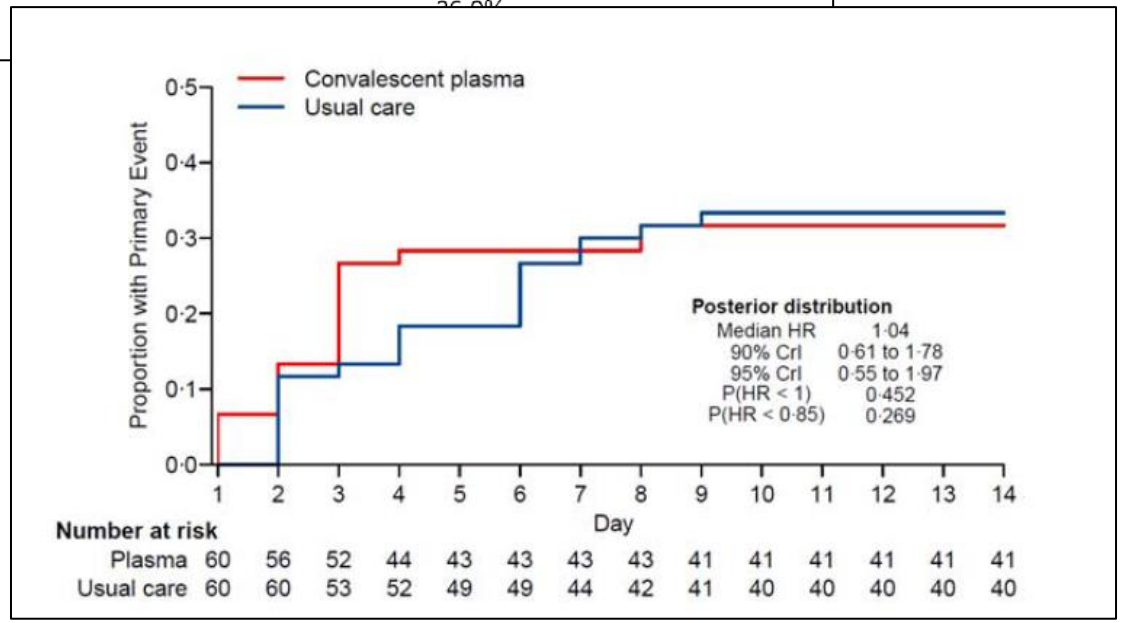
Coriplasm_diapo-mep_v1

Efficacy and safety of convalescent plasma to treat hospitalised COVID-19 patients with or without underlying immunodeficiency: a randomized clinical trial

Lacombe et al, medRxiv, 2022

	Convalescent plasma (n=60)	Usual care (n=60)	Treatment effect
Co-primary outcomes			
WHO-CPS score ≥ 6 at d4	13 (22%)	8 (13%)	+8.0% (90% CrI −3.2 to +19.4)*
Posterior probability of any benefit			11.9%
Posterior probability of moderate or greater benefit×			2.4%
Need for ventilation, additional immunomodulators or death up to d14	19 (32%)	20 (33%)	1.04 (90% CrI 0.61 to 1.78)†
Posterior probability of any benefit			45.2%
Posterior probability of moderate or greater benefit×			



