Episode 312: Clinical consequences of COVID and news on vaccines

Dear colleagues,

This short episode will be arranged in two paragraphs: clinical findings on long-term effects of acute COVID and some news about vaccines.

With many thanks to colleagues who shared some of this material (Patrick Smits; Pierre Van Damme…).

See

First a reminder: Episode 312-0 = COVID highlights during first 2 years by the Royal Society of Medicine

Par 1 New clinical findings on long term effects of COVID

Ep 312-1: Edlows JAMA Network Pediatrics: Overall **6 % neurodevelopmental problems** at 1 year in babies from positive mothers **versus 3 %** if the mother had not been infected. More risk if infection during **third trimester**.

It is a retrospective study in 7700 babies that needs confirmation.

Ep 312-2: Falko Tesch medRxiv 26 Jan 2023: **42% increased risk of new-onset autoimmune diseases** after acute SARS-CoV-2 in Germany

Table 1 Characteristics of COVID-19 and control cohort after matching.

Category	n COVID-19	Percent COVID-19	n Controls	Percent Control
Total	641,407	100	1,907,992	100
Sex				
Male	273,868	42.7	1,092,873	42.7
Female	367,539	57.3	815,119	57.3
Age				
0-17	60,535	9.4	181,210	9.5
18-64	476,085	74.2	1,423,132	74.6
65-79	60,889	9.5	180,060	9.4
80+	43,898	6.8	123,590	6.5
Severity of COVID-19				
Outpatient	590,204	92.0	-	-
Hospital	40,846	6.4	-	-
ICU/Ventilation	10,357	1.6	-	-
Autoimmunity				
Any preexisting autoimmune disease	76,518	11.9	237,035	12.4
First onset of autoimmune disease	6,489	1.1	13376	0.8
Additional autoimmune disease with preexisting autoimmunity	1744	2.3	3324	1.4

Depending on the number of matched controls per individual with COVID-19, each entered the analysis with a weight between 1/3 and 1.

Table 2 shows a long list of auto-immune diseases with increased incidence after COVID, ranging from Hashimoto's thyroiditis to rheumatoid arthritis. The highest RR is for Wegener > Behcet > Guillain-Barré > sarcoidosis > thrombocytopenia purpura > arteritis temporalis …

People with severe COVID have a clearly elevated risk on auto-immunity.

