Episode 280 Long Covid, reinfection and hybrid immunity

Dear colleagues,

A short episode, easily “digestible”, based on a re-arrangement of hint by Patrick Smits

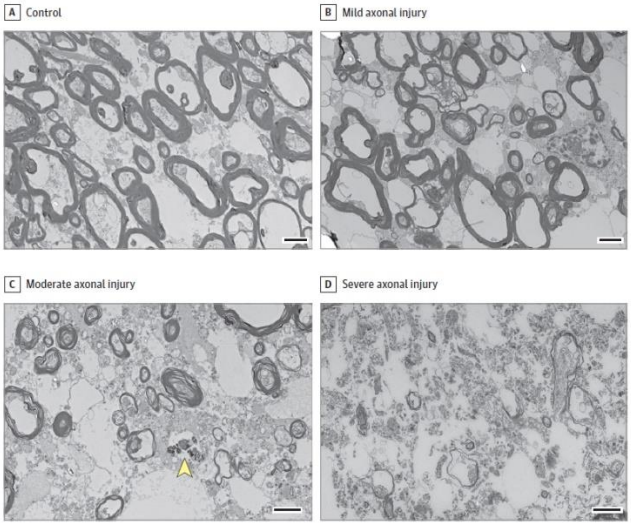
See

LONG COVID

Ep 280-1: Cheng-Ying Ho, JAMA Neurology: **Olfactory damage as reason for anosmia/ageusia?**

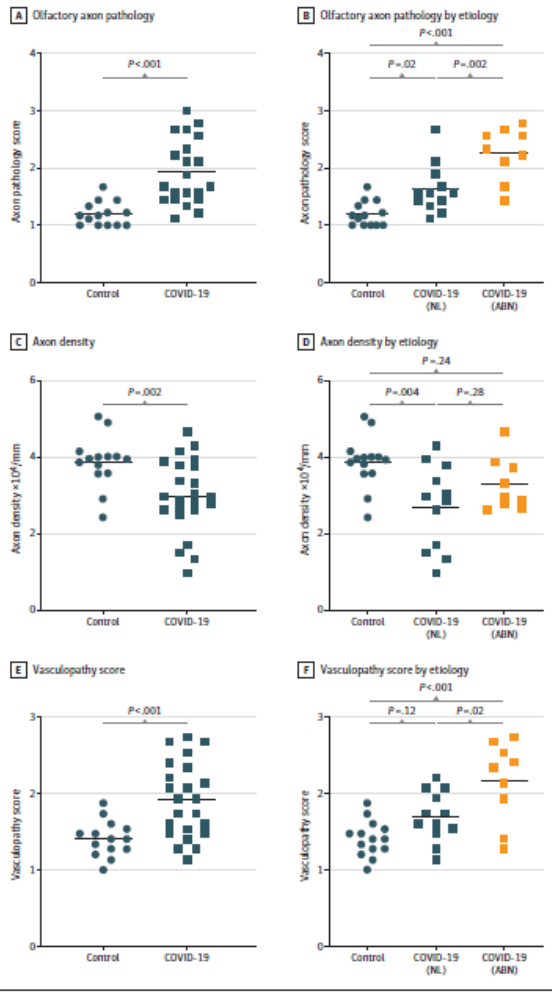
A controlled post-mortem study found that COVID-19 infection is associated with **axon injuries and microvasculopathy in olfactory tissue**, suggesting that this is the basis for severe and even permanent olfactory dysfunction in COVID-19 infection.

Figure 1. Electron Micrographs Demonstrate a Spectrum of Olfactory Axonal Injuries in Patients With COVID-19



A spectrum of axonal degeneration including organelle aggregation, myelin sheath disintegration, myelin sheath vacuolization, and myelin debris can be seen in COVID-19 cases. Scale bars represent 2 µm. The arrowhead indicates myelin debris.

Figure 3. Olfactory Axon Pathology, Axon Losses, and Microvasculopathy Are Significantly Worse in Patients With COVID-19 Than Control Individuals



A, C, and E, Comparisons between individuals with COVID-19 and control individuals (*t* test). Individuals with COVID-19 are further divided into smell normal (NL) and smell abnormal (ABN) groups for the comparisons in B, D, and F (1-way analysis of variance).

