

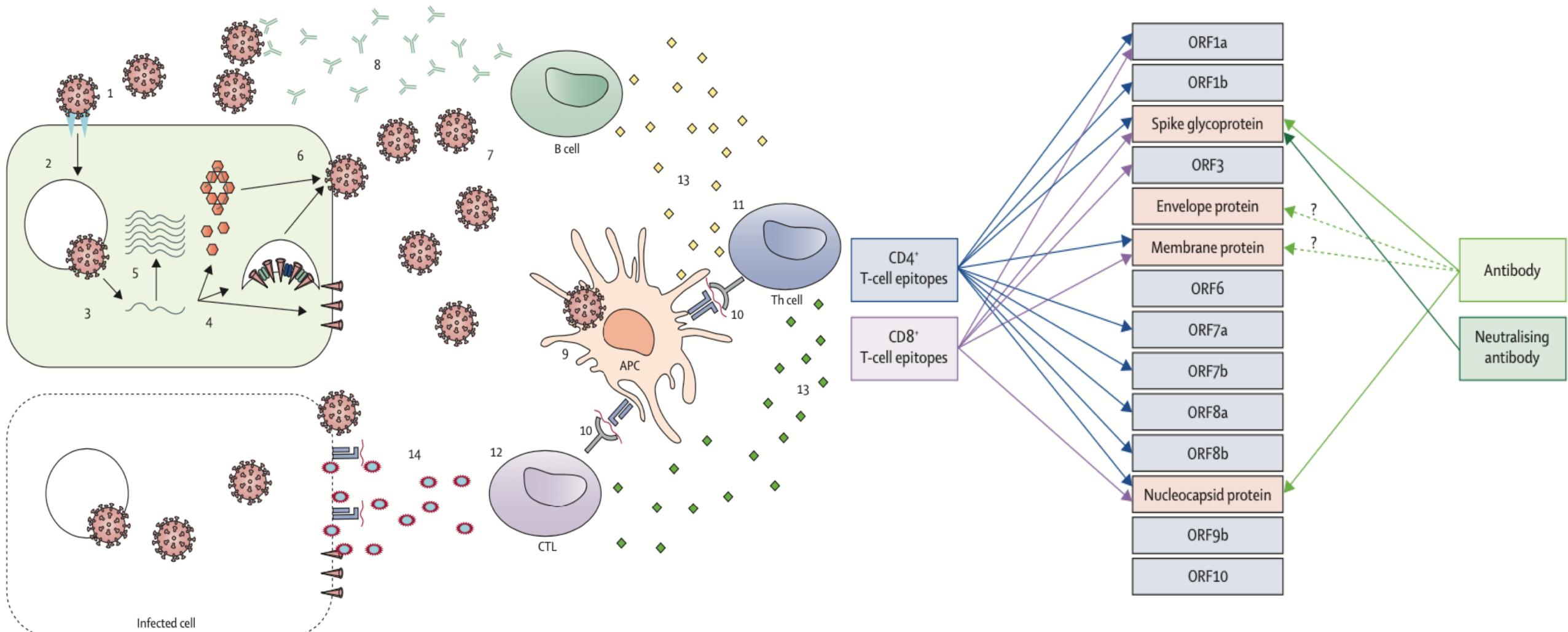
Réponse immunitaire humorale: le Yin et le Yang des anticorps anti-SARS-CoV

Les grandes fonctions de l'immunité:

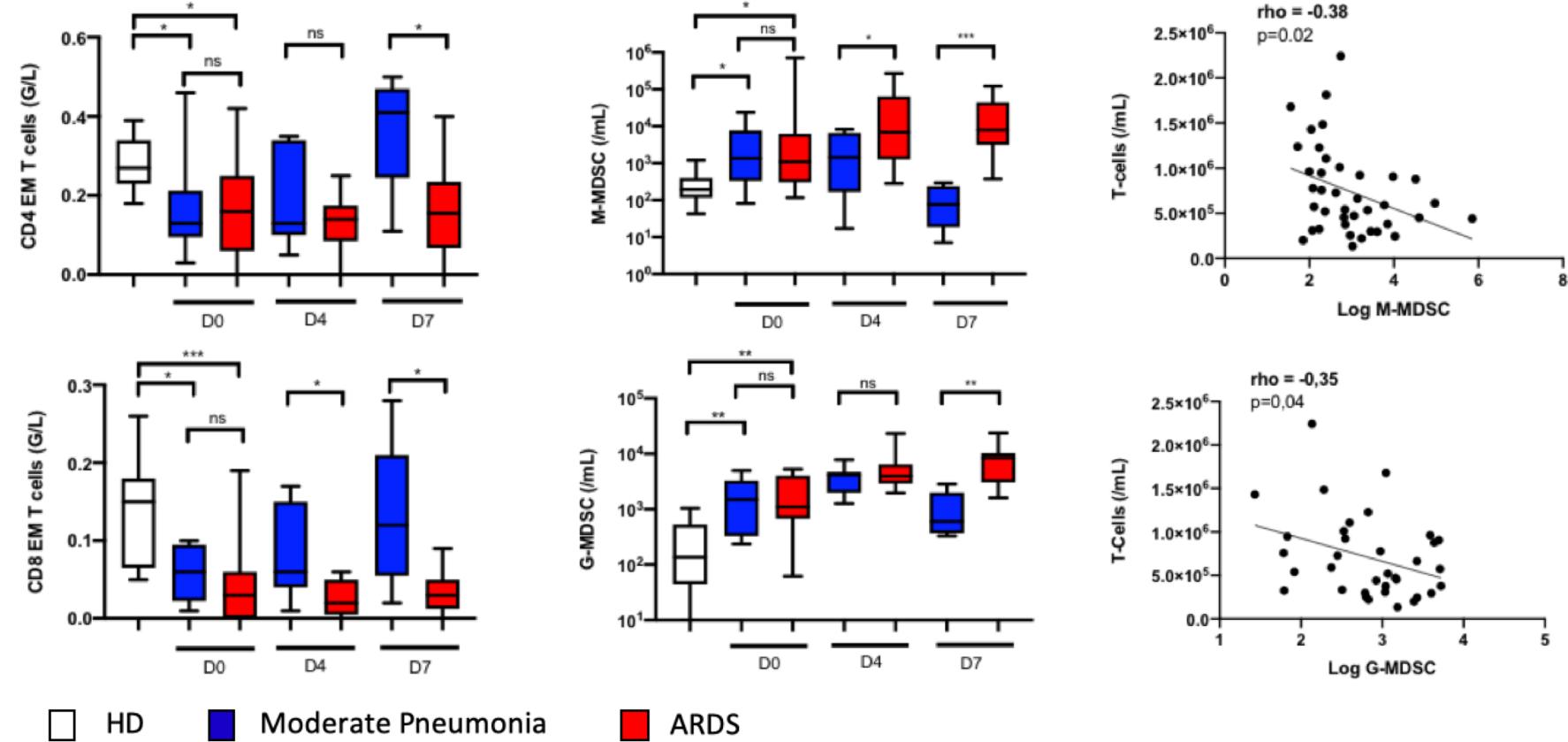
- reconnaître des structures étrangères à l'organisme (= discriminer **soi** et le **non-soi**) grâce à des **récepteurs spécifiques**
- éliminer ces substances étrangères par des **mécanismes effecteurs**
- **mémoriser** ces structures étrangères (mise en jeu de **cellules mémoires**).

Anticorps = effecteurs immuns + biomarqueurs + acteurs immunopathologiques

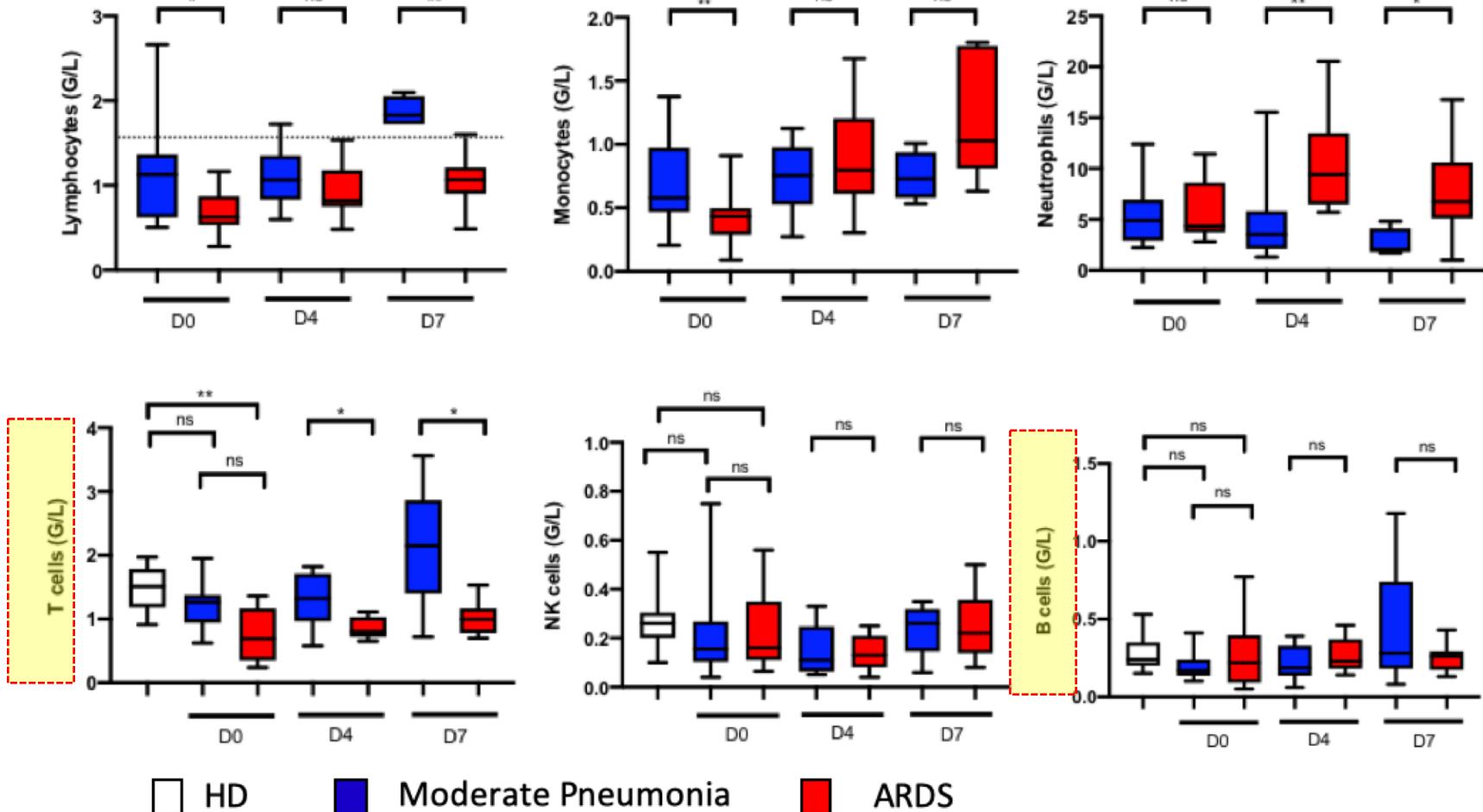
Les antigènes d'intérêt pour la réponse immune adaptative



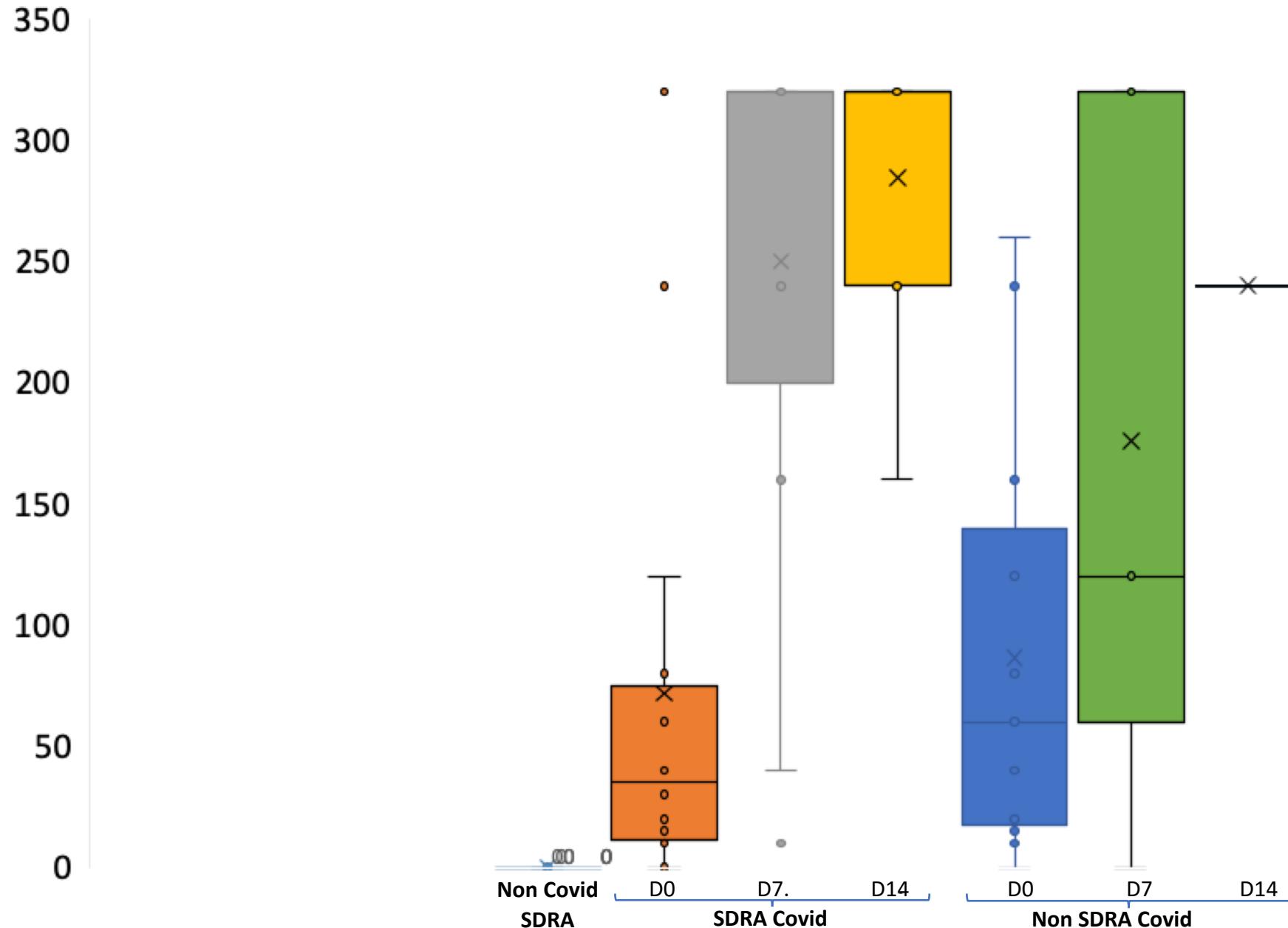
Variations des cellules circulantes chez les patients COVID