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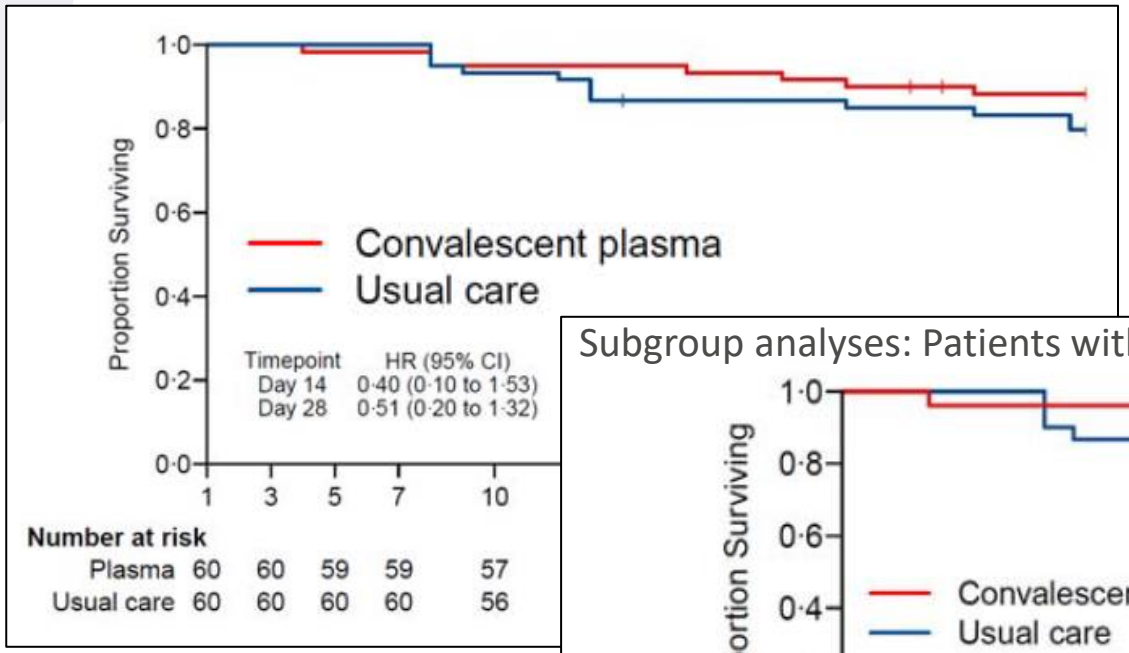
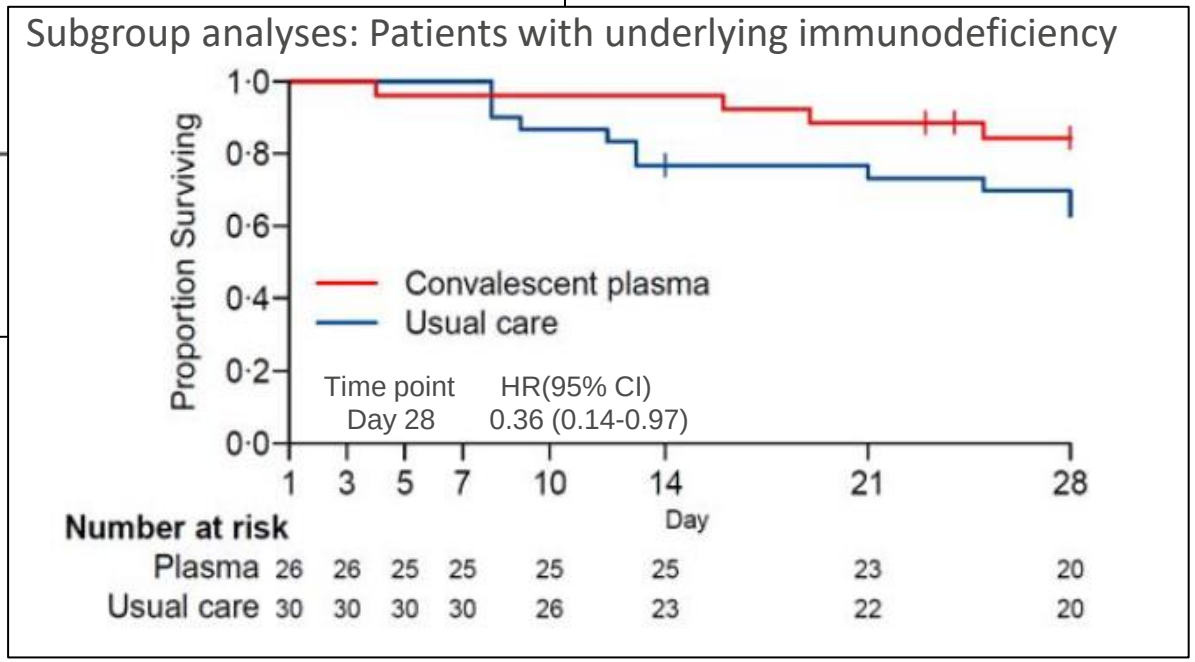