Ep 280-2: Ballering Lancet 6 August 2022: Large cohort of > 4000 COVID and > 8000 matched controls between April 2020 and August 2021 shows **excess of 12.7 % of post COVID symptoms** (after 90-150 days).

	Presence of symptom of at least moderate severity		Substantial increase in symptom severity to at least moderate severity	
	Controls (n=4353)	COVID-19-positive participants (n=1942)	Controls (n=4130)	COVID-19-positive participants (n=1782)
Ageusia or anosmia	37 (0·8%)	158 (8·1%)*	17 (0·4%)	135 (7·6%)*
Difficulties with breathing	38 (0·9%)	68 (3·5%)*	21 (0·5%)	43 (2·4%)*
Chest pain	44 (1·0%)	63 (3·2%)*	24 (0·6%)	43 (2·4%)*
Pain when breathing	13 (0·3%)	20 (1·0%)*	<10 (<0·2%)	16 (0·9%)*
Lump in throat	59 (1·4%)	61 (3·1%)*	24 (0·6%)	42 (2·4%)*
Heavy arms or legs	130 (3·0%)	126 (6·5%)*	65 (1·6%)	75 (4·2%)*
General tiredness	159 (3·7%)	136 (7·0%)*	87 (2·1%)	88 (4·9%)*
Painful muscles	378 (8·7%)	262 (13·5%)*	134 (3·2%)	130 (7·3%)*
Tingling extremities	145 (3·3%)	98 (5·0%)*	65 (1·6%)	52 (2·9%)*
Fever	19 (0·4%)	16 (0·8%)	18 (0·4%)	12 (0·7%)
Wet cough	83 (1·9%)	58 (3·0%)	40 (1·0%)	28 (1·6%)
Dry cough	81 (1·9%)	50 (2·6%)	43 (1·0%)	28 (1·6%)
Headache	239 (5·5%)	166 (8·5%)*	111 (2·7%)	76 (4·3%)
Itchy eyes	143 (3·3%)	96 (4·9%)*	78 (1·9%)	51 (2·9%)
Feeling hot and cold alternately	155 (3·6%)	112 (5·8%)*	70 (1·7%)	63 (2·5%)*
Sore throat	84 (1·9%)	48 (2·5%)	51 (1·2%)	29 (1·6%)
Runny nose	217 (5·0%)	110 (5·7%)	94 (2·3%)	50 (2·8%)
Nausea	128 (2·9%)	72 (3·7%)	74 (1·8%)	37 (2·1%)
Sneezing	210 (4·8%)	101 (5·2%)	74 (1·9%)†	35 (2·1%)‡
Back pain	413 (9·5%)	210 (10·8%)	182 (4·4%)	88 (4·9%)
Stomach pain	108 (2·5%)	53 (2·7%)	58 (1·4%)	25 (1·4%)
Dizziness	93 (2·1%)	46 (2·4%)	56 (1·4%)	25 (1·4%)
Diarrhoea	80 (1·8%)	38 (2·0%)	52 (1·3%)	19 (1·1%)
Total	1275 (29·3%)	790 (40·7%)*	749 (18·1%)	526 (29·6%)*

Data are n (%). Symptoms are ordered according to their relative increase in frequency in COVID-19-positive participants compared with controls. A substantial increase in severity was defined as an increase in symptom severity of at least 1 point on the 5-point scale. *p<0·001. †n=3988; sneezing was assessed in 23 surveys instead of 24. ‡n=1704; sneezing was assessed in 23 surveys instead of 24.

Table 2: **Frequencies of participants who had presence of, or a substantial increase to, symptoms of at least moderate severity at 90–150 days after COVID-19 diagnosis or matched timepoint**

Ep 280-3: Lyudmyla Kompaniyets MMWR 5 August 2022 Post-COVID in US children and adolescents March 2020-Jan 2021

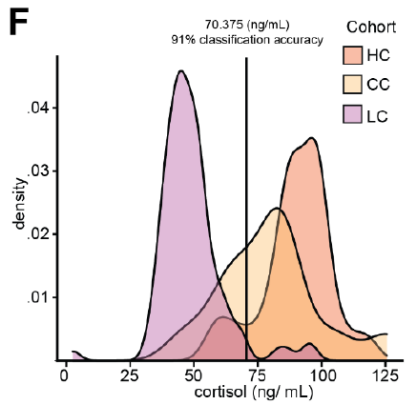
Compared with patients aged 0–17 years without previous COVID-19, those with previous COVID-19 had higher rates of **acute pulmonary embolism (**adjusted hazard ratio = 2.01**), myocarditis and cardiomyopathy** (1.99), **venous thromboembolic event (**1.87), acute and **unspecified renal failure** (1.32), and **type 1 diabetes** (1.23), all of which were rare or uncommon in this study population.