Variations des cellules circulantes chez les patients COVID



Variations du taux global des anticorps neutralisants des patients COVID



Tests sérologiques COVID

Plus de 40 tests validés CE / CNR sur automates de laboratoire: => consulter la plate-forme du ministère de la santé pour leur liste et leur validation <https://covid-19.sante.gouv.fr/tests>

AESKULISA SARS-CoV-2 NP IgG	AESKU Diagnostics
ACCESS	Beckman
ADVIA Centaur SARS-CoV-2T	Siemens Healthcare
Atellica IM SARS-CoV-2 IgG (COV2G)	Vircell
COVID-19 ELISA IgG	Euroimmun
ELISA anti-SARS	Roche
Elecsys LIAISON@SARS	DIASORIN
PLATELIA	BIORAD
VIDAS	BIOMERIEUX

environ 80 tests rapides ou autotest validés CE / CNR => consulter la plate-forme du ministère de la santé pour leur liste et leur validation <https://covid-19.sante.gouv.fr/tests>



Exemple du test ELECSYS ROCHE:

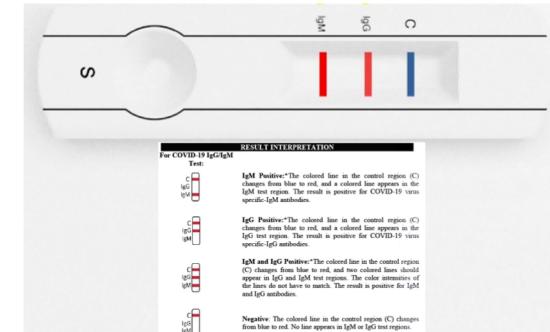
A total of 10,453 samples from diagnostic routine and blood donors obtained before December 2019 were tested with the Elecsys® Anti-SARS-CoV-2 assay.

Cohort	N	Reactive	Specificity % (95 % CI)
Diagnostic routine	6305	12	99.81 % (99.67 – 99.90 %)
Blood donors	4148	9	99.78 % (99.59 – 99.90 %)
Overall	10453	21	99.80 % (99.69 – 99.88 %)

Correlation to serum neutralization⁴⁵

The Elecsys® Anti-SARS-CoV-2 assay was compared to a VSV-based pseudo-neutralization assay⁴⁶ in 46 clinical samples from individual patients.

		Pseudo-NT*	
		Positive	Negative
Elecsys® Anti-SARS-CoV-2	Reactive	38	0
	Non-reactive	6	2
Percent Positive Agreement	86.4 % (95 % CI 73.3 % – 93.6 %)		
Percent Negative Agreement	100 % (95 % CI: 34.2 – 100 %)		
Percent Overall Agreement	87.0 % (95 % CI 74.3 % – 93.9 %)		



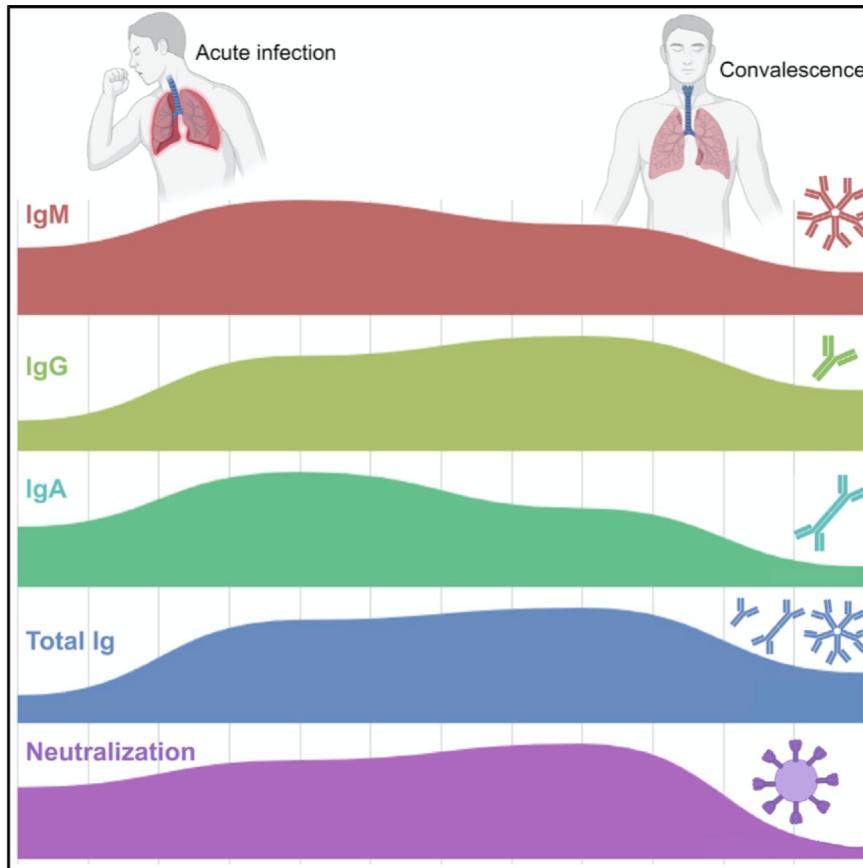
Variations quantitatives de la réponse humorale

Cell Reports
Medicine

Report

Cross-Sectional Evaluation of Humoral Responses against SARS-CoV-2 Spike

Graphical Abstract



Authors

Jérémie Prévost, Romain Gasser,
Guillaume Beaudoin-Bussières, ...,
Renée Bazin, Michel Roger, Andrés Finzi

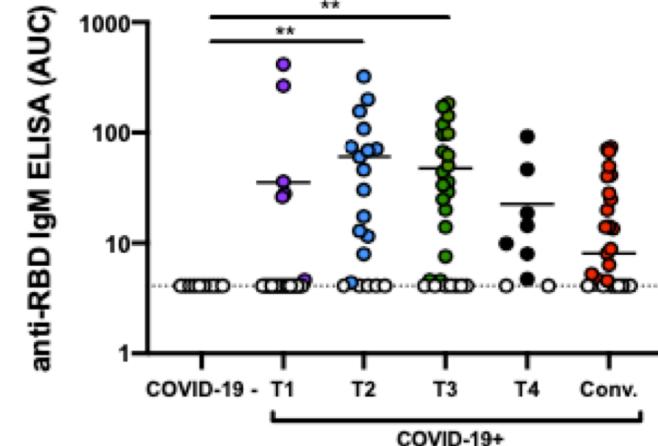
Correspondence

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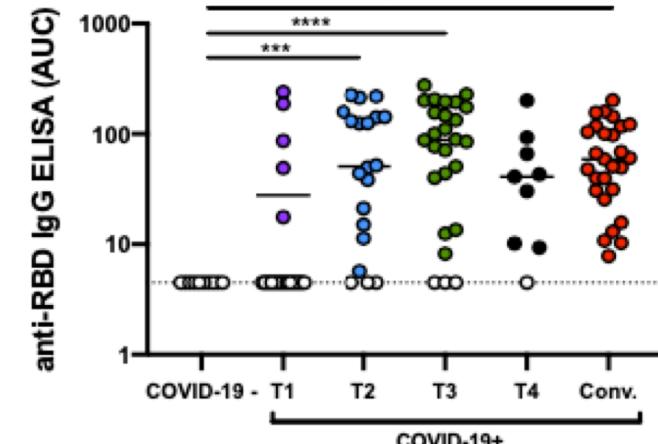
In Brief

Prévost et al. report a cross-sectional study on a cohort of 106 COVID-19 patients and show that most infected individuals are able to elicit a sustained antibody response over time. However, plasma neutralizing capacity wanes after infection resolution, but its implication on protection from re-infection remains unknown.

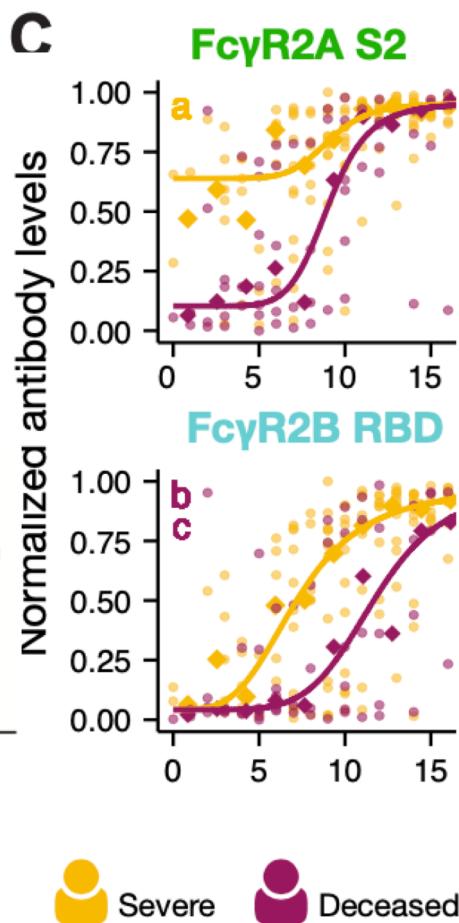
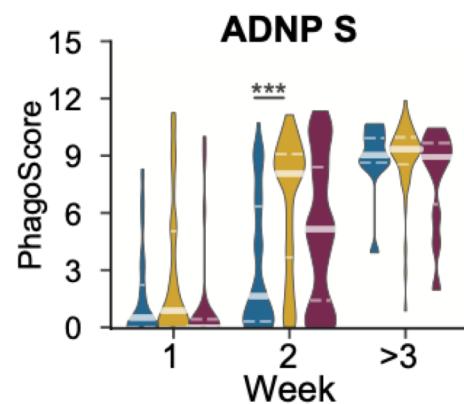
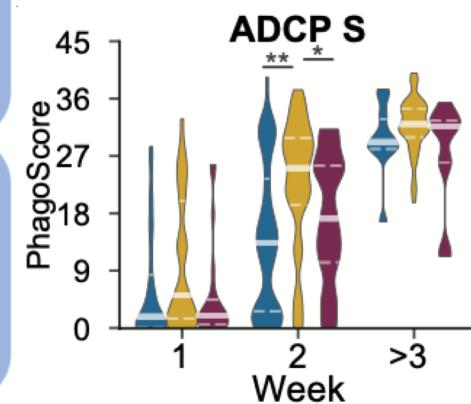
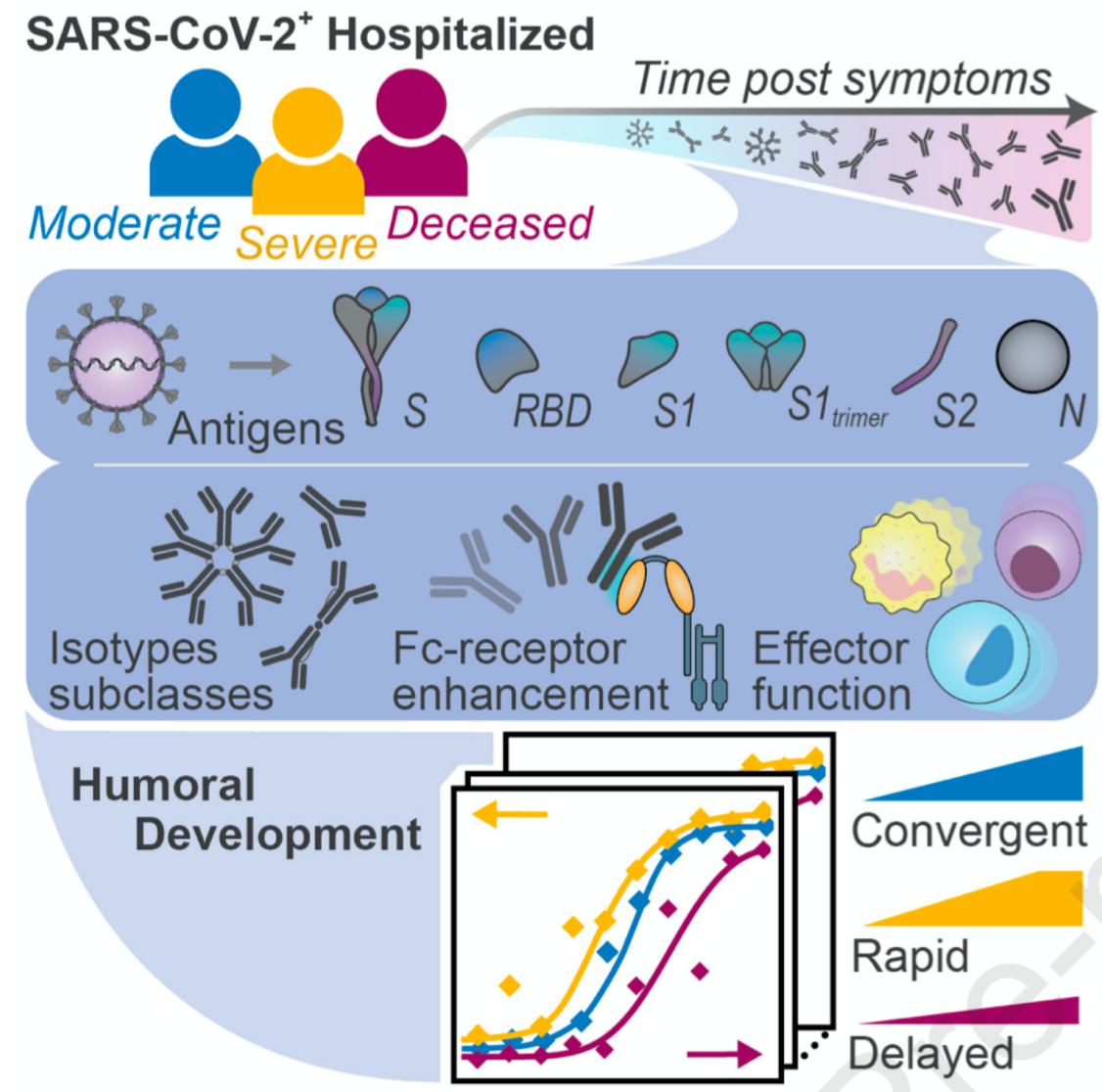
Seropositivity (%):	0%	25%	75%	76.2%	77.8%	70.4%
Mean:	4.09	35.4	60.6	47.7	22.5	19.7