Subgroup analyses: Patients with underlying immunodeficiency



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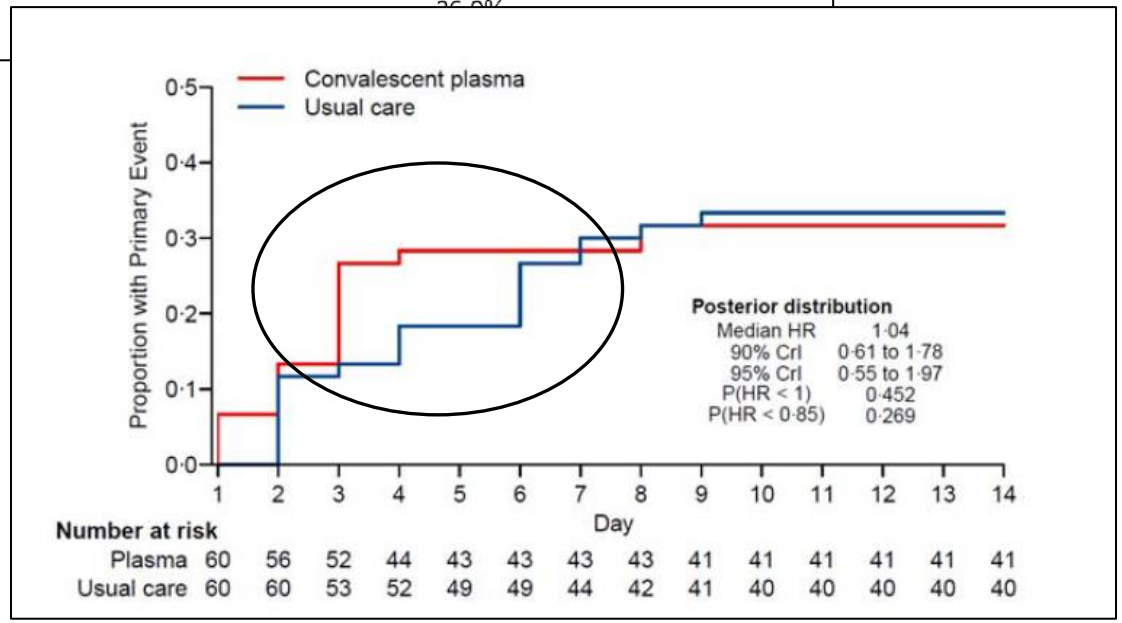
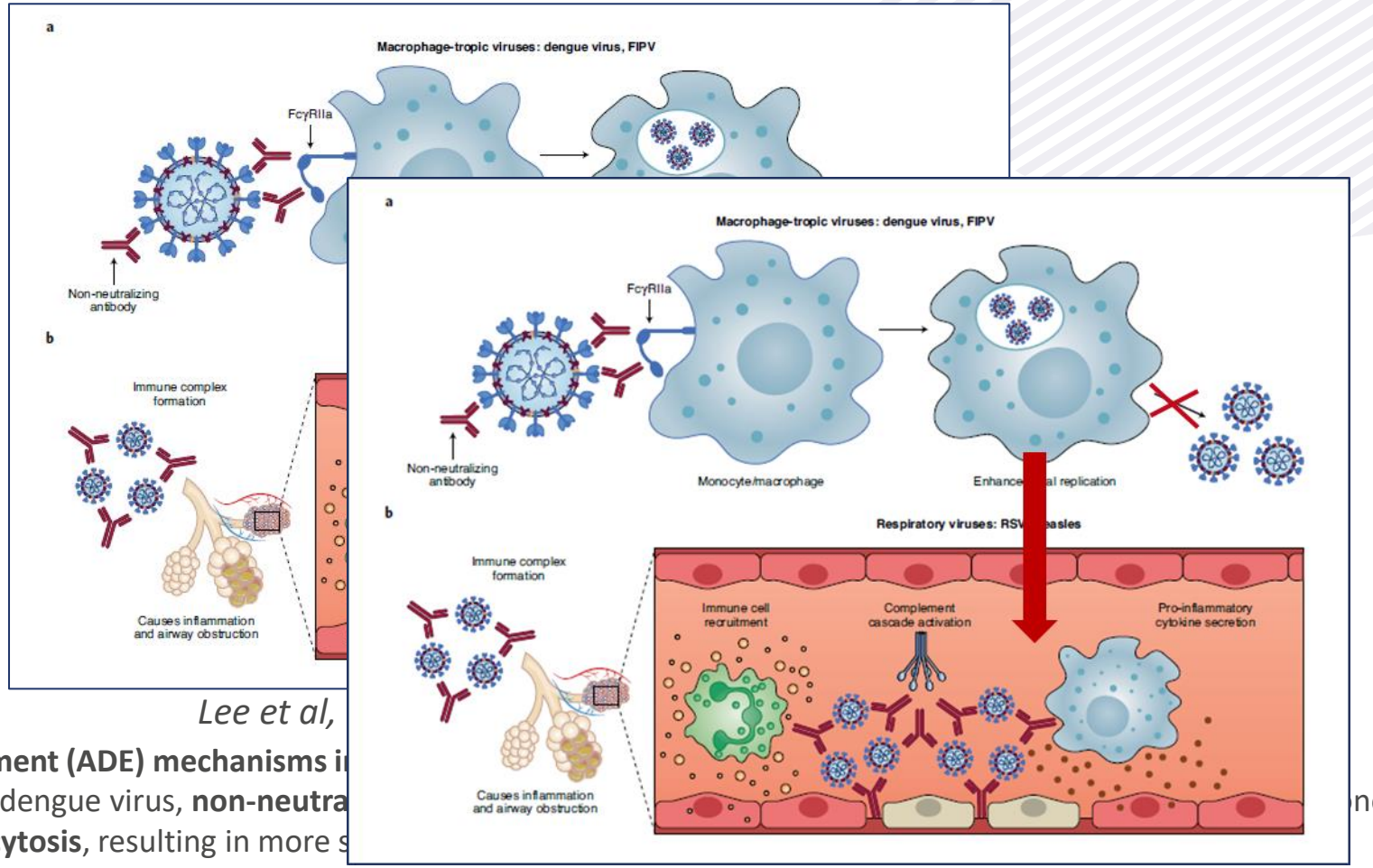
Posterior probability of any benefit			45.2%
Posterior probability of moderate or greater benefit×			



