EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

COVID-19 vaccines and therapeutics
An update to the PCWP/HCPWP

Dr. Marco Cavaleri
Head of Office Biological Health Threats and Vaccine Strategy, EMA

An agency of the European Union

Therapeutics update: 4 monoclonal antibodies products with neutralising activity received scientific opinion to support emergency use before approval and have started rolling review

Currently under rolling review

- Bamlanivimab and etesevimab
- Regdanvimab
- REGN-COV2 (casirivimab / imdevimab)
- Sotrovimab

Marketing authorisation application submitted

- Olumiant *

Authorised for use in the European Union

- Veklury

CoVIg-19 PLASMA ALLIANCE

Working Together to Fight COVID-19 with Immunoglobulin (Ig) Therapy

- Anti-Coronavirus Immunoglobulin (ITAC) Phase 3 Trial
- National Institute of Allergy and Infectious Diseases (NIH)
- Did not meet endpoints of efficacy in hospitalised adults with COVID-19

EMA advises against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials

Share

News 22/03/2021

- In the EU, ivermectin tablets are approved for treating some parasitic worm infestations while ivermectin skin preparations are approved for treating skin conditions such as rosacea.
- Ivermectin is also authorised for veterinary use for a wide range of animal species for internal and external parasites.
- There have been media reports suggesting Ivermectin could be used for the treatment of COVID-19.
- EMA review conclusions do not support its use for COVID-19 outside clinical trials

Source: https://www.ema.europa.eu/en/news/ema-advises-against-use-ivermectin-prevention-treatment-covid-19-outside-randomised-clinical-trials

Inhaled corticosteroids: insufficient evidence on use to treat COVID-19

- Recent study suggests that inhaled budesonide might be an effective treatment of COVID-19 in adults.
- For the ITT population, the primary outcome occurred in 11 (15%) participants in the usual care group and 2 (3%) participants in the budesonide group (difference in proportion 0·123, 95% CI 0·033–0·213; p=0·009).

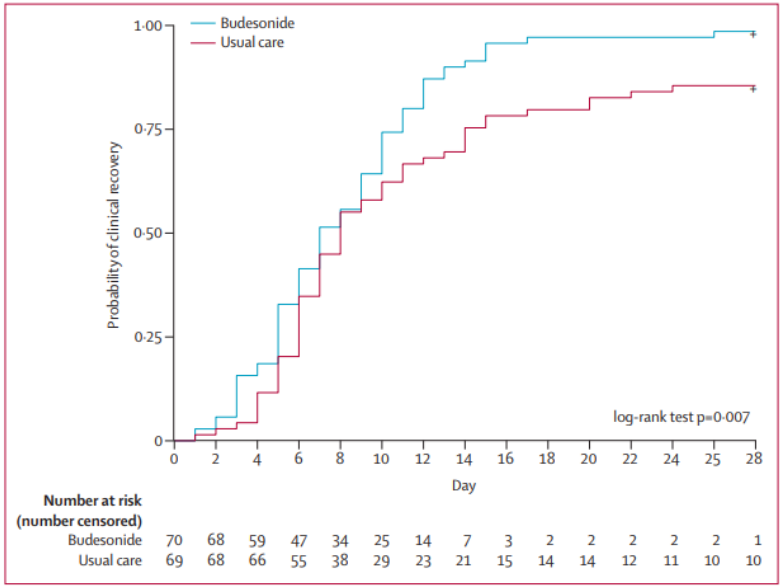
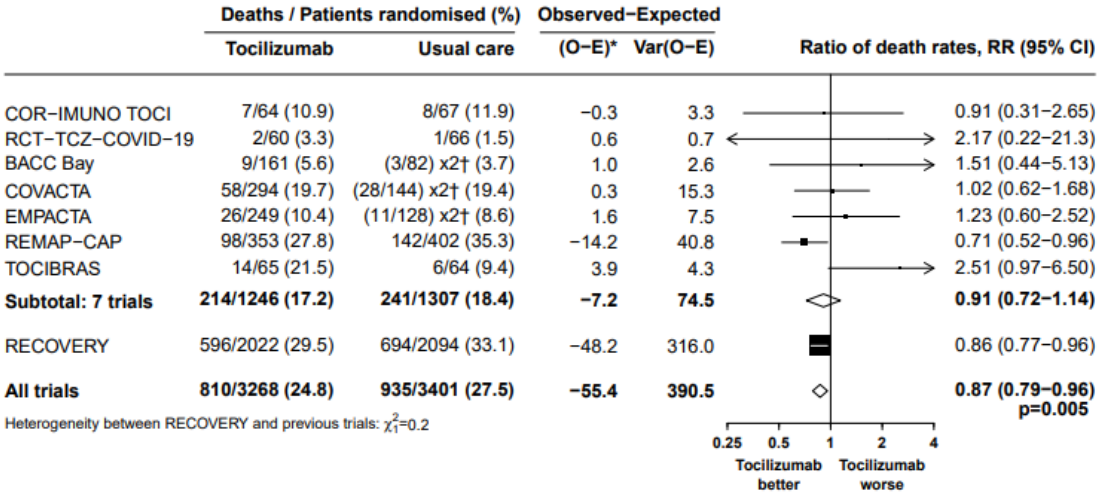