Seropositivity (%):	0%	20.8%	85%	88.5%	88.9%	100%
Mean:	4.49	27.8	86.5	104.6	55.3	72.1



Variations qualitatives de la réponse humorale



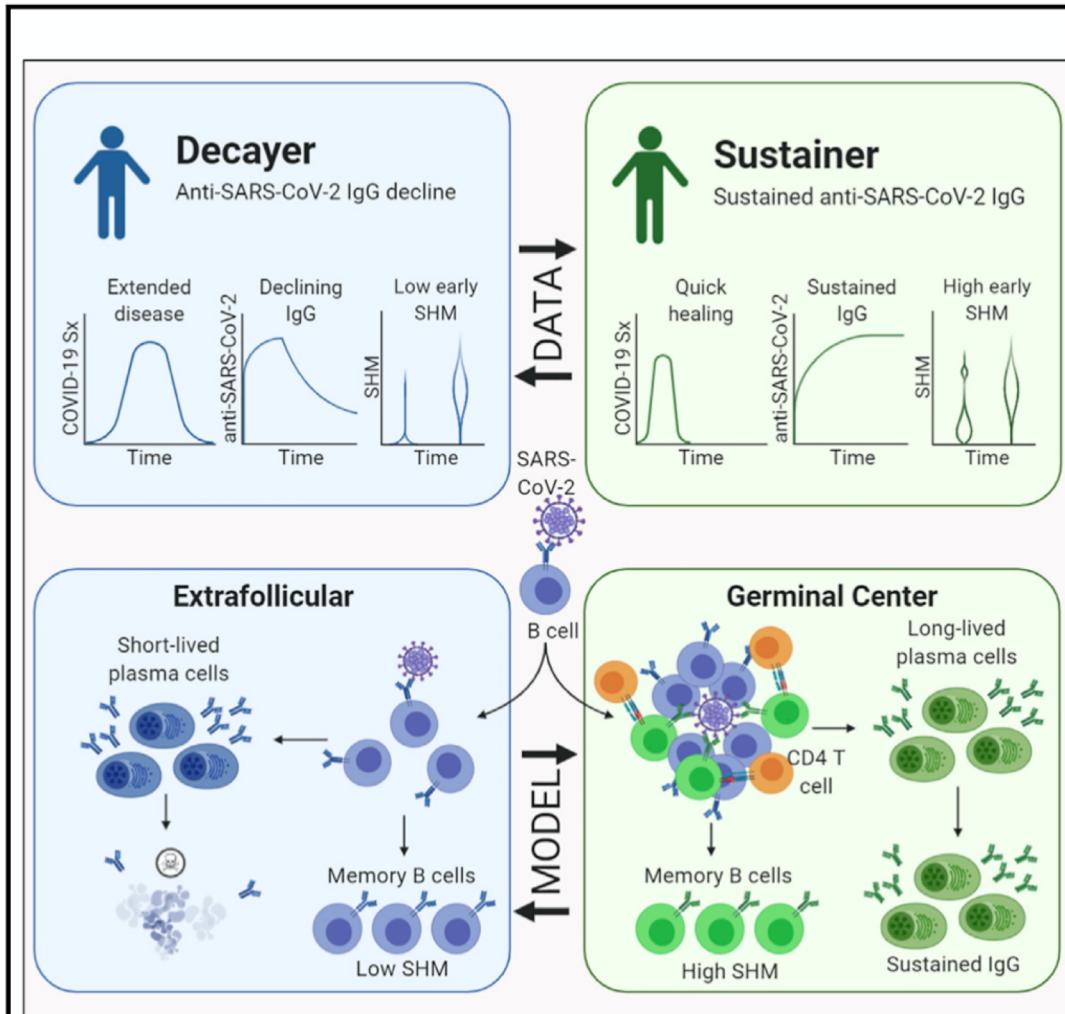
Tomer Zohar, et al. Compromised humoral functional evolution tracks with SARS-CoV-2 mortality.

PII:S0092-8674(20)31459-
8DOI:<https://doi.org/10.1016/j.cell.2020.10.052>

To appear in **CELL** (Nov 2020, ref CELL 11717)

Variations qualitatives de la réponse humorale Cell

Quick COVID-19 Healers Sustain Anti-SARS-CoV-2 Antibody Production



Yuezhou Chen, Adam Zuiani,
Stephanie Fischinger, ...,
Douglas A. Lauffenburger, Galit Alter,
Duane R. Wesemann

Correspondence
dwesemann@bwh.harvard.edu

In Brief

Longitudinal analyses of antibody responses to SARS-CoV-2 demonstrate that individuals with sustained virus-specific IgG production have shorter disease trajectories, with a subset demonstrating increased somatic hypermutation and higher levels of activated CD4⁺ cells.

Variations qualitatives de la réponse humorale

> **Science**. 2020 Aug 28;369(6507):1119–1123. doi: 10.1126/science.abd2321. Epub 2020 Jul 13.

Structural basis of a shared antibody response to SARS-CoV-2

Meng Yuan # 1 , Hejun Liu # 1 , Nicholas C Wu # 1 , Chang-Chun D Lee 1 , Xueyong Zhu 1
, Fangzhu Zhao 2 3 4 , Deli Huang 2 , Wenli Yu 1 , Yuanzi Hua 1 , Henry Tien 1 , Thomas F Rogers
5 , Elise Landais 2 3 6 , Devin Sok 3 4 6 , Joseph G Jardine 3 6 , Dennis R Burton 2 3 4 7 , Ian A
Wilson 8 3 4 9

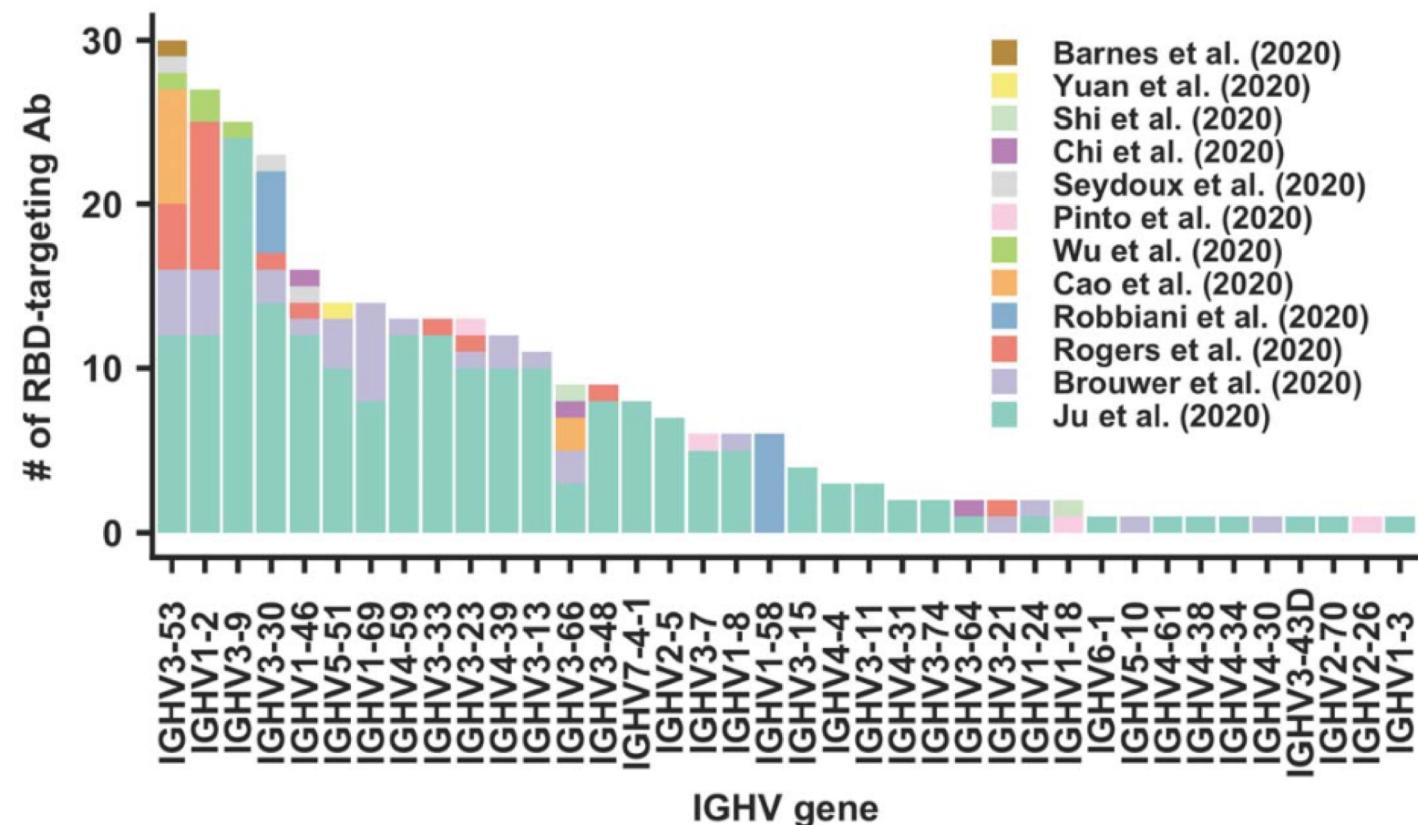
> Cell Rep. 2020 Oct 20;33(3):108274. doi: 10.1016/j.celrep.2020.108274. Epub 2020 Sep 29

An Alternative Binding Mode of IGHV3-53 Antibodies to the SARS-CoV-2 Receptor Binding Domain

Nicholas C Wu ¹, Meng Yuan ², Hejun Liu ², Chang-Chun D Lee ², Xueyong Zhu ², Sandhya Bangaru ², Jonathan L Torres ², Tom G Caniels ³, Philip J M Brouwer ³, Marit J van Gils ³, Rogier W Sanders ⁴, Andrew B Ward ⁵, Ian A Wilson ⁶

Les anticorps neutralisants anti-SARS CoV-2 expriment volontiers des clonotypes partagés

=> une partie de la réponse immune humorale adaptée est ainsi CONVERGENTE

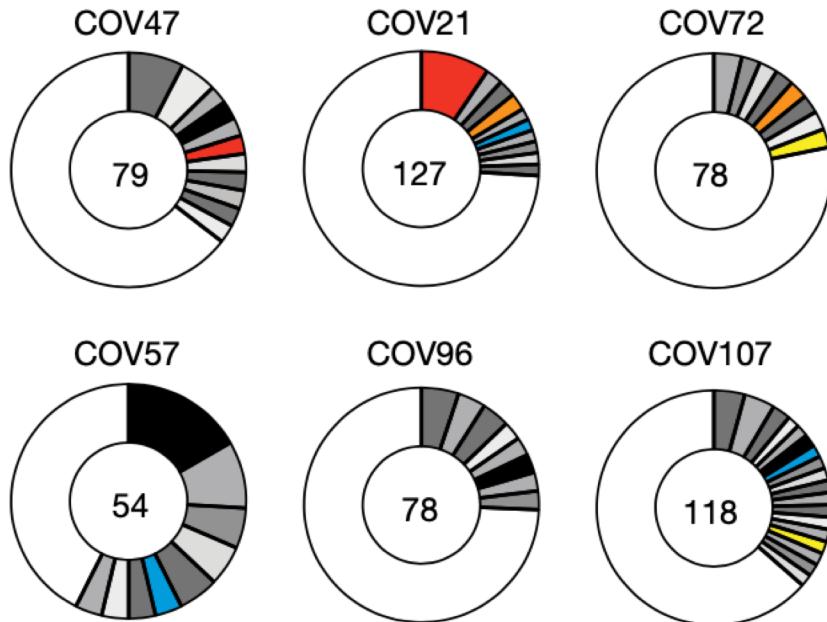


Variations qualitatives de la réponse humorale

> Nature. 2020 Aug;584(7821):437-442. doi: 10.1038/s41586-020-2456-9. Epub 2020 Jun 18.