« Antibody-dependant enhancement »: aggravation médiée par les anticorps ?

Une manifestation transitoire associé à un effet anti-viral?



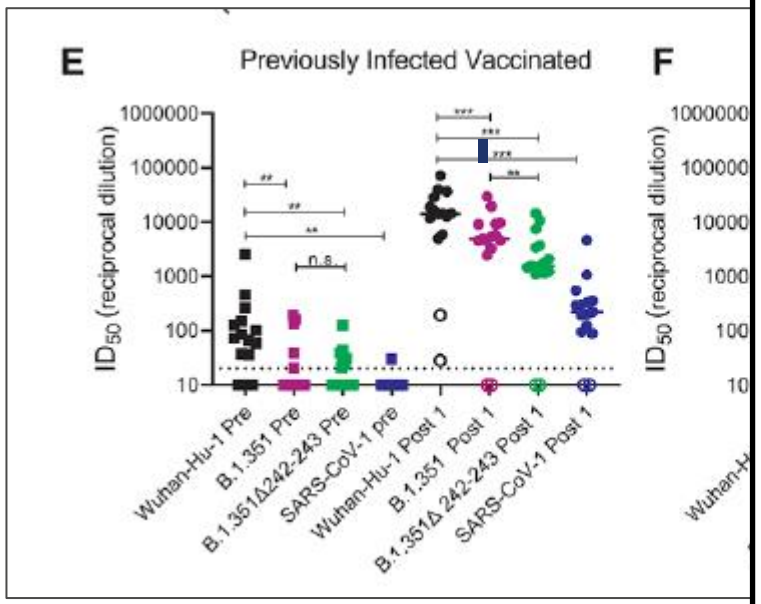
Lee et al,

Two main antibody-dependent enhancement (ADE) mechanisms i
a: For **macrophage-tropic viruses** such as dengue virus, **non-neutra** nocytes or macrophages via **FcγRIIa-mediated endocytosis**, resulting in more s
B: For **non-macrophage-tropic viruses** such as RSV and measles, non-neutralizing antibodies can **form immune complexes** with viral antigens inside airway tissues, resulting in the secretion of **pro-inflammatory cytokines**, immune cell recruitment and **activation of the complement** cascade within lung tissue. The **ensuing inflammation** can lead to airway obstruction and can cause **acute respiratory distress syndrome** in severe cases.
Early evidence suggested that immune complex formation, complement deposition and local immune activation present the most likely ADE in COVID-19.

