COVID-19 et antiviraux ?
Ou une histoire du repositionnement

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES
10 ANS

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CHRU de Lille

28 et **29** SEPTEMBRE 2021
UIC-P - Espaces Congrès - 16, rue Jean Rey - 75015 Paris

Inserm
CHU LILLE
Université de Lille
FACULTÉ DE MÉDECINE Henri Warembourg

Sous l'égide de :

Liens d'intérêt

- Pfizer
- MSD
- Novartis
- Eumédica
- Gilead
- Correvio

Y a-t-il une place pour les antiviraux dans la COVID-19 ?

A-Oui

B-Non

Si oui, pour quelle(s) indication(s) ?

A-Malade ambulatoire sans facteur de risque

B-Malade ambulatoire avec facteur de risque

C-Malade hospitalisé sans O2

D-Malade hospitalisé sous O2 bas débit

E-Malade hospitalisé sous O2 haut débit

F-Malade hospitalisé intubé/ventilé

Quels critères vous paraissent utiles pour décider de la prescription d'un antiviral?

A-Notion de facteur de risque

B-Durée des symptômes

C-Charge virale

D-Sérologie

E-Séquençage de la souche virale

SRAS : le coronavirus émergent par lequel tout a commencé. Modèle de bouffée épidémique.

Traitement « compassionnel » Lopi/r+ribavirine

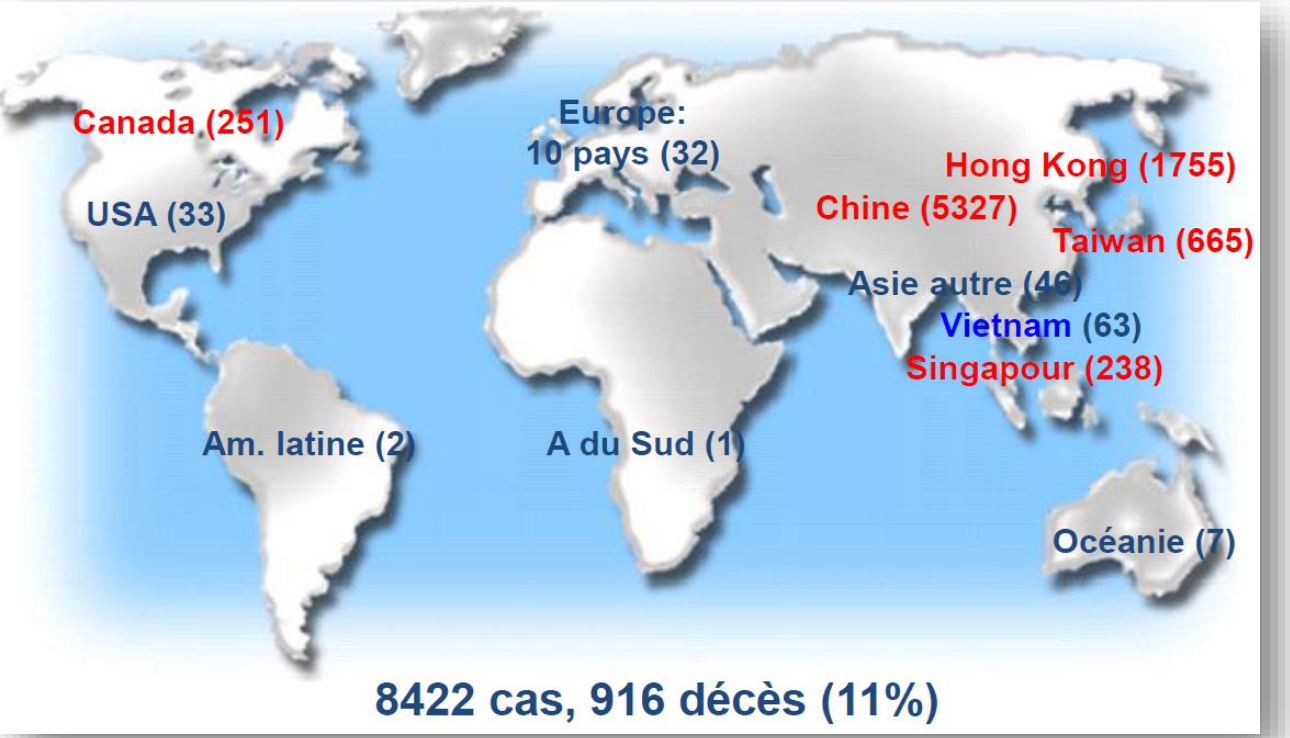


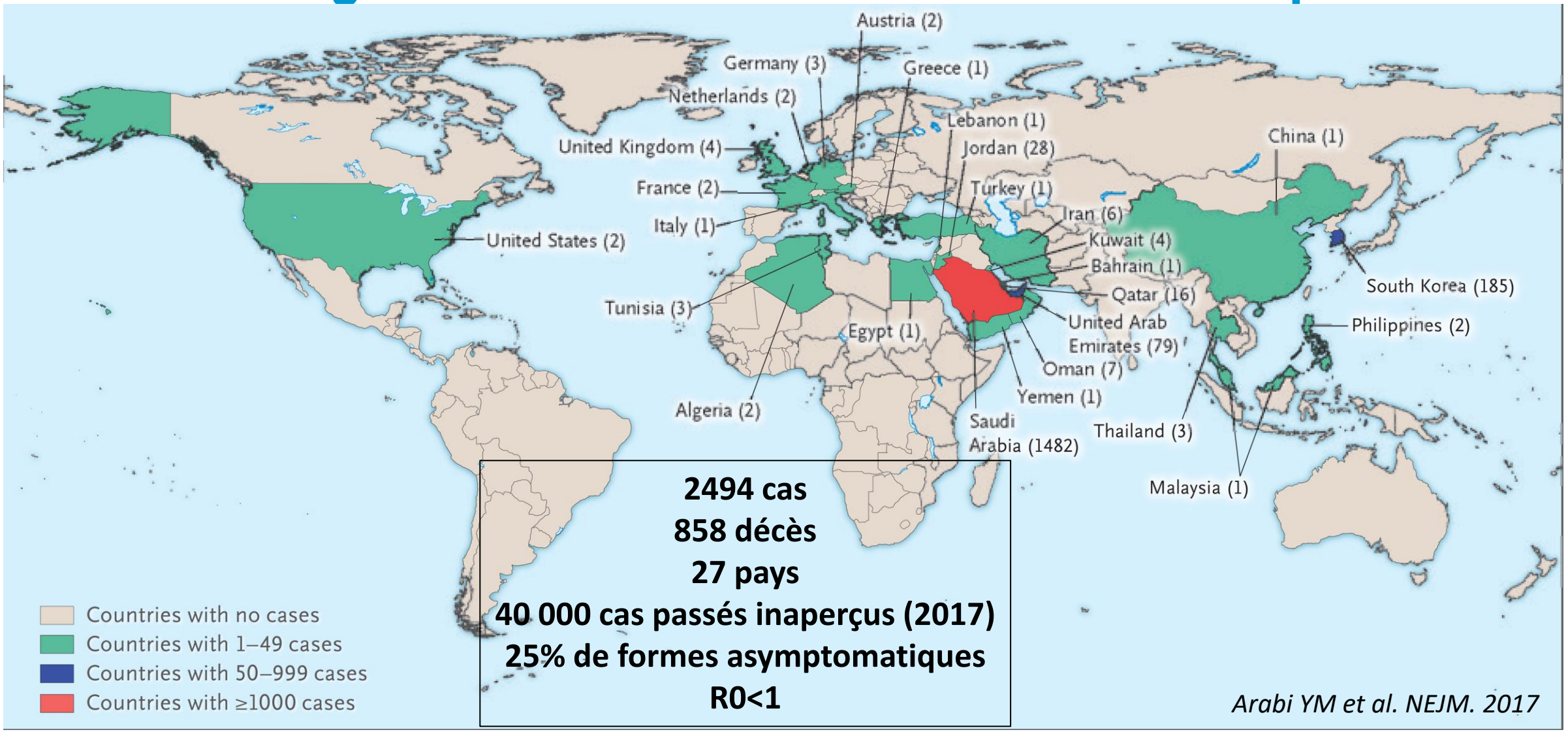
Table 1 Baseline characteristics and 21 day adverse outcome (death or development of ARDS requiring intensive care) of historical controls and treatment group

	Historical controls (n = 111)	Treatment group (n = 41)	p value
Mean (SD) age (years)	42.1 (14.7)	39.4 (15.2)	0.32
Male:female ratio	48:63	10:31	0.039
Active co-morbid condition	22 (19.8%)	6 (14.6%)	0.464
Chronic hepatitis B infection	11 (9.9%)	1 (2.4%)	0.182
Mean (SD) duration of symptoms to admission (days)	2.61 (2.3)	1.85 (1.5)	0.05
Apparently normal chest radiograph on admission	23 (20.7%)	11 (26.8%)	0.511
Multilobar involvement on initial chest radiograph	29 (26.1%)	5 (12.2%)	0.081
NPA RT-PCR positive at diagnosis	41 (36.9%)	14 (34.1%)	0.850
Mean (SD) haemoglobin (g/dl)	13.3 (1.6)	13.5 (1.4)	0.468
Mean (SD) initial total peripheral WBC count ($\times 10^9$/l)	6.4 (2.2)	6.7 (3.0)	0.420
Mean (SD) initial lymphocyte count ($\times 10^9$/l)	1.0 (0.5)	0.9 (0.3)	0.297
Mean (SD) initial platelet count ($\times 10^9$/l)	169 (44)	199 (77)	0.023
Median (IRQ) initial LDH (IU/l)	401 (344–467)	276 (197–336)	<0.001
Median (IRQ) cumulative pulse methylprednisolone dose (g)	1.5 (1.0–3.0)	2.0 (0–3.0)	0.477
Development of ARDS or death within 21 days	32 (28.8%)	1 (2.4%)	<0.001
Death/ARDS at day 21	7 (6.3%)/25 (22.5%)	0 (0%)/1 (2.4%)	–

NPA = nasopharyngeal aspirate; WBC = white blood cell; LDH = lactate dehydrogenase; ARDS = acute respiratory distress syndrome.

Chu CM et al. Thorax. 2004

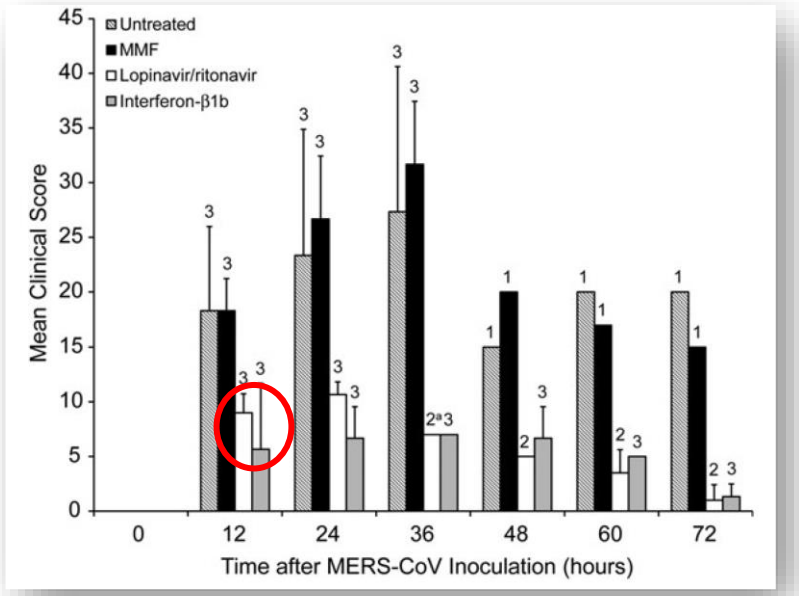
Emergence du MERS et modèle endémique

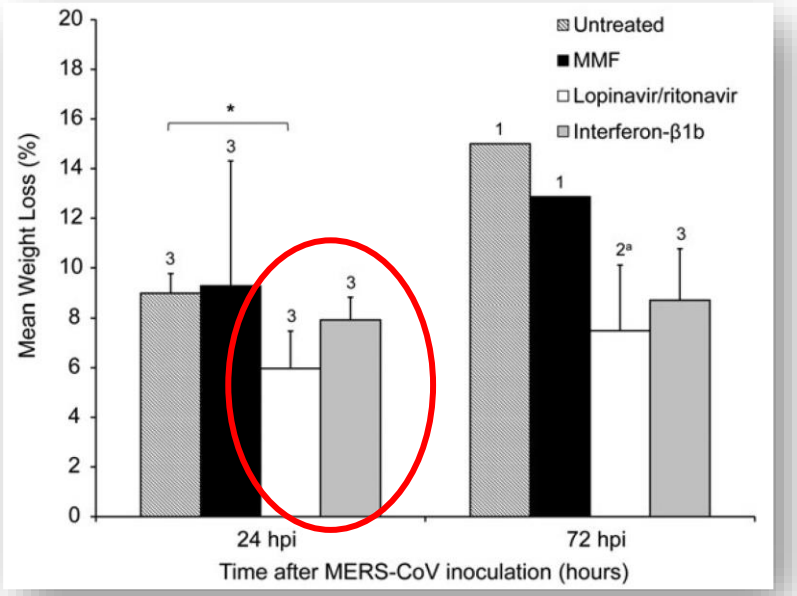


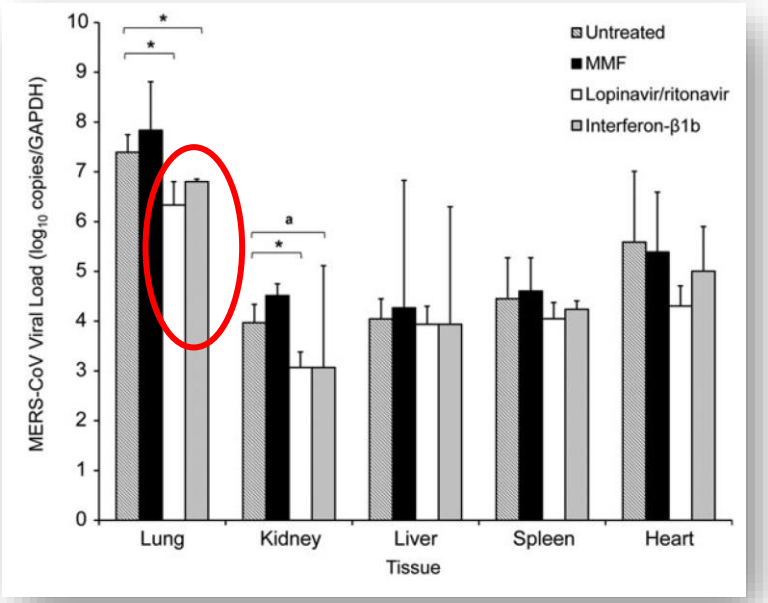
2494 cas
858 décès
27 pays
40 000 cas passés inaperçus (2017)
25% de formes asymptomatiques
R0<1

Arabi YM et al. NEJM. 2017

Lopi/rito et interféron β1b dans un modèle primate de MERS-CoV







Score clinique significativement meilleur

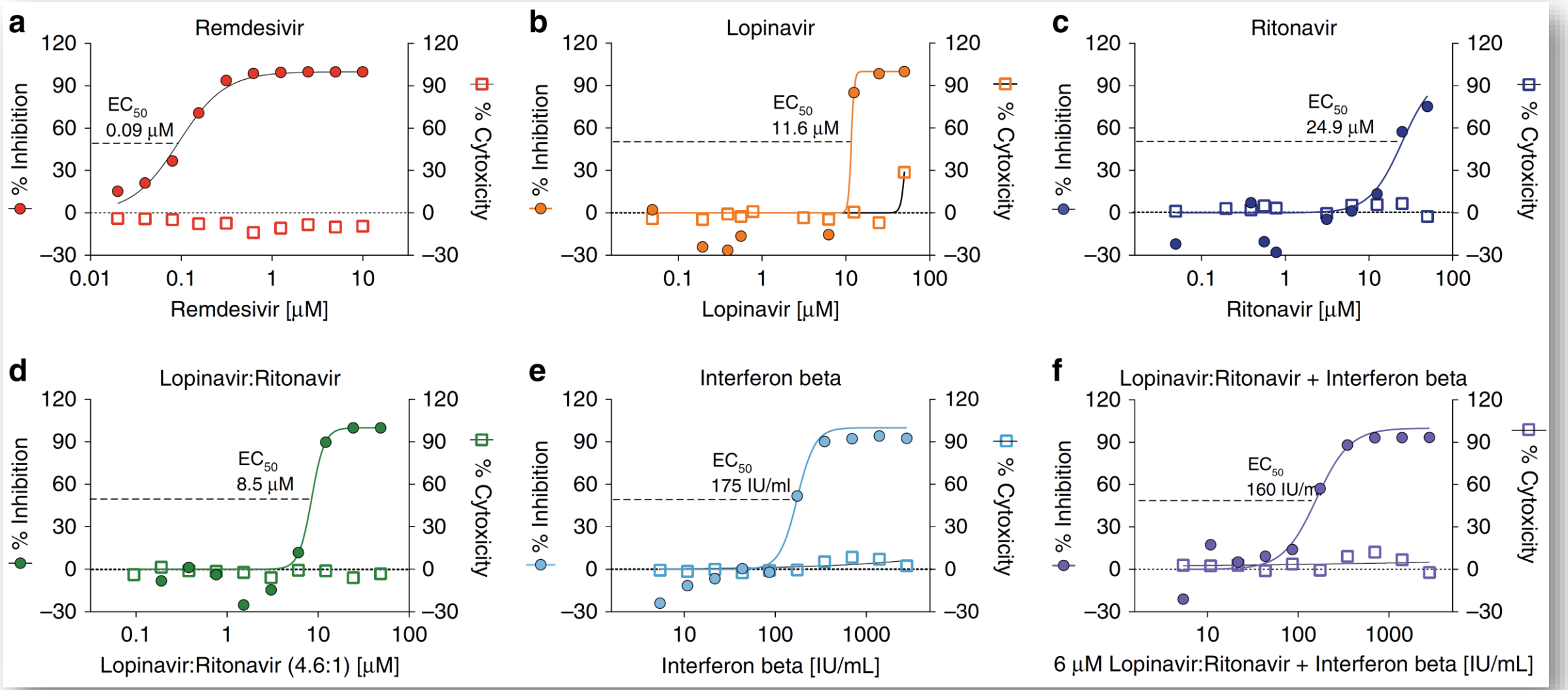
Significativement moins de perte de poids

