COVID-19:quelles sérologies ? Pourquoi ? Pour qui ? Et quand ?

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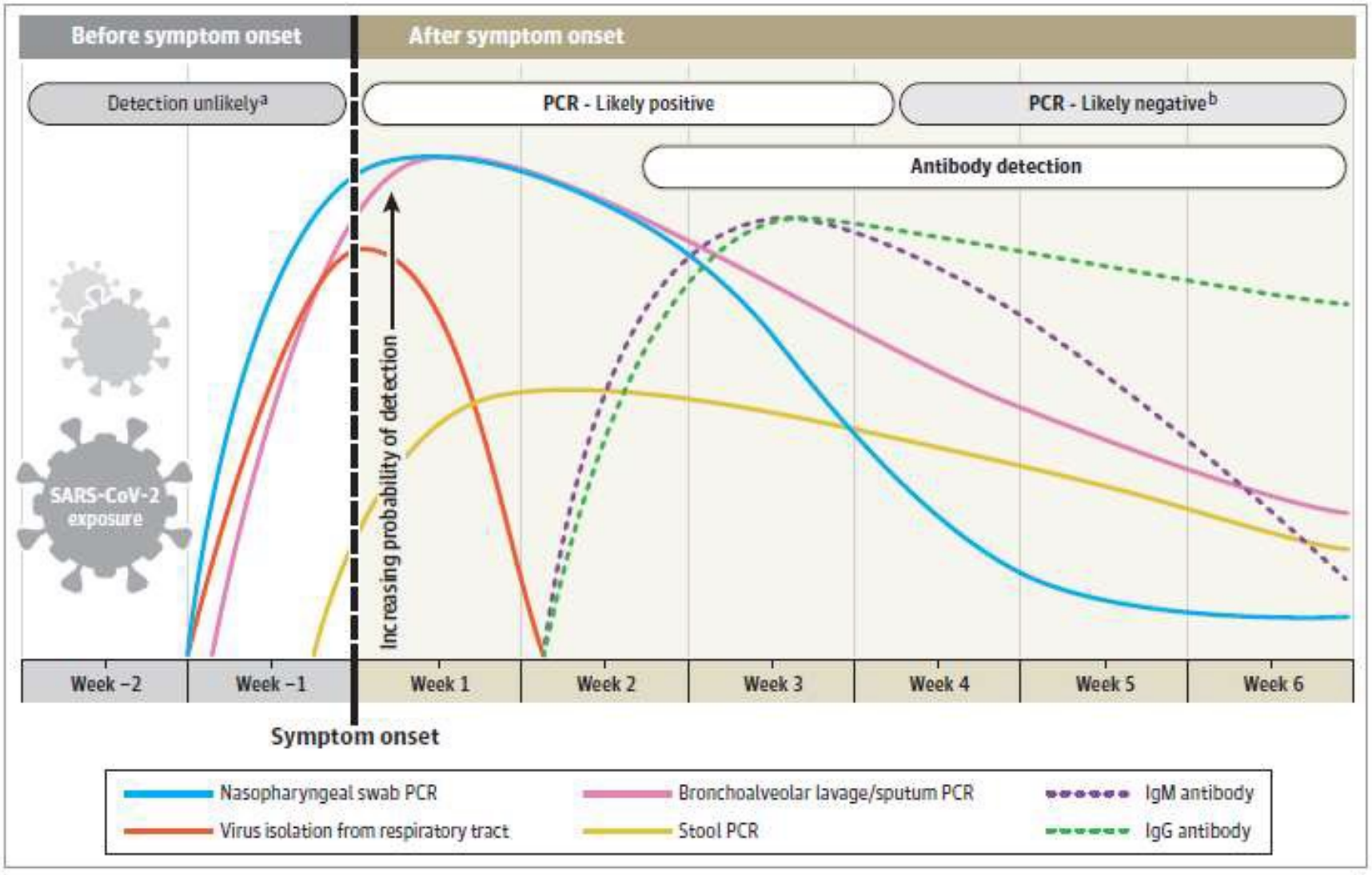
Chaire Prévention, Vaccination, Contrôle de l'Infection PRESAGE

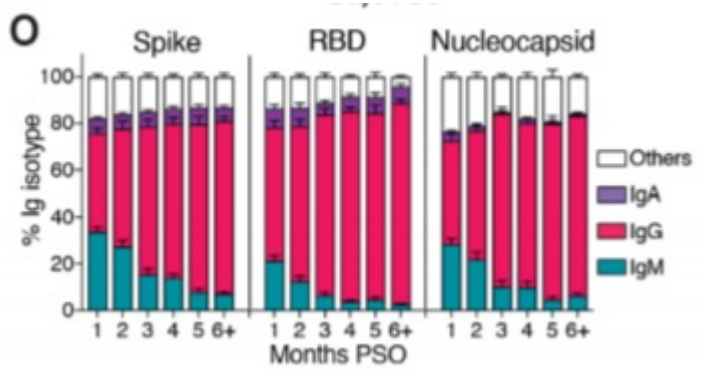
Sérologie et COVID-19

Figure. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset



91-99% des personnes infectées seroconvertissent

AC anti Spike mais aussi dirigés contre d'autres antigènes viraux tels que la Nucléocapside



Sethuraman et al., JAMA 2020
J. M. Dan et al., Science 10.1126/science.abf4063

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers

S.F. Lumley, D. O'Donnell, N.E. Stoesser, P.C. Matthews, A. Howarth, S.B. Hatch, B.D. Marsden, S. Cox, T. James, F. Warren, L.J. Peck, T.G. Ritter, Z. de Toledo, L. Warren, D. Axten, R.J. Cornall, E.Y. Jones, D.I. Stuart, G. Screaton, D. Ebner, S. Hoosdally, M. Chand, D.W. Crook, A.-M. O'Donnell, C.P. Conlon, K.B. Pouwels, A.S. Walker, T.E.A. Peto, S. Hopkins, T.M. Walker, K. Jeffery, and D.W. Eyre, for the Oxford University Hospitals Staff Testing Group*

December 23, 2020, at NEJM.org.