Figure 2: **Time to self-reported clinical recovery of per-protocol population using data censoring for primary outcome**

Source: https://www.thelancet.com/action/showPdf?pii=S2213-2600%2821%2900160-0

Meta-analysis of studies on Tocilizumab

- In hospitalised COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes.
- These benefits were seen regardless of the amount of respiratory support and were additional to the benefits of systemic corticosteroids.



	Deaths / Patients randomised (%)		Observed−Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O−E)*	Var(O−E)	
COR−IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	−0.3	3.3	0.91 (0.31−2.65)
RCT−TCZ−COVID−19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22−21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44−5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62−1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60−2.52)
REMAP−CAP	98/353 (27.8)	142/402 (35.3)	−14.2	40.8	0.71 (0.52−0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97−6.50)
Subtotal: 7 trials	**214/1246 (17.2)**	**241/1307 (18.4)**	**−7.2**	**74.5**	**0.91 (0.72−1.14)**
RECOVERY	596/2022 (29.5)	694/2094 (33.1)	−48.2	316.0	0.86 (0.77−0.96)
All trials	**810/3268 (24.8)**	**935/3401 (27.5)**	**−55.4**	**390.5**	**0.87 (0.79−0.96) p=0.005**

Heterogeneity between RECOVERY and previous trials: χ^2_1=0.2

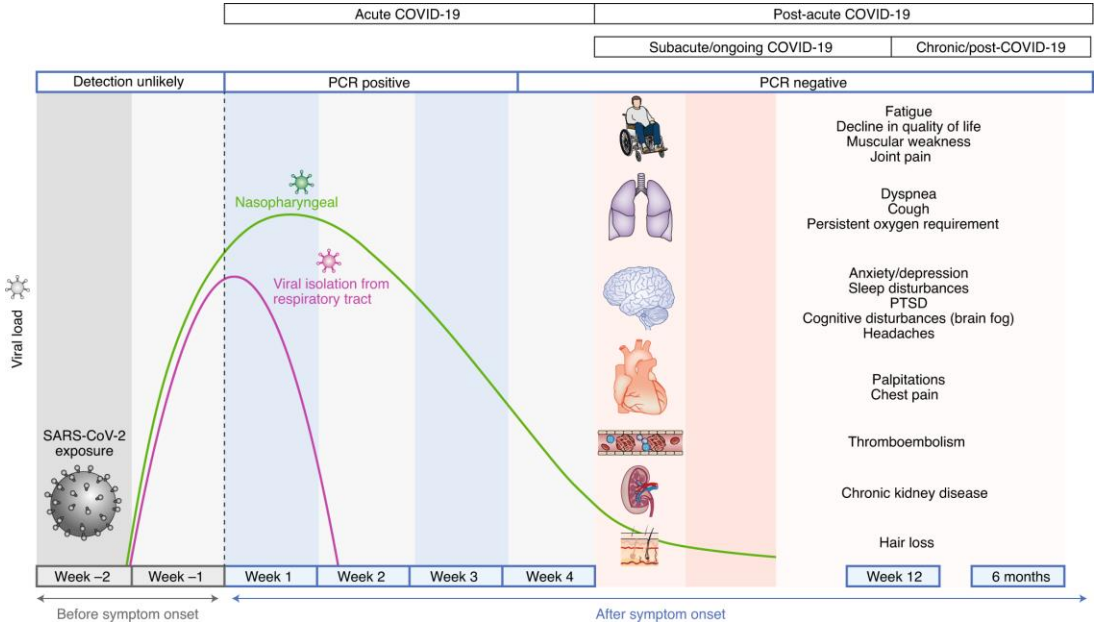
0.25 0.5 1 2 4

Tocilizumab better | Tocilizumab worse

Source: https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2900676-0

Long-Covid development

- Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms.
- Post-acute COVID-19 (long-Covid) is defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms.



Source: https://www.nature.com/articles/s41591-021-01283-z

Observational study on reinfection

- A population-level study conducted in Denmark in 2020 assessed the protection against reinfection with SARS-CoV-2 among 3 million PCR-tested individuals.
- Table shows protection by sex, age group, and time since first infection.