Implication?

COVID-19 prevention strategies, including vaccination for all eligible persons aged ≥6 months, are critical to preventing SARS-CoV-2 infection and subsequent illness, and reducing the public health impact of post-COVID symptoms and conditions among persons aged 0–17 years.

Ep 280-4: Hon Klein 10 August 2022 Distinctive immune profiling in long COVID

Most striking = **low cortisol** levels in long COVID(LC): about half of convalescent covid (CC) and healthy controls (HC)

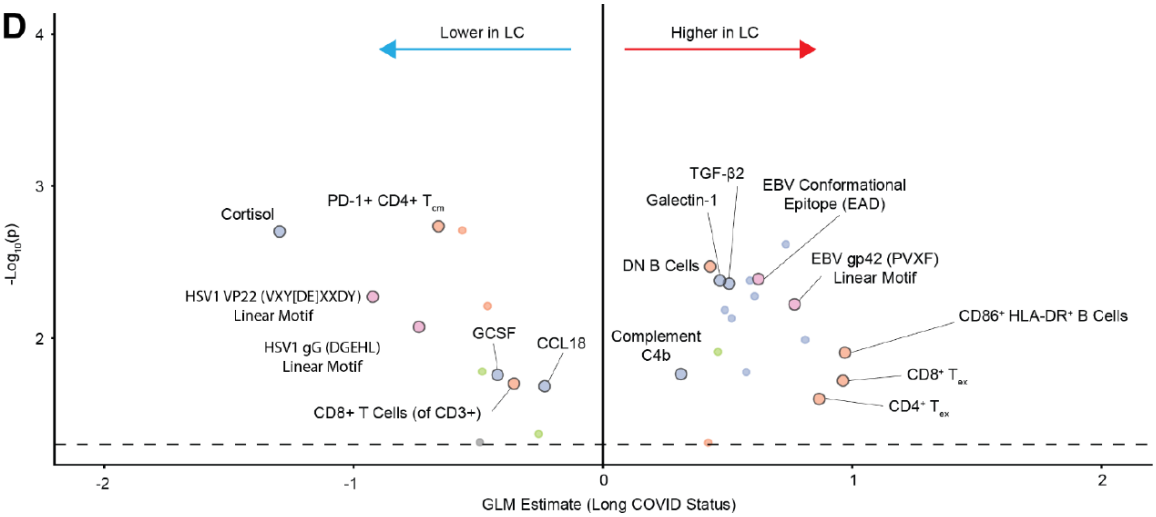


Changes in circulating mononuclear cells:

- increases in non-classical monocytes, activated B cells, double-negative B cells, exhausted T cells, and IL-4/IL-6 secreting CD4 T cells,
- decreases in conventional Dendritic Cells type 1 and central memory CD4 T

Changes in antibodies:

- elevated to SARS-CoV-2 antigen
- elevated to herpes lytic antigens
- NO change in auto-Ab



Suggestive of <u>persistent SARS-CoV-2 antigen</u>, <u>reactivation of latent herpesviruses</u>, and <u>chronic inflammation</u>, but not consistent with auto-immunity.

BREAKTHROUGH, VACCINE and HYBRID Immunity during OMICRON

Ep 280-5: Sharon Tan NEJM 11 August 2022: Effectiveness of BNT162b2 Vaccine against Omicron in Children 5 to 11 Years of Age in Singapore Jan-April 2022

Table 2. Effectiveness of BNT162b2 Vaccine against SARS-CoV-2 Infection and Hospitalization.*