Durée de protection variable

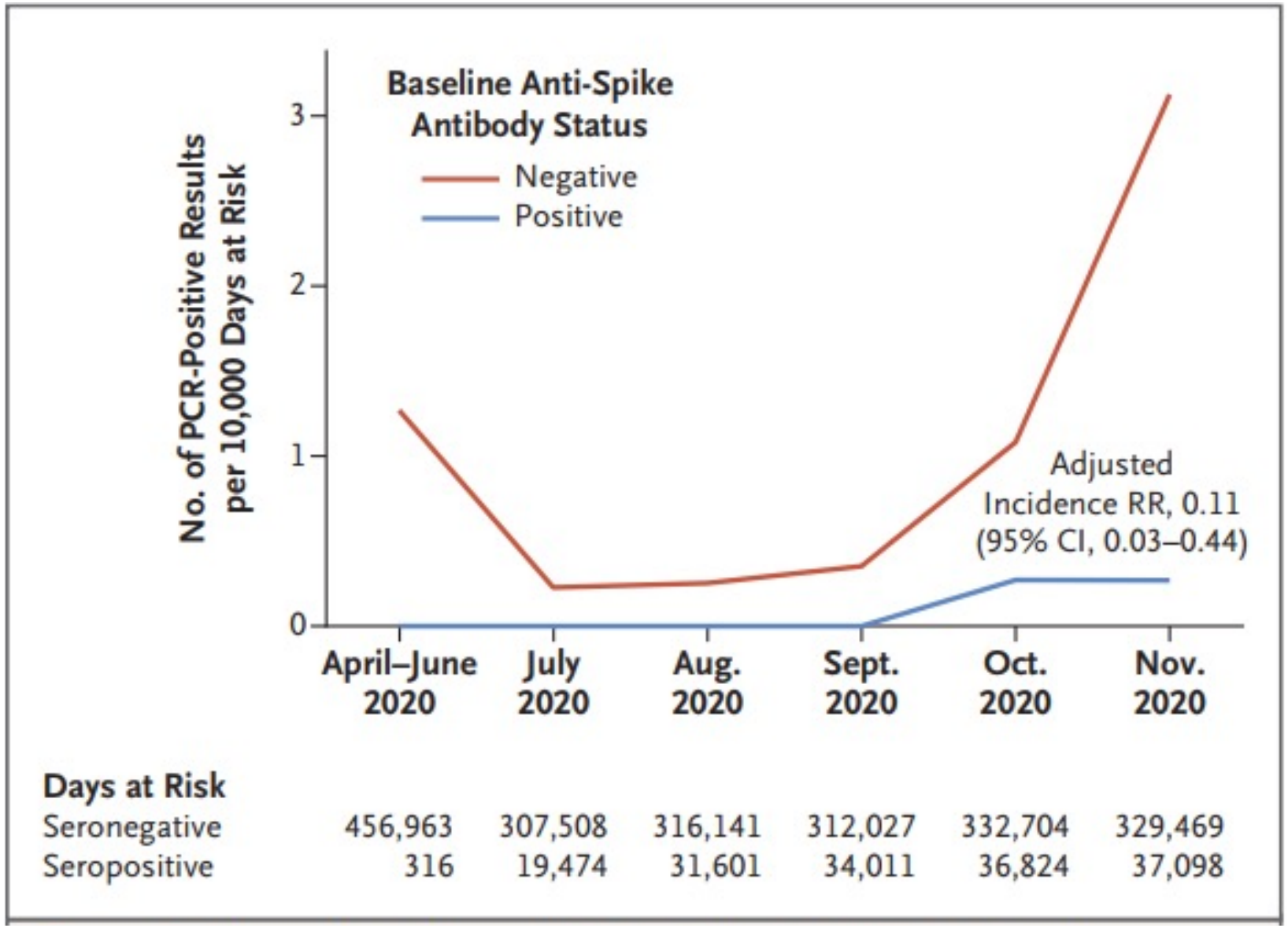


Figure 1. Observed Incidence of SARS-CoV-2–Positive PCR Results According to Baseline Anti-Spike IgG Antibody Status.

The incidence of polymerase-chain-reaction (PCR) tests that were positive for SARS-CoV-2 infection during the period from April through November 2020 is shown per 10,000 days at risk among health care workers according to their antibody status at baseline. In seronegative health care workers, 1775 PCR tests (8.7 per 10,000 days at risk) were undertaken in symptomatic persons and 28,878 (141 per 10,000 days at risk) in asymptomatic persons; in seropositive health care workers, 126 (8.0 per 10,000 days at risk) were undertaken in symptomatic persons and 1704 (108 per 10,000 days at risk) in asymptomatic persons. RR denotes rate ratio.

	Number of infections during follow-up		Infection rate*		Adjusted rate ratio (95% CI)†	Estimated protection (95% CI)	p value‡
	Exposed individuals	Unexposed individuals	Exposed individuals	Unexposed individuals			
Overall	138	53 991	5·64	30·94	0·212 (0·179–0·251)	78·8% (74·9–82·1)	..
Sex							
Female	78	30 225	5·68	30·87	0·209 (0·167–0·261)	79·1% (73·9–83·3)	0·84
Male	60	23 766	5·59	31·03	0·216 (0·168–0·279)	78·4% (72·1–83·2)	..
Age group, years							
0–34	49	26 829	5·92	38·13	0·173 (0·131–0·229)	82·7% (77·1–86·9)	<0·0001
35–49	32	12 071	5·16	31·92	0·199 (0·141–0·282)	80·1% (71·8–85·9)	..
50–64	26	10 111	4·25	27·42	0·187 (0·127–0·274)	81·3% (72·6–87·3)	..
≥65	31	4980	8·01	16·92	0·529 (0·372–0·753)	47·1% (24·7–62·8)	..
Time in follow-up, months							
3–6	84	37 357	5·57	27·28	0·207 (0·167–0·256)	79·3% (74·4–83·3)	0·67
≥7	54	16 634	2·66	14·48	0·223 (0·171–0·291)	77·7% (70·9–82·9)	..

*Rate of infection per 100 000 person-days of follow-up. †Adjusted for sex, age group, test frequency, and start month of follow-up. ‡p value from likelihood ratio tests comparing models with and without interaction terms to capture evidence of effect heterogeneity across subgroups.

***Table 2*: Protection against reinfection with SARS-CoV-2 by sex, age group, and time since first infection, in the alternative cohort analysis**

Immunité naturelle protège des réinfections: durée des AC

https://doi.org/10.1016/S0140-6736(21)00575-4

Sérologie et vaccins

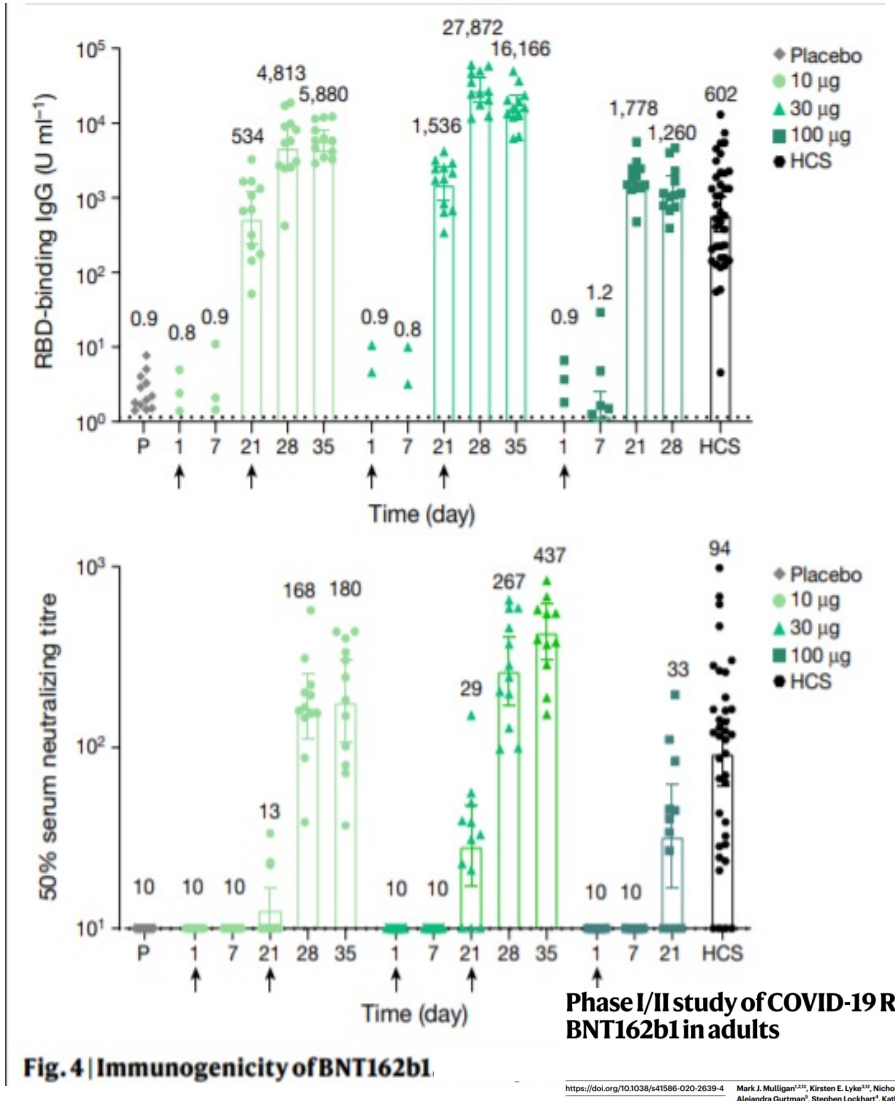
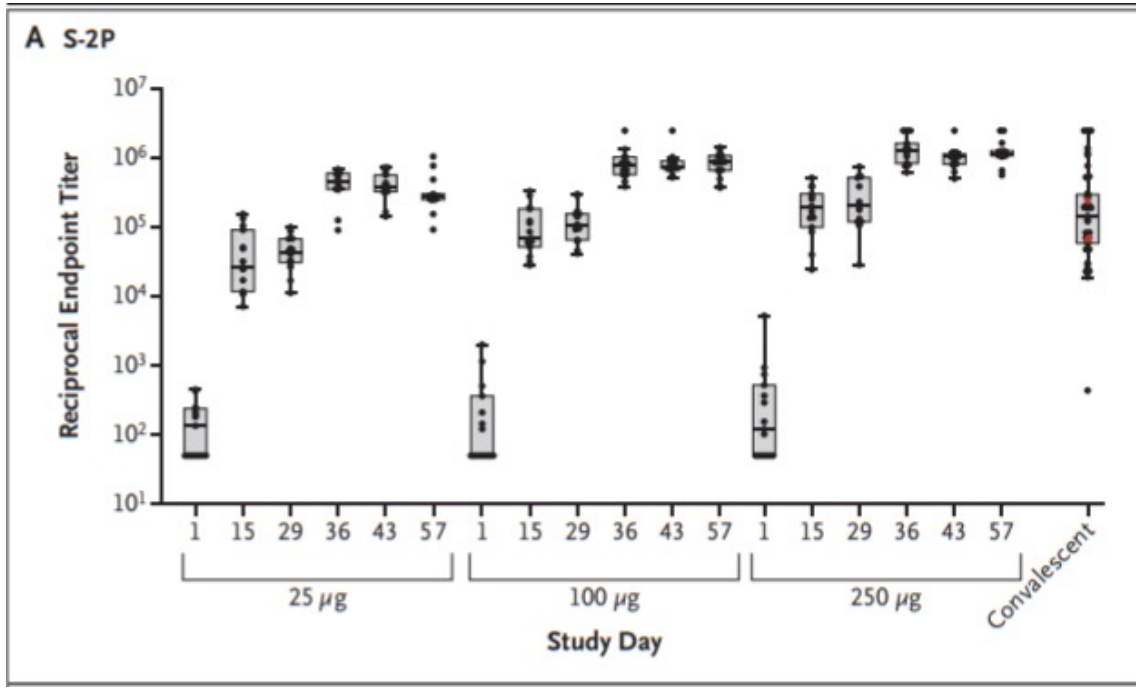