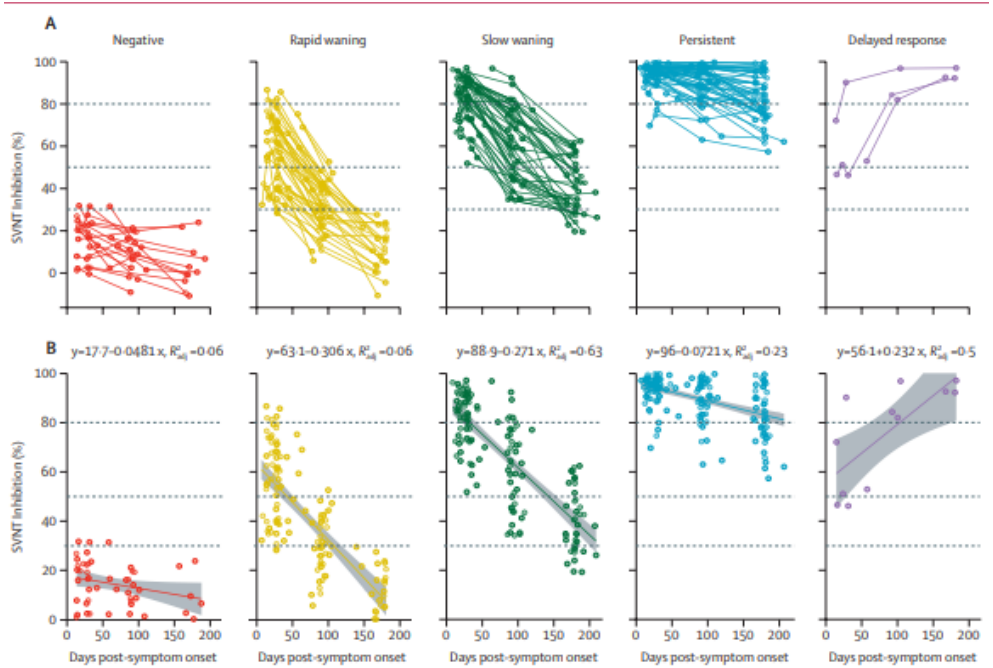
	Number of infections during follow-up		Infection rate*		Adjusted rate ratio (95% CI)†	Estimated protection (95% CI)	p value‡
	Exposed individuals	Unexposed individuals	Exposed individuals	Unexposed individuals			
Overall	138	53 991	5·64	30·94	0·212 (0·179–0·251)	78·8% (74·9–82·1)	..
Sex							
Female	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.

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

COVID-19 immunity study: duration of immunity and antibody response

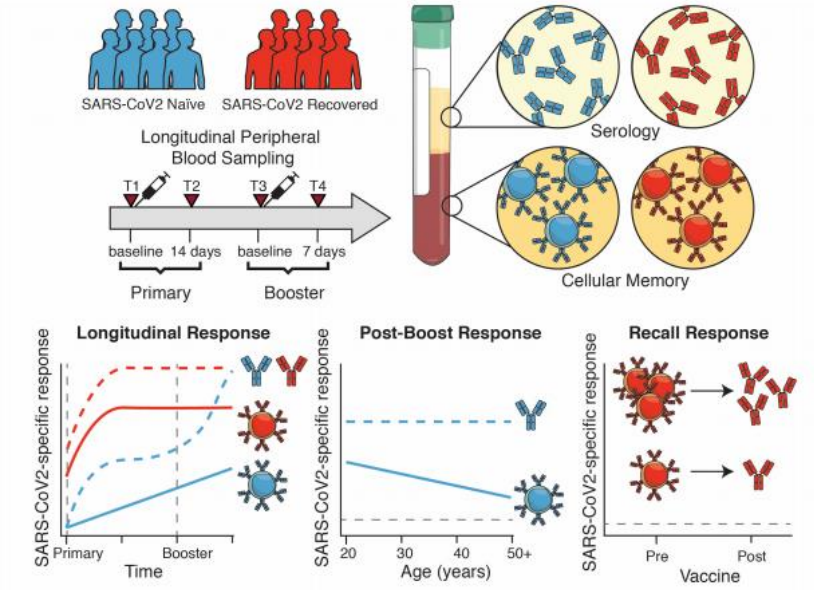
- Neutralising antibody response dynamics in patients who have recovered from COVID-19 vary greatly, and prediction of immune longevity can only be accurately determined at the individual level.