Intérêt de la collecte de plasma chez les convalescents vaccinés

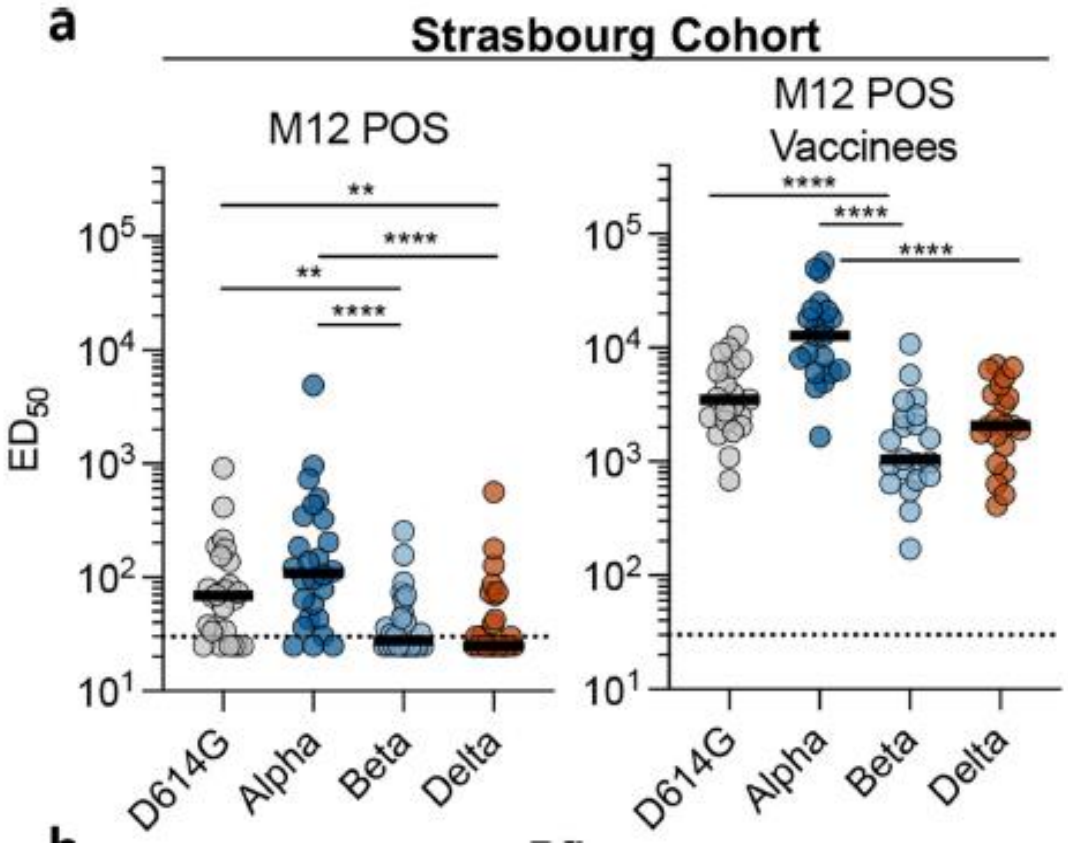
Plasma à très haut titre capable de neutraliser des variants auxquels le donneur n'a pas été exposé