Fig. 4 | Immunogenicity of BNT162b1

Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults

https://doi.org/10.1038/s41586-020-2639-4
Received: 29 June 2020
Accepted: 4 August 2020
Published online: 12 August 2020

Mark J. Mulligan[1,2,3], Kirsten E. Lyke[1,2], Nicholas Kitchin[1,2], Judith Absalon[1,2], Alejandra Gurtman[3], Stephen Lockhart[4], Kathleen Neuzil[5], Vanessa Raabe[1,2], Ruth Bailey[4], Kena A. Swanson[3], Ping Li[3], Kenneth Koury[3], Warren Kalina[3], David Cooper[3], Camila Fontes-Garfias[3], Pei-Yong Shi[3], Özlem Türeci[6], Kristin R. Tompkins[5], Edward E. Walsh[5,10], Robert Frenck[5], Ann R. Falsey[5,10], Philip R. Dormitzer[3], William C. Gruber[4], Uğur Şahin[6] & Kathrin U. Jansen[3]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R.N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, A.J. Pruijssers, A. McDermott, B. Flach, N.A. Doria-Rose, K.S. Corbett, K.M. Morabito, S. O'Dell, S.D. Schmidt, P.A. Swanson II, M. Padilla, J.R. Mascola, K.M. Neuzil, H. Bennett, W. Sun, E. Peters, M. Makowski, J. Albert, K. Cross, W. Buchanan, R. Pikaart-Tautges, J.E. Ledgerwood, B.S. Graham, and J.H. Beigel, for the mRNA-1273 Study Group*

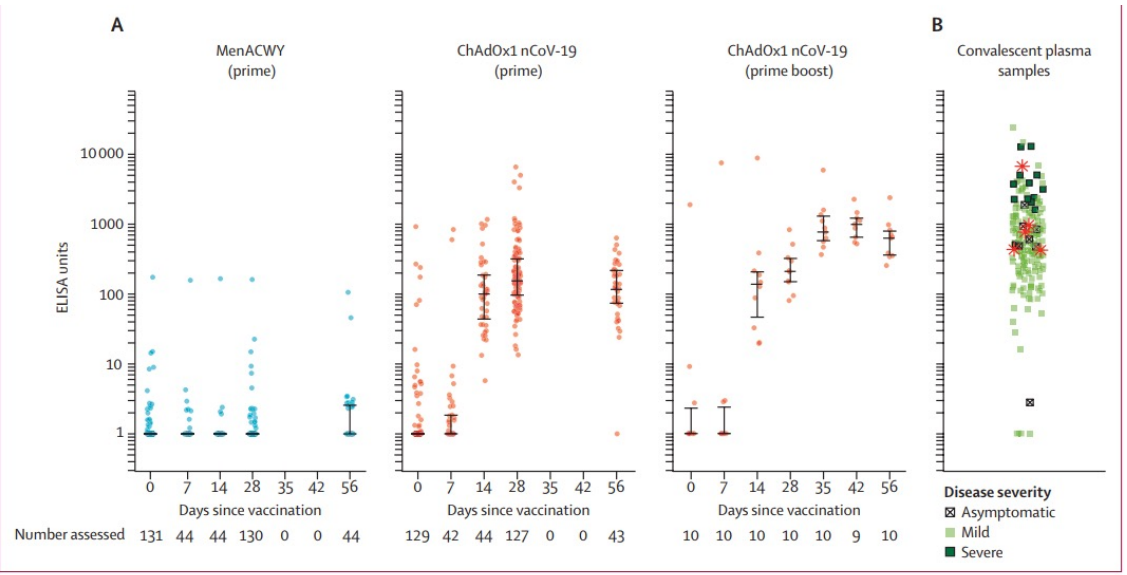
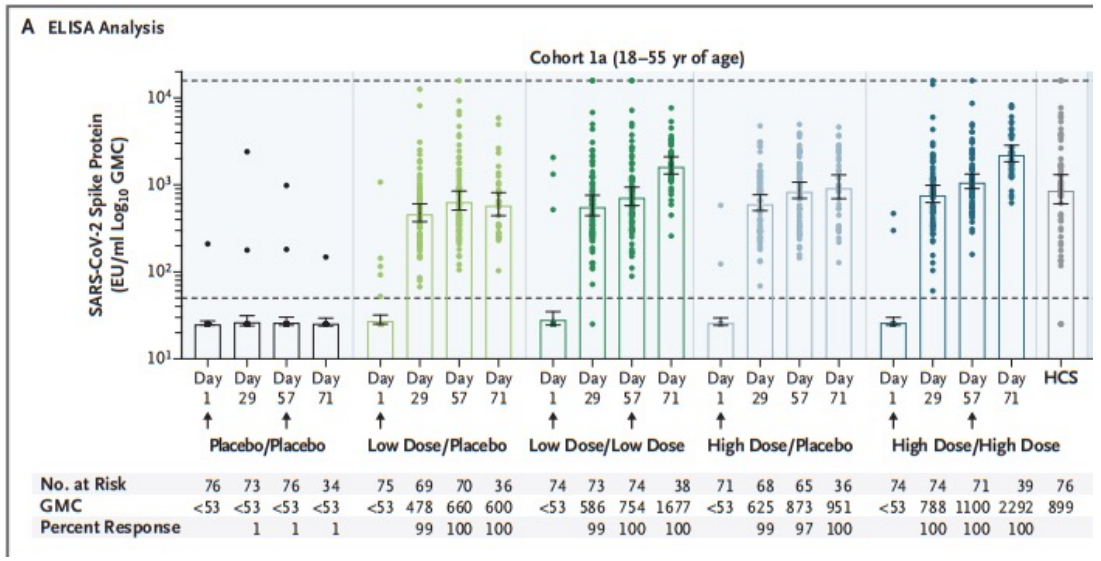