Source: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00025-2/fulltext

Immune responses after mRNA vaccination

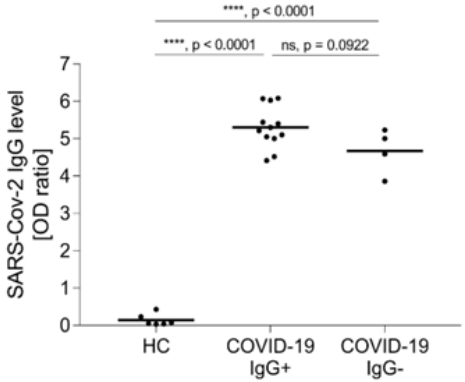
- Longitudinal Analysis Reveals Distinct Antibody and Memory B Cell Responses in SARS-CoV2 Naïve and Recovered Individuals Following mRNA Vaccination

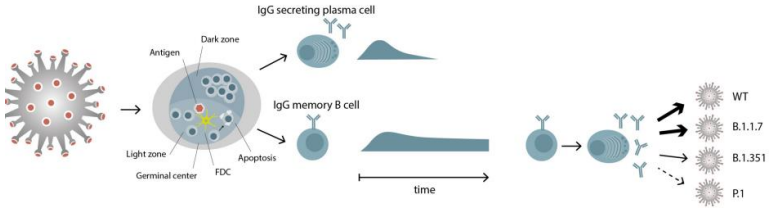


Source: https://www.medrxiv.org/content/10.1101/2021.03.03.21252872v1

Detecting past Covid19 infection using memory-b-cells

- Memory-B-cell differentiation into antibody-producing cells is a more sensitive method for detecting previous infection than measuring serum antibodies.
- Circulating SARS-CoV-2 IgG memory B cells persist, even in the absence of specific serum IgG; produce neutralizing antibodies; and show differential cross-reactivity to emerging variants of concern.





Source: https://www.medrxiv.org/content/10.1101/2021.05.15.21257210v1

Vaccine updates

Currently under rolling review

- CVnCoV
- NVX-CoV2373
- Sputnik V (Gam-COVID-Vac)
- COVID-19 Vaccine (Vero Cell) Inactivated

Marketing authorisation application submitted

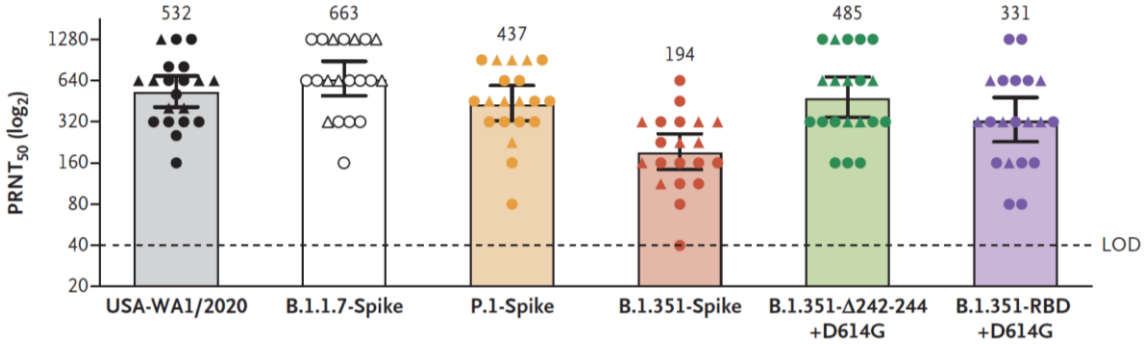
No marketing authorisation applications currently under evaluation

Authorised for use in the European Union

- Comirnaty
- COVID-19 Vaccine Moderna
- Vaxzevria (previously COVID-19 Vaccine AstraZeneca)
- COVID-19 Vaccine Janssen

BioNTech/Pfizer vaccine and virus variants

- In a randomized, placebo-controlled clinical trial involving approximately 44,000 participants, immunization conferred 95% efficacy.
- The figure shows the immune response of the vaccine to different SARS-CoV-2 variants.
- The vaccine showed a response to all variants.



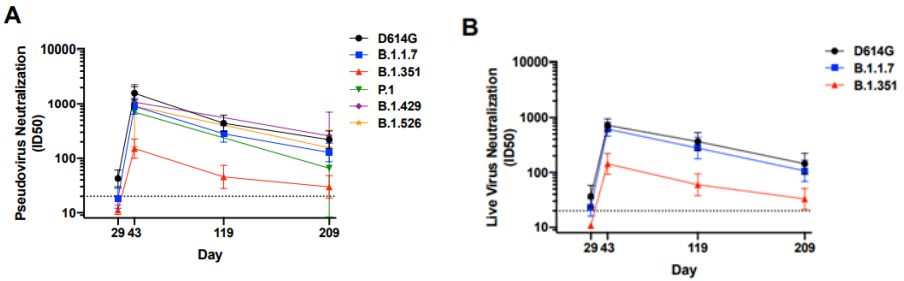
USA-WA1/2020 – wild type; B.1.1.7-Spike – UK variant; P.1-Spike – Brazilan variant; B.1.351-spike – South African variant

Source: https://www.nejm.org/doi/full/10.1056/NEJMc2102017

Moderna vaccine and virus variants

- At the peak of response to the second dose, all subjects had robust responses to all variants.
- Binding and functional antibodies against variants persisted in most subjects, albeit at low levels, for 6 months after the primary series of the vaccine.