mRNA vaccination boosts cross-vari
antibodies elicited by SARS-CoV-2 in



Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization

Planas et al, Science, 2021



Plasma issus de convalescents (pre-omicron) vaccinés

Considerable escape of SARS-CoV-2 Omicron to antibody neutralizatio

Planas et al, Nature, 2021

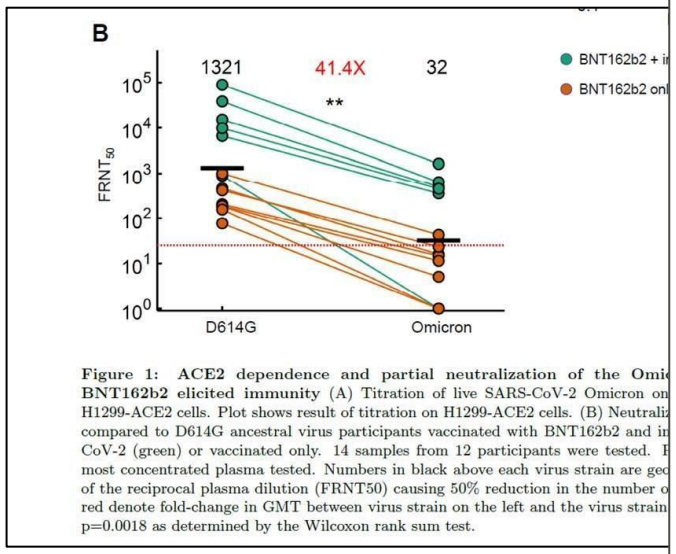
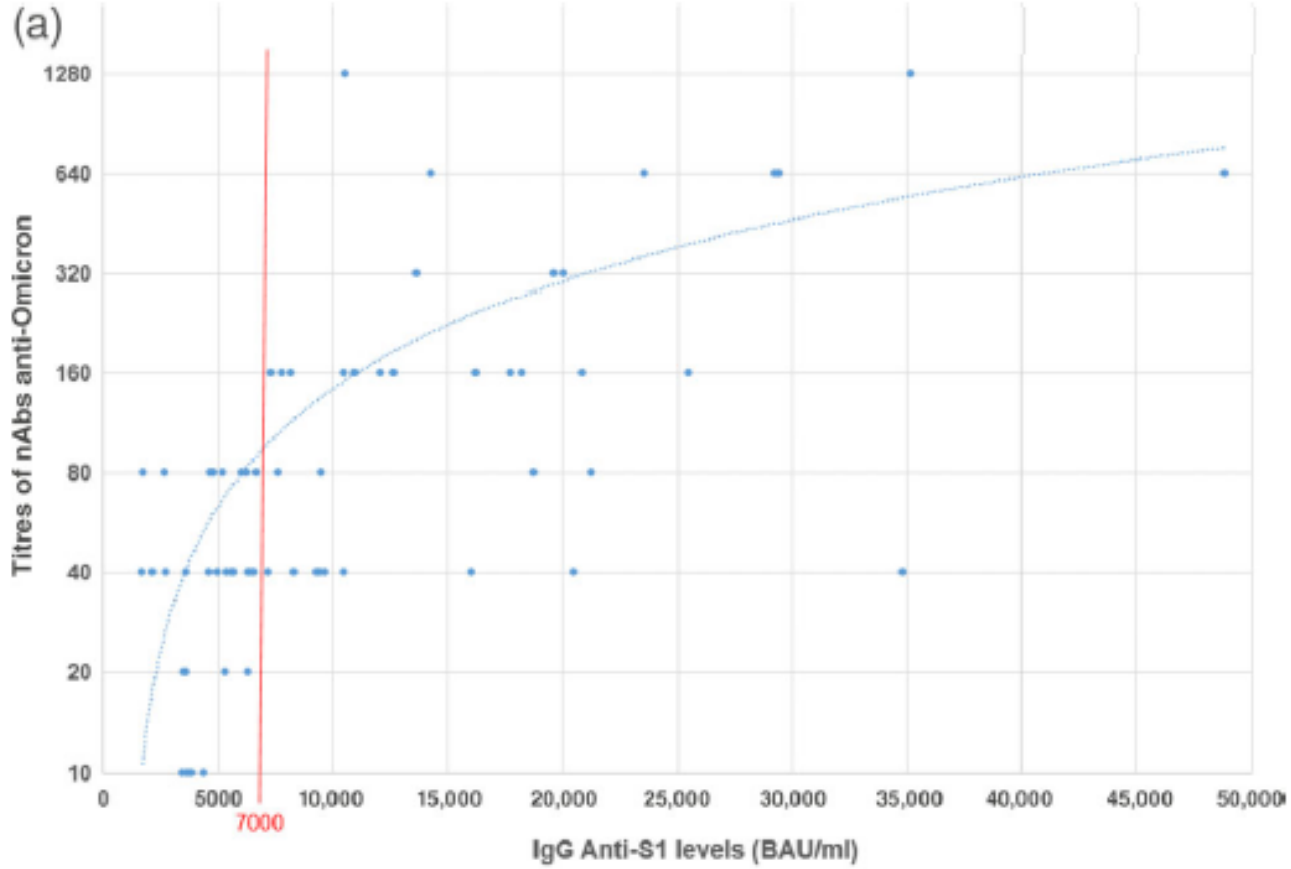