Convergent antibody responses to SARS-CoV-2 in convalescent individuals

Davide F Robbiani ^{1 2}, Christian Gaebler ³, Frauke Muecksch ⁴, Julio C C Lorenzi ³, Zijun Wang ³, Alice Cho ³, Marianna Agudelo ³, Christopher O Barnes ⁵, Anna Gazumyan ³, Shlomo Finkin ³, Thomas Hägglöf ³, Thiago Y Oliveira ³, Charlotte Viant ³, Arlene Hurley ⁶, Hans-Heinrich Hoffmann ⁷, Katrina G Millard ³, Rhonda G Kost ⁸, Melissa Cipolla ³, Kristie Gordon ³, Filippo Bianchini ³, Spencer T Chen ³, Victor Ramos ³, Roshni Patel ³, Juan Dizon ³, Irina Shimeliovich ³, Pilar Mendoza ³, Harald Hartweger ³, Lilian Nogueira ³, Maggi Pack ³, Jill Horowitz ³, Fabian Schmidt ⁴, Yiska Weisblum ⁴, Eleftherios Michailidis ⁷, Alison W Ashbrook ⁷, Eric Waltari ⁹, John E Pak ⁹, Kathryn E Huey-Tubman ⁵, Nicholas Koranda ⁵, Pauline R Hoffman ⁵, Anthony P West Jr ⁵, Charles M Rice ⁷, Theodora Hatzioannou ⁴, Pamela J Bjorkman ¹⁰, Paul D Bieniasz ^{11 12}, Marina Caskey ¹³, Michel C Nussenzweig ^{14 15}



Suivi de clonotypes stéréotypés

- CDR3 normal length / SHM similar to conventional memory cells / low hydrophobicity
- Public clonotypes: IGHV1-58/IGKV3-20 and IGHV3-30-3/IGKV1-39 (found in different individuals, sequence identities of up to 99% and 92%)

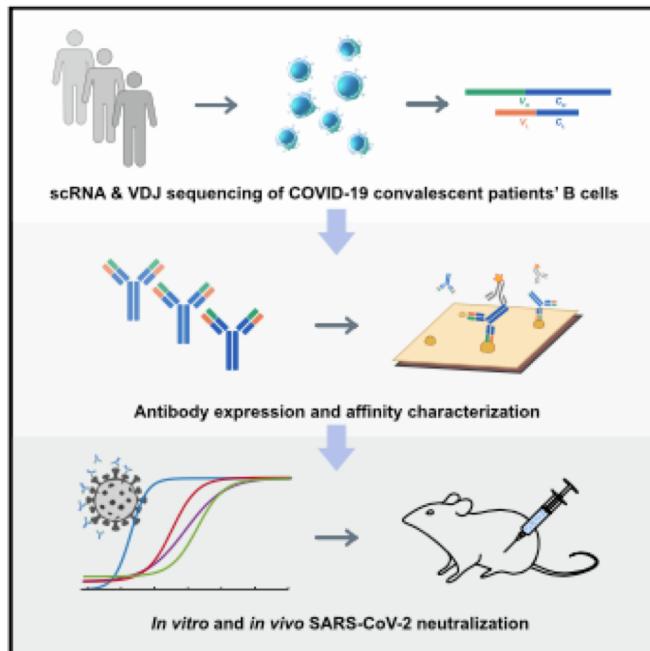
	Heavy				Light		
	IGHV	IGHD	IGHJ	CDRH3	IGLV	IGLJ	CDRL3
COV21	IGHV1-58*01	IGHD2-15*01	IGHJ3*02	AAPHCSGGSCLDAFDI	IGKV3-20*01	IGKJ1*01	QQYGSSPWT
	IGHV1-58*01	IGHD2-15*01	IGHJ3*02Y.....	IGKV3-20*01	IGKJ1*01
COV57	IGHV1-58*02	IGHD2-15*01	IGHJ3*02	.N.....Y.G...	IGKV3-20*01	IGKJ1*01M
	IGHV1-58*02	IGHD2-15*01	IGHJ3*02	...Y.....N....	IGKV3-20*01	IGKJ1*01
COV107	IGHV1-58*01	IGHD2-2*01	IGHJ3*02ST..F....	IGKV3-20*01	IGKJ1*01N....
	IGHV1-58*01	IGHD2-15*01	IGHJ3*02	...Y.....S....	IGKV3-20*01	IGKJ1*01
	IGHV3-30-3*01	IGHD5-18*01	IGHJ4*02	ARDGIVDTAMVTWFDY	IGKV1-39*01	IGKJ1*01	QQSYSTPPWT
COV21	IGHV3-30-3*01	IGHD5-24*01	IGHJ4*02	...-QGMATTY-...	IGKV1-39*01	IGKJ1*01N....
	IGHV3-30-3*01	IGHD5-18*01	IGHJ4*02L.....	IGKV1-39*01	IGKJ1*01
COV72	IGHV3-30-3*01	IGHD5-18*01	IGHJ5*01	...SD...S.....	IGKV1-39*01	IGKJ1*01
	IGHV3-30-3*01	IGHD5-18*01	IGHJ5*01	...SD.....	IGKV1-39*01	IGKJ1*01

Variations qualitatives de la réponse humorale

Article
Cell

Suivi de clonotypes stéréotypés

Potent Neutralizing Antibodies against SARS-CoV-2 Identified by High-Throughput Single-Cell Sequencing of Convalescent Patients' B Cells



Yunlong Cao, Bin Su, Xianghua Guo, ...,
Chengfeng Qin, Ronghua Jin,
X. Sunney Xie

Correspondence

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qincf@bmi.ac.cn (C.Q.),
ronghuajin_youan@126.com (R.J.),
sunneyxie@pku.edu.cn (X.S.X.)

In Brief

Neutralizing antibodies, which could effectively block virus entry into host cells, are urgently needed for intervention against COVID-19. Using high-throughput single-cell RNA sequencing, Cao et al. identified fourteen potent neutralizing antibodies from 60 convalescent patients' B cells. The most potent antibody, BD-368-2, exhibits high therapeutic and prophylactic efficacy in SARS-CoV-2-infected mice.

Neutralizing Abs against SARS-CoV virus have stereotyped CDR3s...

Highlights

- 8,558 IgG⁺ antigen-binding clonotypes were identified by high-throughput scRNA/VDJ-seq
- 14 potent SARS-CoV-2 neutralizing antibodies were found from 60 convalescent patients
- BD-368-2 showed high therapeutic and prophylactic efficacy in SARS-CoV-2-infected mice
- Neutralizing antibodies can be directly selected based on predicted CDR3_H structures

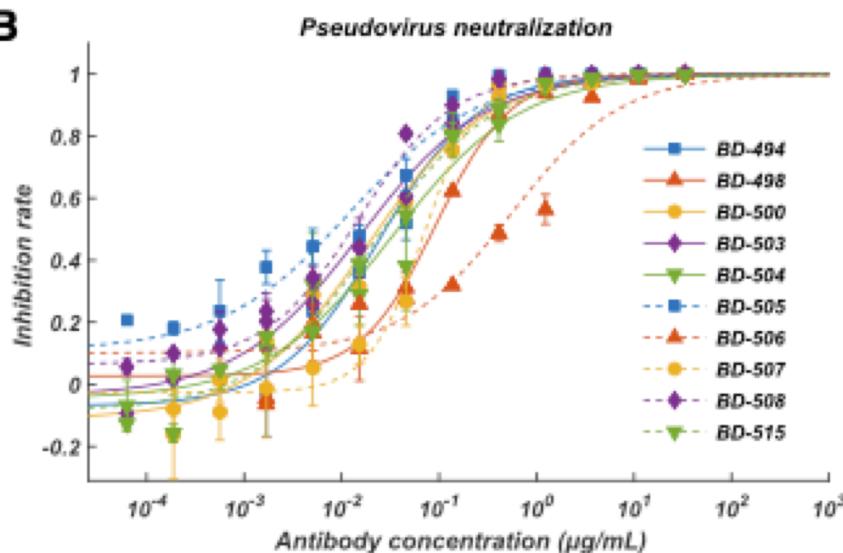
Variations qualitatives de la réponse humorale

Suivi de clonotypes stéréotypés

A

Ab Name	Batch	CDR3 _H	CDR3 _L
m396	/	A R D T V M G G G M D V	Q V W D S S S D Y V
BD-494	1	A R D L V V Y G M D V	Q Q L N S Y P F T
BD-495	1	A R D P I R N G M D V	Q Q Y D N L P R T
BD-498	2	A R D L V V Y G M D V	Q Q L N S Y P L T
BD-500	3	A R D A M S Y G M D V	Q Q S Y S T P P D T
BD-501	3	A R D R V V Y G M D V	Q Q Y D N L P P T
BD-503	5	A R D A A V Y G I D V	Q Q S Y T T P L F T
BD-504	5	A R D L I S R G M D V	Q Q S Y T T P L F T
BD-505	5	A R D R V V Y G M D V	H Q Y D N L P P T
BD-506	6	A R D L V S Y G M D V	Q Q L N S Y P L T
BD-507	6	A R D L V V Y G M D V	Q Q L N S N P P I T
BD-508	6	A R D A Q N Y G M D V	Q Q S Y S T P P Y T

B



C

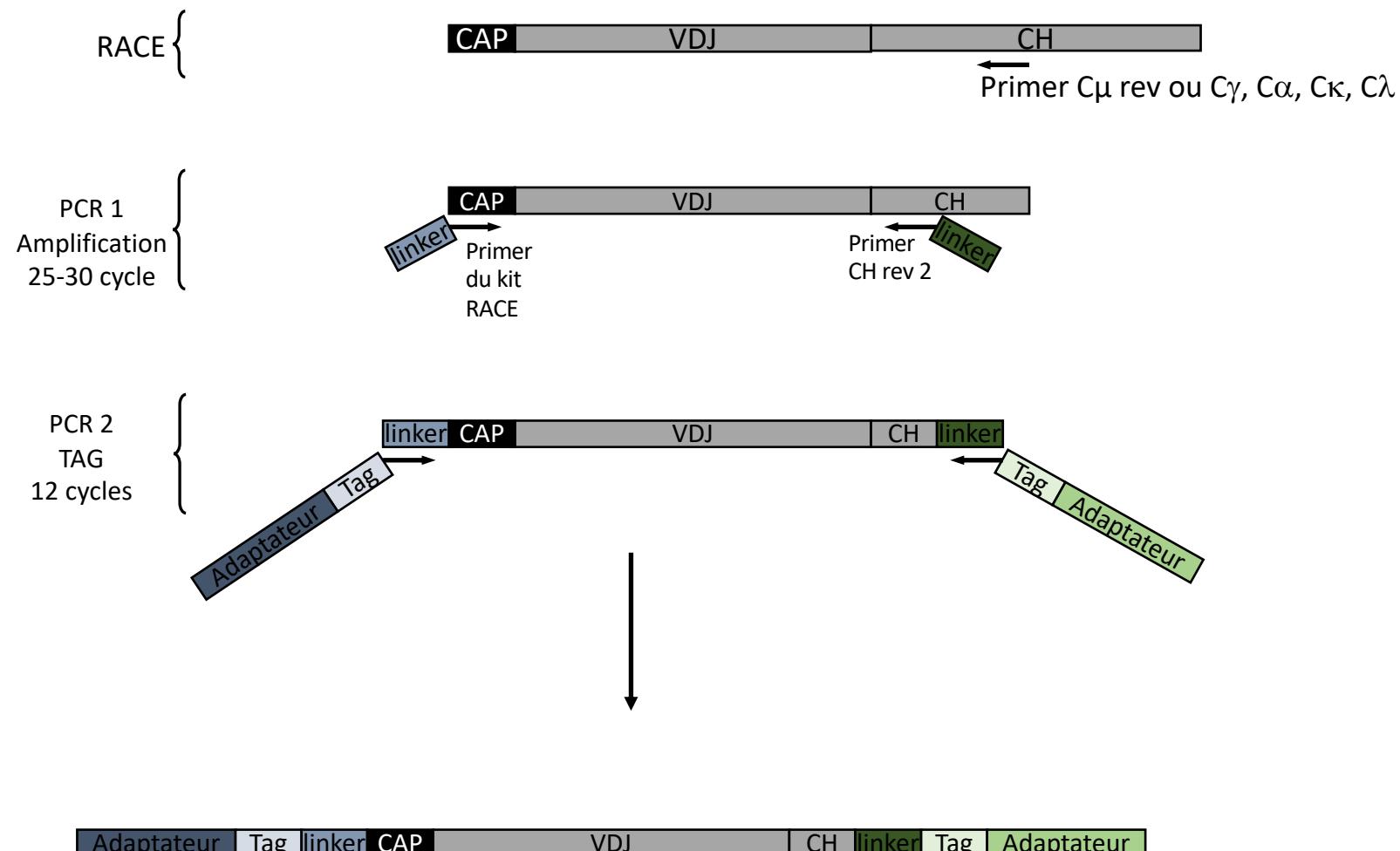
Characterization of the mAbs identified by CDR3_H structure similarity