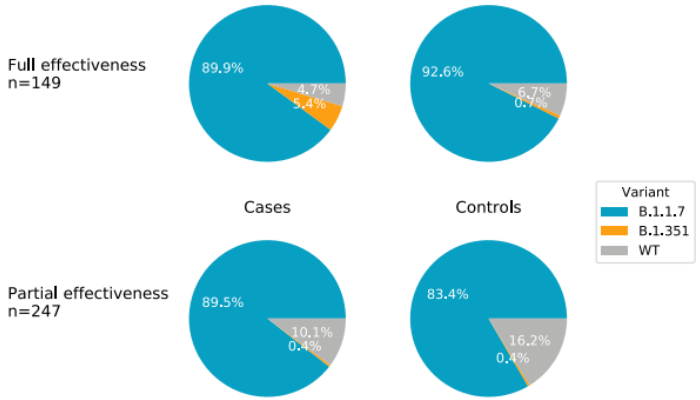
Assay	Variant	% of sera with detectable antibodies			
		Day 29	Day 43	Day 119	Day 209
Pseudovirus Neutralization	D614G	83%	100%	100%	100%
	B.1.1.7	33%	100%	100%	96%
	B.1.351	8%	100%	71%	54%
	P.1	*nt*	100%	*nt*	85%
	B.1.429	*nt*	100%	*nt*	100%
	B.1.526	*nt*	100%	*nt*	88%
Live Virus FRNT Neutralization	D614G	67%	100%	100%	100%
	B.1.1.7	54%	100%	100%	88%
	B.1.351	8%	100%	79%	58%

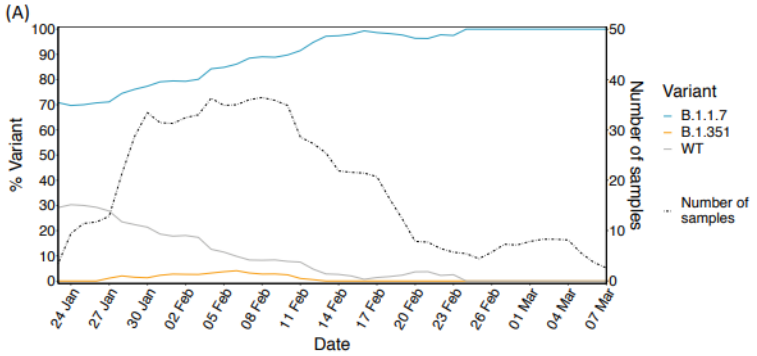


Source: https://www.biorxiv.org/content/10.1101/2021.05.13.444010v1

Evidence for increased breakthrough rates of SARS-CoV-2 variants in individuals vaccinated with Pfizer-BioNTech

- The study suggests that vaccine breakthrough infection may be more frequent with variants of concern.
- However, incidence remains low and vaccine effectiveness remains high among those fully vaccinated.





Source: https://www.medrxiv.org/content/10.1101/2021.04.06.21254882v2

Effectiveness of COVID-19 vaccines against the Indian variant

- The study showed high levels of vaccine effectiveness against symptomatic disease after two doses.
- These estimates were only modestly lower than vaccine effectiveness against the B.1.1.7 variant.

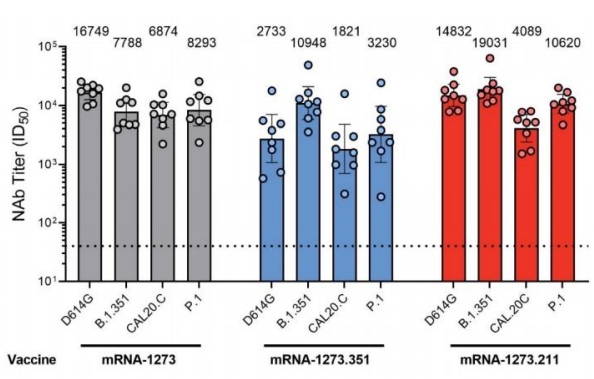
Table 2. Vaccine effectiveness against S-gene target negative (B.1.1.7) and S-gene target positive (B.1.617.2)