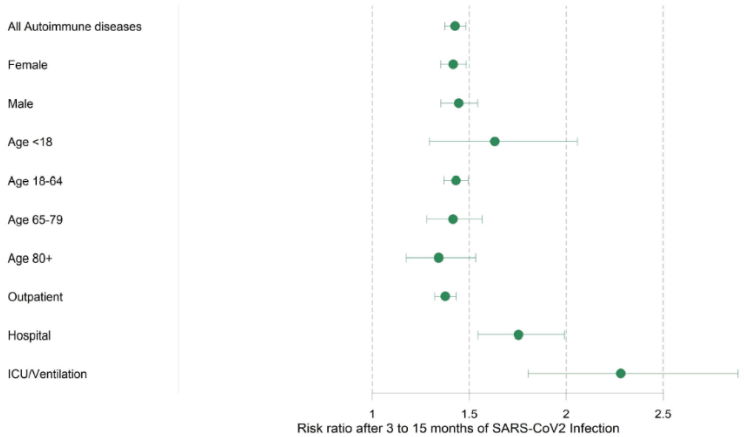
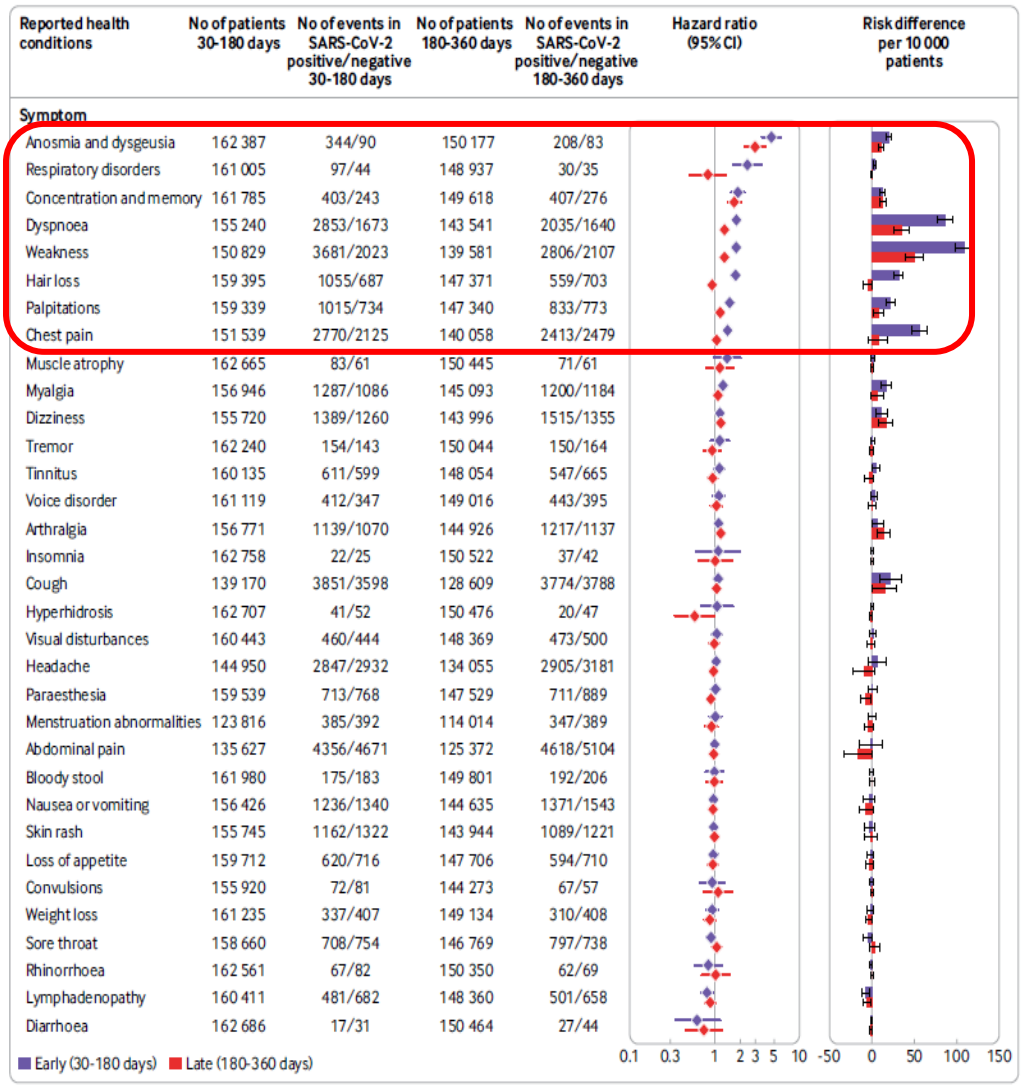


Figure 2 Forest plot comparing incident rate ratios for any first-onset autoimmune disease 3 to 15 months after SARS-CoV-2 infection by subgroup. The severity of COVID-19 was operationalized as only outpatient care, usual hospital care and ICU/ventilation-intensive care unit and mechanical ventilation.

Ep 312-3: Mizrak Barak BMJ Jan 2023: Long COVID in a large Israeli cohort (with test-negative controls)

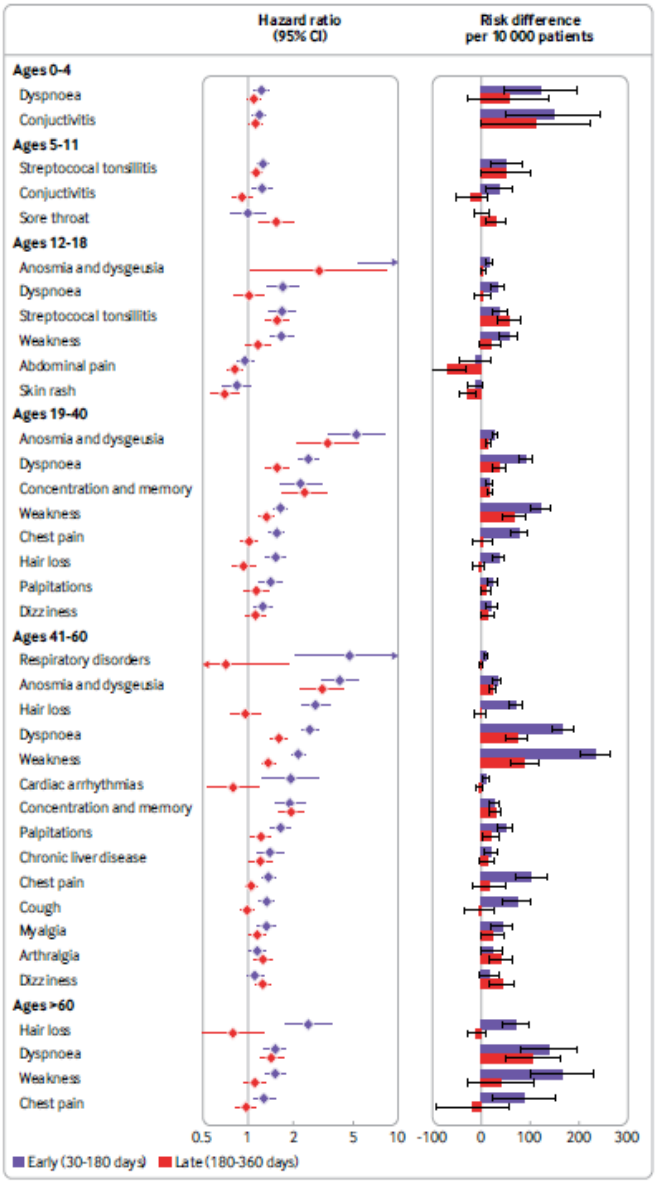
Main findings:

- Patients with mild covid-19 had an increased risk for **a small number of health outcomes**, most of which resolved within a year from diagnosis



Reported health conditions	No of patients 30-180 days	No of events in SARS-CoV-2 positive/negative 30-180 days	No of patients 180-360 days	No of events in SARS-CoV-2 positive/negative 180-360 days
Symptom				
Anosmia and dysgeusia	162 387	344/90	150 177	208/83
Respiratory disorders	161 005	97/44	148 937	30/35
Concentration and memory	161 785	403/243	149 618	407/276
Dyspnoea	155 240	2853/1673	143 541	2035/1640
Weakness	150 829	3681/2023	139 581	2806/2107
Hair loss	159 395	1055/687	147 371	559/703
Palpitations	159 339	1015/734	147 340	833/773
Chest pain	151 539	2770/2125	140 058	2413/2479
Muscle atrophy	162 665	83/61	150 445	71/61
Myalgia	156 946	1287/1086	145 093	1200/1184
Dizziness	155 720	1389/1260	143 996	1515/1355
Tremor	162 240	154/143	150 044	150/164
Tinnitus	160 135	611/599	148 054	547/665
Voice disorder	161 119	412/347	149 016	443/395
Arthralgia	156 771	1139/1070	144 926	1217/1137
Insomnia	162 758	22/25	150 522	37/42
Cough	139 170	3851/3598	128 609	3774/3788
Hyperhidrosis	162 707	41/52	150 476	20/47
Visual disturbances	160 443	460/444	148 369	473/500
Headache	144 950	2847/2932	134 055	2905/3181
Paraesthesia	159 539	713/768	147 529	711/889
Menstruation abnormalities	123 816	385/392	114 014	347/389
Abdominal pain	135 627	4356/4671	125 372	4618/5104
Bloody stool	161 980	175/183	149 801	192/206
Nausea or vomiting	156 426	1236/1340	144 635	1371/1543
Skin rash	155 745	1162/1322	143 944	1089/1221
Loss of appetite	159 712	620/716	147 706	594/710
Convulsions	155 920	72/81	144 273	67/57
Weight loss	161 235	337/407	149 134	310/408
Sore throat	158 660	708/754	146 769	797/738
Rhinorrhoea	162 561	67/82	150 350	62/69
Lymphadenopathy	160 411	481/682	148 360	501/658
Diarrhoea	162 686	17/31	150 464	27/44

- **Children** (below 11) **had fewer outcomes**, which mostly resolved in the late period, highest risk in mid-age group; sex had a minor effect on risk of outcomes.



- Findings remained consistent across SARSCoV-2 variants: between March 2020-Oct 2021 (WT to Delta, omicron not included)

- Breakthrough infections (after vaccination): lower risk for dyspnoea and similar risk for other outcomes was observed in vaccinated patients with BTI compared with unvaccinated patients

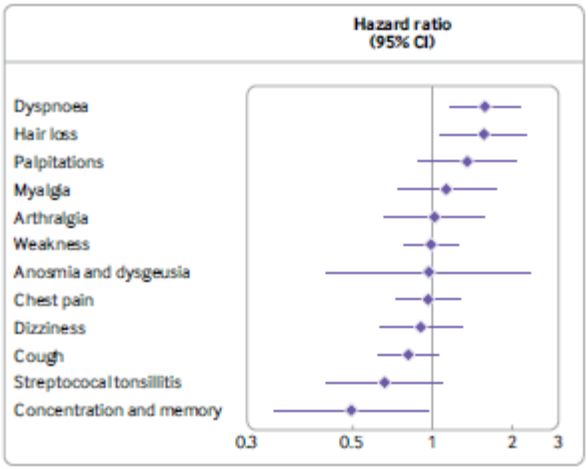


Fig 7 | Hazard ratios (with 95% confidence intervals) for long covid health outcomes 30-90 days after infection for unvaccinated versus vaccinated patients. Health outcomes that were significantly related to SARS-CoV-2 infection were assessed in vaccinated and unvaccinated patients (supplementary tables 8a-b)