mAbs	Batch	Viral protein binding		Pseudovirus neutralization		VDJ combination				CDR3 _H similar structure
		Enrichment antigen	K _D (RBD) (nM)	IC ₅₀ ($\mu\text{g/mL}$)	IC ₅₀ ($\mu\text{g/mL}$)	V _H	J _H	V _L	J _L	
BD-494	1	Spike	0.69	0.024	0.12	IGHV3-53	IGHJ6	IGKV1-9	IGKJ3	2dd8H
BD-495	1	Spike	> 50	18	> 30	IGHV3-66	IGHJ6	IGKV1D-33	IGKJ1	2dd8H
BD-498	2	Spike	2.5	0.092	0.32	IGHV3-66	IGHJ6	IGKV1-9	IGKJ5	2dd8H
BD-500	3	RBD	2.3	0.018	0.13	IGHV3-53	IGHJ6	IGKV1D-39	IGKJ5	2dd8H
BD-501	3	RBD	> 50	> 30	> 30	IGHV3-53	IGHJ6	IGKV1D-33	IGKJ5	2dd8H
BD-503	5	RBD	0.24	0.016	0.12	IGHV3-53	IGHJ6	IGKV1D-39	IGKJ3	2dd8H
BD-504	5	RBD	0.32	0.033	0.27	IGHV3-66	IGHJ6	IGKV1-9	IGKJ3	2dd8H
BD-505	5	RBD	1.2	0.012	0.10	IGHV3-53	IGHJ6	IGKV1D-33	IGKJ5	2dd8H
BD-506	6	RBD	2.7	0.55	3.4	IGHV3-53	IGHJ6	IGKV1-9	IGKJ4	2dd8H
BD-507	6	RBD	1.3	0.070	0.18	IGHV3-53	IGHJ6	IGKV1-9	IGKJ3	2dd8H
BD-508	6	RBD	1.9	0.015	0.069	IGHV3-53	IGHJ6	IGKV1D-39	IGKJ2	2ghwD
BD-515	3	RBD	0.041	0.022	0.15	IGHV3-66	IGHJ4	IGKV1D-33	IGKJ5	2ghwD

Neutralizing Abs against SARS-CoV virus have stereotyped CDR3s...

Suivi des répertoires immuns Ig/BCR par 5'RACE

❖ protocole 5'RACE

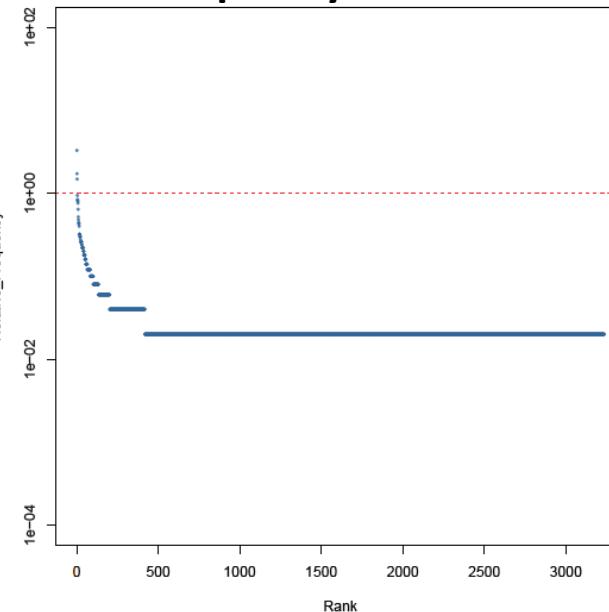


Librairies à séquencer sur MiSeq

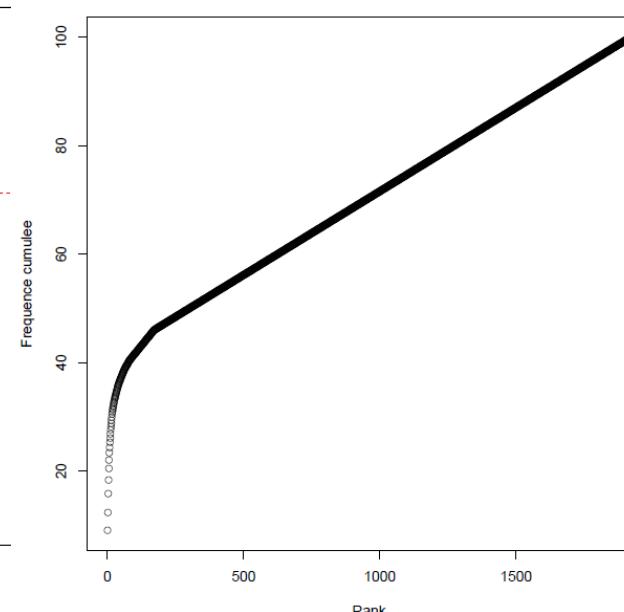
Suivi des répertoires immuns Ig/BCR par 5'RACE

Nature des résultats obtenus:

Clone frequency distribution

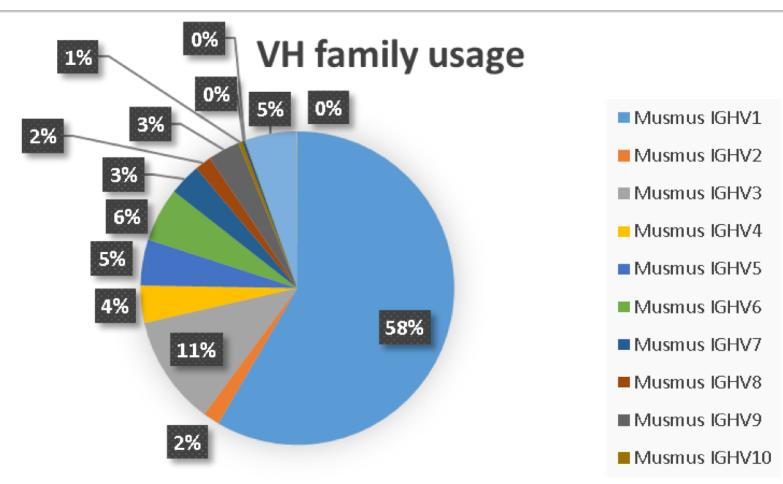
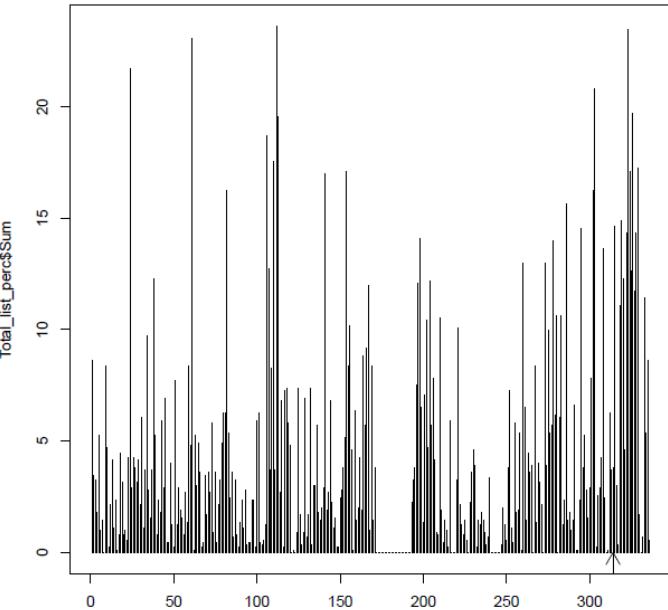


Cumulated Clone frequency



SHM analysis for SHM level and position

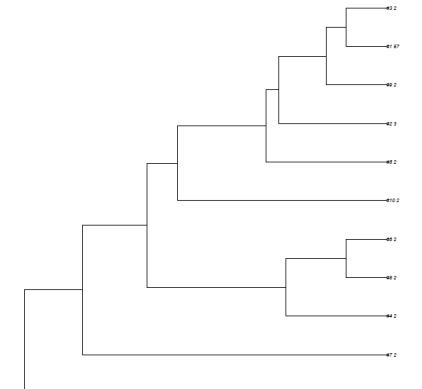
Example file 1	
FR1_mut_freq	1,18534832
FR2_mut_freq	0,69172427
FR3_mut_freq	4,16672089
CDR1_mut_freq	0,90960143
CDR2_mut_freq	1,98386366
CDR3_mut_freq	1,90434673
V_mut_freq	3,974049
V_region_Corrected_Max_V_mut_Freq	0,98832549
V_region_Corrected_Max_V_mut_Nbr	4,2029703
V_region_Corrected_Mean_V_mut_Freq	0,73090765
V_region_Corrected_Mean_V_mut_Nbr	2,95465981
FR1_Corrected_Mean_V_mut_Freq	0,03801353
CDR1_Corrected_Mean_V_mut_Freq	0,02211387
FR2_Corrected_Mean_V_mut_Freq	0,02807159
CDR2_Corrected_Mean_V_mut_Freq	0,05975793
FR3_Corrected_Mean_V_mut_Freq	0,57058303
CDR3_Corrected_Mean_V_mut_Freq	0,27465194
CDR3_Transversions	0,69306931
Pnucleotides	0,65024337
Nnucleotides	5,51278603
TrimmedNucleotides	13,380364



Diversity quantification

	Total clones count	Shannon Diversity Index	Clonality Index	Gini Index	Clones >1%
96_R_Mu	1921	0,860	0,140	0,399	8

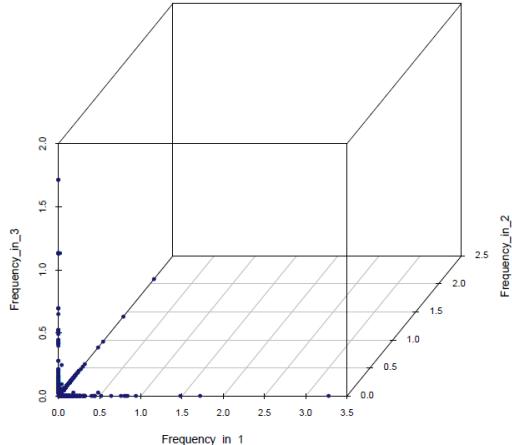
Intraclonal évolution



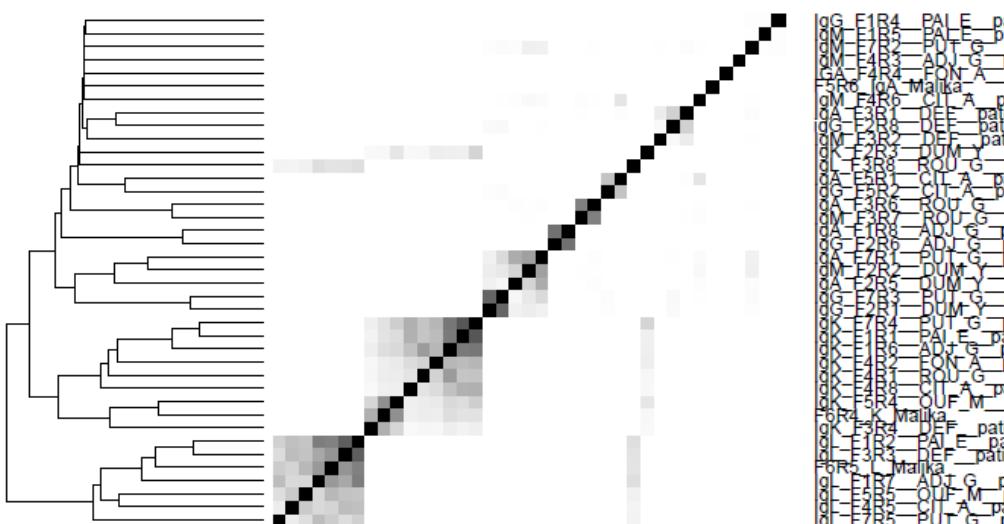
Suivi des répertoires immuns Ig/BCR par 5'RACE

Nature des résultats obtenus:

Identification de clones partagés entre échantillons

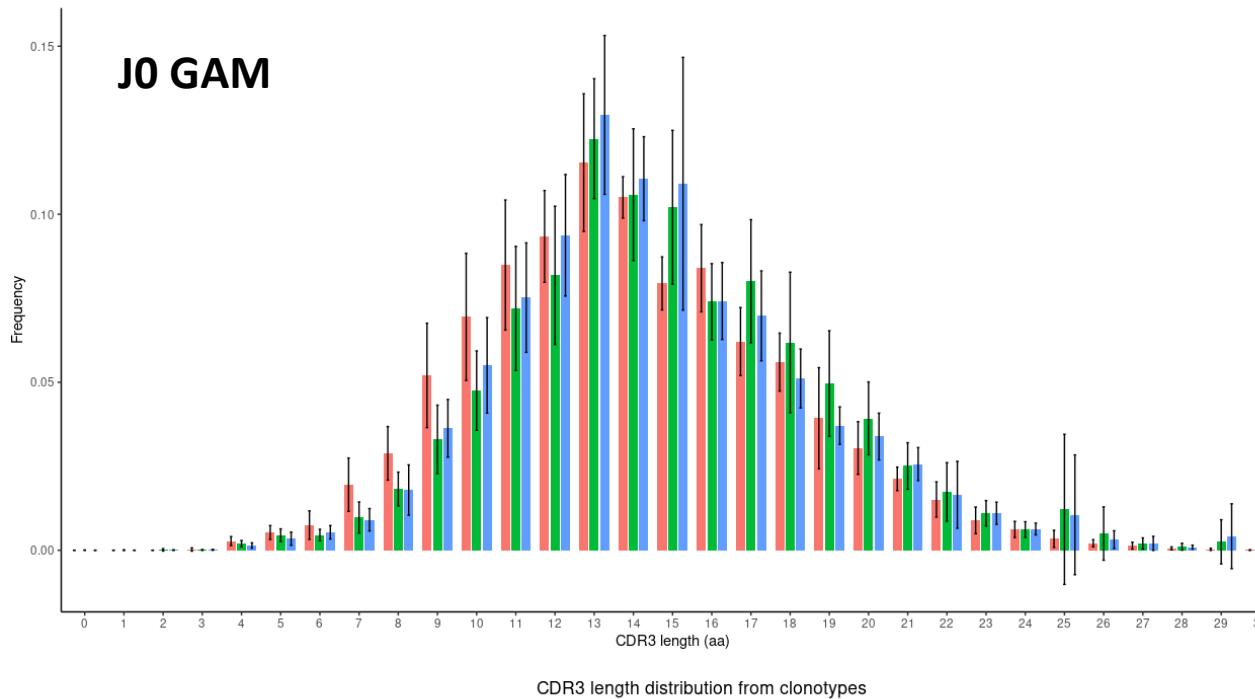


Analyse de Similarité entre répertoire

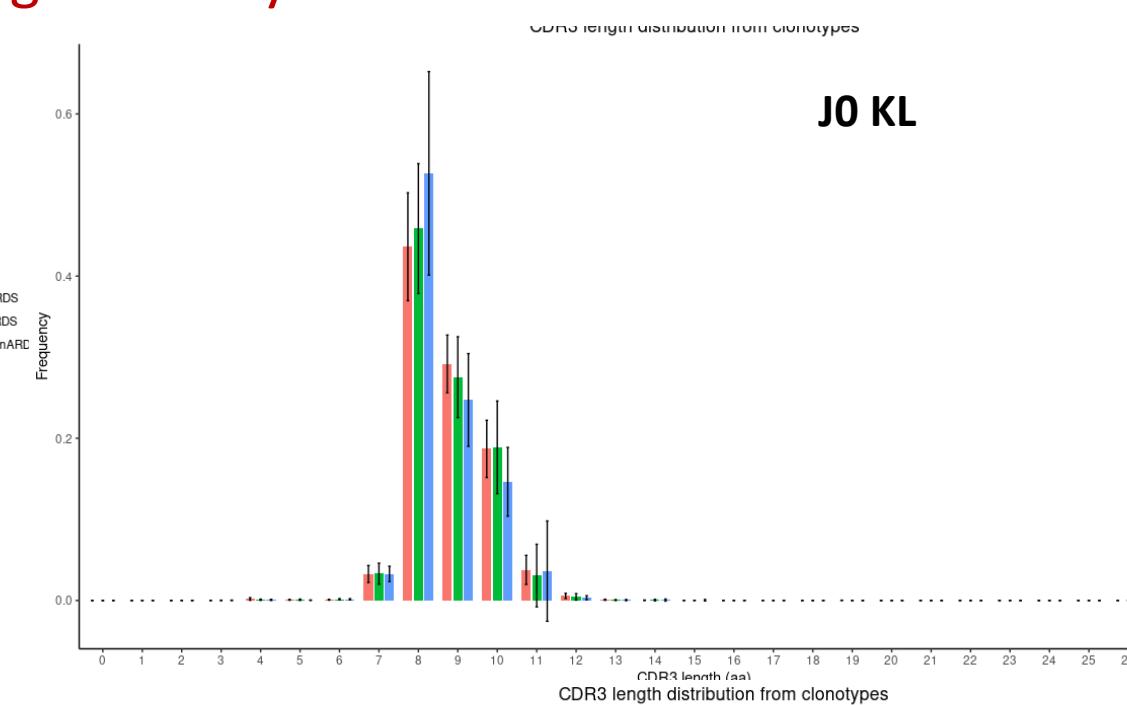


Nature des résultats obtenus: variations de longueur moyenne CDR3 au cours du Covid-19

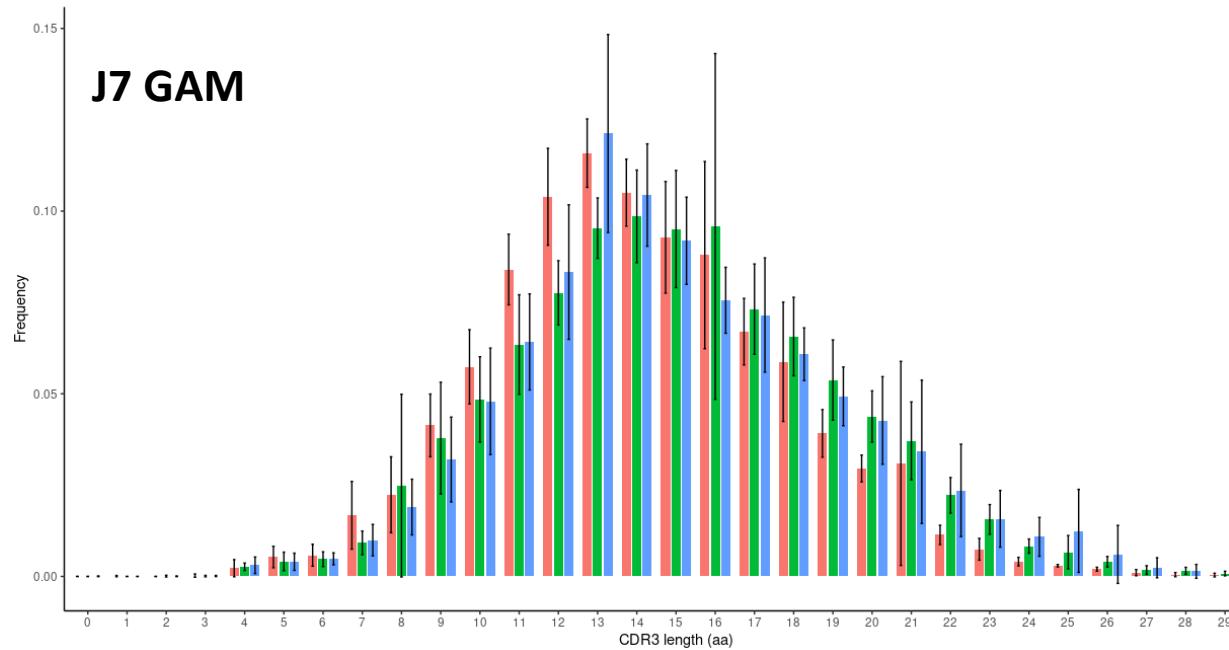
J0 GAM



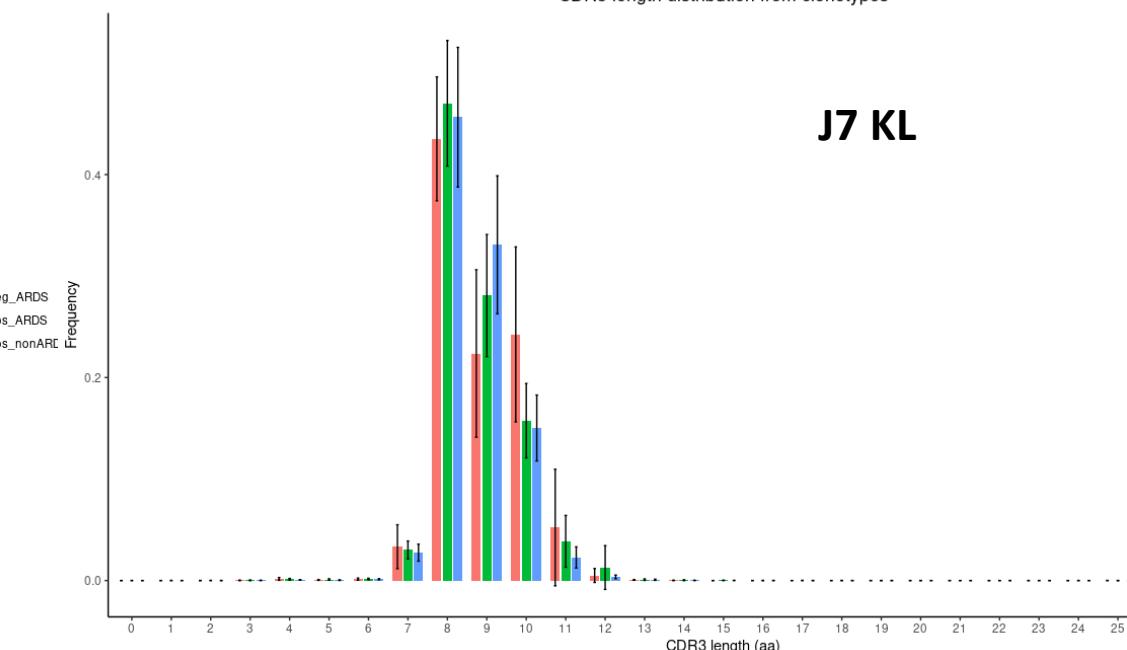
J0 KL



J7 GAM

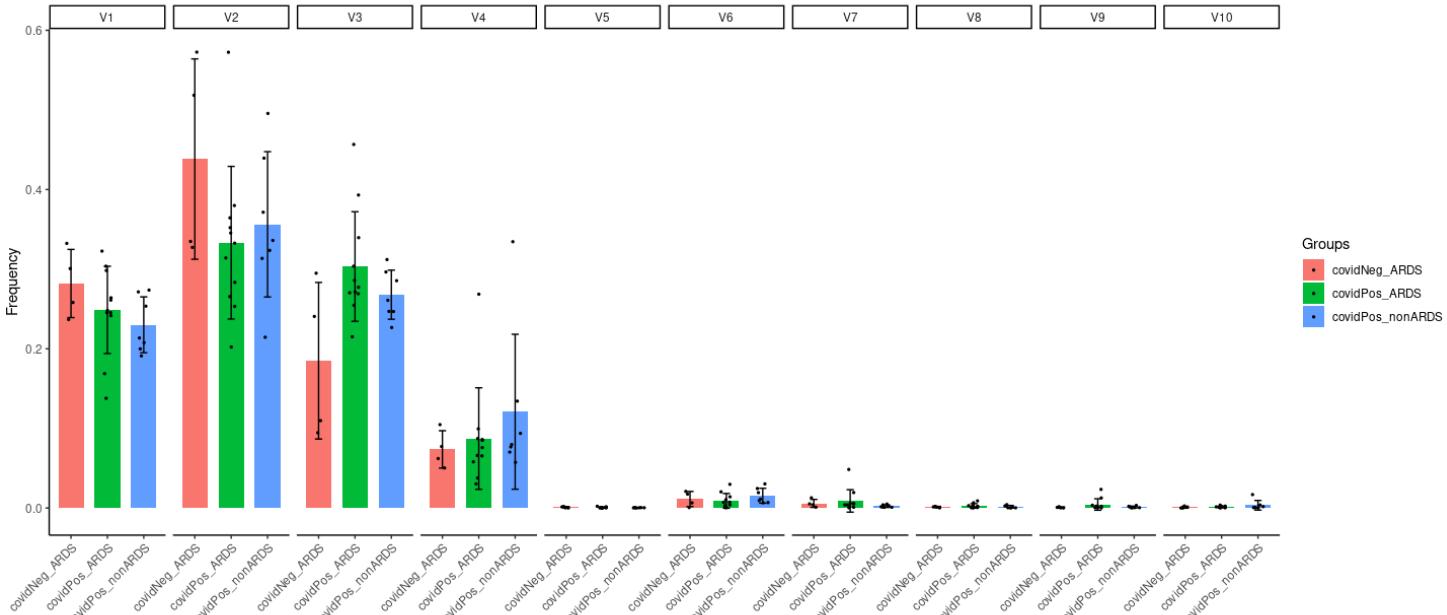
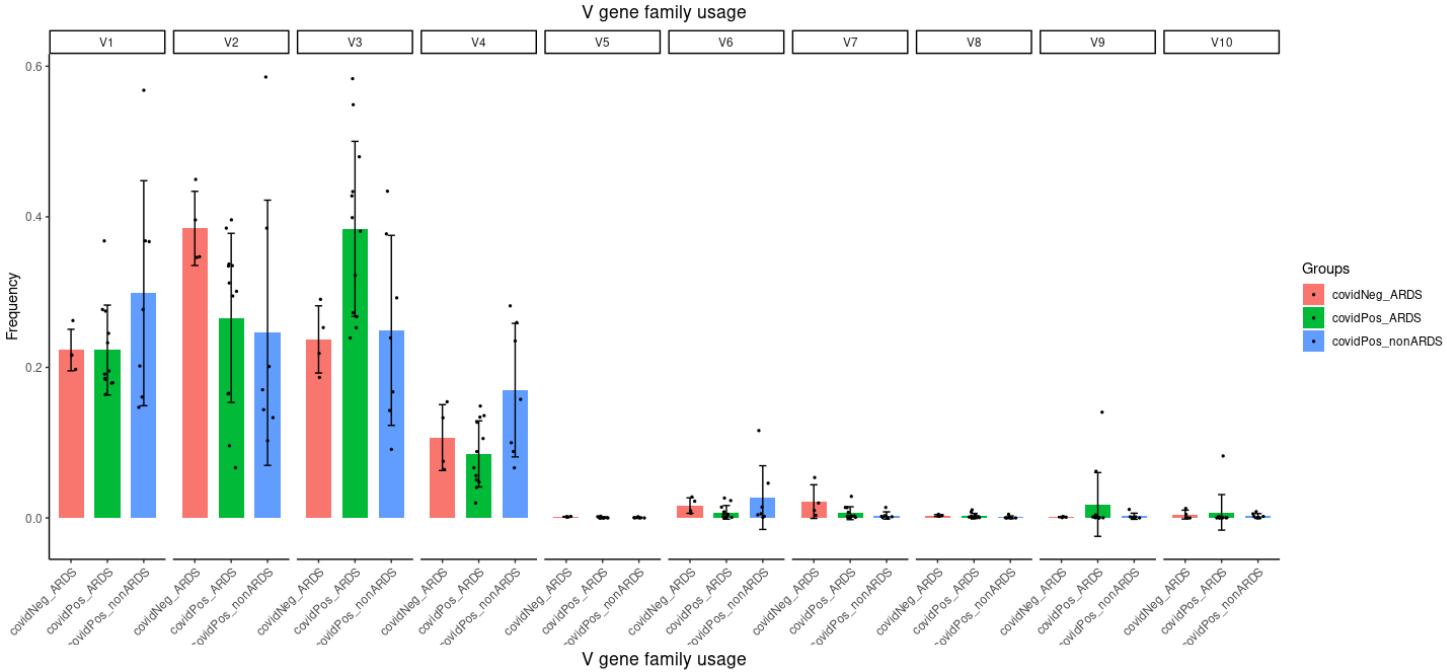