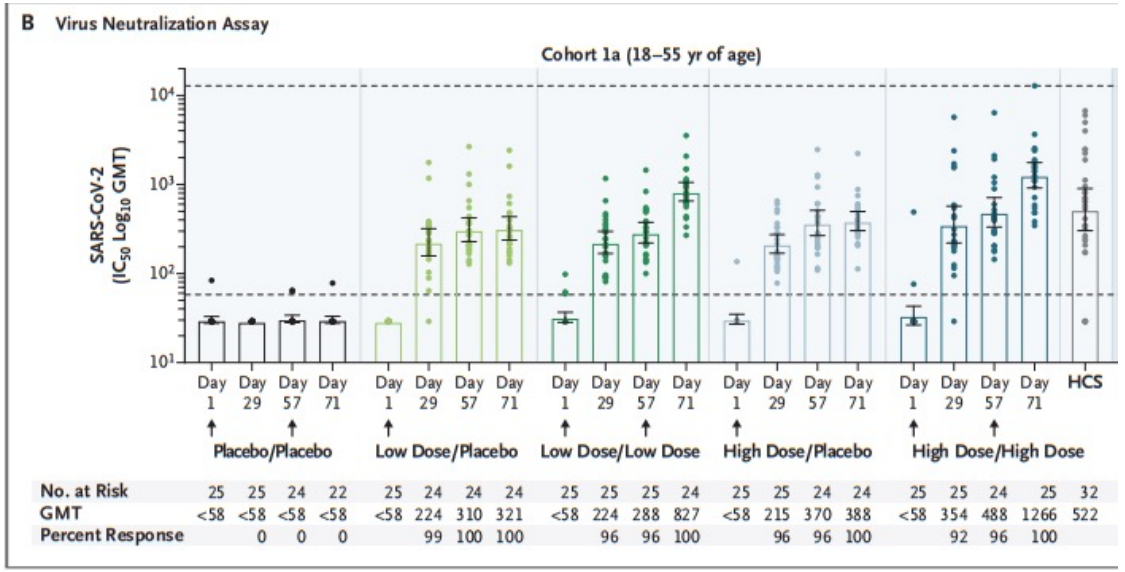
Figure 3: SARS-CoV-2 IgG response by standardised ELISA to spike protein in trial participants (A) and in 180 convalescent plasma samples from 172 patients with PCR-confirmed COVID-19 and eight asymptomatic health-care workers (B)

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

Pedro M Folegatti, Katie J Ewer*, Parvinder K Aley, Brian Angus, Stephan Becker, Sandra Belij-Rammerstorfer, Duncan Bellamy, Sagida Bibi, Mustapha Bittaye, Elizabeth A Clutterbuck, Christina Dold, Saul N Faust, Adam Finn, Amy L Flaxman, Bassam Hallis, Paul Heath, Daniel Jenkin, Rajeka Lazarus, Rebecca Makinson, Angela M Minassian, Katrina M Pollock, Maheshi Ramasamy, Hannah Robinson, Matthew Snape, Richard Tarrant, Merryn Voysey, Catherine Green*, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard*, on behalf of the Oxford COVID Vaccine Trial Group†*

AC anti Spike: ≈ 15 j après la 1ere dose
AC neutralisants en moindre quantité que les AC totaux



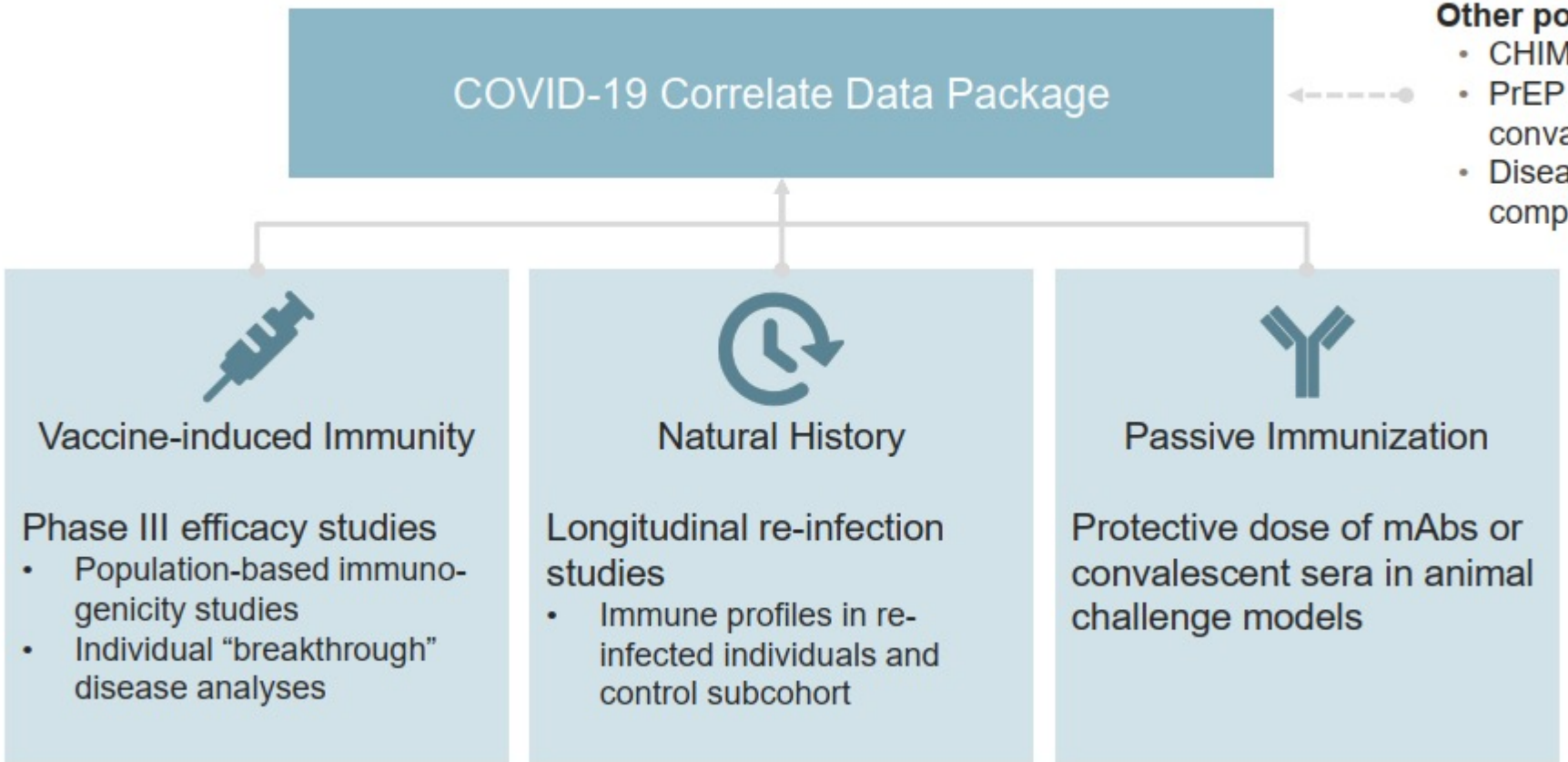


ORIGINAL ARTICLE

Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine

J. Sadoff, M. Le Gars, G. Shukarev, D. Heerwegh, C. Truyers, A.M. de Groot, J. Stoop, S. Tete, W. Van Damme, I. Leroux-Roels, P.-J. Berghmans, M. Kimmel, P. Van Damme, J. de Hoon, W. Smith, K.E. Stephenson, S.C. De Rosa, K.W. Cohen, M.J. McElrath, E. Cormier, G. Scheper, D.H. Barouch, J. Hendriks, F. Struyf, M. Douoguih, J. Van Hoof, and H. Schuitemaker