Group	Person-Days at Risk†	Cases of SARS-CoV-2 Infection			Crude Incidence Rate			Vaccine Effectiveness (95% CI)‡		
		All Confirmed Cases§	PCR-Confirmed Cases	Hospitalizations	All Confirmed Cases§	PCR-Confirmed Cases	Hospitalizations	All Confirmed Cases§	PCR-Confirmed Cases	Hospitalizations
		number			*number of confirmed infections/ 1 million person-days at risk*			*percent*		
Unvaccinated	5,118,468	16,909	2425	146	3303.5	473.8	30.0	Reference	Reference	Reference
Partially vaccinated	5,340,205	16,006	2089	100	2997.3	391.2	19.1	13.6 (11.7–15.5)	24.3 (19.5–28.9)	42.3 (24.9–55.7)
Fully vaccinated	7,405,066	20,514	828	42	2770.3	111.8	6.6	36.8 (35.3–38.2)	65.3 (62.0–68.3)	82.7 (74.8–88.2)

* Partial vaccination was defined as at least 1 day after the first dose of vaccine and up to 6 days after the second dose, and full vaccination at least 7 days after the second dose. PCR denotes polymerase chain reaction, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† The total number of person-days at risk for the hospitalization outcome was 4,869,127 in the unvaccinated group, 5,231,353 in the partially vaccinated group, and 6,338,164 in the fully vaccinated group.
‡ Vaccine effectiveness was calculated as 1 minus the incidence rate ratio. The incidence rate ratio is obtained from the exponentiated coefficients of separate Poisson regressions on all confirmed infections, infections confirmed by means of PCR testing only, and severe infections resulting in hospitalization. The covariates of age (in years), ethnic group (Chinese, Malay, Indian, or other), sex (male or female), housing type (public housing with one or two rooms, three rooms, four rooms, or five rooms; private housing; or other housing), and calendar dates during the study period were included in the regression to control for potential confounding. Vaccine effectiveness in the partially vaccinated and fully vaccinated groups was reported with the unvaccinated group as the reference. Confidence intervals have not been adjusted for multiplicity and should not be used to infer statistical significance.
§ "All confirmed cases" refers to all reported SARS-CoV-2 infections confirmed by PCR testing, rapid antigen testing, or both.

Ep 280-6: Christian Holm SSRN 10 August 2022 **Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron** in Denmark April-June 2022

High protection against BA.5 by hybrid immunity = prior omicron infection in triple-vaccinated individuals, and similar vaccine effectiveness for BA.5 infection as currently for BA.2.

Table 2 Protection against BA.5 and BA.2 infection after a prior positive SARS-CoV-2 PCR test, April to June, 2022, Denmark.

	Cases	Test-negative controls	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Estimated protection, % (95% CI)
	BA.5 cases				**protection against BA.5**
Exposure: prior omicron infection					
Exposed	96 (2.0)	29,832 (18.1)	0.092 (0.075; 0.112)	0.064 (0.052; 0.079)	93.6 (92.1; 94.8)
Unexposed	4,713 (98.0)	134,537 (81.9)	1	1	
Exposure: prior delta infection					
Exposed	41 (0.8)	2,996 (1.5)	0.554 (0.407; 0.755)	0.531 (0.387; 0.730)	46.9 (27.0; 61.3)
Unexposed	4,962 (99.2)	200,953 (98.5)	1	1	
Exposure: prior alpha infection					
Exposed	30 (0.6)	1,702 (1.2)	0.503 (0.350; 0.723)	0.346 (0.238; 0.502)	65.4 (49.8; 76.2)
Unexposed	4,713 (99.4)	134,537 (98.8)	1	1	
	BA.2 cases				**protection against BA.2**
Exposure: prior omicron infection					
Exposed	249 (0.8)	29,832 (18.1)	0.037 (0.033; 0.042)	0.037 (0.033; 0.042)	96.3 (95.8; 96.7)
Unexposed	30,367 (99.2)	134,537 (81.9)	1	1	
Exposure: prior delta infection					
Exposed	101 (0.3)	2,996 (1.5)	0.215 (0.176; 0.262)	0.228 (0.187; 0.278)	77.2 (72.2; 81.3)
Unexposed	31,512 (99.7)	200,953 (98.5)	1		
Exposure: prior alpha infection					
Exposed	99 (0.3)	1,702 (1.2)	0.258 (0.210; 0.316)	0.255 (0.208; 0.313)	74.5 (68.7; 79.2)
Unexposed	30,367 (99.7)	134,537 (98.8)	1	1	