Ep 312-4: Lucie Bernard-Raichon Nat Med Nov 2022: Severe COVID causes gut microbiome **dysbiosis** and secondary **systemic infections**, because of epithelial damage and bacterial translocation

It is a complex paper that shows a **decrease of diversity**, with overgrowth of the family of **Akkermansiaceae** (= mucin-degrading bacteria) both in experimentally infected mice and hospitalized patients.

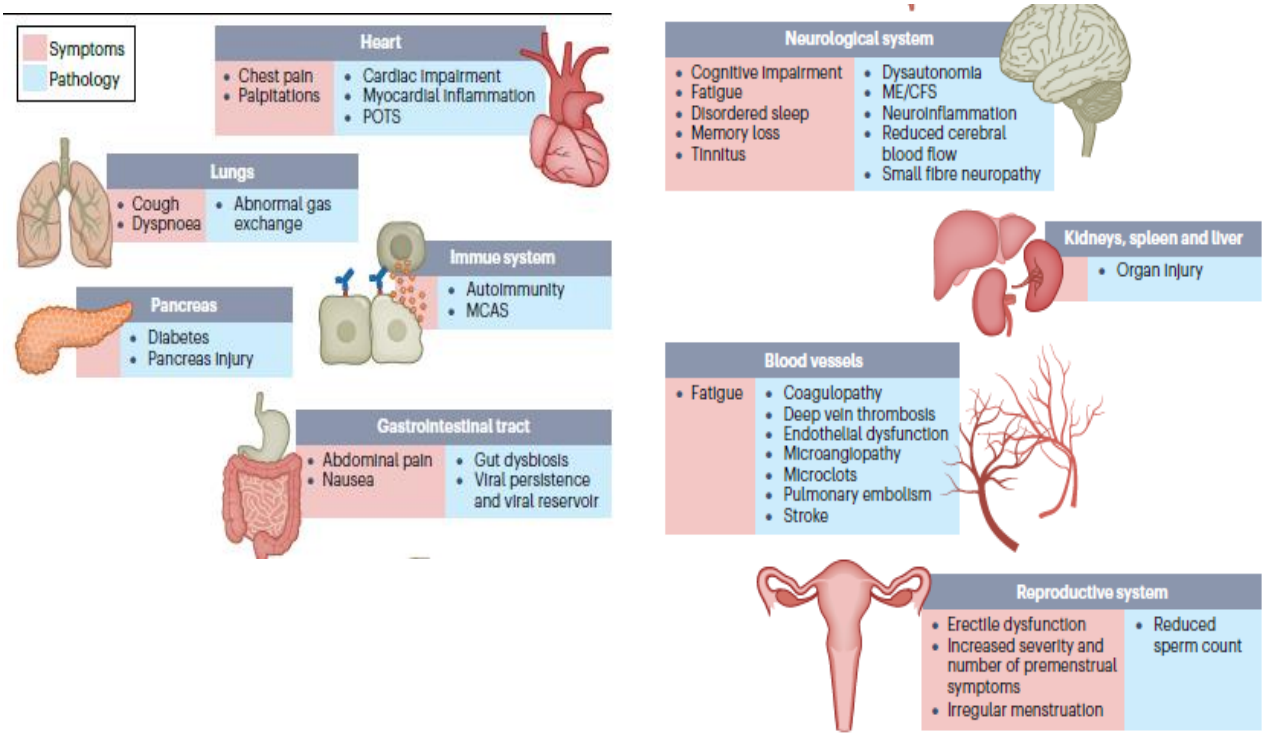
There is an associated **increase of mucin-producing Globlet cells and a decrease of Paneth cells**, which produce anti-microbial and anti-viral factors such as lysozyme.

In patients, microorganisms from the dysbiotic gut microbiome translocate into the blood with **dangerous systemic infections of drug-resistant microbes** , plausibly due to a combination of the immunocompromising effects of the viral infection and antibiotic-driven depletion of commensal gut microbes with loss of gut barrier integrity.