Anticorps et protection



Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis

Deborah Cromer, Megan Steain, Arnold Reynaldi, Timothy E Schlub, Adam K Wheatley, Jennifer A Juno, Stephen J Kent, James A Triccas, David S Khoury*, Miles P Davenport*

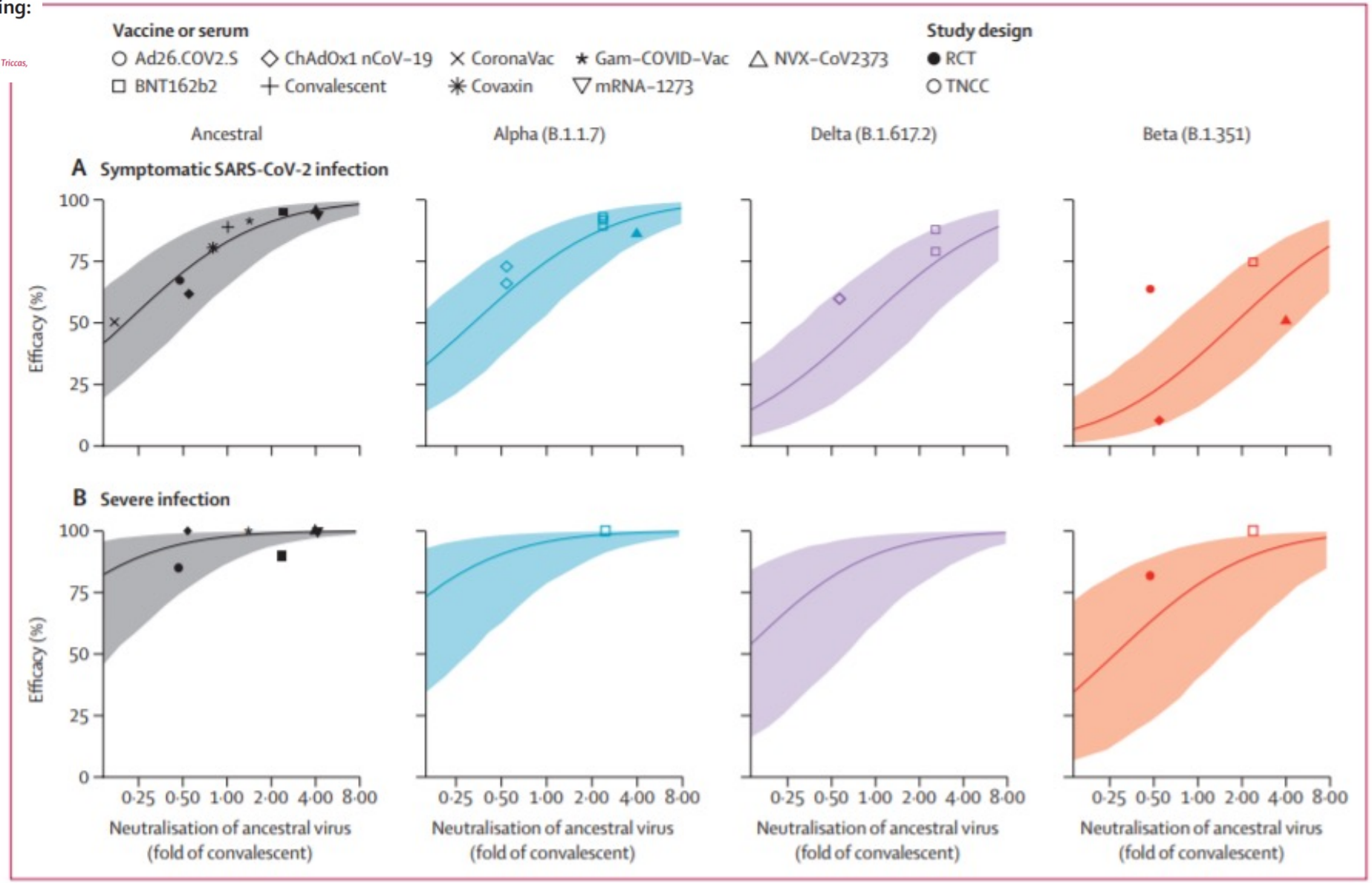
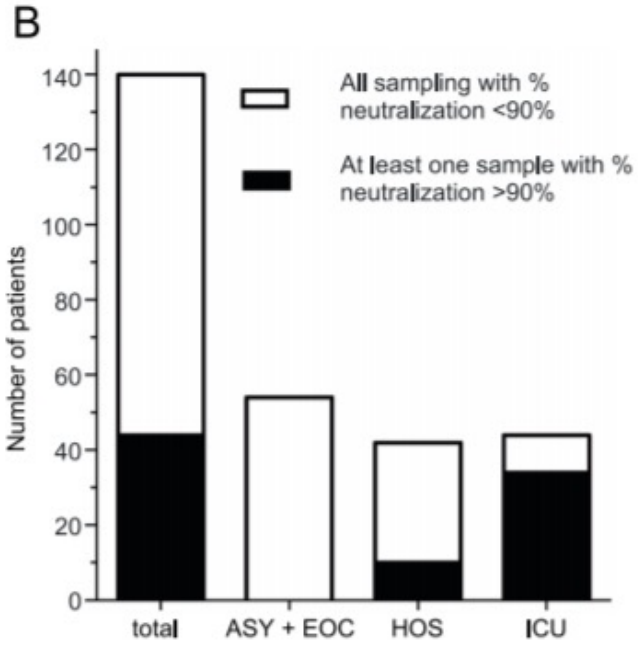


Figure 2: **Predicting vaccine efficacy against SARS-CoV-2 variants**

https://doi.org/10.1016/ S2666-5247(21)00267-6

Qui dit AC ne dit pas toujours AC neutralisants



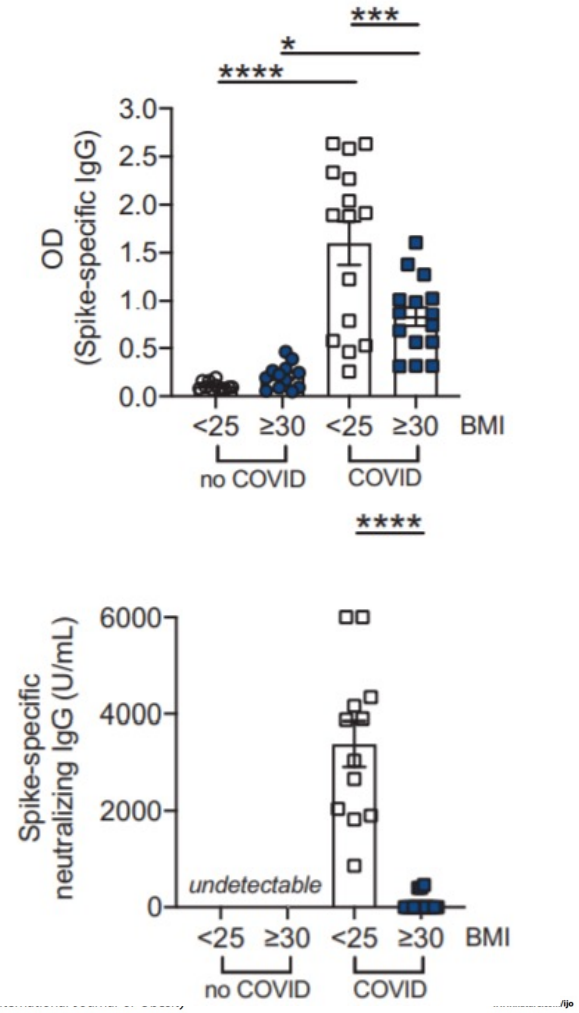
www.nature.com/cmi Cellular & Molecular Immunology