Charge virale significativement plus faible

Chan J et al. JID. 2015

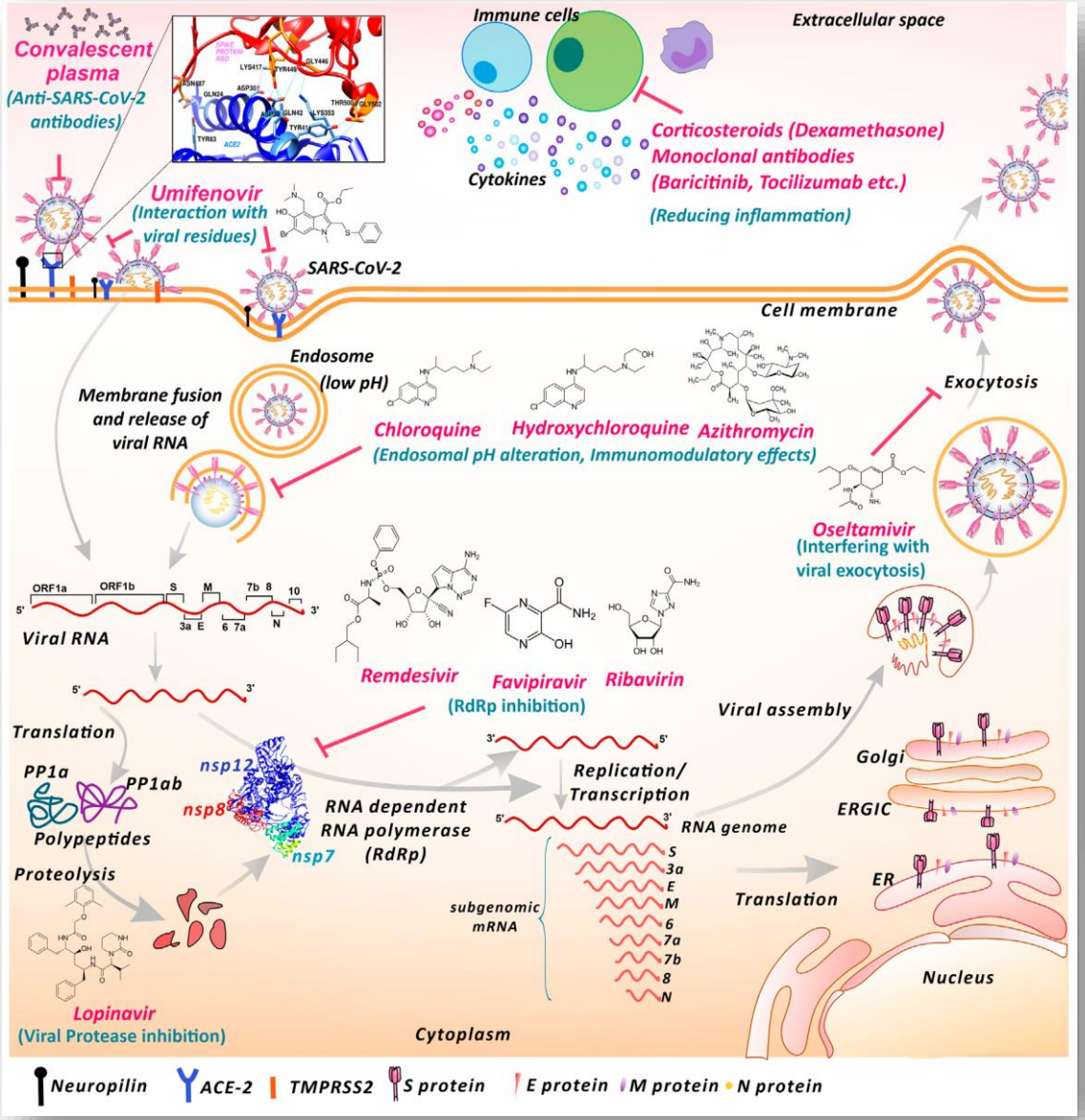
NB: -lopinavir/r validée in vitro sur SARS et MERS. *(WU CY et al. PNAS 2004; de Wilde AH et al. AAC 2014)*
-rationnel interféron : restauration immunité. Le MERS exprime des protéines anti IFN

Remdesivir et MERS (spectre large sur coronavirus)

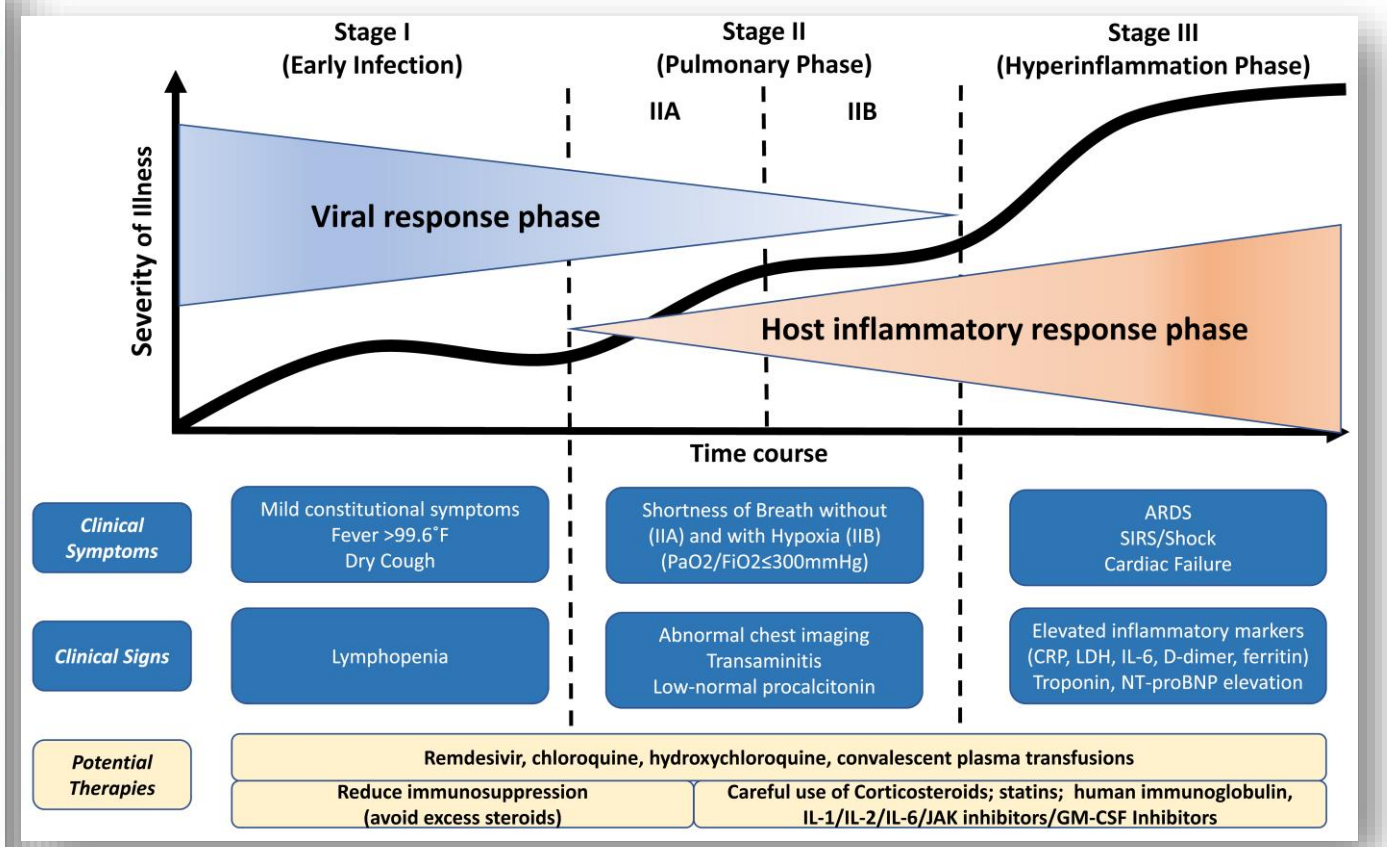


Sheahan TP et al. Nature Communications. 2020.

COVID-19 et fenêtre d'opportunité antivirale

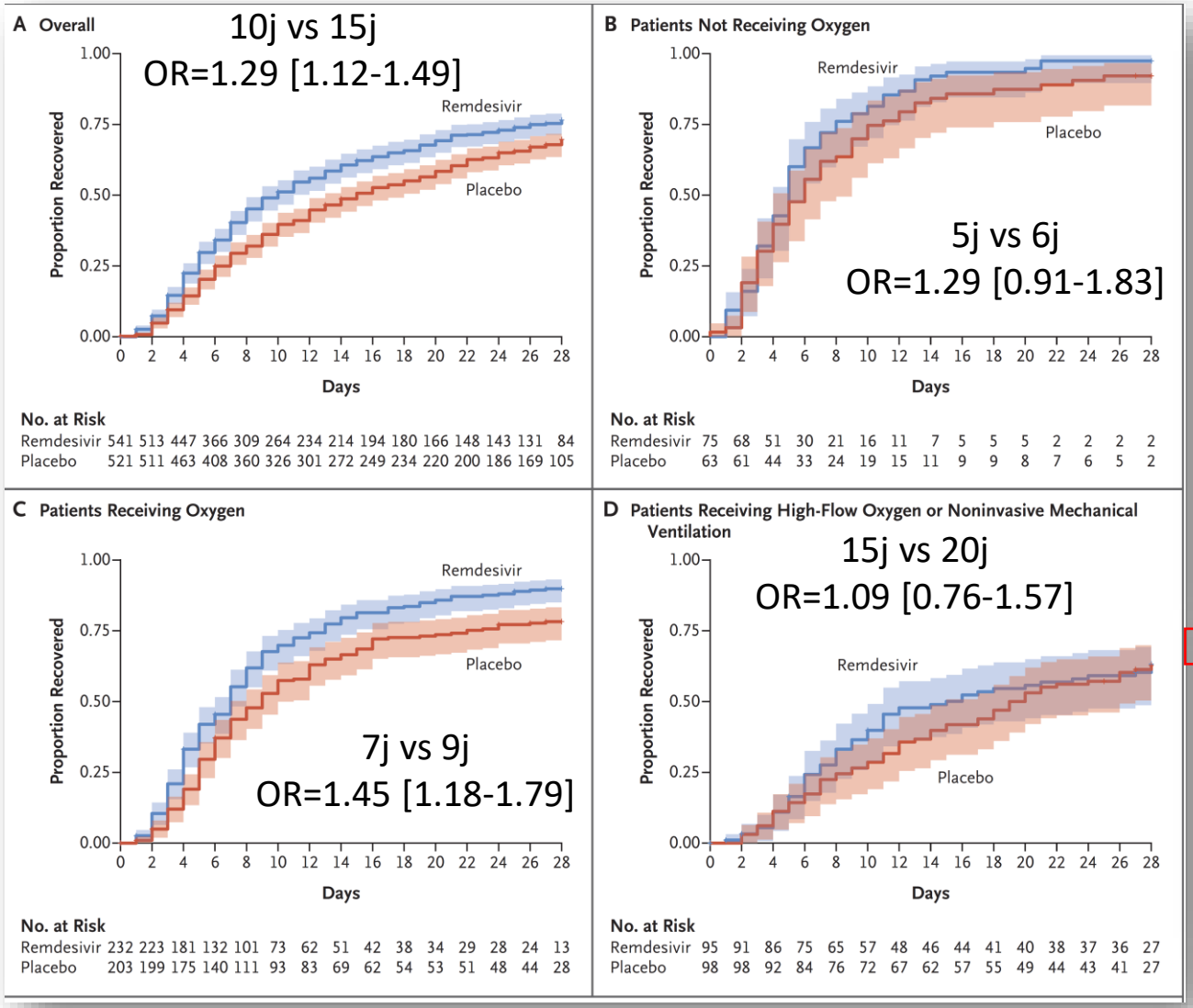


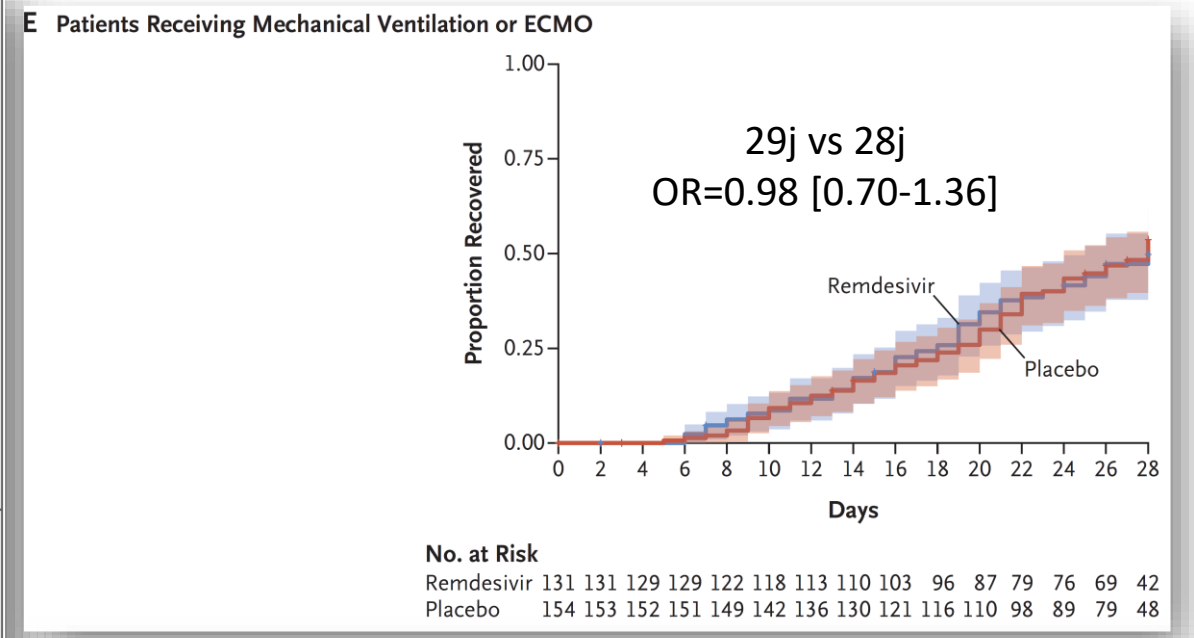
Indari O et al. Frontiers pharmacol. 2021