J7 KL



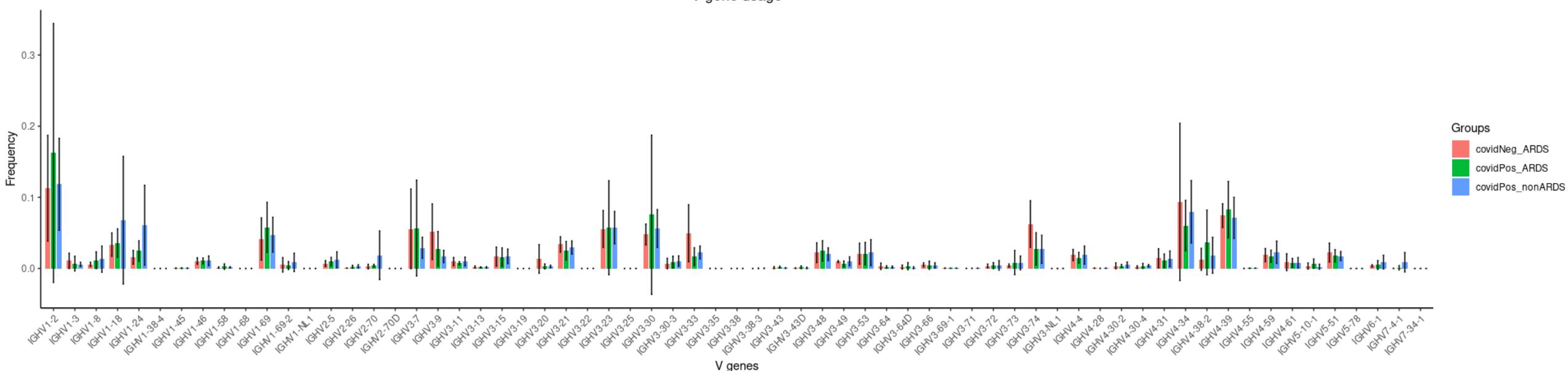
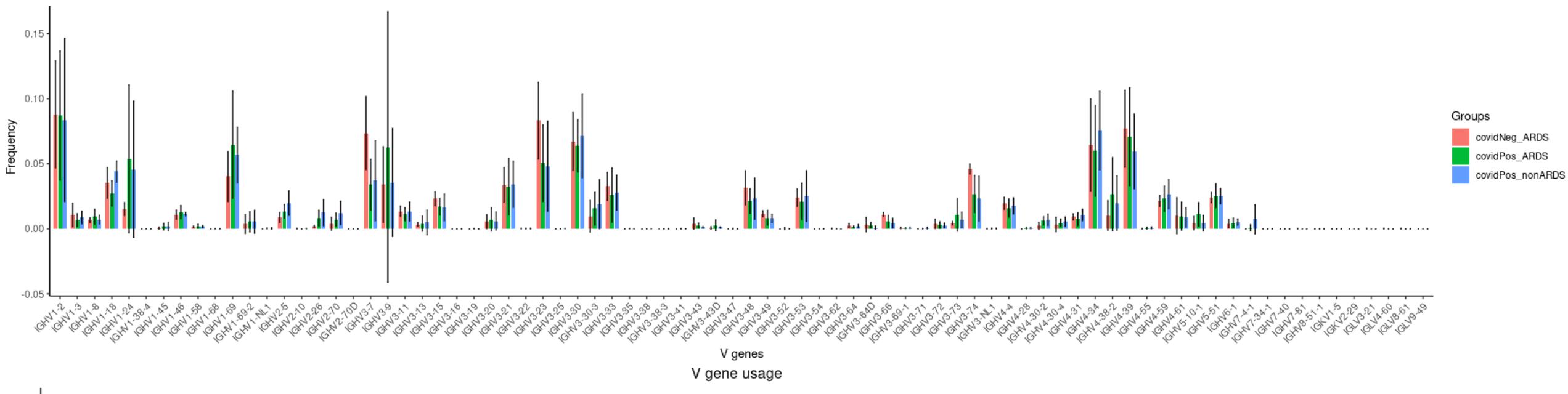
Suivi des répertoires immuns Ig/BCR par 5'RACE

Variation d'usage des V analysés par familles:



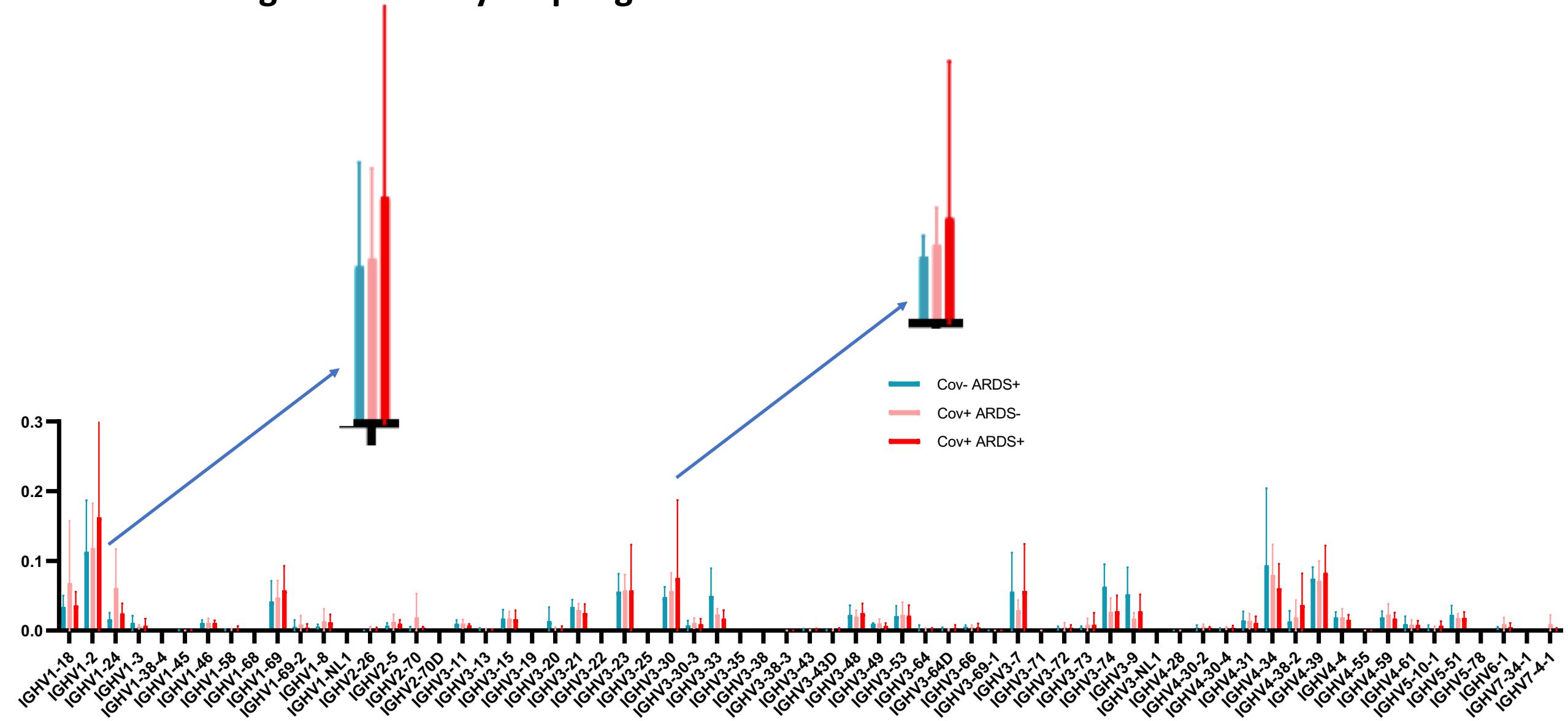
Suivi des répertoires immuns Ig/BCR par 5'RACE

Variation d'usage des V analysés par gène:



Suivi des répertoires immuns Ig/BCR par 5'RACE

Variation d'usage des V analysés par gène:



Suivi des répertoires immuns Ig/BCR par 5'RACE

Variation d'usage des V analysés par clonotype:

Suivi des répertoires immuns Ig/BCR par 5'RACE

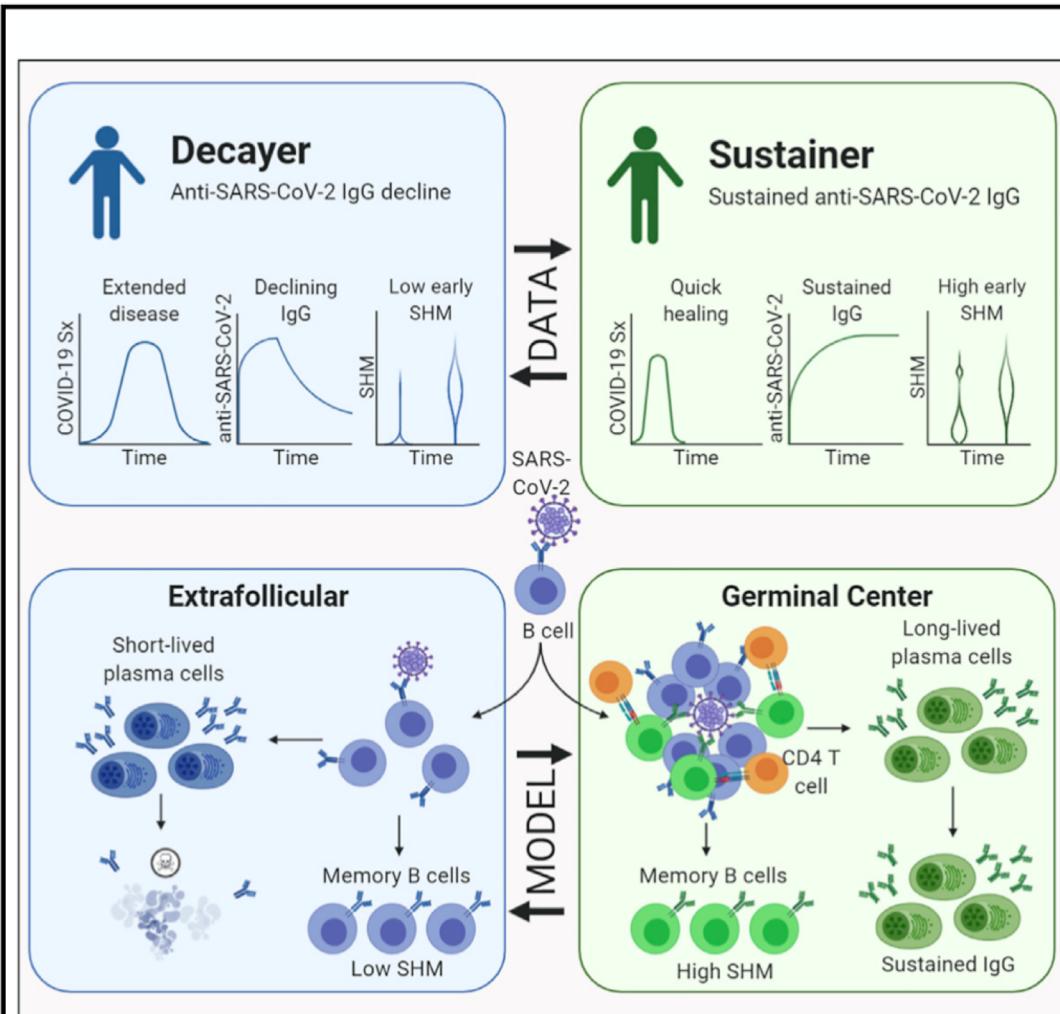
Variation d'usage des V analysés par clonotype:

Fluctuation dynamique de clonotypes en expansion



Variations qualitatives de la réponse humorale Cell

Quick COVID-19 Healers Sustain Anti-SARS-CoV-2 Antibody Production



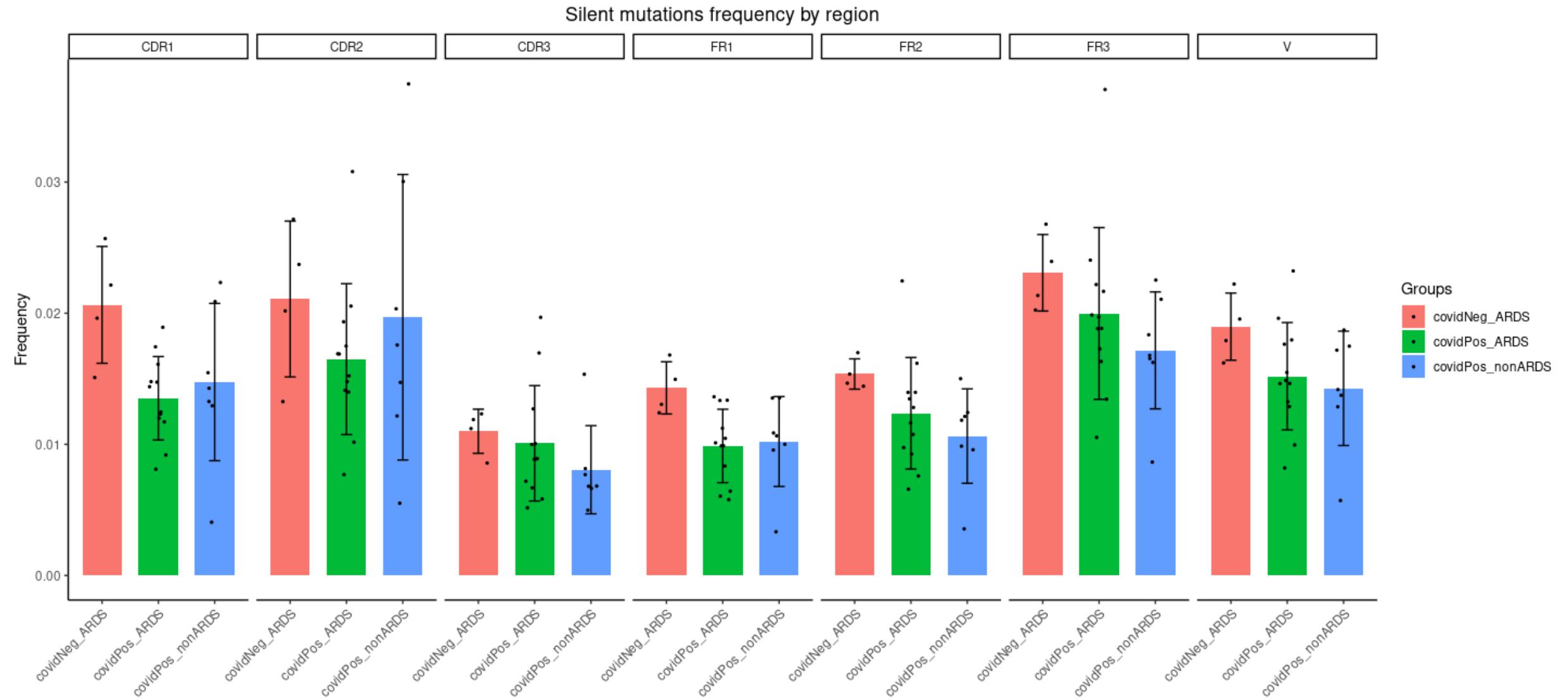
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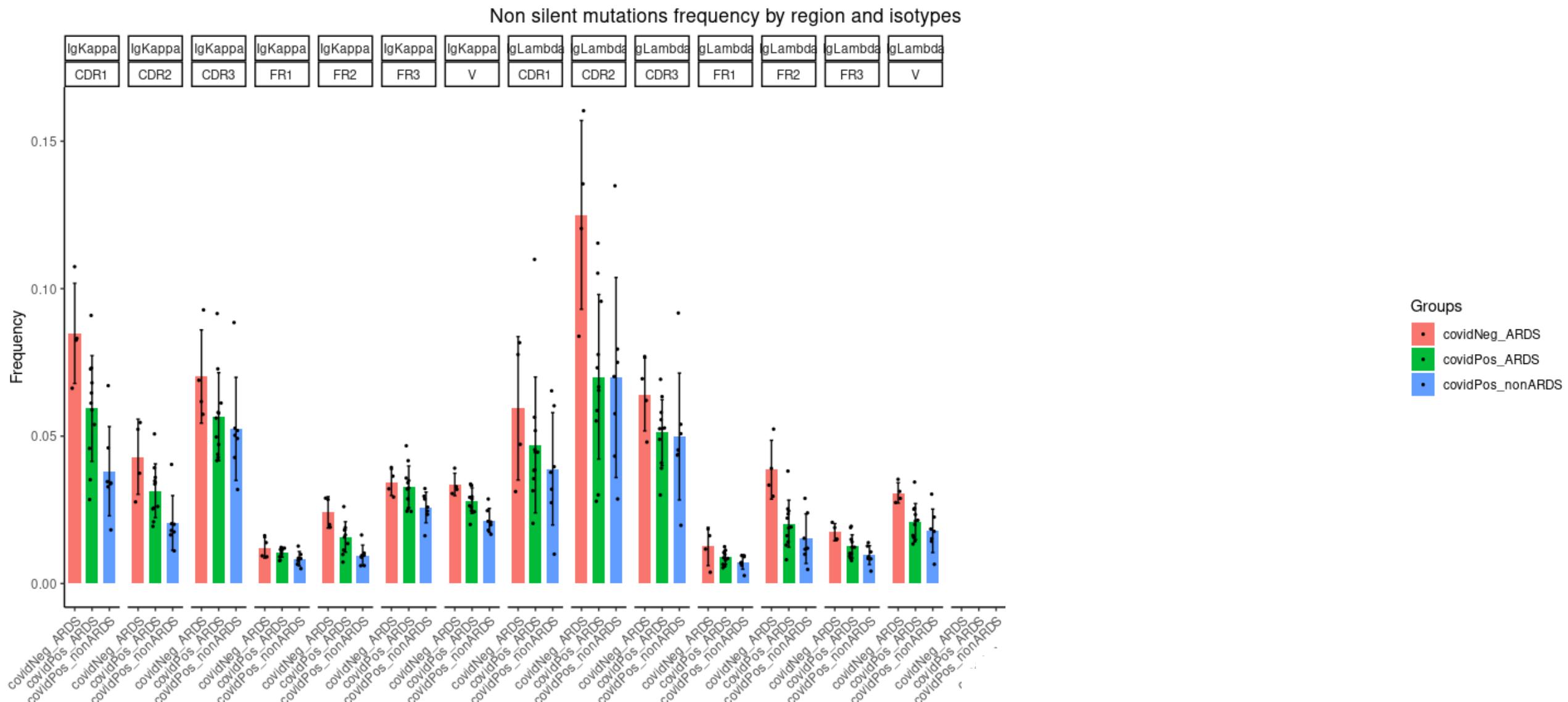
In Brief

Longitudinal analyses of antibody responses to SARS-CoV-2 demonstrate that individuals with sustained virus-specific IgG production have shorter disease trajectories, with a subset demonstrating increased somatic hypermutation and higher levels of activated CD4⁺ cells.

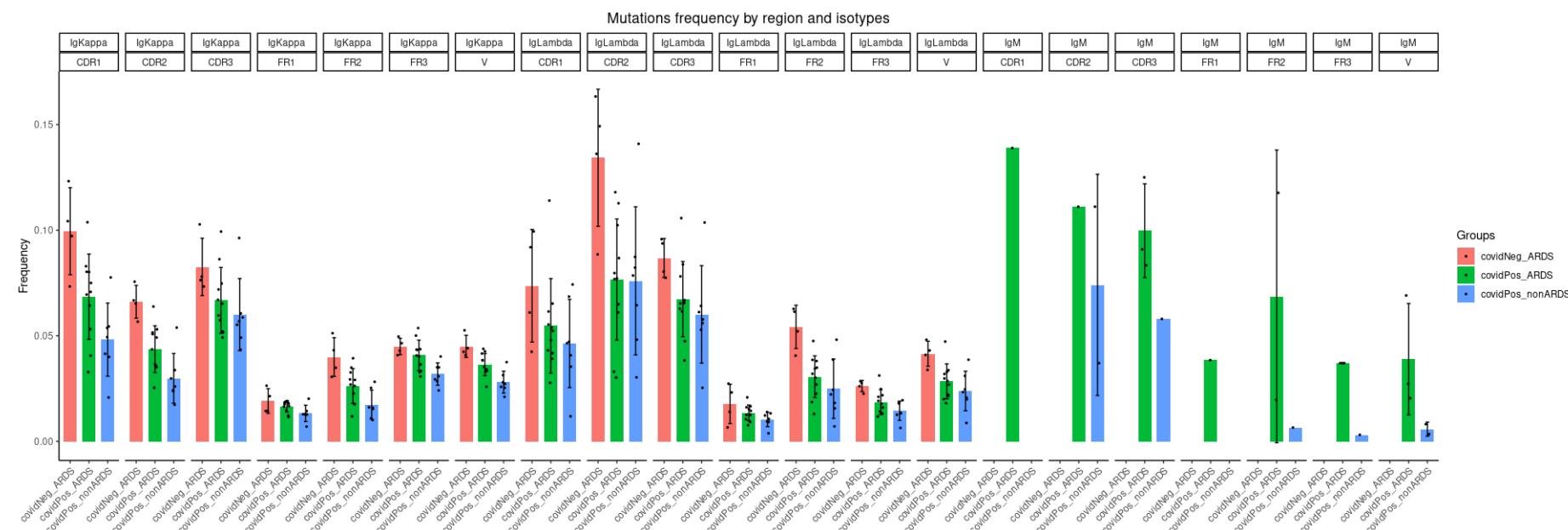
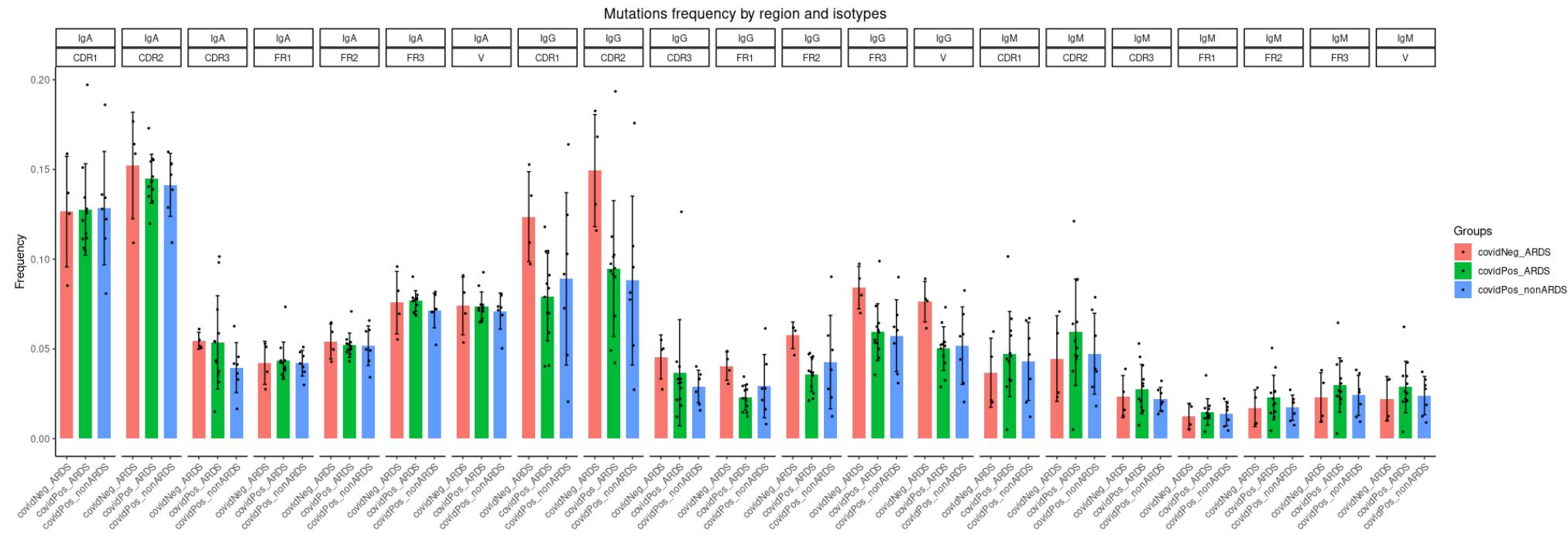
Nature des résultats obtenus: expansions B au cours du Covid-19 et baisse SHM



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Take-home messages

- En matière d'anticorps anti-CoV2, la qualité prime sur la quantité
- Intérêt du suivi des classes et des sous-classes, ainsi que des fonctions effectrices pour évaluer la protection conférée par ces anticorps
- Aucune donnée publiée actuelle ne laisse craindre l'existence d'anticorps facilitant l'évolution de l'infection (phénomène ADE, antibody-dependent enhancement)
- Mesurer l'impact de l'immunisation sur le répertoire des cellules B mémoires circulantes constitue une autre méthode attractive d'immunomonitoring *via* le suivi de clonotypes IgH définis

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Control of the Immune B-cell Response and
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