ARTICLE OPEN

A longitudinal study of SARS-CoV-2-infected patients reveals a high correlation between neutralizing antibodies and COVID-19 severity

Vincent Legros[1,2], Solène Denolly[1], Manon Vogrig[3,4], Bertrand Boson[1], Eglantine Siret[1], Josselin Rigaill[3,4], Sylvie Pillet[3,5], Florence Grattard[3,5], Sylvie Gonzalo[3], Paul Verhoeven[3,5], Omran Allatif[1], Philippe Berthelot[5,6], Carole Pélissier[7], Guillaume Thiery[8], Elisabeth Botelho-Nevers[5,6], Guillaume Millet[9], Jérôme Morel[10], Stéphane Paul[4,5], Thierry Walzer[1], François-Loïc Cosset[1], Thomas Bourlet[3,5] and Bruno Pozzetto[3,5]

Cellular & Molecular Immunology (2021) 18:318–327; https://doi.org/10.1038/s41423-020-00588-2

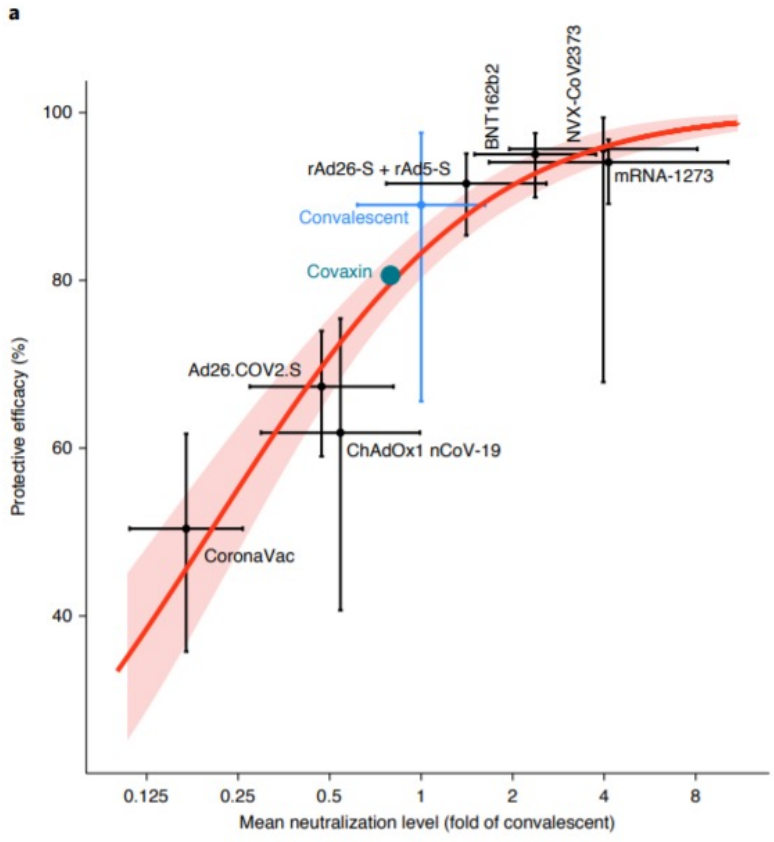


ARTICLE OPEN

Clinical Research

The majority of SARS-CoV-2-specific antibodies in COVID-19 patients with obesity are autoimmune and not neutralizing

Daniela Frasca[1,2,4], Lisa Reidy[3,4], Maria Romero[1], Alain Diaz[1], Carolyn Cray[3], Kristin Kahl[3] and Bonnie B. Blomberg[1,2]



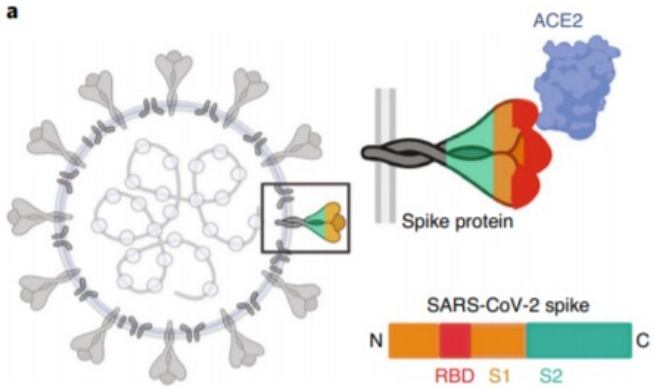
Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection

David S. Khoury[1,9], Deborah Cromer[1,9], Arnold Reynaldi[1], Timothy E. Schlub[1,2], Adam K. Wheatley[3], Jennifer A. Juno[3], Kanta Subbarao[3,4], Stephen J. Kent[3,5,6], James A. Triccas[7,8] and Miles P. Davenport[1]

Quelles sérologies?

- Détecter les AC neutralisants!
  - PAS en routine!
  - Laboratoire P3, SARS-CoV-2= « gold standard », « time consuming », onéreux
  - Neutralisation de pseudovirus: variable d'un technique à l'autre, onéreux

- Détecter des Ac anti Spike (anti S1), anti RBD, anti N
  - Faisable en routine
  - Parfois assez loin des Ac neutralisants!
  - Mais variable technique à l'autre++++
  - Besoin d'uniformisation pour les unités!
  - Trop souvent fait à tort et à travers: couteux++++



WHO International Standard for evaluation of the antibody response to COVID-19 vaccines: call for urgent action by the scientific community

Ivana Knezevic, Giada Mattiuzzo, Mark Page, Philip Minor, Elwyn Griffiths, Micha Nuebling, Vasee Moorthy

	Geometric mean titre	95% CI	Unit
Neutralising antibody activity	1300	981–1719	IU/mL
Anti-receptor-binding domain IgG	502	382–660	BAU/mL
Anti-S1 IgG	588	398–870	BAU/mL
Anti-Spike IgG	476	418–542	BAU/mL
Anti-nucleoprotein IgG	747	214–2606	BAU/mL

The research reagent 20/130 has been calibrated to the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code 20/136) as part of a multicentre collaborative study. IU=International Units. BAU=binding antibody units.

Table 2: **Calibration of research reagent 20/130 in International Standard unitage**

Clinical Microbiology and Infection 27 (2021) 981–986

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

How to interpret and use COVID-19 serology and immunology tests

David S.Y. Ong [1, 2, *], Paraskevi C. Fragkou [3], Valentijn A. Schweitzer [4], Roy F. Chemaly [5], Charalampos D. Moschopoulos [3], Chrysanthi Skevaki [6], on behalf of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Respiratory Viruses (ESGREV)

rview principles of serological and immunological tests

	Detection targets	Advantages	Limitations	When to apply
Lateral flow immunoassay (LFIA)	IgM, IgA, IgG or total antibodies	- Suitable as point-of-care test - Rapid and easy testing	- Heterogeneous performance with overall limited sensitivity during acute phase of disease - Only qualitative results - Not suitable for rapid testing - Need for trained laboratory staff - Batchwise workup in laboratory process	- Population-based epidemiological surveillance - For individual patient care in case of unavailability of molecular diagnostic tests, inconclusive molecular test results, late presentations during disease course or late-onset post-infectious complications - Implications for interpretation after vaccination and correlation with protective immunity remain to be determined
Enzyme-linked immunosorbent assay (ELISA) Chemiluminescence immunoassay (CLIA)		- Overall higher sensitivity in comparison to LFIA - Suitable for high throughput and automation - Some assays generate quantitative results		
Plaque reduction neutralization tests (i.e. conventional virus neutralization test)	Total antibodies (that can inhibit viral replication)	- Presumably high correlation with protective immunity - Gold standard for quantification of neutralizing antibodies	- Only in biosafety level 3 laboratories possible - Time consuming test	- To increase scientific understanding regarding immunity - Implications for interpretation after vaccination and correlation with protective immunity remain to be determined
Pseudo-neutralizing antibody assays/ surrogate virus neutralization test (sVNT)		- High correlation with plaque reduction neutralization tests - Rapid and safe (no need for live biological material)	- Not considered as gold standard for quantification of neutralizing antibodies	
ELISpot	Antigen-specific T cells (producing a specific cytokine, e.g. IFNγ)	- Quantitative measurements - Commonly used for evaluation of immunity in vaccination trials	- No information regarding exact cytokine-producing cell types	- To increase scientific understanding regarding immunity - Implications for interpretation after vaccination and correlation with protective immunity remain to be determined
Flow cytometry	Different cell types, including T cells	- Identification of specific cell subpopulations and presence of polyfunctional cells	- Test is (relatively) complex	

"T-cell responses against SARS-CoV-2 have also been detected in recovered COVID-19 patients with no detectable antibodies, indicating that, in some cases, cellular immunity could be maintained independently of antibody responses"

Au final.....