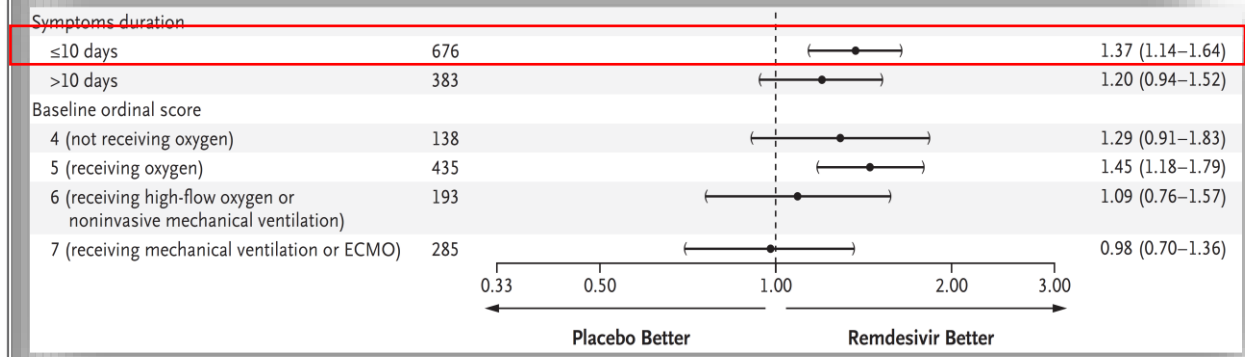


Siddiqui HK et al. J Heart Lung Transplant. 2020

ACCT1 : time to recovery. Remdesivir

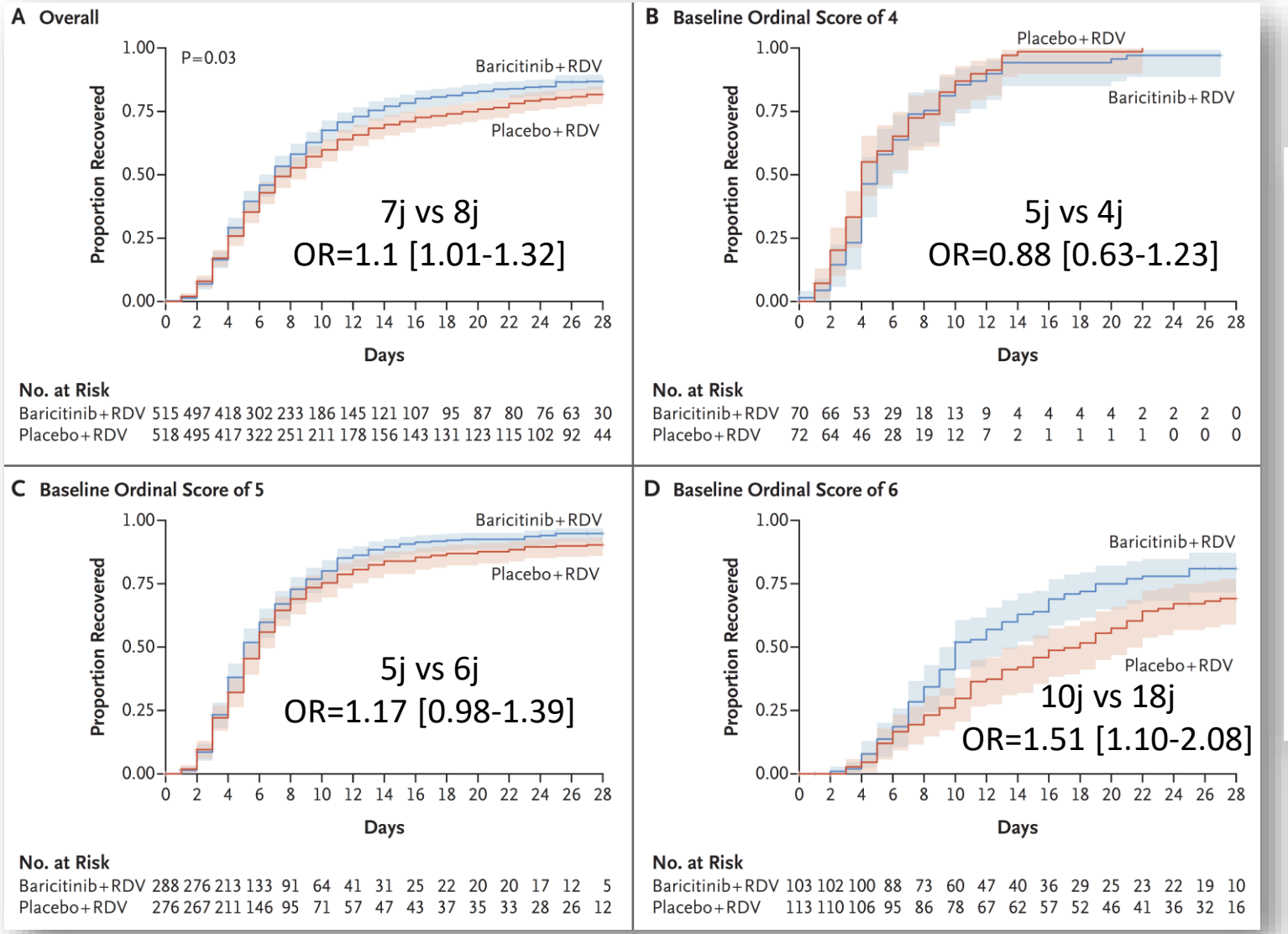


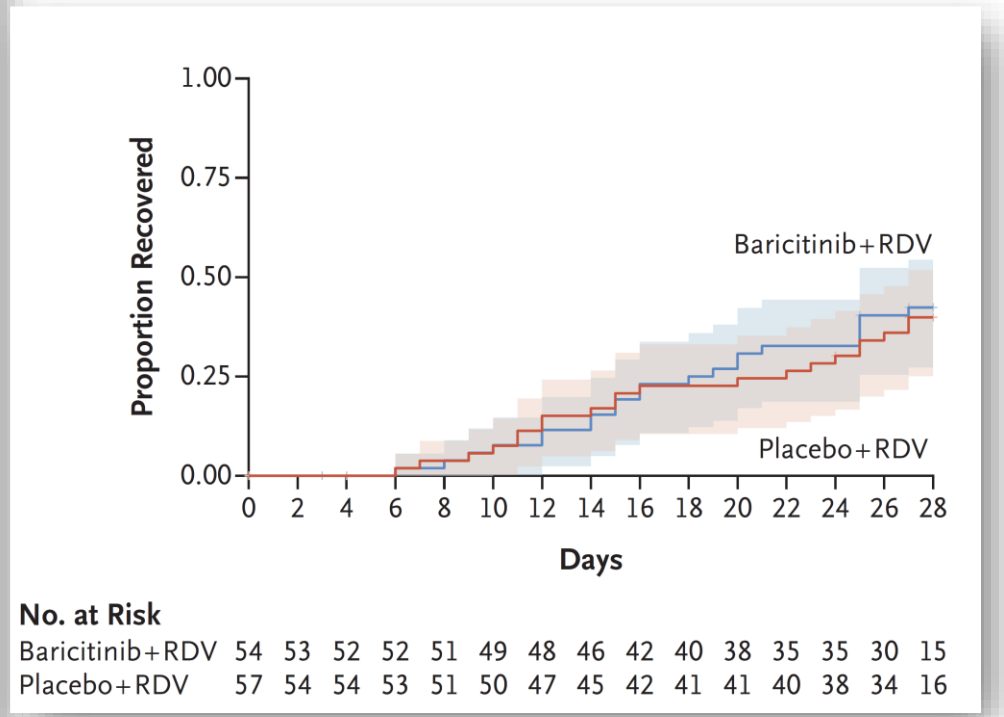




Beigel JH et al. NEJM. 2020

ACCT2 : time to recovery. Remdesivir+/-baricitinib





Kalil AC et al. NEJM. 2021

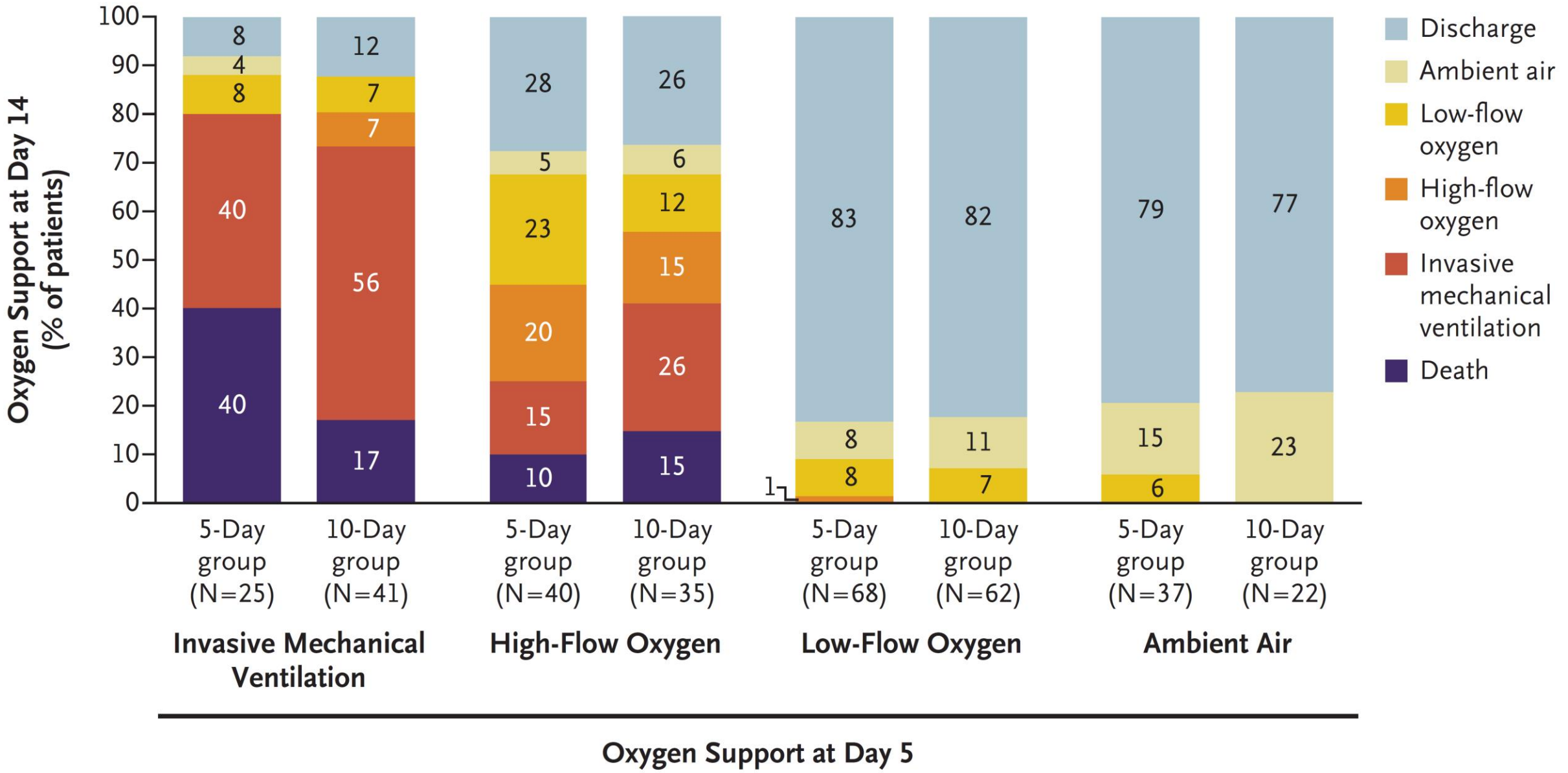
Essai Simple : Remdesivir 5j vs 10j. Statut clinique J14

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)	Baseline-Adjusted Difference (95% CI)*
Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)			P=0.14†
1: Death	16 (8)	21 (11)	
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)	
3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen	9 (4)	10 (5)	
4: Hospitalized, requiring low-flow supplemental oxygen	19 (10)	14 (7)	
5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care	11 (6)	13 (7)	
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	3 (2)	
7: Not hospitalized	120 (60)	103 (52)	
Time to clinical improvement (median day of 50% cumulative incidence‡)	10	11	0.79 (0.61 to 1.01)

65% amélioration 2 points
Vs
54%

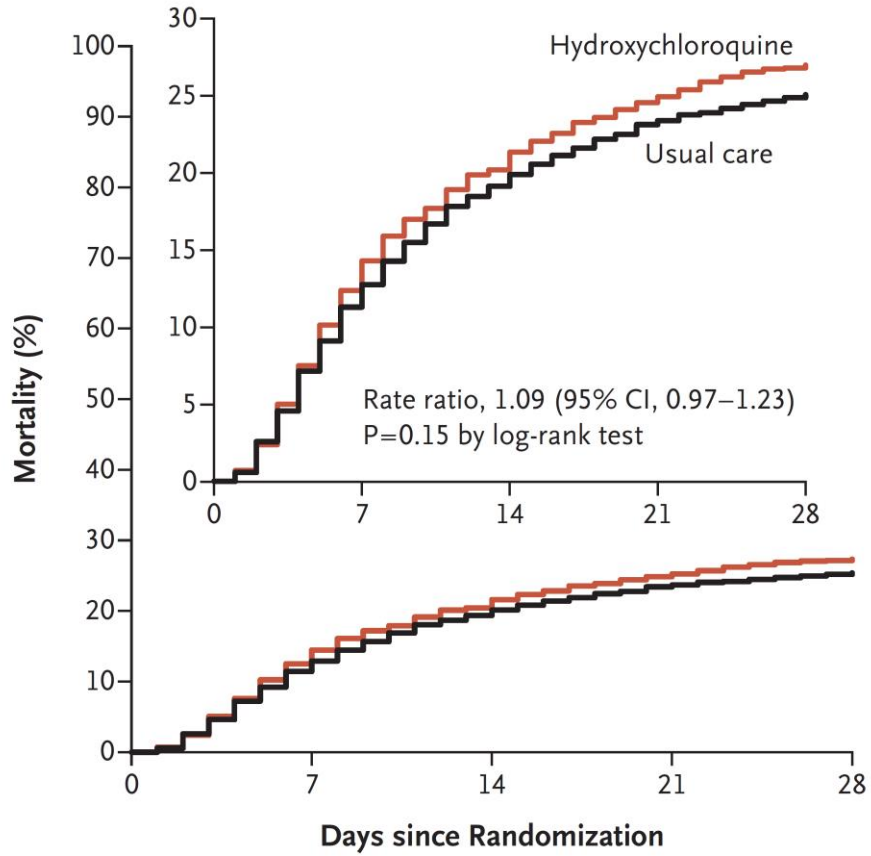
Exclusion patients ventilés/ECMO

Goldman JD et al. NEJM. 2020



Goldman JD et al. NEJM. 2020

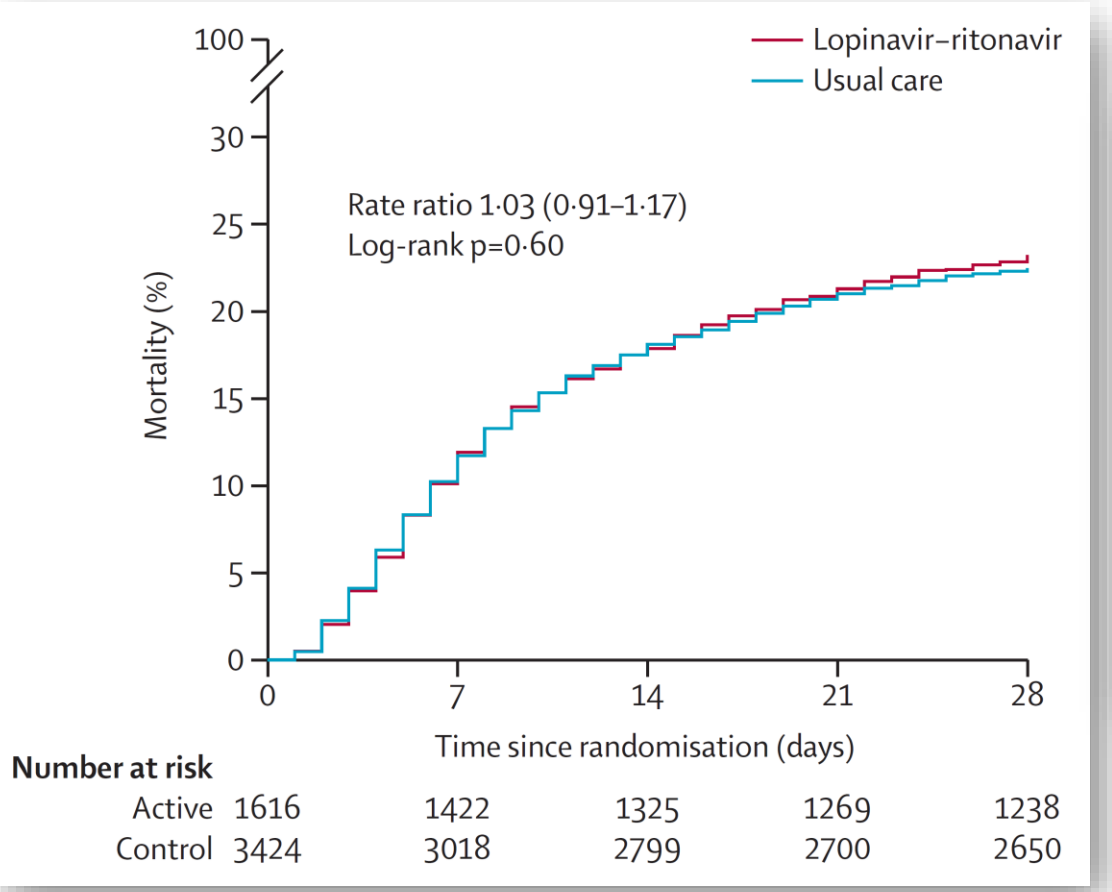
Recovery OH-chloroquine. Mortalité J28



Outcome	Hydroxychloroquine (N=1561)	Usual Care (N=3155)	Rate or Risk Ratio (95% CI)
	no./total no. (%)		
Primary outcome: 28-day mortality	421/1561 (27.0)	790/3155 (25.0)	1.09 (0.97–1.23)*
Secondary outcomes			
Discharge from hospital in ≤28 days	931/1561 (59.6)	1983/3155 (62.9)	0.90 (0.83–0.98)*
Invasive mechanical ventilation or death†	399/1300 (30.7)	705/2623 (26.9)	1.14 (1.03–1.27)‡
Invasive mechanical ventilation	128/1300 (9.8)	225/2623 (8.6)	1.15 (0.93–1.41)
Death	311/1300 (23.9)	574/2623 (21.9)	1.09 (0.97–1.23)