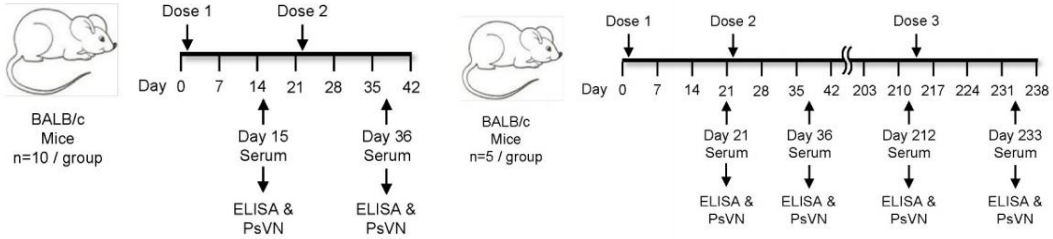
Vaccination status	Test negative controls	B.1.1.7 or S-gene target negative			B.1.617.2 or S-gene target positive		
		cases	cases:controls	aVE(%)	cases	cases:controls	aVE(%)
Unvaccinated	58253	4891	0.084	base	695	0.012	base
Any vaccine							
Dose 1	32703	1481	0.045	51.1 (47.3 to 54.7)	279	0.009	33.5 (20.6 to 44.3)
Dose 2	8483	74	0.009	86.8 (83.1 to 89.6)	27	0.003	80.9 (70.7 to 87.6)
BNT162b2							
Dose 1	7036	344	0.049	49.2 (42.6 to 55.0)	49	0.007	33.2 (8.3 to 51.4)
Dose 2	6412	28	0.004	93.4 (90.4 to 95.5)	13	0.002	87.9 (78.2 to 93.2)
ChAdOx1							
Dose 1	25667	1137	0.044	51.4 (47.3 to 55.2)	230	0.009	32.9 (19.3 to 44.3)
Dose 2	2071	46	0.022	66.1 (54.0 to 75.0)	14	0.007	59.8 (28.9 to 77.3)

Source: [Effectiveness of COVID-19 vaccines against the B.1.617.2 variant (khub.net)]

Variant SARS-CoV-2 mRNA vaccines under development

- A primary vaccination series of mRNA-1273.351 was effective at increasing neutralizing antibody titers against the B.1.351 lineage.
- mRNA-1273.211 was most effective at providing broad cross-variant neutralization in mice.
- Both mRNA-1273.351 and mRNA-1273.211 are currently being evaluated in additional pre-clinical challenge models and in phase 1/2 clinical studies.