CellPress
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Trends in
Microbiology

Review

COVID-19 Antibody Tests: A Valuable Public Health Tool with Limited Relevance to Individuals

Rachel West,[1] Amanda Kobokovich,[1] Nancy Connell,[1] and Gigi Kwik Gronvall [1,*]

SAUF….

- HAS mai 2020: la détection d'anticorps sériques, témoins d'une primo-infection par le virus SARS-CoV-2, par méthode automatisable et/ou test diagnostique rapide (TDR) ou test rapide d'orientation diagnostique (TROD), reste indiquée dans quatre situations

  - Le diagnostic initial de patients symptomatiques graves hospitalisés, en cas de tableau clinique ou scanographique évocateur d'infection par le SARS-CoV-2 et de test RT-PCR négatif
  - Le diagnostic de rattrapage de patients symptomatiques graves hospitalisés mais n'ayant pas pu faire l'objet d'un test RT-PCR avant sept jours
  - Le diagnostic initial de patients symptomatiques sans signe de gravité suivis en ville en cas de tableau clinique évocateur d'infection par le SARS-CoV-2 et de test RT-PCR négatif
  - Le diagnostic de rattrapage de patients présentant des symptômes évocateurs d'une infection par le SARS-CoV-2 (y compris des symptômes prolongés de Covid-19) sans signe de gravité pour lesquels un diagnostic biologique initial n'a pas été établi.

https://www.has-sante.fr/jcms/p_3273496/fr/covid-19-quelle-utilite-aujourd-hui-pour-les-tests-serologiques

SAUF…

- Pour guider le schéma vaccinal en primo-vaccination:

« Le 3 juin dernier, la HAS a ajouté une indication aux tests sérologiques de type TROD en contexte de dépistage pré-vaccinal. Elle recommande ainsi de les proposer lors du premier rendez-vous vaccinal aux ***personnes immunocompétentes*** *(possédant la capacité à produire une réponse immunitaire normale),* ***sans facteurs de risque de développer une forme grave de la maladie*** *(jeunes adultes) et* ***sans antécédent connu ou confirmé d'infection au SARS-CoV-2*** *afin de déterminer leur schéma vaccinal. »*

« La stratégie vaccinale pour les personnes immunodéprimées ***ne doit pas*** *s'appuyer sur un test sérologique »*

https://www.has-sante.fr/jcms/p_3273496/fr/covid-19-quelle-utilite-aujourd-hui-pour-les-tests-serologiques

SAUF…..

- Pour proposer des stratégies de prophylaxie (AC monoclonaux) chez des sujets non ou peu répondeurs à haut risque de forme grave de COVID-19:

« L'association casirivimab et imdevimab est indiquée en ***prophylaxie post-exposition de la COVID-19*** *et* ***en prophylaxie pré-exposition de la COVID-19*** *chez les patients adultes et les enfants âgés de 12 ans et plus, n'ayant pas développé du fait de leur immunodépression une réponse vaccinale satisfaisante à un schéma complet de vaccination* ***[i.e patients non-répondeurs (séronégatifs ou titre d'anticorps anti-S <30 BAU) ou faiblement répondeurs (titre d'anticorps anti-S <260 BAU)]*** *ET appartenant à l'un des sous-groupes à très haut risque de forme sévère de COVID-19 tels que définis par l'ANRS-Maladies Infectieuses Emergentes: »*

Receveurs de greffes d'organes solides; Receveurs d'une greffe allogénique de cellules souches hématopoïétiques
Hémopathies lymphoïdes : leucémies lymphoïdes chroniques traitées ou non, lymphomes non hodgkiniens et myélomes sous traitement, y compris les patients receveurs de thérapie Cellulaire génique de type CAR-T cell (Chimeric antigen receptor T cell) ou d'anticorps thérapeutiques bi-phénotypiques
Patients recevant un traitement par anticorps anti-CD20 ou inhibiteurs de BTK (Bruton Tyrosine Kinase) ou azathioprine, cyclophosphamide et mycophenolate mofetil
Sujets porteurs d'un déficit immunitaire primitif; Patients séronégatifs après un schéma vaccinal complet ou non éligibles à la vaccination ***et*** *qui présentent une immunodépression sévère* ***et*** *qui sont à haut risque de forme grave de COVID-19.*

- Et pour la 3ème dose?