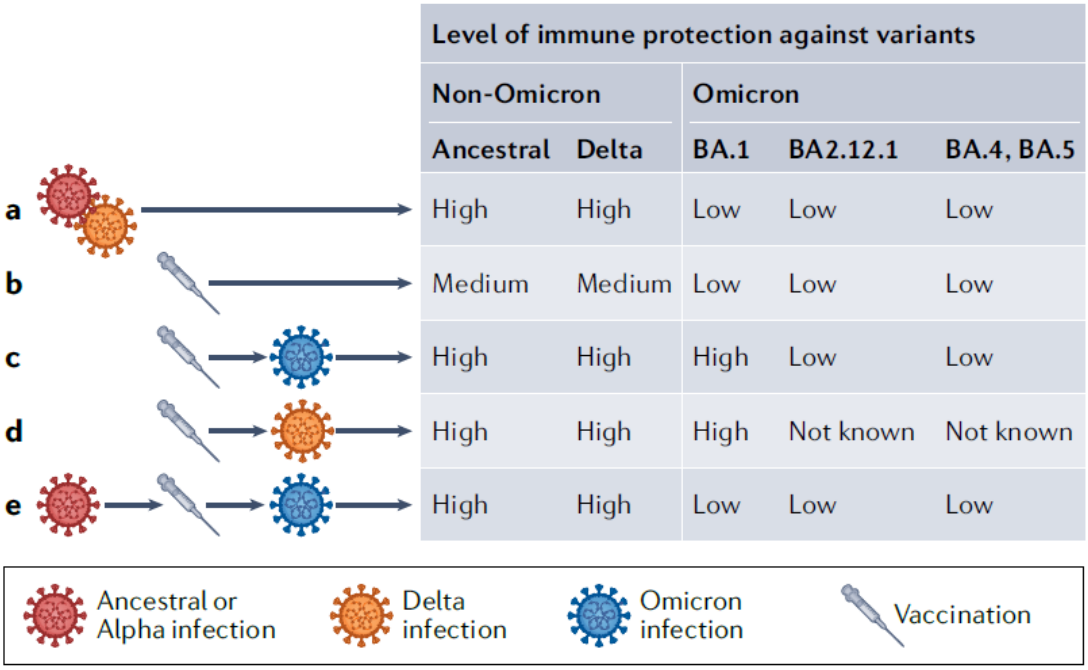
All participants had received 3 mRNA COVID-19 vaccine doses. Cases were infected with either BA5 or BA.2 during the outcome period from April 10, 2022 to June 20, 2022. OR denotes odds ratio; CI denotes confidence interval. Unexposed individuals had no positive PCR tests before the start of follow-up on April 10, 2022. *adjusted for age group, time (week number), sex, region and comorbidity.

BA.5 infection was associated with an increased risk of hospitalization, but low overall

Table 4 Severity of BA.5: risk of hospitalisation after infection, April to June, 2022, Denmark.

Exposure (type of infection)	Hospitalised for COVID-19	Cases not hospitalised[¤]	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Main analysis				
BA.2	487 (1.4)	35,343 (98.6)	1	1
BA.5	87 (1.4)	6,067 (98.6)	1.04 (0.83; 1.31)	1.65 (1.16; 2.34)

Ep 280-7: Suryawanshi Nature Review of Immunology August 2022 **Complex picture of hybrid immunity**



Protection after different immune-conferring events.
a | Emerging Omicron sub- variants escape immunity conferred by infection with non- Omicron SARS- CoV-2 variants.
b | A second dose of mRNA vaccine gives moderate protection for non- Omicron and limited protection against Omicron variants 6–8 months post- vaccination.
c | Hybrid immunity elicited by BA.1 breakthrough infection in vaccinated individuals (2 doses) provides cross-variant protection but causes neutralization escape for newly emerging Omicron variants.
d | Hybrid immunity generated by Delta infection in vaccinated individuals elicits broader protection against non-micron and Omicron (BA.1) variants.
e | Compared with B.1.617.2, immune imprinting generated by infection with Wuhan/B.1.1.7 , vaccination (3 doses) and Omicron reinfection decreases Omicron neutralizing antibodies and T cell recognition, which may increase chances of Omicron reinfection. Consistent with Reynolds et al..

Ep 280-8: Sarah Zhang in the Atlantic: A common language discussion on how long the Coronavirus can keep reinfection us? Well, probably indefinitely….

Best wishes,

Guido