Recovery collaborative group. NEJM. 2020

Recovery Lopi/rito. Mortalité J28



	Lopinavir–ritonavir (n=1616)	Usual care (n=3424)	RR (95% CI)	p value
Primary outcome				
28-day mortality	374 (23%)	767 (22%)	1·03 (0·91–1·17)	0·60
Secondary outcomes				
Discharged from hospital within 28 days	1113 (69%)	2382 (70%)	0·98 (0·91–1·05)	0·53
Receipt of invasive mechanical ventilation or death*	449/1556 (29%)	871/3280 (27%)	1·09 (0·99–1·20)	0·092
Invasive mechanical ventilation	152/1556 (10%)	279/3280 (9%)	1·15 (0·95–1·39)	0·15
Death	350/1556 (22%)	712/3280 (22%)	1·04 (0·93–1·16)	0·54

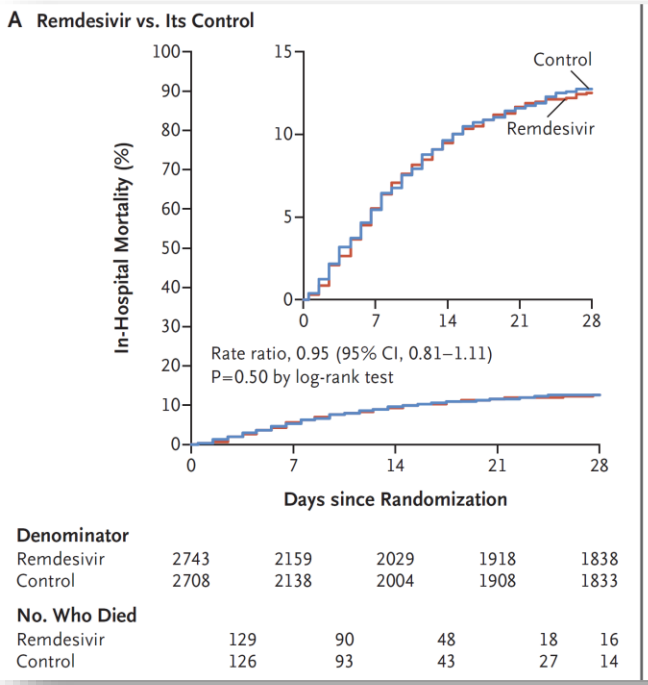
Recovery collaborative group. Lancet. 2020

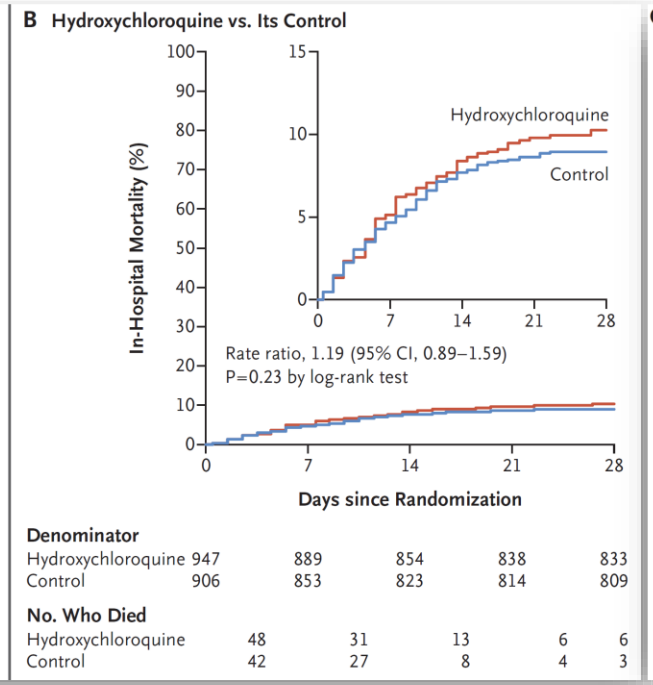
RemapCap en réa

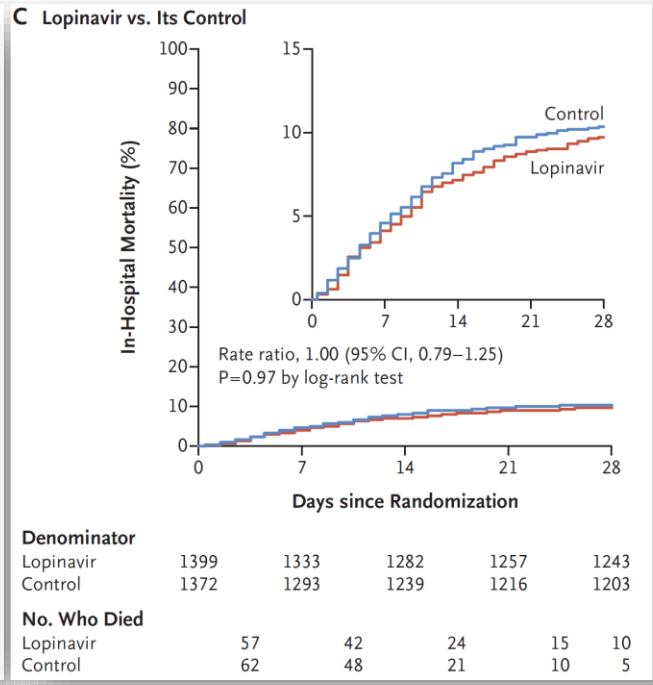
Outcome/analysis	Lopinavir-ritonavir (*N* = 255)	Hydroxychloroquine (*N* = 50)	Combination therapy (*N* = 27)	Control (*N* = 362)
Primary outcome, organ support-free days (OSFDs)				
Median (IQR)	4 (− 1, 15)	0 (− 1, 9)	− 1 (− 1, 7)	6 (− 1, 16)
Adjusted OR—median (95% CrI)	0.73 (0.55, 0.99)	0.57 (0.35, 0.83)	0.41 (0.24, 0.72)	1
Probability of futility, %	99.9	> 99.9	> 99.9	–
Probability of harm compared to control, %	98	99.9	> 99.9	–
Subcomponents of OSFDs				
In-hospital deaths, n (%)	88/249 (35.3%)	17/49 (34.7%)	13/26 (50%)	106/353 (30%)
OSFDs in survivors, median (IQR)	14 (7, 17)	4 (0, 13)	8 (0, 13)	14 (3, 18)
Primary analysis of hospital survival				
Adjusted OR—median (95% CrI)	0.65 (0.45–0.95)	0.56 (0.30–0.89)	0.36 (0.17–0.73)	1
Probability of harm compared to control, %	98.5	99.4	99.8	–
Secondary analysis of primary outcome				
Adjusted OR—median (95% CrI)	0.76 (0.57, 1.02)	0.59 (0.35, 0.88)	0.45 (0.25, 0.78)	1
Probability of futility, %	99.9	> 99.9	> 99.9	–
Probability of harm compared to control, %	96.3	99.6	99.8	–
Secondary analysis of hospital survival				
Adjusted OR—median (95% CrI)	0.66 (0.46, 0.96)	0.58 (0.32, 0.91)	0.38 (0.18, 0.76)	1
Probability of harm compared to control, %	98.5	99.2	99.7	–

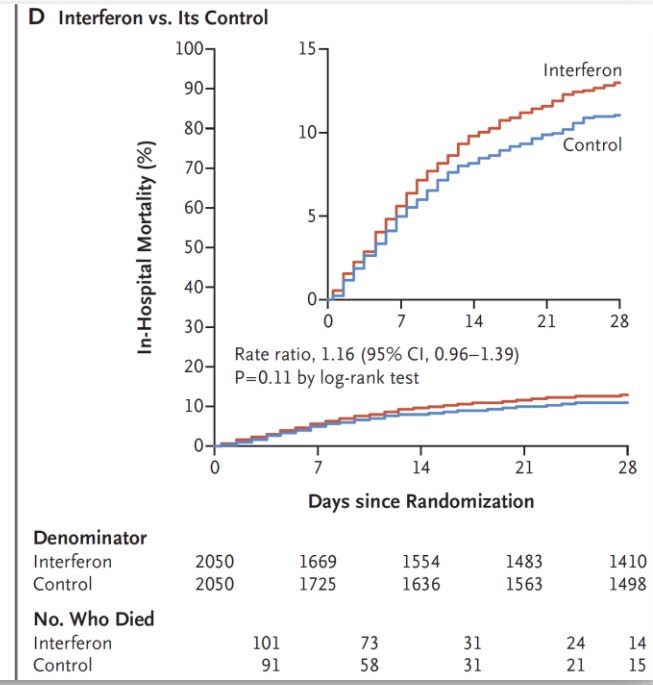
WHO Solidarity Trial Consortium. NEJM 2021

Solidarity. Mortalité hospitalière





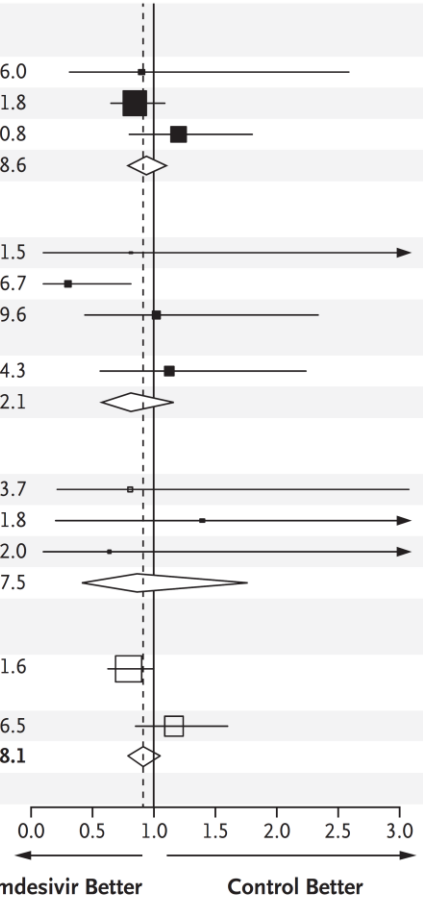




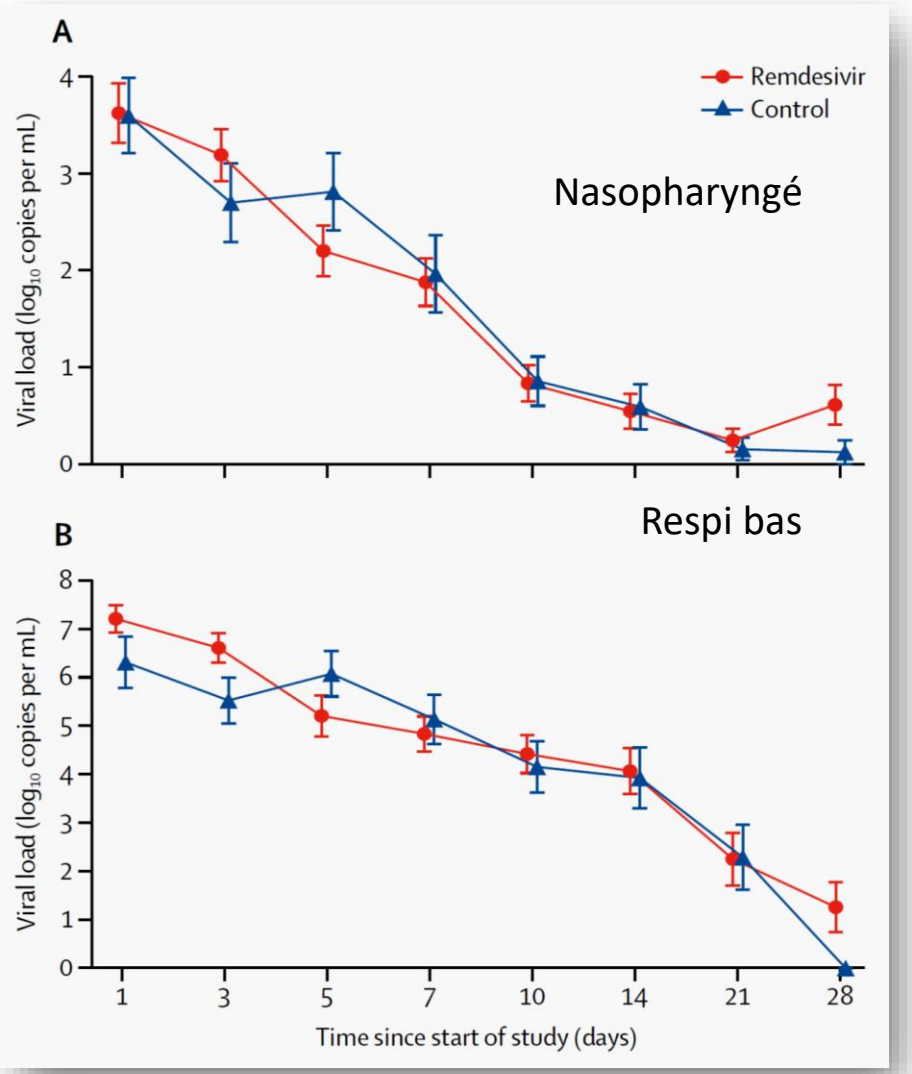
WHO Solidarity Trial Consortium. NEJM 2021

Un manque d'efficacité intrinsèque ou une fenêtre antivirale dépassée ?

Subgroup	Remdesivir	Control	Observed–Expected No. of Deaths in Remdesivir Group: Value	Observed–Expected No. of Deaths in Remdesivir Group: Variance	Rate Ratio for Death (99% CI; 95% CI for totals)
	no. of deaths reported/no. of patients (%)				
Solidarity (stratified according to oxygen use and ventilation)					
No supplemental oxygen	11/661 (2.0)	13/664 (2.1)	−0.6	6.0	0.90 (0.31–2.58)
Low-flow or high-flow oxygen	192/1828 (12.2)	219/1811 (13.8)	−16.9	101.8	0.85 (0.66–1.09)
Ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Stratified total: Solidarity	301/2743 (12.5)	303/2708 (12.7)	−10.0	148.6	0.94 (0.80–1.10)
ACTT-1 (stratified according to 4 ordinal score levels)					
No supplemental oxygen	3/75 (4.1)	3/63 (4.8)	−0.3	1.5	0.82 (0.10–6.61)
Low-flow oxygen	9/232 (4.0)	25/203 (12.7)	−8.0	6.7	0.30 (0.11–0.81)
High-flow oxygen or noninvasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 (0.44–2.34)
Invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.8	14.3	1.13 (0.57–2.23)
Stratified total: ACTT-1	59/533 (11.1)	77/518 (14.9)	−6.4	32.1	0.82 (0.58–1.16)
Trials with few deaths (and randomization ratio of 2:1)					
Wuhan: low-flow oxygen	11/129 (8.5)	(7/68)×2 (10.3)	−0.8	3.7	0.81 (0.21–3.07)
Wuhan: high-flow oxygen or ventilation	11/29 (37.9)	(3/10)×2 (30.0)	0.6	1.8	1.40 (0.20–9.52)
International: no supplemental oxygen	5/384 (1.3)	(4/200)×2 (2.0)	−0.9	2.0	0.64 (0.10–3.94)
Stratified total: 2:1 trials	27/542 (5.0)	(14/278)×2 (5.0)	−1.1	7.5	0.86 (0.42–1.77)
Risk groups (calculated by summation of relevant strata)					
Lower risk: strata with no ventilation	231/3309 (7.0)	282/3277 (8.6)	−27.6	121.6	0.80 (0.63–1.01)
Higher risk	156/509 (30.6)	126/505 (25.0)	10.1	66.5	1.16 (0.85–1.60)
Stratified total	**387/3818 (10.1)**	**408/3782 (10.8)**	**−17.5**	**188.1**	**0.91 (0.79–1.05)**
Heterogeneity between trials (Solidarity vs. ACTT-1 vs. 2:1 trials): χ^2_2=0.5					P=0.20