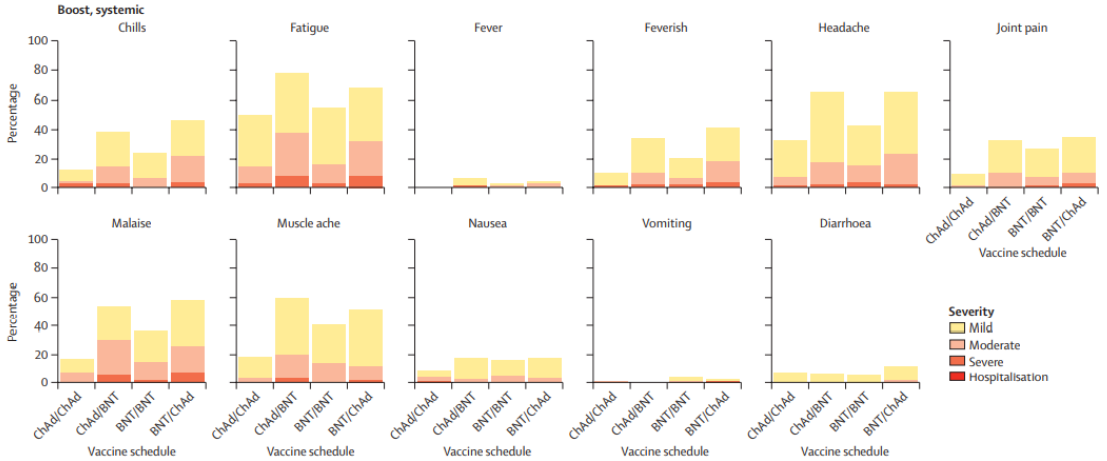




Source: https://doi.org/10.1101/2021.04.13.439482

Heterologous prime-boost – vaccinating with different vaccines

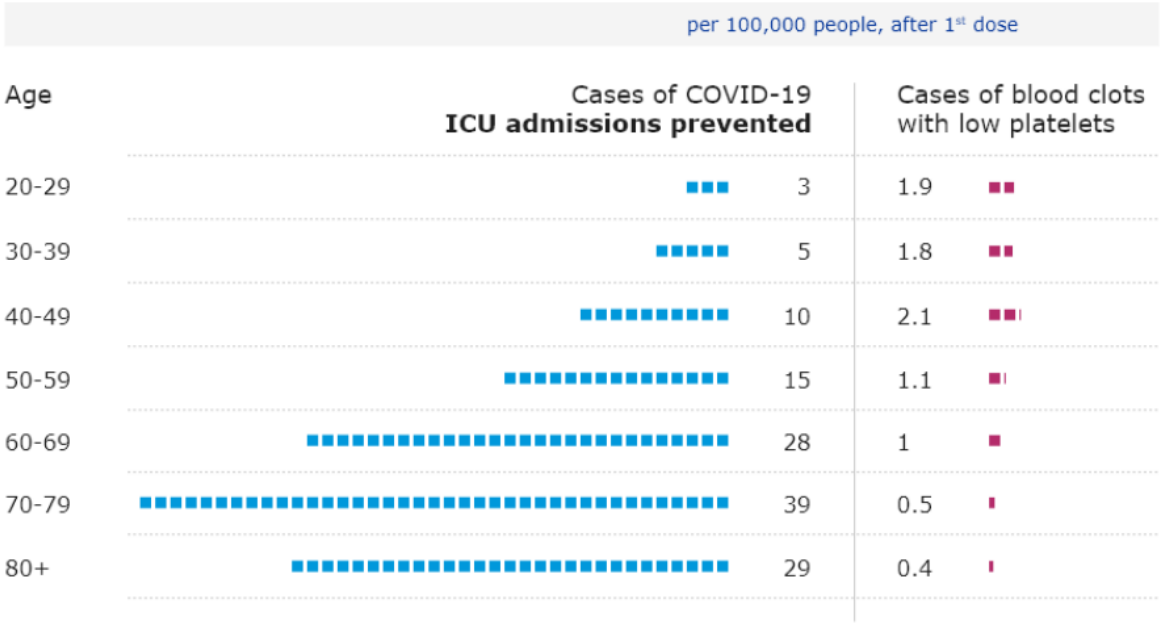
- Com-COV is a UK multi-centre, participant-masked, randomised heterologous prime-boost COVID-19 vaccination study comparing all four permutations of the Astra Zeneca and Pfizer-BioNTech vaccines.



Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01115-6/fulltext

Risk contextualisation of vaccination with Vaxzevria

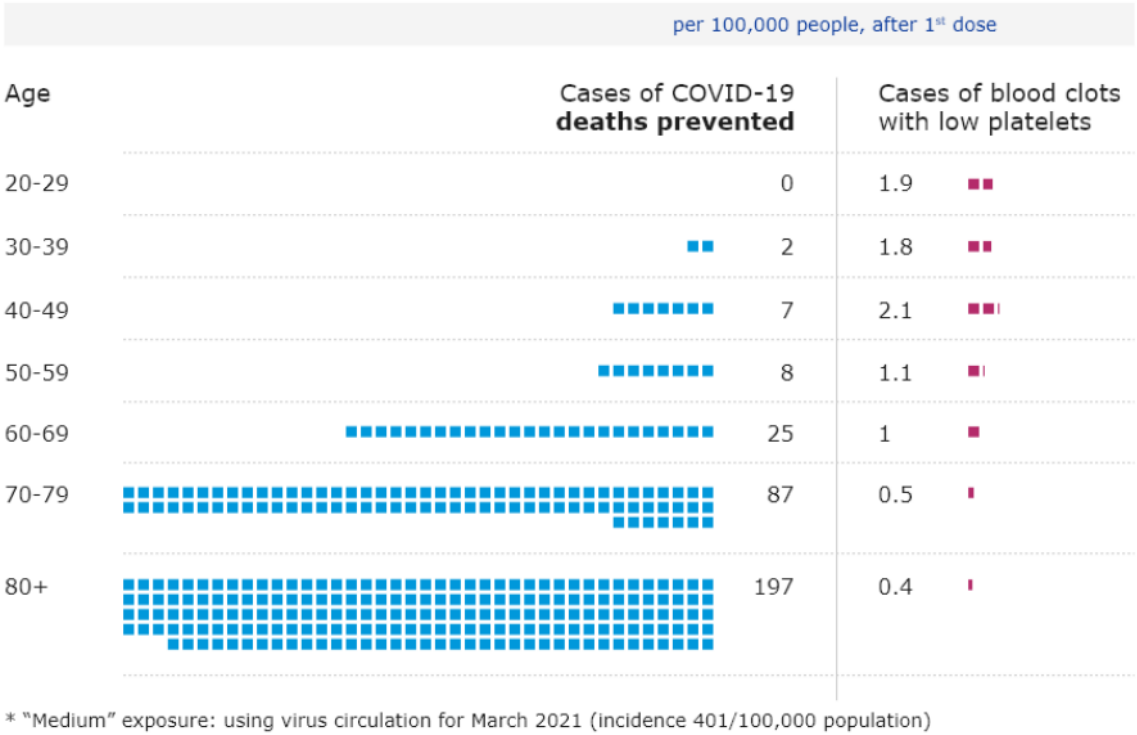
Medium infection rate*



Source: https://www.ema.europa.eu/en/documents/chmp-annex/annex-vaxzevria-art53-visual-risk-contextualisation_en.pdf