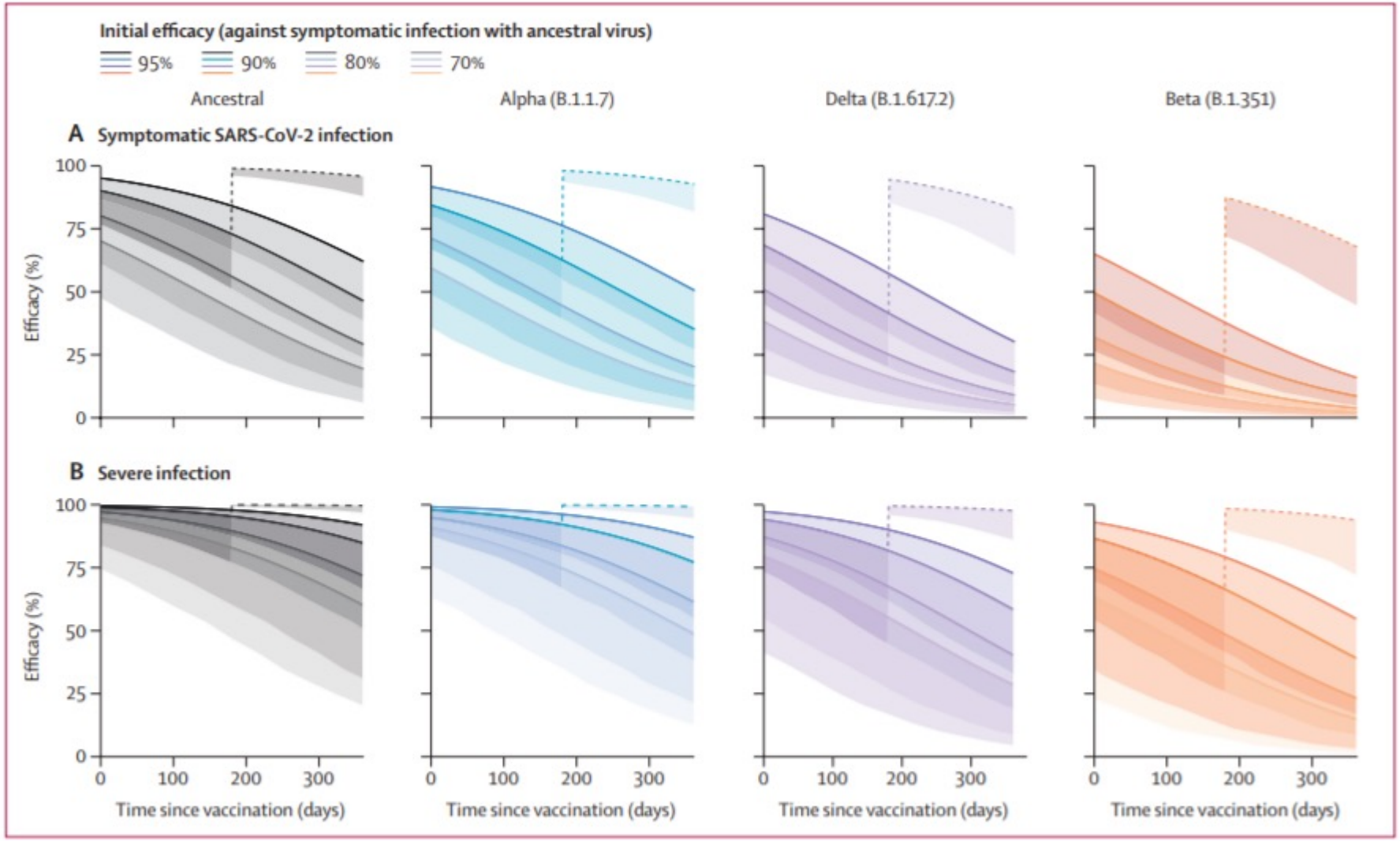

Figure 4: **Predicted protection from SARS-CoV-2 infection and the effect of an additional booster dose at 6 months**
The predicted protection over time is shown for four hypothetical vaccines that initially provide 95%, 90%, 80%, or 70% protection against symptomatic infection with the ancestral virus. It is assumed that neutralisation decays with a half-life of 108 days and variant neutralisation decreases as estimated (appendix p 23). Solid lines are mean model predictions, and shading indicates the lower bound of the 95% CI (indicating the minimal predicted efficacy). The dashed line indicates the predicted effect of boosting previously infected individuals with BNT162b2 or mRNA-1273 6 months after their primary infection (geometric mean of all boosting studies; appendix p 24) and assumes decay after boosting is the same as after initial infection or primary vaccination.

Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis

Deborah Cromer, Megan Steain, Arnold Reynaldi, Timothy E Schlub, Adam K Wheatley, Jennifer A Juno, Stephen J Kent, James A Triccas, David S Khoury*, Miles P Davenport*

La suite?

- Corrélats de protection universels nécessaires, y compris pour le développement de nouveaux vaccins
- Combinaison de 2 tests automatisables?
- Seuil d'AC anti RBD et anti Spike corrélé à la neutralisation et valable dans toutes les populations?????

ARTICLES
https://doi.org/10.1038/s41591-021-01540-1
nature medicine
Check for updates

OPEN

Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection

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Table 2 | Outputs from generalized additive models, with immune marker values associated with 50%, 60%, 70%, 80%, and 90% VE against symptomatic infection

Assay units	*P* value $_{\text{immune marker}}$	*P* value $_{\text{baseline risk score}}$	No. cases	No. noncase	50% VE (95% CI)	60% VE (95% CI)	70% VE (95% CI)	80% VE (95% CI)	90% VE (95% CI)
Anti-spike IgG									
AU/ml	0.003	<0.001	52	1155	4446 (NC, 12822)	8413 (NC, 22232)	17538 (NC, 37929)	40923 (16748, 125017)	139306 (57276, NC)
BAU/ml					29 (NC, 83)	54 (NC, 143)	113 (NC, 245)	264 (108, 806)	899 (369, NC)
Anti-RBD IgG									
AU/ml	0.018	<0.001	52	1155	2193 (NC, 13614)	6266 (NC, 29105)	20700 (NC, 56620)	63383 (16903, NC)	295781 (90567, NC)
BAU/ml					17 (NC, 109)	50 (NC, 232)	165 (NC, 452)	506 (135, NC)	2360 (723, NC)
Normalized live-virus neutralization assay									
NF_{50}	<0.001	<0.001	36	412	68 (NC, 129)	91 (NC, 175)	135 (48, 267)	247 (101, NC)	938 (294, NC)
Pseudovirus neutralization assay									
ID_{50}	0.005	<0.001	47	828	NC	22 (NC, 76)	57 (NC, 183)	185 (NC, NC)	982 (303, NC)
IU/ml					NC	3 (NC, 11)	8 (NC, 26)	26 (NC, NC)	140 (43, NC)

ID_{50}: neutralization dilution for 50% virus inhibition; NC: not computed; AU/ml: arbitrary units per mL; BAU/ml: binding antibody units per ml (WHO international standard 20/136), IU/ml: international units per ml (WHO international standard 20/136). Where CIs were outside the range of values of the assay the limits are reported as NC. VE estimates and CIs are those shown in Fig. 4, at every 10% increment in the *y* axis. The two-sided *P* value for each immune marker (column 2) is from the generalized additive models in Fig. 1, showing the strength of the relationship between the antibody value and infection. The *P* values were not adjusted for multiple comparisons.

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Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial

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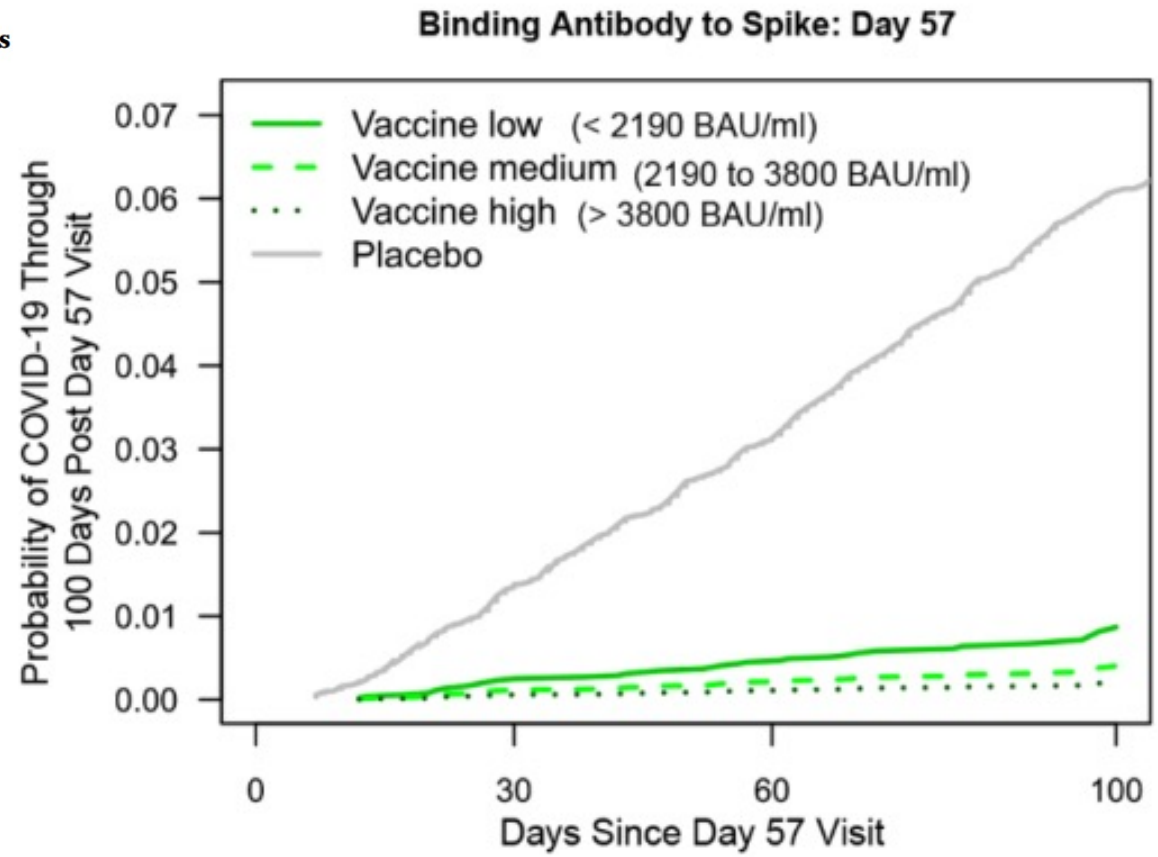

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