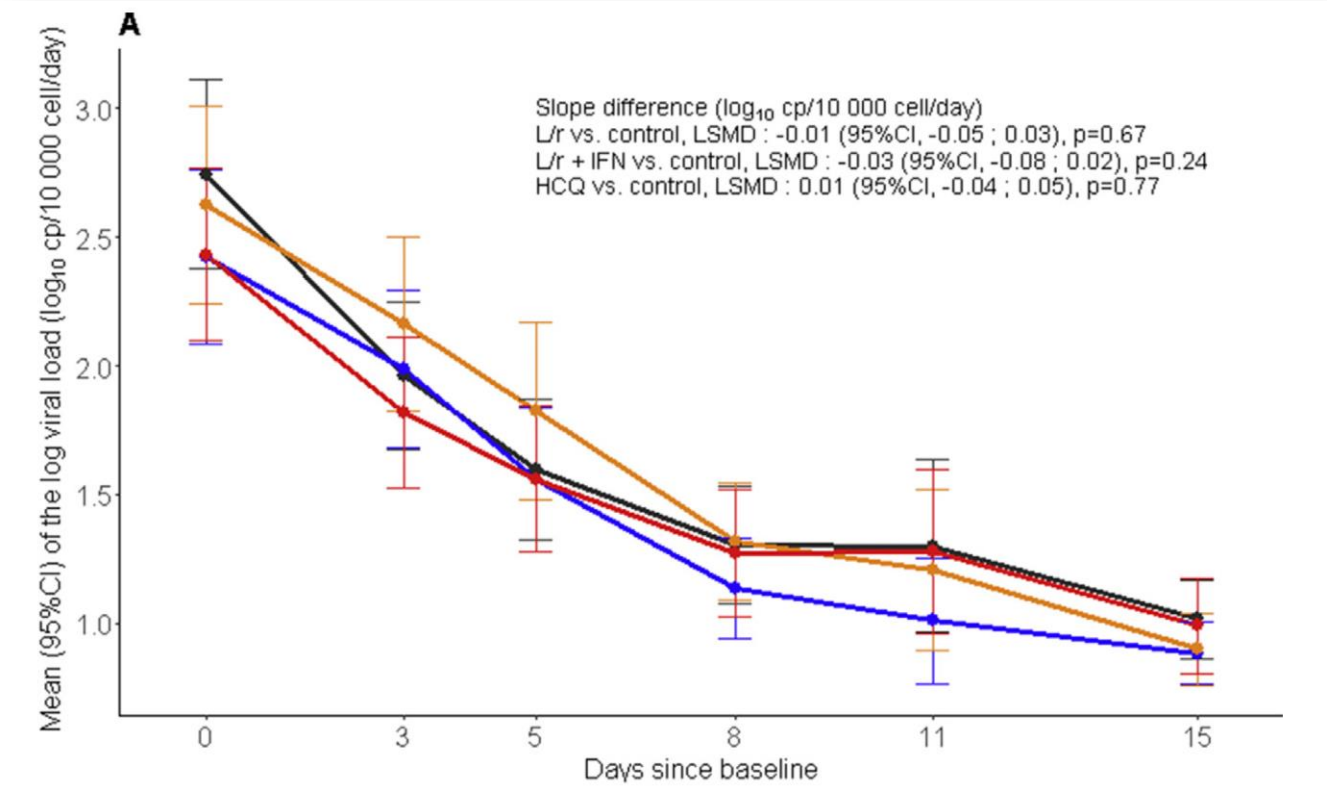


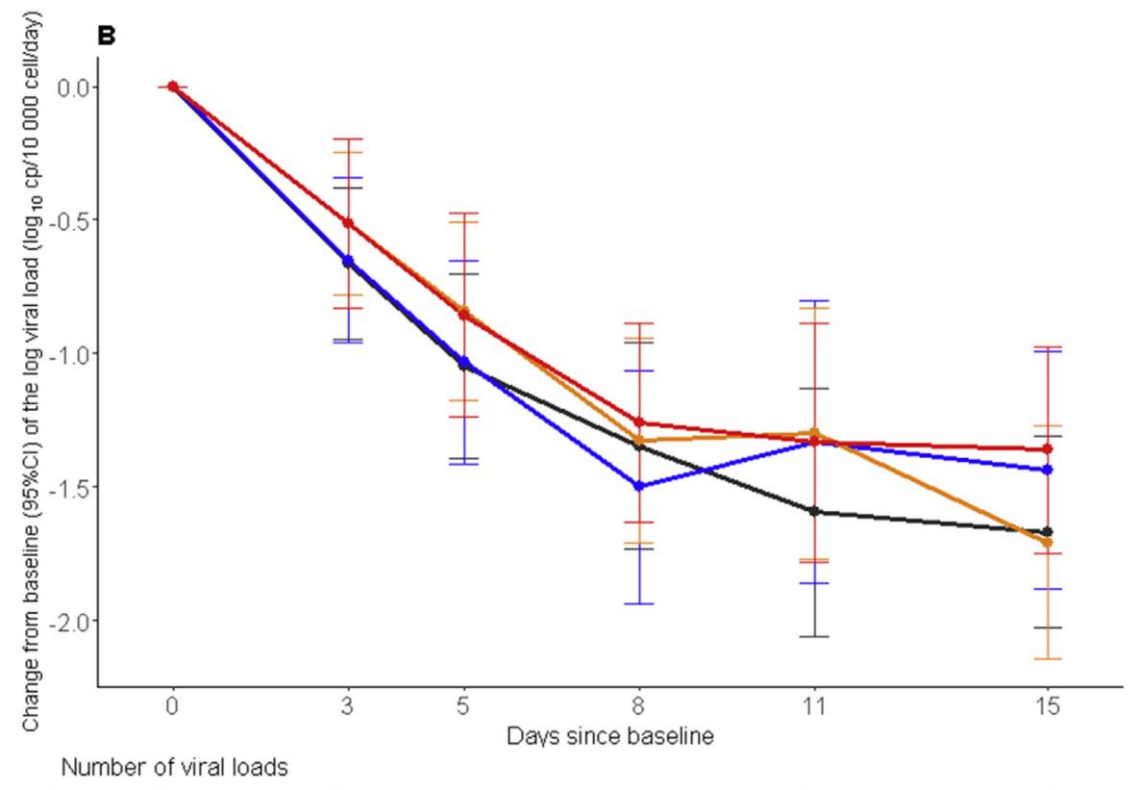
Solidarity. NEJM. 2020



Wang Y et al. Lancet. 2020

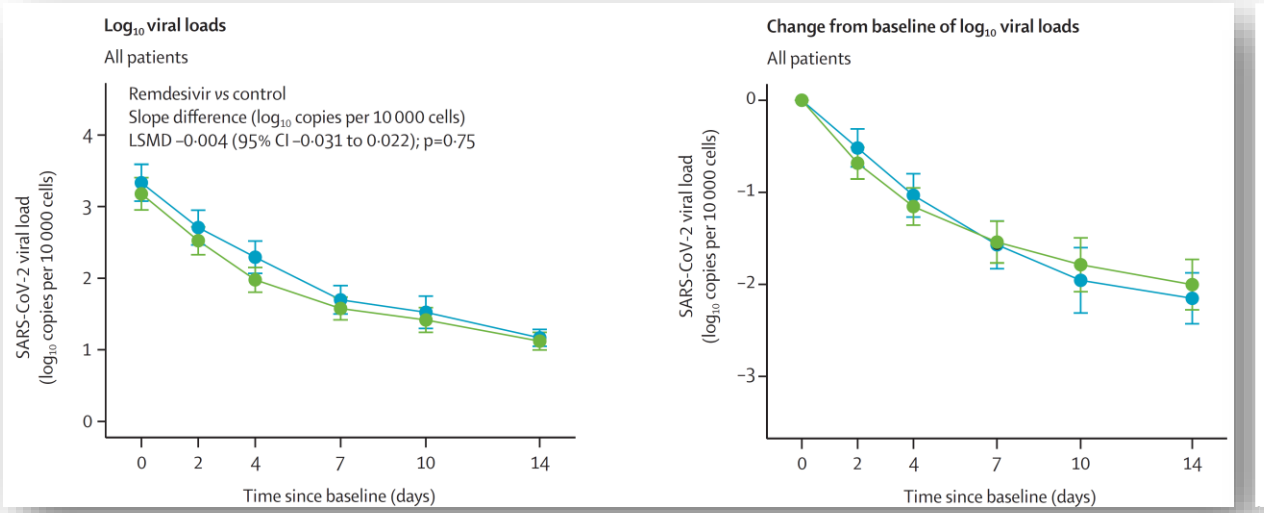
Charges virales Discovery bras OH-Cholroquine; Lopi/r +/- IFN

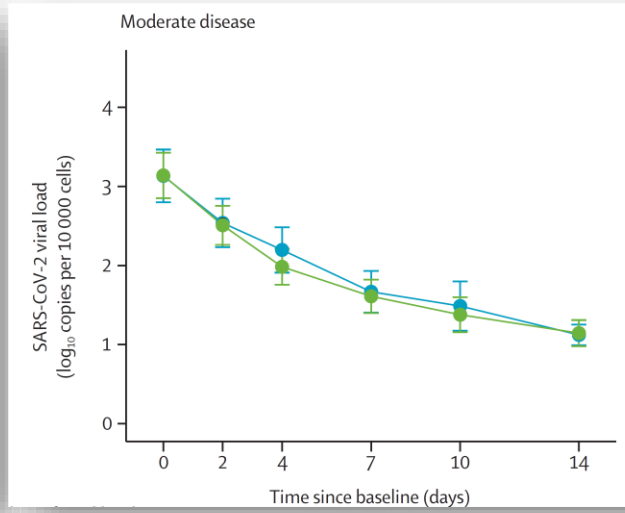


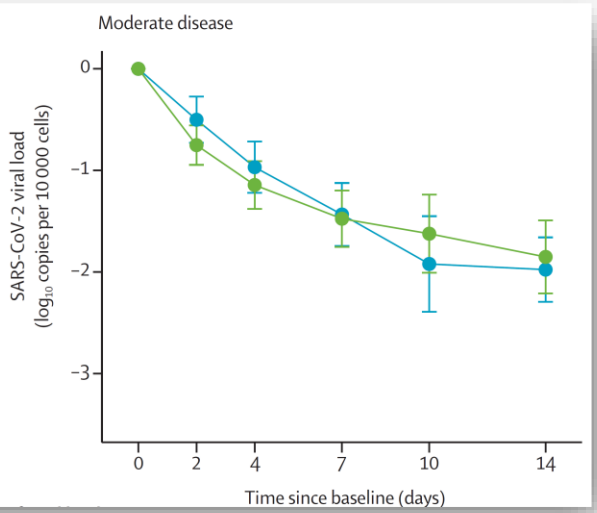


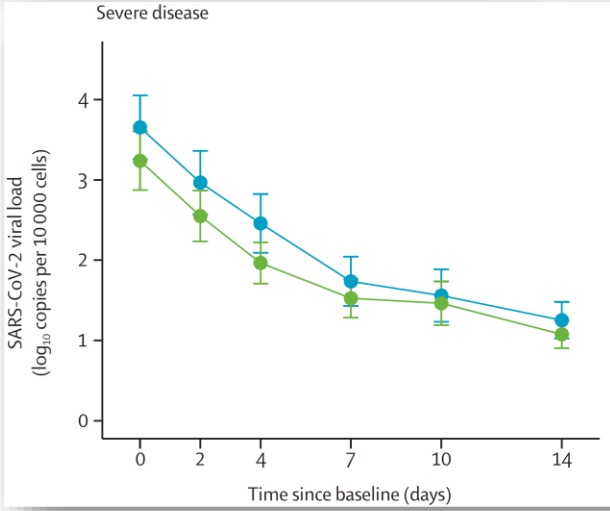
Ader F et al. CMI. 2020

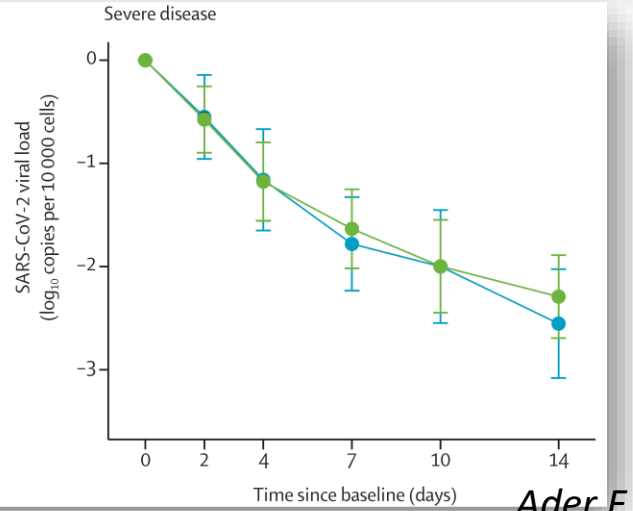
Quid des charges virales ? Discovery bras Remdesivir