Figure 1: ACE2 dependence and partial neutralization of the Omi BNT162b2 elicited immunity (A) Titration of live SARS-CoV-2 Omicron on H1299-ACE2 cells. Plot shows result of titration on H1299-ACE2 cells. (B) Neutraliz compared to D614G ancestral virus participants vaccinated with BNT162b2 and in CoV-2 (green) or vaccinated only. 14 samples from 12 participants were tested. most concentrated plasma tested. Numbers in black above each virus strain are ge of the reciprocal plasma dilution (FRNT50) causing 50% reduction in the number o red denote fold-change in GMT between virus strain on the left and the virus strain p=0.0018 as determined by the Wilcoxon rank sum test.

Cele et al, Nature, 2021

Gallian et al, Vox Sanguinis,2022



COVIC-19 Efficacy of early transfusion of very high Ab titre convalescent plasma in vulnerable COVID-19 patients

Features of this COVIC-19 Trial

- Very **early treatment** with CCP, outpatient treatment
- CCP with **very high amount of neutralizing antibodies**
- **Vulnerable patient population at high risk of severe COVID-19**
- Monitoring of **variants of concern**

Supporte
SUPPORTing high quality evaluation of covid-19 convalescent plasma throughout EUROPE

COVID-19 (PCR confirmed) **≤ 7 days within start of symptoms** in **vulnerable patients**

Cohort 1: COVID-age ≥ 70 years
(based on ALAMA Risk Calculator)
n = 339

Cohort 2: immunocompromised patients
(aquired or congential immune deficiency)
N=339

1:1

Control
Standard of Care

High-Titre CCP +
Standard of Care

1:1

High-Titre CCP +
Standard of Care

Control
Standard of Care

Primary endpoint: Hospitalization due to progressive COVID-19, O_2 requirement, death within 28 days from random.