Risk contextualisation of vaccination with Vaxzevria

Medium infection rate*

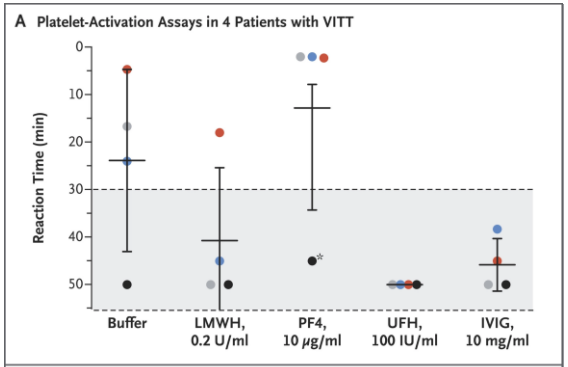


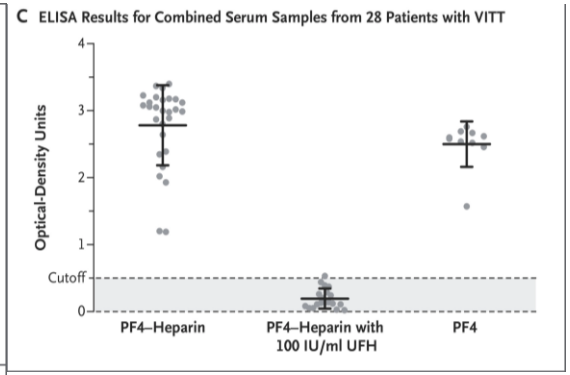
* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)

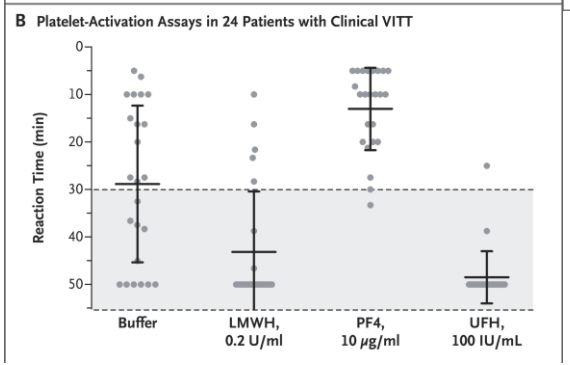
Source: https://www.ema.europa.eu/en/documents/chmp-annex/annex-vaxzevria-art53-visual-risk-contextualisation_en.pdf

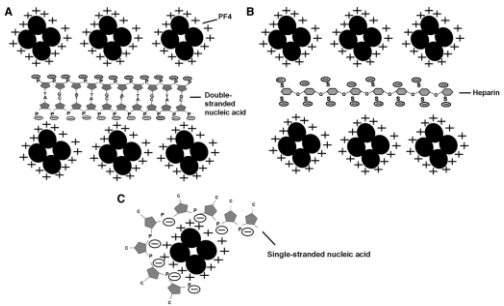
Anti-platelet factor 4 (PF4)/polyanion antibody complexes formation

- Interactions between the vaccine and platelets or between the vaccine and PF4 could play a role in pathogenesis.
- One possible trigger of these PF4-reactive antibodies could be free DNA in the vaccine.
- DNA and RNA form multimolecular complexes with PF4, which bind antibodies from patients with heparin-induced thrombocytopenia and also induce antibodies against PF4–heparin in a murine model.



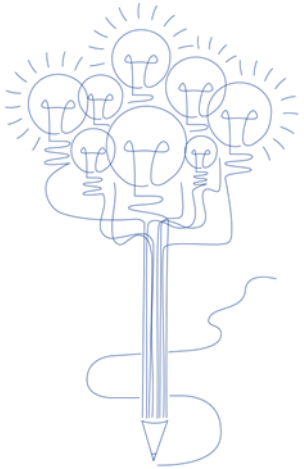






Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3709655/

Summary of activities



194 therapeutics in discussion with EMA

56 vaccines identified for interaction

Rapid scientific advice proceeding for advanced vaccines and therapeutics (89 completed – 15 in the pipeline)

Timing of vaccines third dose, variant vaccines development

Second generation vaccines and options for demonstration of efficacy

Discussions ongoing with Curevac, Sinovac and Gamaleya for EU approval

Clinical networks for vaccines, VACCELARATE and therapeutics, EU RESPONSE