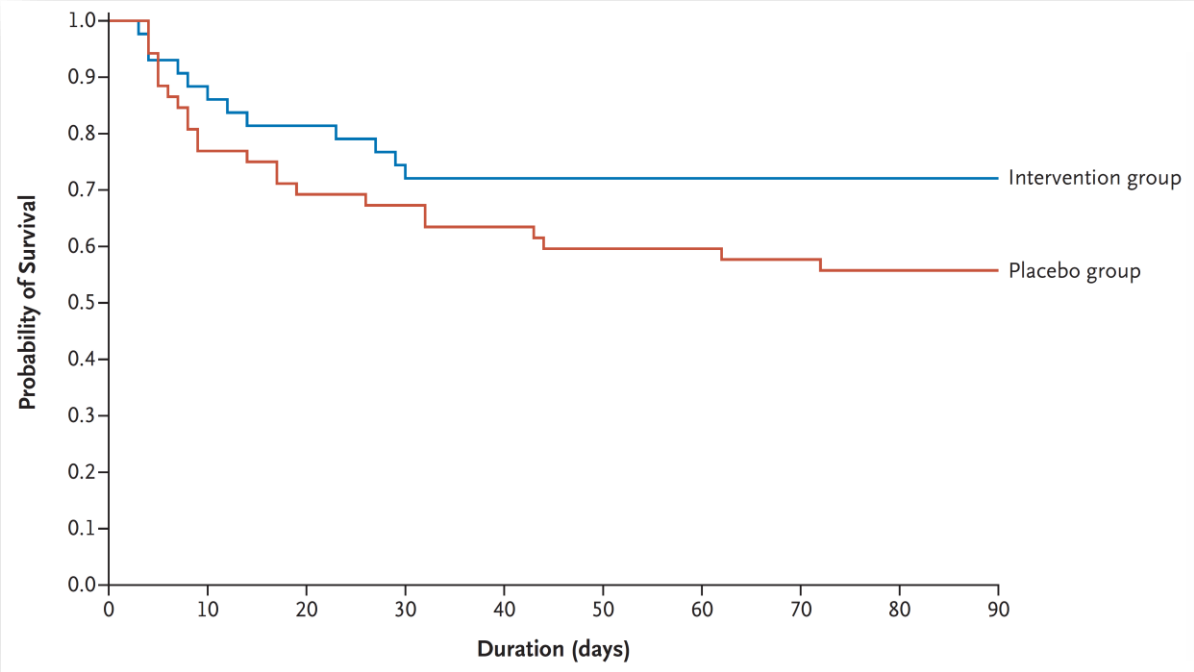






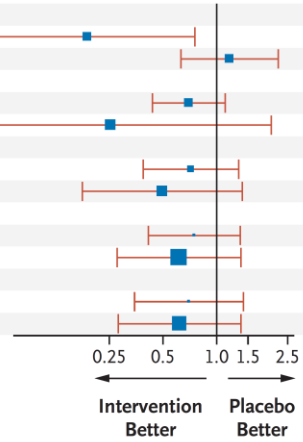
Ader F et al. Lancet Inf Dis. 2021

Et pourtant dans le MERS : essai Miracle Lopi/rito + IFN β1b



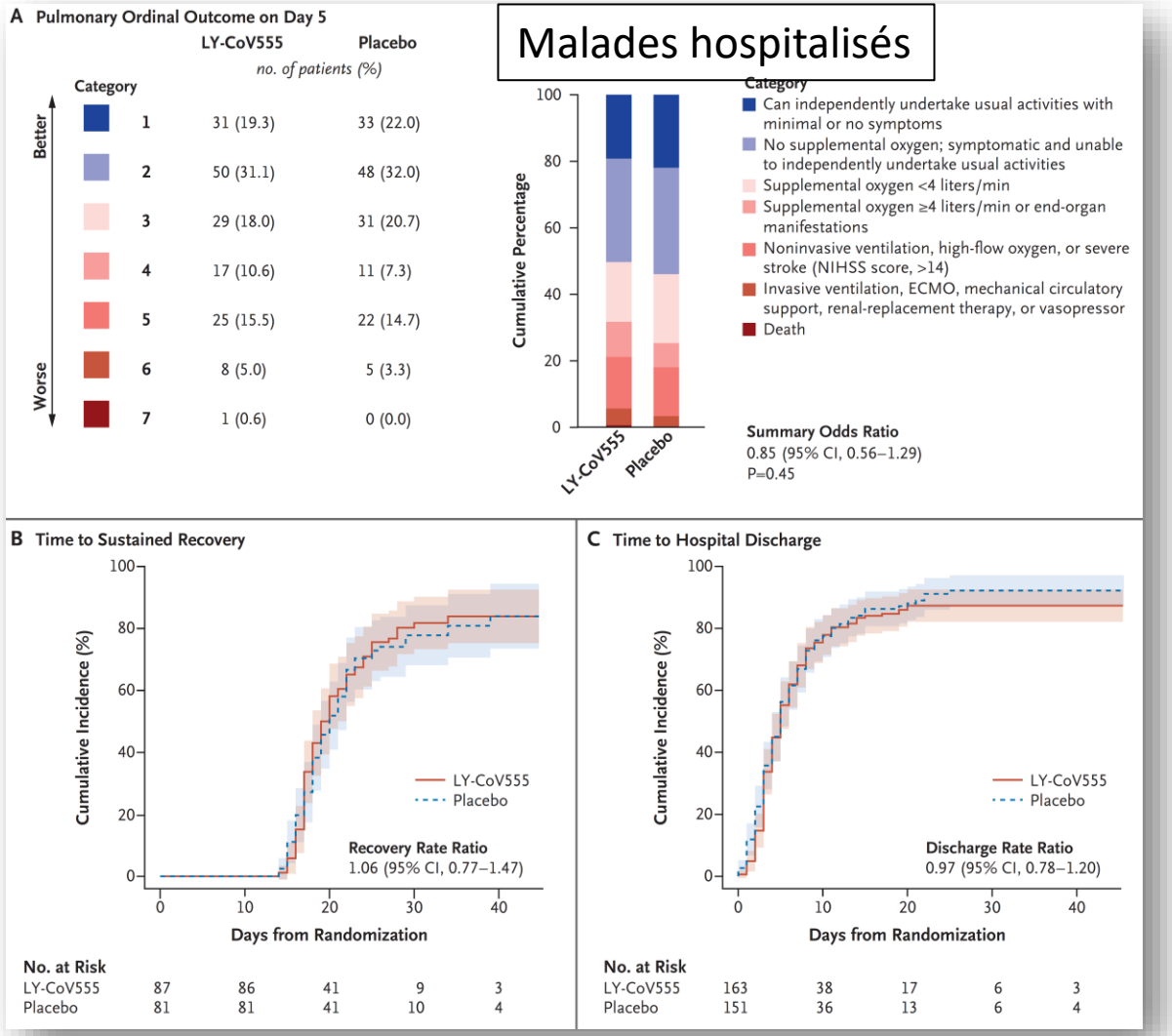
B

Subgroup	Intervention Group	Placebo Group	Relative Risk (95% CI)	P Value for Interaction	FDR
	no. of patients with event/ no. of patients (%)				
Time from onset of symptoms to enrollment				0.006	0.03
≤7 days	2/23 (9)	12/26 (46)	0.19 (0.05–0.75)		
>7 days	10/20 (50)	11/26 (42)	1.18 (0.63–2.21)		
APACHE II score				0.30	0.75
>20	11/21 (52)	18/24 (75)	0.70 (0.44–1.12)		
≤20	1/22 (5)	5/28 (18)	0.25 (0.03–2.02)		
Mechanical ventilation				0.54	0.82
Yes	8/18 (44)	13/21 (62)	0.72 (0.39–1.33)		
No	4/25 (16)	10/31 (32)	0.50 (0.18–1.39)		
Vasopressor therapy				0.70	0.82
Yes	5/8 (62)	10/12 (83)	0.75 (0.41–1.36)		
No	7/35 (20)	13/40 (32)	0.62 (0.28–1.37)		
Renal-replacement therapy				0.82	0.82
Yes	5/10 (50)	10/14 (71)	0.70 (0.35–1.41)		
No	7/33 (21)	13/38 (34)	0.62 (0.28–1.37)		

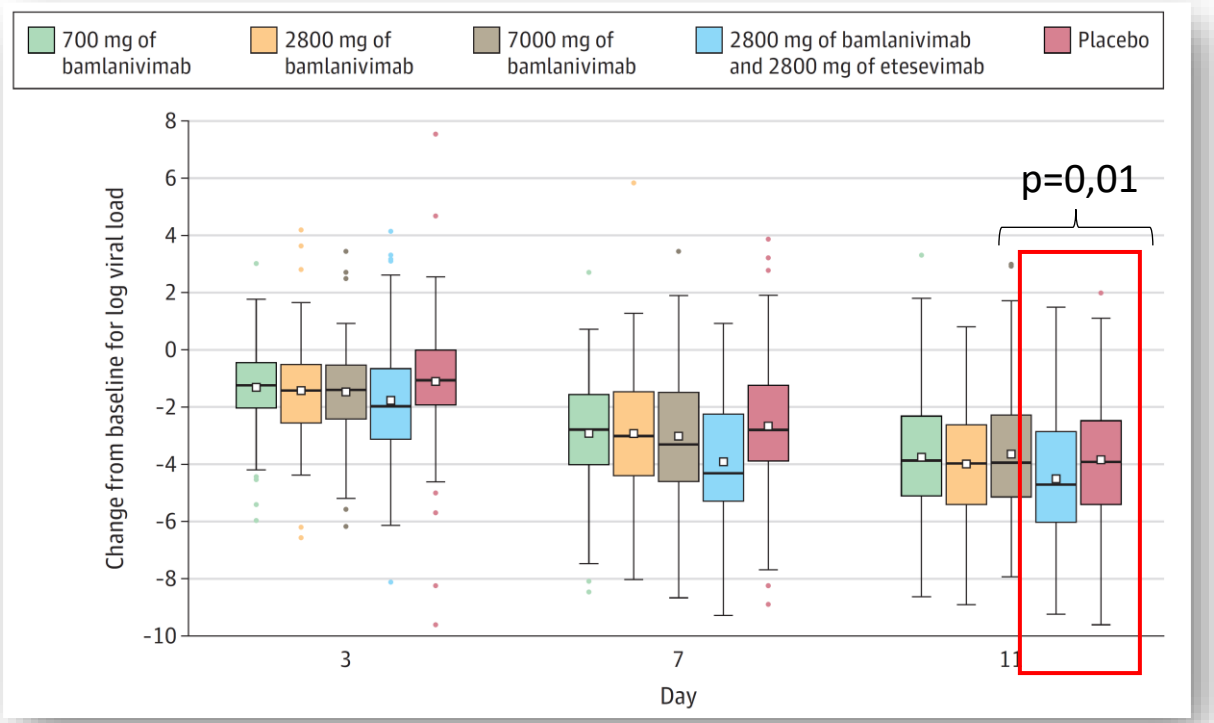


Arabi M et al. NEJM. 2020

Ac monoclonaux : en association et précocement



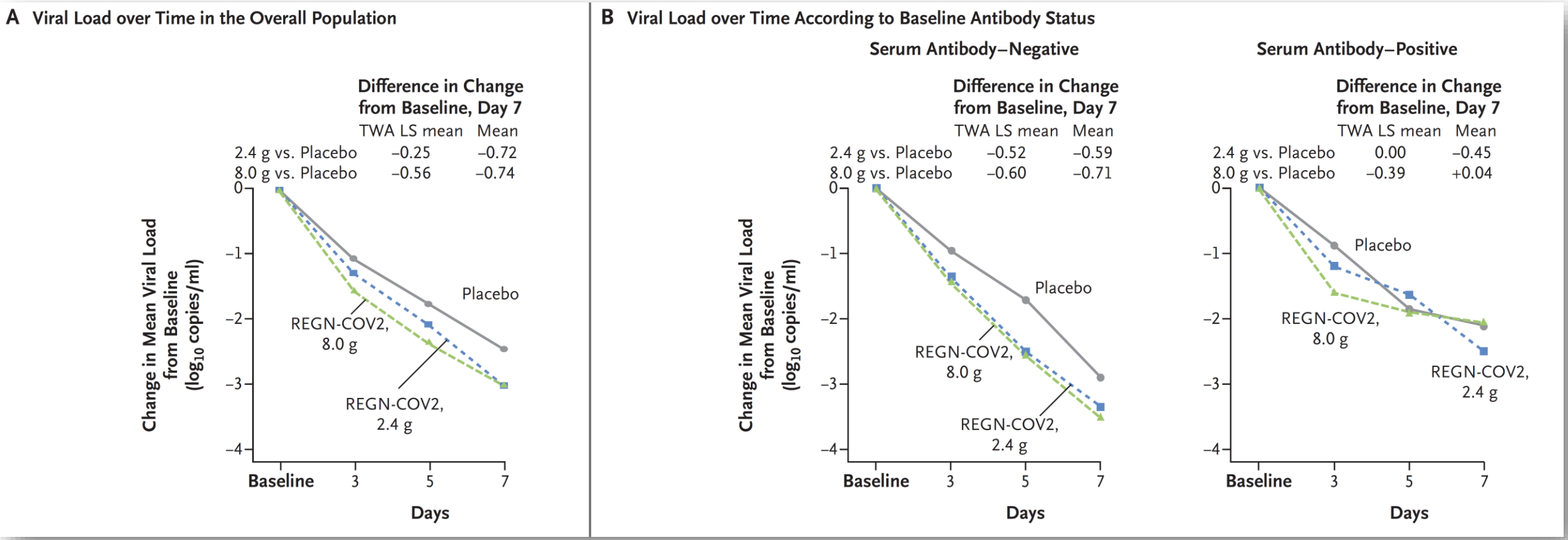
ACTIV3/TICO LY CoV555 study group. NEJM 2020



- Mild to moderate
- A J3 de la PCR
- En pratique à J4 des symptômes
- Patients ambulatoires

Gottlieb LR et al. JAMA. 2021

REGN-COV2 en ambulatoire : diminution de la CV chez les séronégatifs



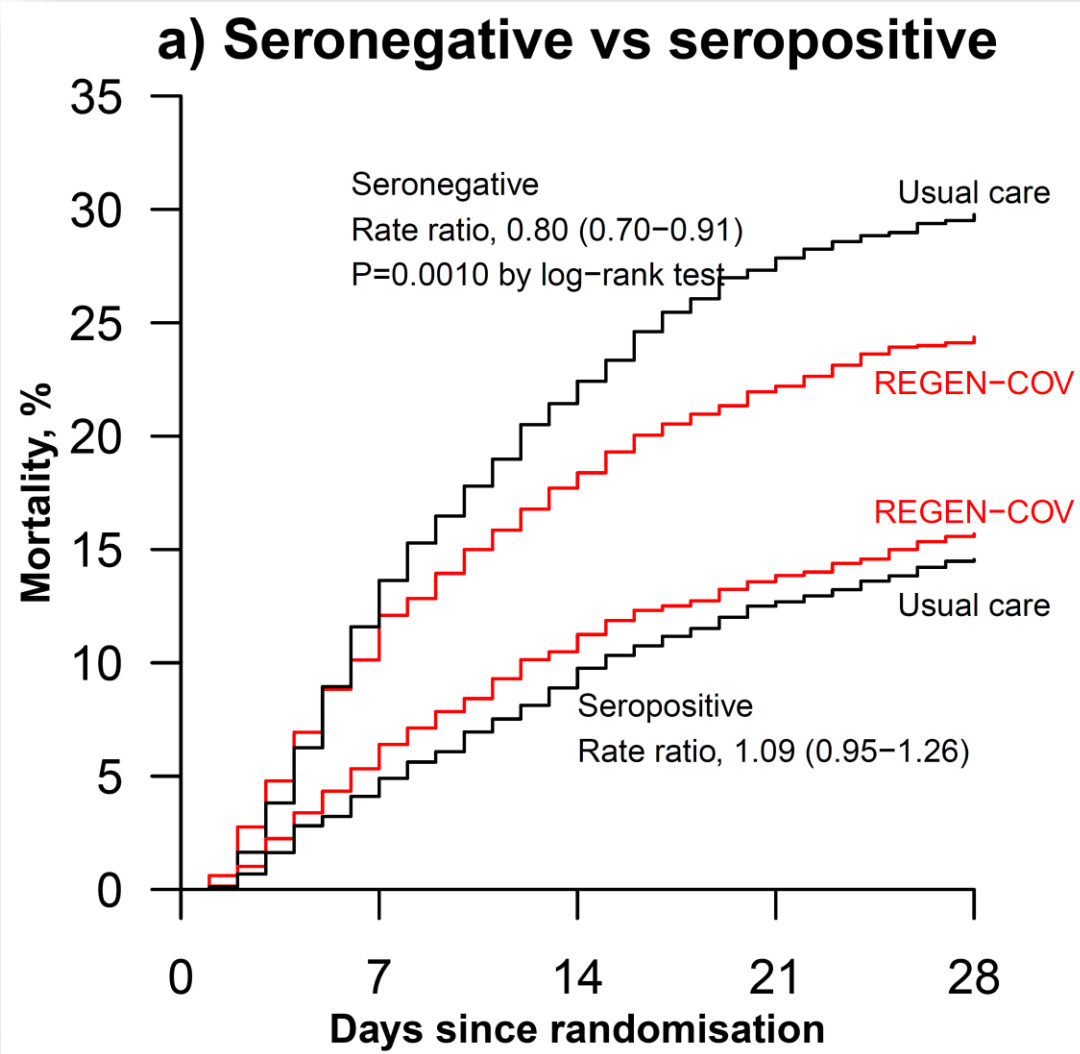
Weinreich DM et al. NEJM. 2020

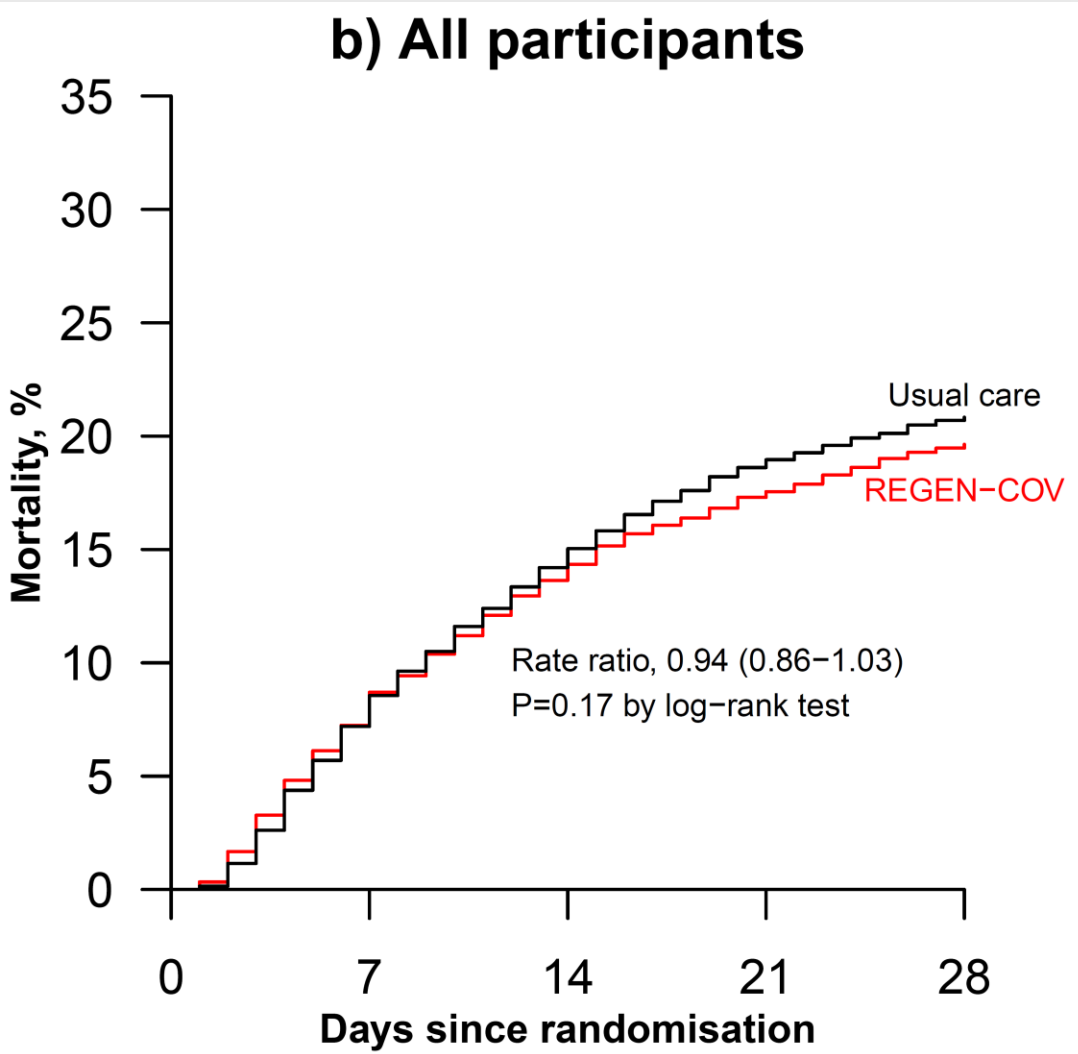
REGN-COV2 chez les malades hospitalisés : un intérêt chez les séronégatifs ?