COVIC-19

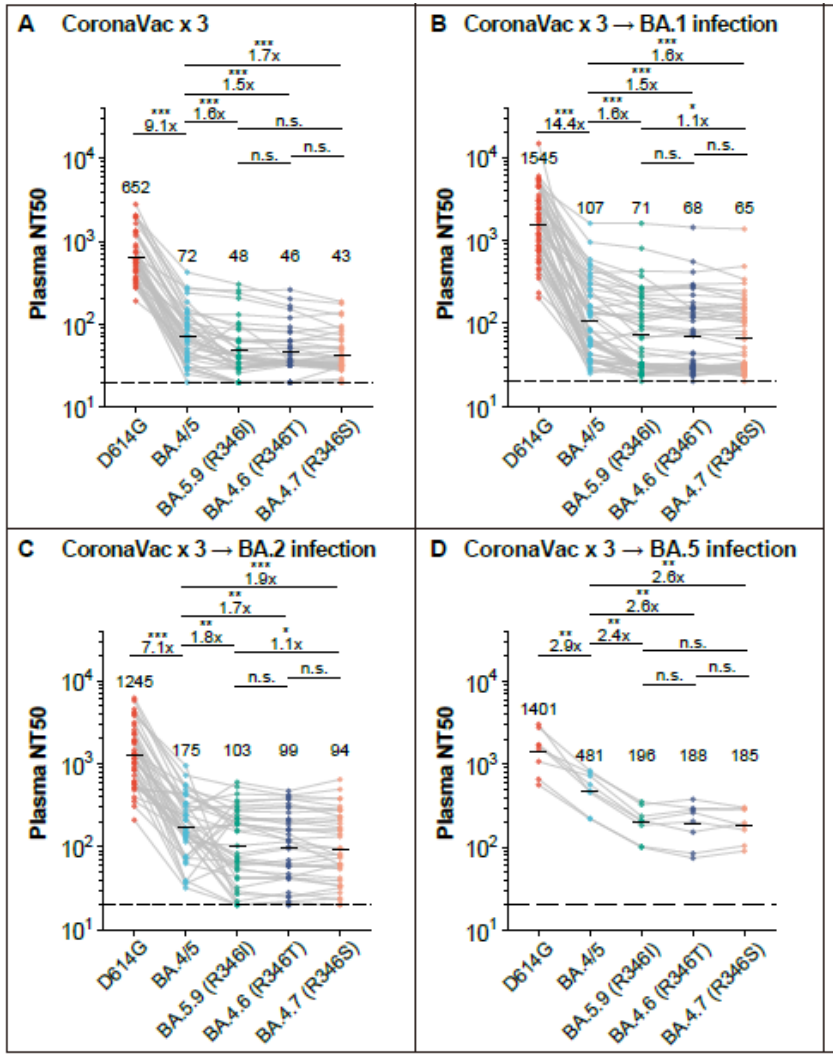
Intervention

- **CCP (2 units, 200-350 ml)** (if possible on day 1).
- **Very high titre neutralizing antibodies (defined threshold)**
  - **≥ 1:640 PRNT against Delta, Omicron or any future variants**
  - **≥ 20.000 U/ml Elecsys Assay (Roche)**
  - **≥ 4.000 U/ml QuantiVac IgG ELISA (Euroimmun)**
- **CCP donors: history of SARS-CoV-2 + vaccination**

Les prochains variants: plus d'anticorps monoclonaux efficaces ?

Jian et al, MedRxiv, 2022

Further humoral immunity evasion of emerging SARS-CoV-2 BA.4 and BA.5 subvariants



E Therapeutic monoclonal antibodies

Pseudovirus IC50 (ng/mL)	BA.4/5	BA.5.9 (R346I)	BA.4.6 (R346T)	BA.4.7 (R346S)
Etesevimab (LY-CoV016)	*	*	*	*
Bamlanivimab (LY-CoV555)	*	*	*	*
Bebtelovimab (LY-CoV1404)	0.8	1.3	1.0	1.4
Casirivimab (REGN10933)	*	*	*	*
Imdevimab (REGN10987)	520	2701	2195	1362
Tixagevimab (COV2-2196)	*	*	*	*
Cilgavimab (COV2-2130)	23	*	*	*
Amubarvimab (BRII-196)	7124	4023	4356	3395
Romlusevimab (BRII-198)	*	*	*	*
Sotrovimab (S309)	1055	4780	3543	2899
Adintrevimab (ADG-2)	*	*	*	*
Etesevimab+ Bamlanivimab	*	*	*	*
Casirivimab+ Imdevimab	709	3498	4388	2420
Tixagevimab+ Cilgavimab	40	*	*	*
Amubarvimab+ Romlusevimab	*	7695	8307	5209

<100	100~1,000	>1,000	* >10,000

Le plasma convalescent COVID-19: une immunothérapie efficace?

Preuves croissantes de l'efficacité de PCC à haut titre pour le traitement de la COVID-19 chez:

- Les patients immunosupprimés
- Les patients vulnérables lorsque le PCC est administré précocement

Un intérêt particulier:

- Début de pandémie: avant les vaccins, les anticorps monoclonaux,…
- Émergence de variants immuno-résistants

Une solution thérapeutique disponible rapidement, peu couteuse et continuellement adaptable

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And all the involved clinicians

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Thibaud Bocquet
Sophie Lecam
Brigitte Bonneaudeau
Lucile Malard
Anne-Marie Fillet
Cathy Bliem
And all EFS colleagues ensuring the collection, testing and issuing of CCP

Etablissement Français du Sang

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Dragoslav Domanovic, EBA

And last but not the least!, our blood donors

Et le soutien de la Fondation de la Recherche Médicale, Reacting, Sorbonne Université, l'Etablissement Français du Sang and l'Union Européenne (ESI, H2020)