Table 2: Effect of allocation to REGEN-COV on key study outcomes among seronegative participants

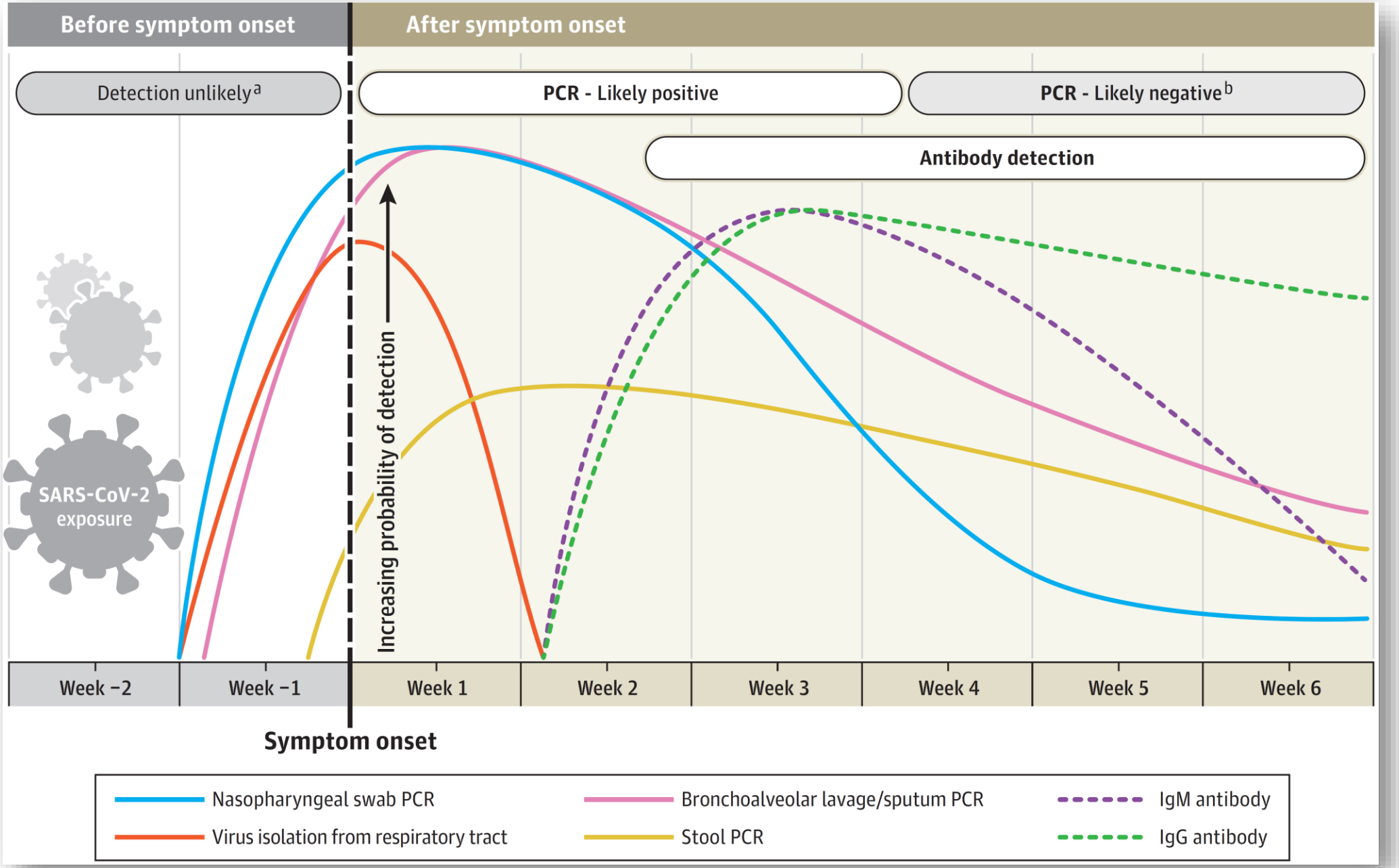
	REGEN-COV (n=1633)	Usual Care (n=1520)	RR (95% CI)
Primary outcome			
Mortality at 28 days	396 (24%)	451 (30%)	0.80 (0.70-0.91)
Secondary outcomes			
Median duration of hospitalisation, days	13 (7 to >28)	17 (7 to >28)	-
Discharged from hospital within 28 days	1046 (64%)	878 (58%)	1.19 (1.08-1.30)
Invasive mechanical ventilation or death*	487/1599 (30%)	542/1484 (37%)	0.83 (0.75-0.92)
Invasive mechanical ventilation	189/1599 (12%)	200/1484 (13%)	0.88 (0.73-1.06)
Death	383/1599 (24%)	434/1484 (29%)	0.82 (0.73-0.92)
Subsidiary outcomes			
Use of ventilation †	355/1267 (28%)	370/1143 (32%)	0.87 (0.77-0.98)
Non-invasive ventilation	341/1267 (27%)	360/1143 (31%)	0.85 (0.75-0.97)
Invasive mechanical ventilation	89/1267 (7%)	119/1143 (10%)	0.67 (0.52-0.88)
Successful cessation of invasive mechanical ventilation ‡	9/34 (26%)	12/36 (33%)	0.86 (0.36-2.03)
Renal replacement therapy §	68/1616 (4%)	64/1498 (4%)	0.98 (0.71-1.38)

Recovery collaborative group. medRxiv. Non reviewed



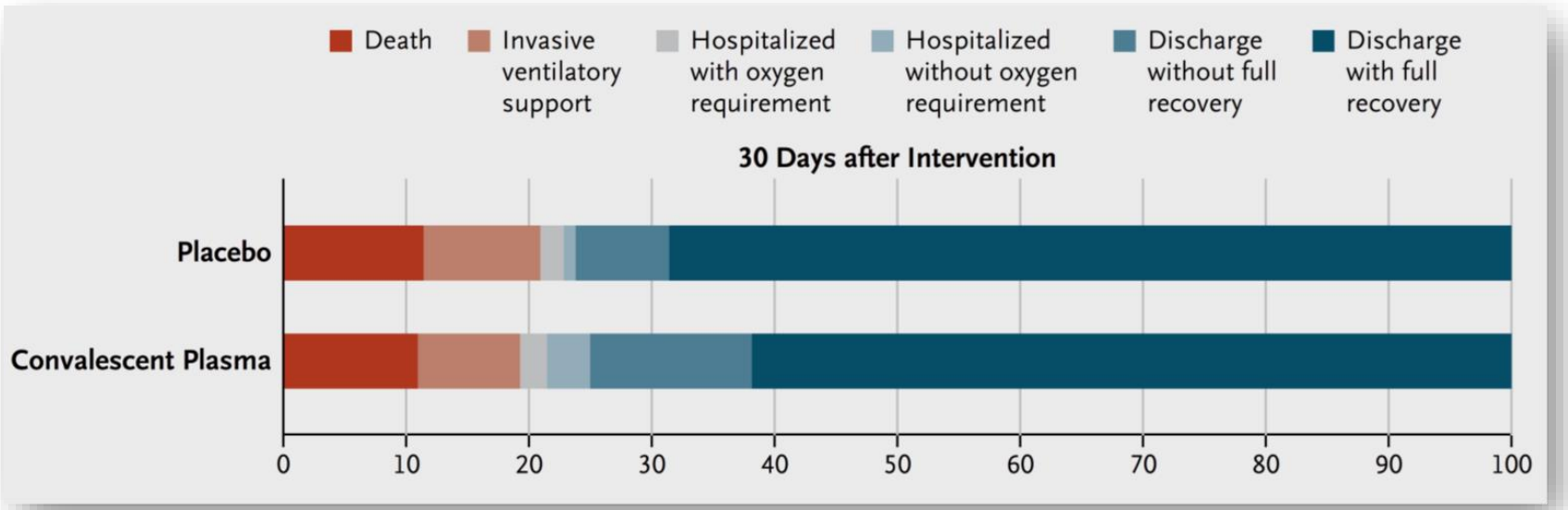


Recovery collaborative group. medRxiv. Non reviewed

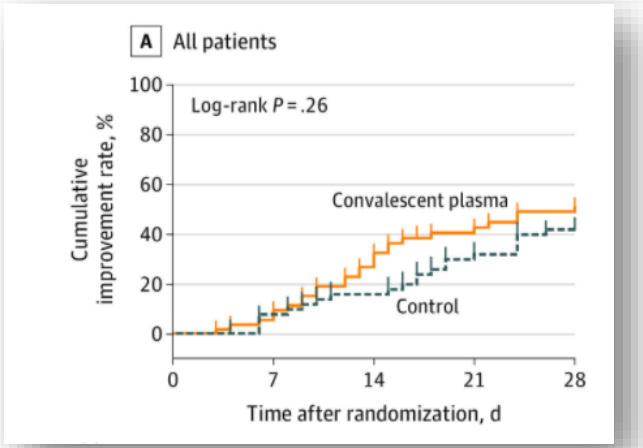


Sethuraman N et al. JAMA. 2020

Plasmathérapie : pas d'effet sur population « tout venant »

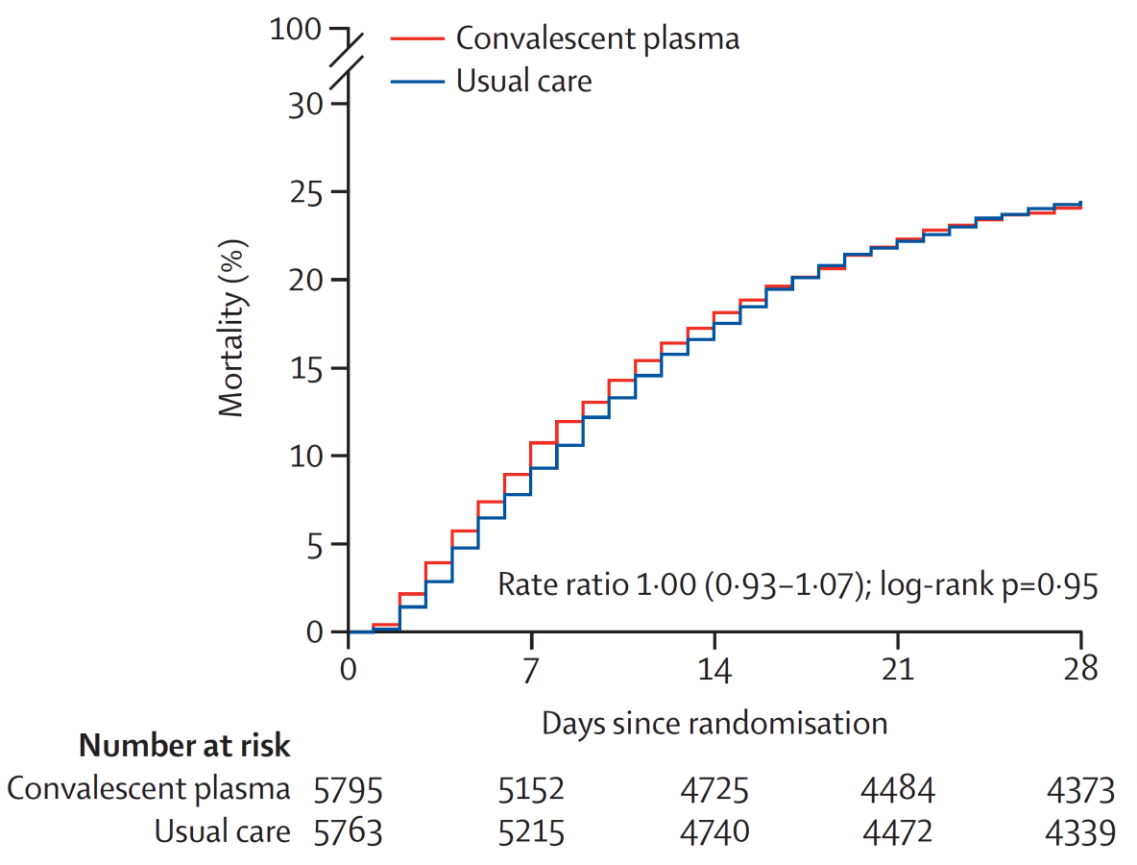


Randomisé contre placebo. 2/1.
Formes sévères hypoxémiantes.
Délai médian J8
1/3 de réa
>90% corticoïdes
Echelle ordinale à J30
Simonovich VA et al. NEJM. 2020

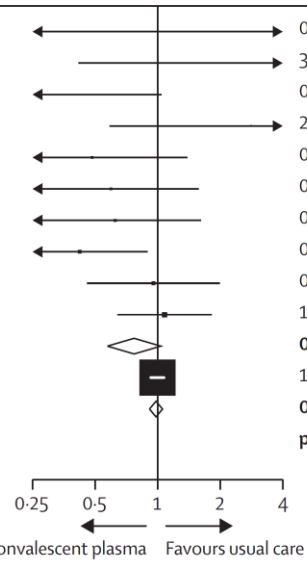


Randomisé en ouvert. 1/1.
Formes sévères voire « critiques ».
Délai médian J30 (!)
40% corticoïdes (après rando)
Amélioration J28 échelle ordinale
Li L et al. JAMA. 2020

Plasmathérapie : pas d'effet sur population « tout venant »

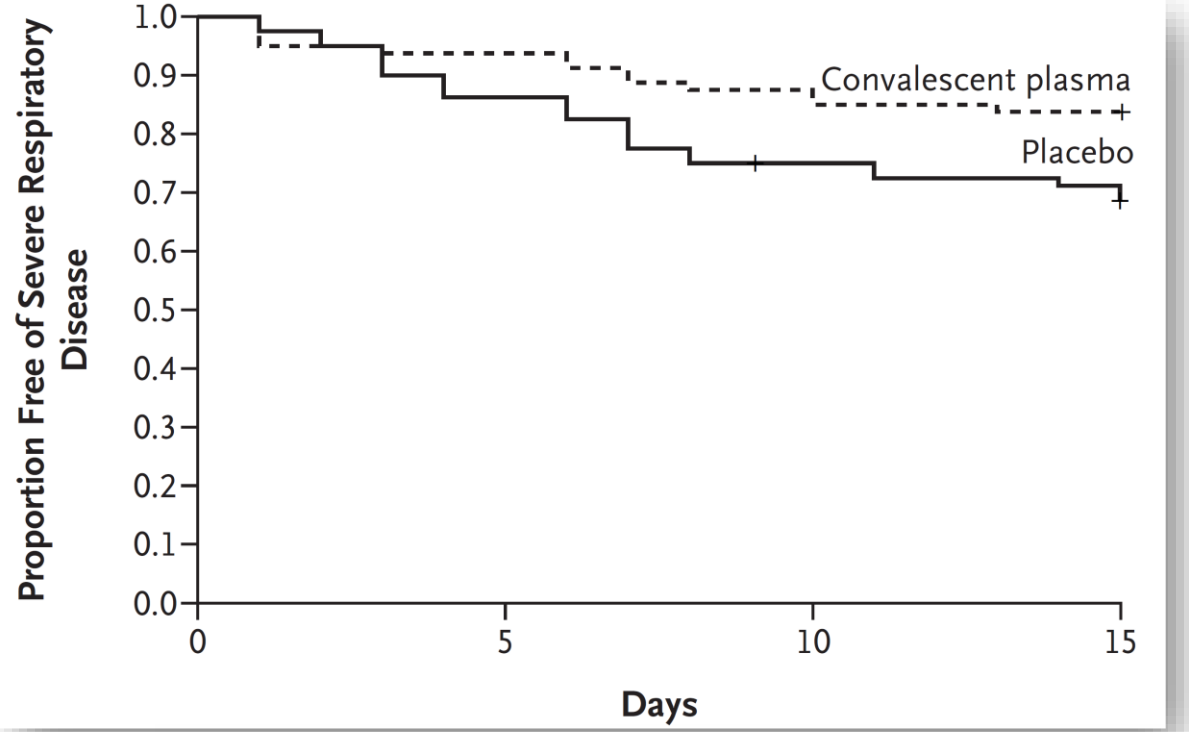


	Deaths/patients randomised (%)		Observed minus expected deaths*		Ratio of death rates, RR (95% CI)
	Convalescent plasma group	Usual care group	(O–E)	Var (O–E)	
AlQahtani et al (2020)[16]	1/20 (5%)	2/20 (10%)	−0·5	0·7	0·50 (0·05–5·06)
Bajpai et al (2020)[15]	3/14 (21%)	1/15 (7%)	1·1	0·9	3·32 (0·42–26·4)
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



Recovery collaborative group. Lancet. 2021

Mais un bénéfice si administration précoce



- Randomisé en double aveugle contre placebo. 2/1.
- H72 d'hospitalisation
- >75 ans sans comorbidité ou >64 ans avec comorbidité
- « Hauts » titres en IgG anti-S
- Développement d'une forme sévère à J15
- Interruption précoce par défaut de recrutement
- *Libster R et al. NEJM. 2021*

End Point	Convalescent Plasma (N=80)	Placebo (N=80)	Relative Risk (95% CI)
	no./total no. (%)		
Primary end point: severe respiratory disease	13/80 (16)	25/80 (31)	0.52 (0.29–0.94)

Corrélé à la positivation en Ac

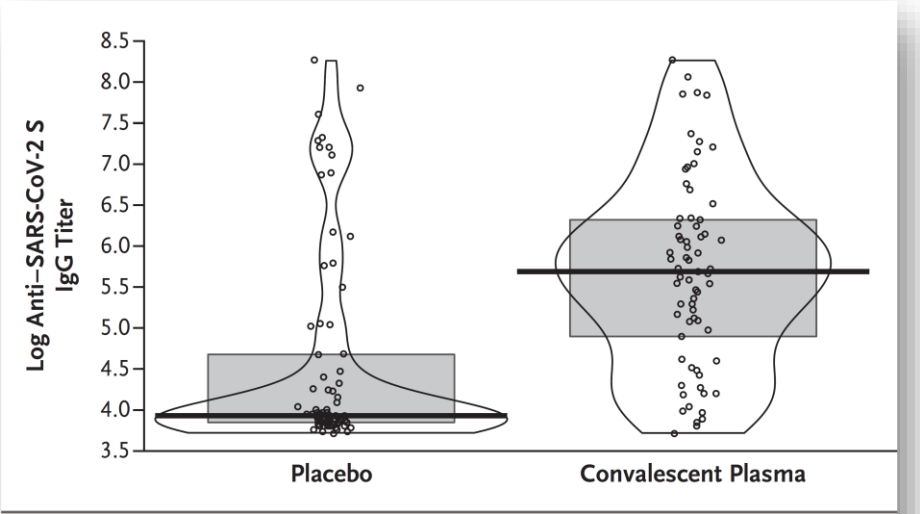


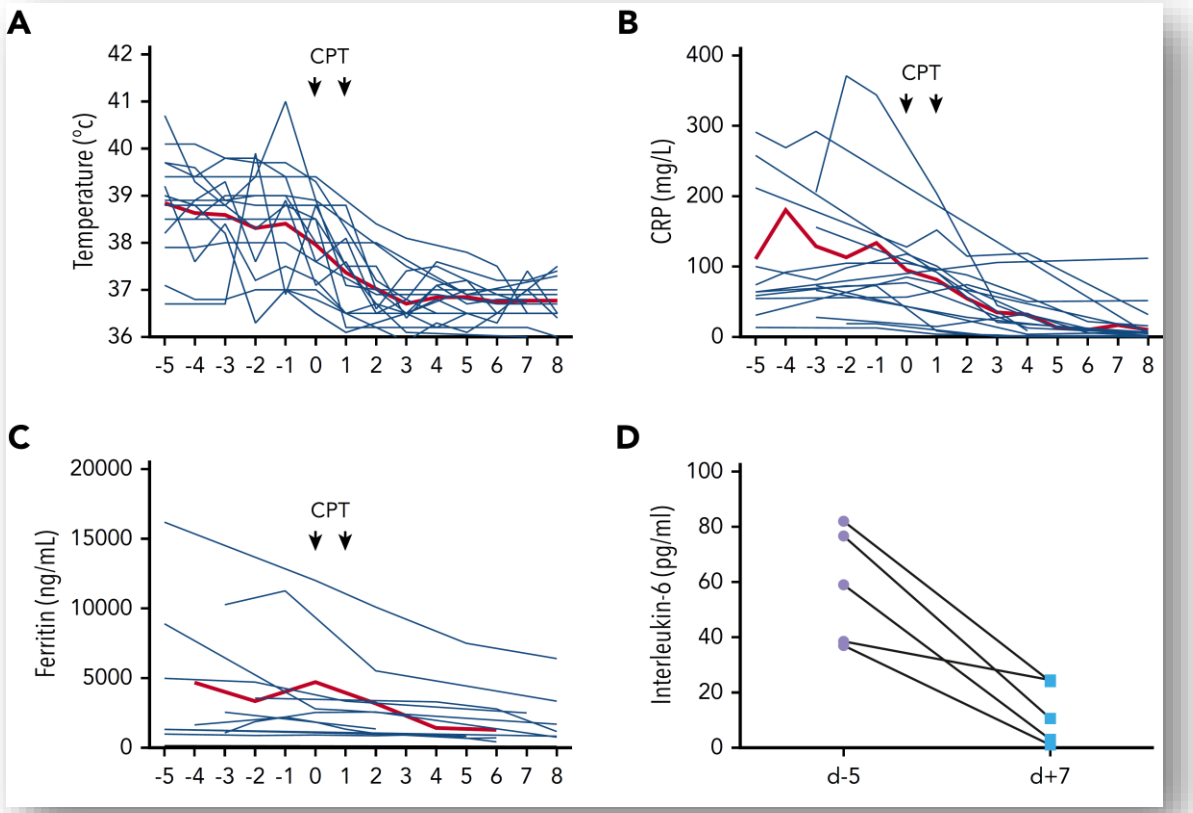
Figure 2. SARS-CoV-2 Serum Titers, According to Trial Group.

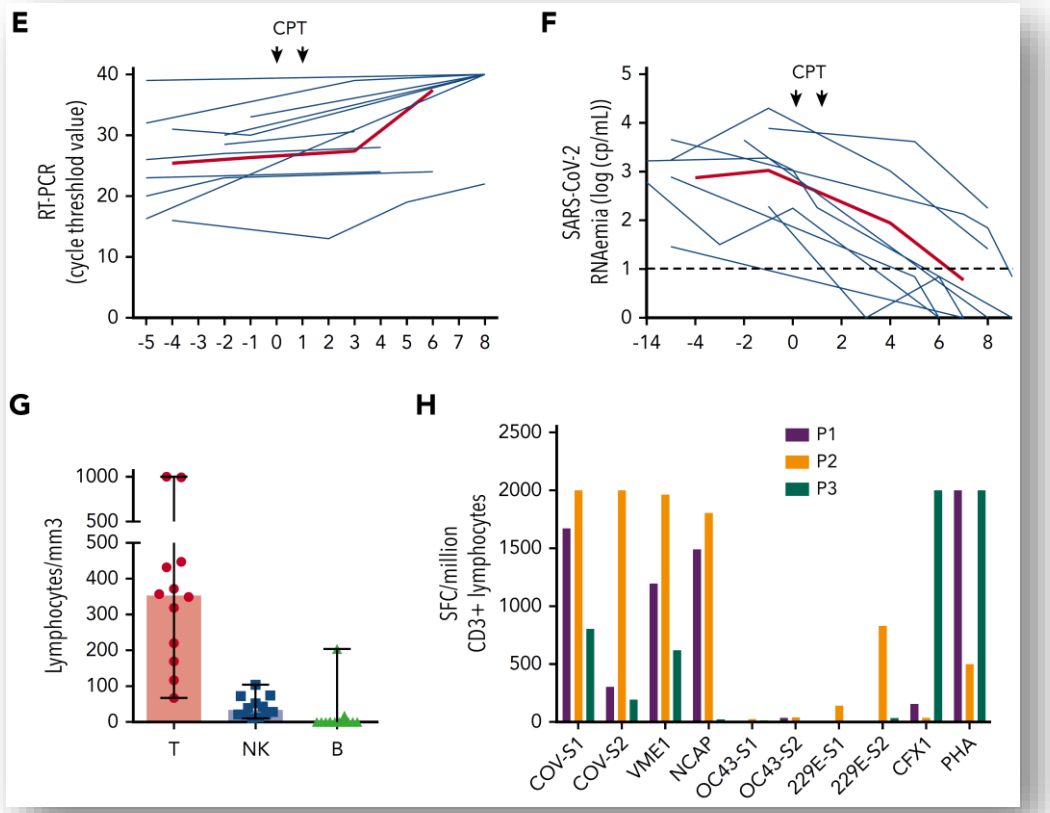
Table 3. Primary End Point, According to Donor SARS-CoV-2 S IgG Titer.

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

Libster R et al. NEJM. 2021

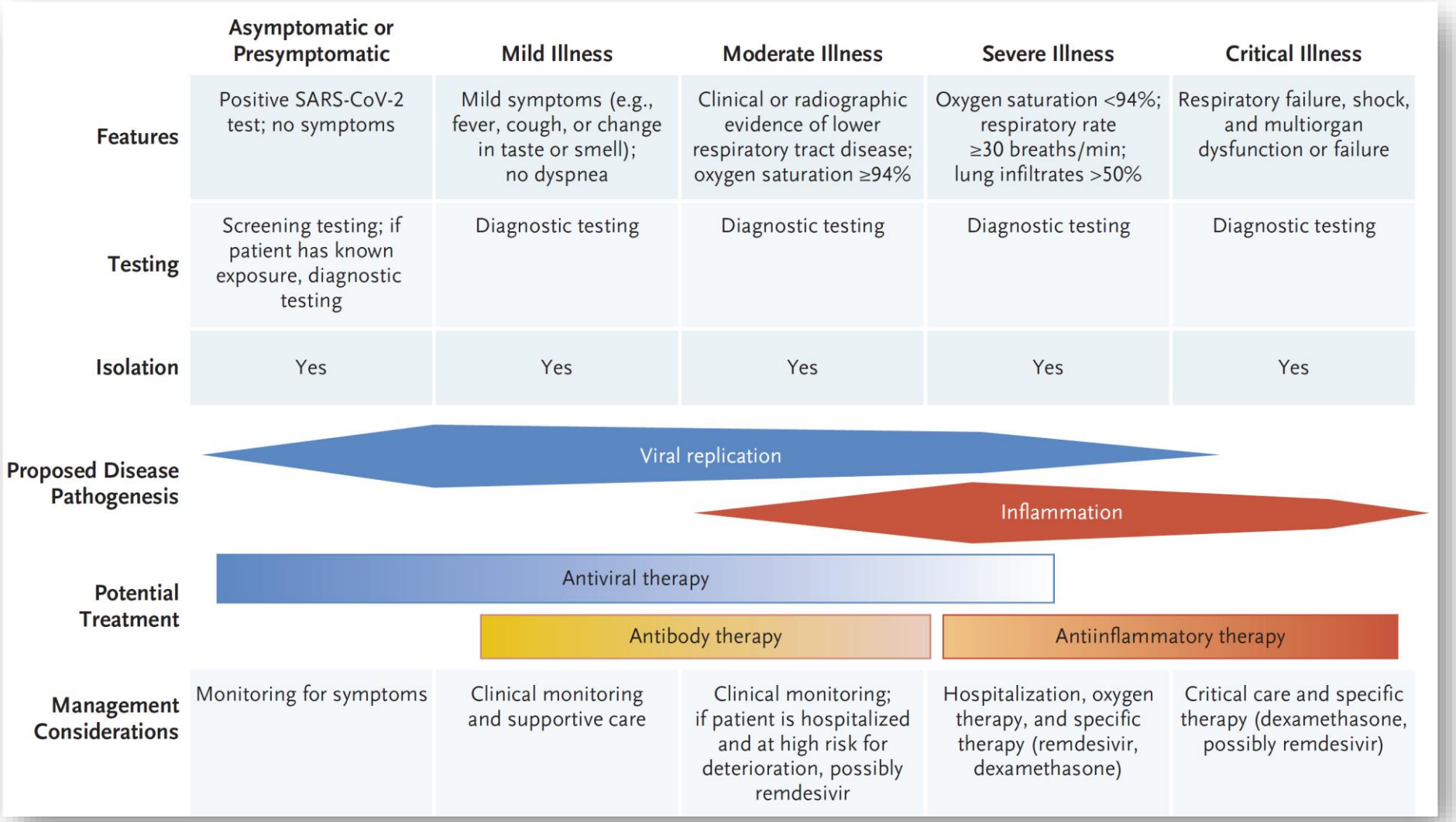
Et en cas de lymphopénie B, avec réplication virale persistante, sans Ac anti-SARS CoV2





Hueso T et al. Blood. 2020

Une rationalisation du traitement en fonction de la phase de traitement



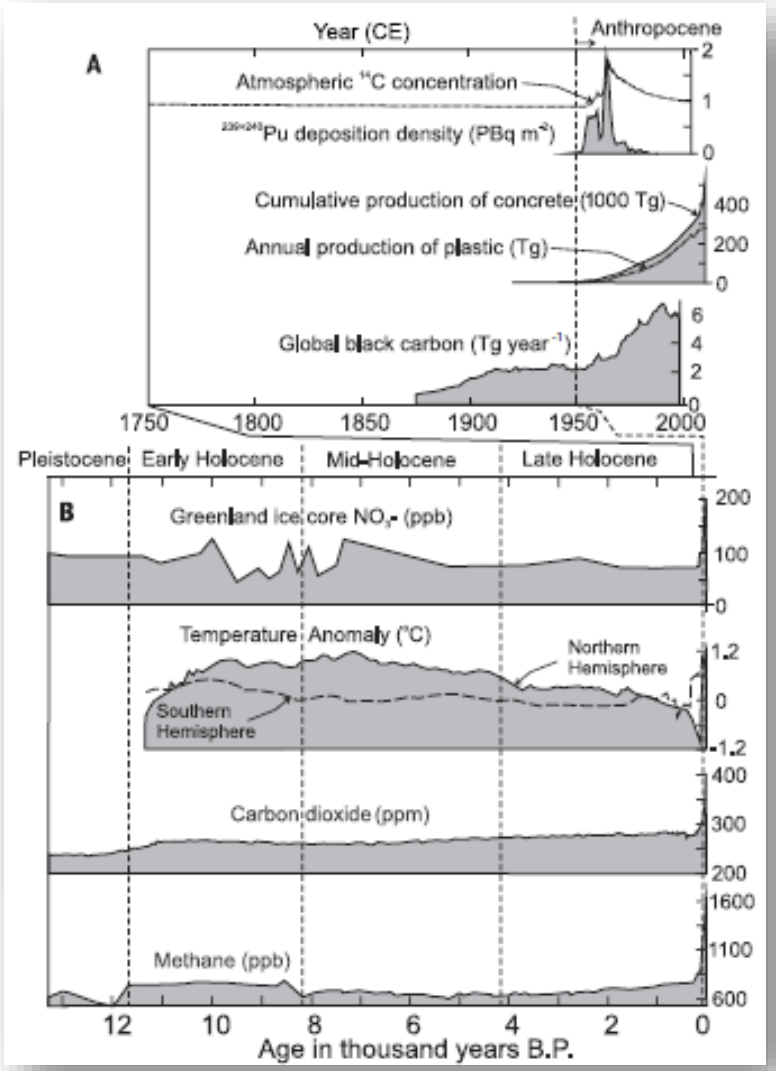
Gandhi RT et al. NEJM nov 2020

Rochwerg B et al. BMJ.

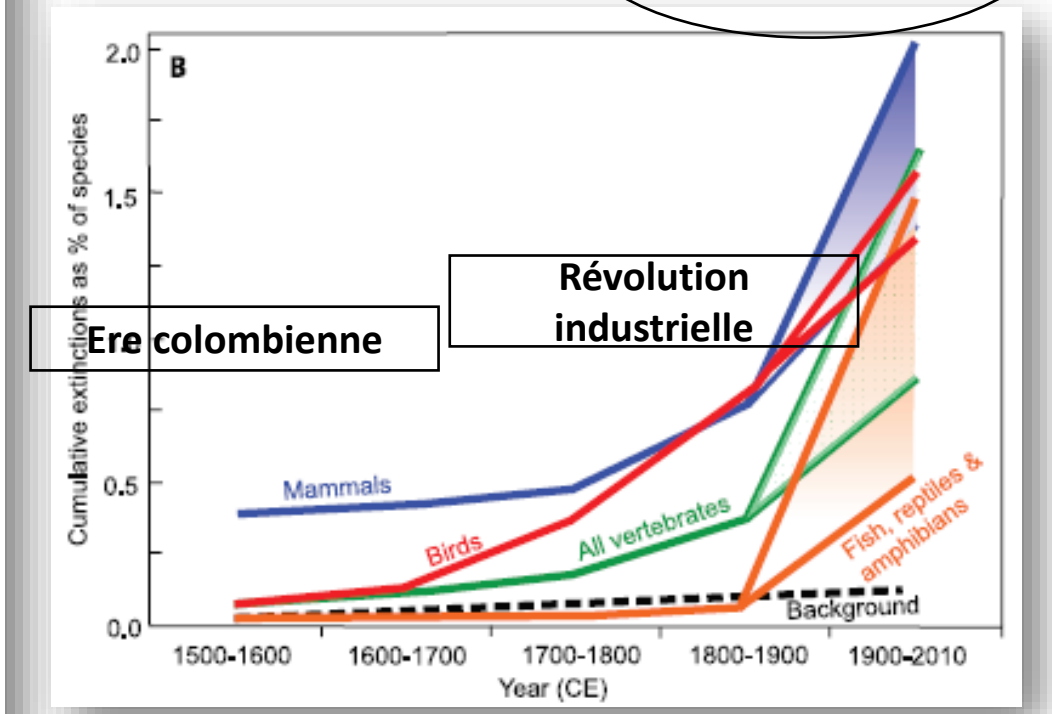
Conclusion

- Les leçons du sepsis depuis deux décennies : one size does not fit all
- COVID-19 : une maladie hétérogène
- Dans laquelle l'approche doit aussi être personnalisée
  - Immunomodulation
  - Approches antivirales
- Aucun traitement antiviral n'a pour l'instant démontré son intérêt franc pour les patients sévères
  - Problème de fenêtre antivirale ? D'activité intrinsèque ?
- Quid de la faisabilité en ambulatoire pour être dans la fenêtre d'opportunité antivirale ?
- Une niche de patients pour les malades hospitalisés ?
  - Immunodéprimés
  - Séronégatifs
  - Avec réplication virale persistante ?

L'homme, l'anthropocène et les émergences à venir



Great acceleration



Waters CN et al. Science, 2016.

Et pour l'avenir ?

Intensive Care Med (2021) 47:896–898
https://doi.org/10.1007/s00134-021-06460-9

EDITORIAL

Check for updates

Do not just sit there, do something … but do no harm: the worrying aspects of COVID-19 experimental interventions

Mervyn Singer[1*] and Andre Kalil[2]