These findings are **reminiscent** of AIDS patients, chemotherapy for cancer and inflammatory bowel disease

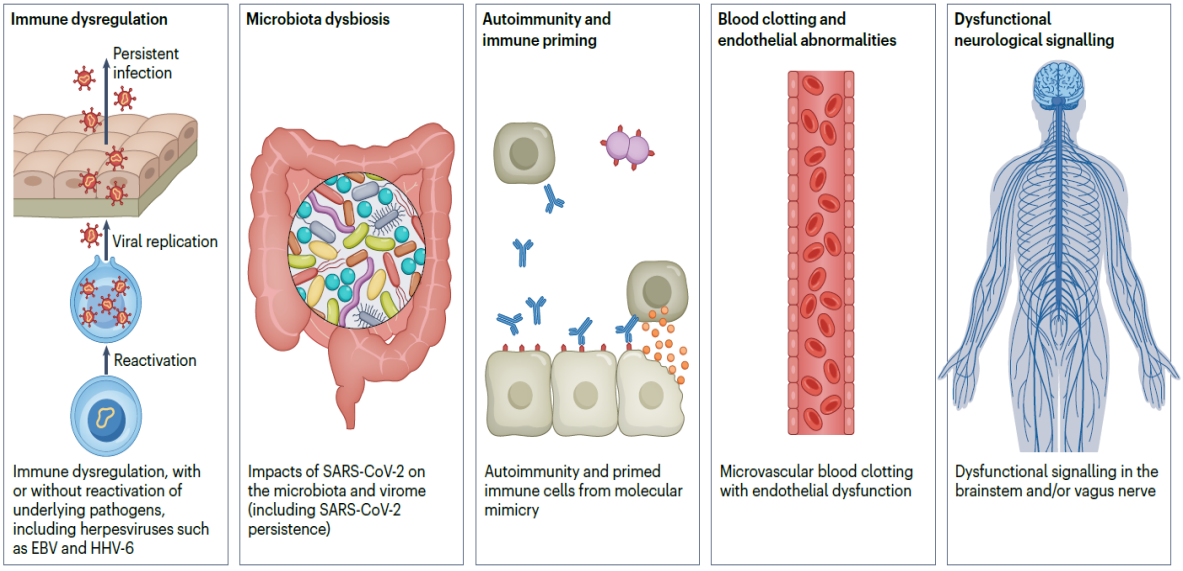
Ep 312-5: Hannah Davis Nat Rev Microbiol Jan 2023: Long-COVID findings, mechanisms, recommendations

Long COVID symptoms and the impacts on numerous organs with differing pathology.
The presentation of pathologies is often overlapping, which can exacerbate management challenges.



MCAS, mast cell activation syndrome;
ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome;
POTS, postural orthostatic tachycardia syndrome.

Hypothesized mechanisms of long COVID pathogenesis



EBV, Epstein–Barr virus; HHV-6, human herpesvirus 6

Par 2 News on vaccines

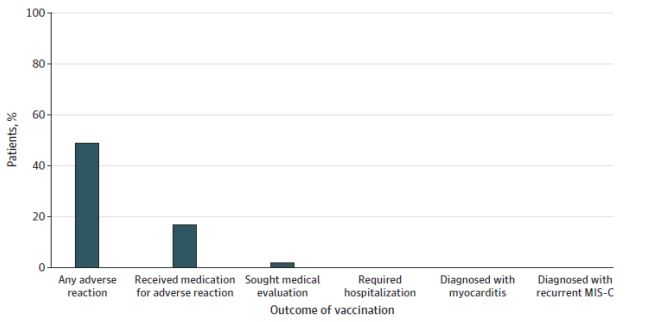
Reassuring news for children with MISC: **COVID-19 vaccine for children after MIS-C appears safe**

Remember Ep 310-2 and -3: some common features between MISC and post RNA vaccine myocarditis: similar inflammatory markers, but also high circulating levels of Spike protein.

Ep 312-6: Matthew D. Elias JAMA Open Pediatrics Jan 2023

In 385 patients with a history of MIS-C, 48.1% were vaccinated for COVID-19: "normal" proportion with mild side effects, but **none experienced serious adverse reactions, including a diagnosis of myocarditis or MIS-C recurrence**.

Figure. COVID-19 Vaccination Adverse Reaction Summary Among 185 Patients With a History of Multisystem Inflammatory Syndrome in Children (MIS-C)



Reassuring news about stroke after Pfizer vaccine in 65+

Ep 312-6: Carol Goh CY SAGE Journal June 2022: A probable case of vaccine-induced thrombotic thrombocytopenia in a 76 year old after Pfizer mRNA (Sorry only abstract, I have no access to full paper)

Ep 312-7: Reuters 18 Jan 2023: **EU drug regulator has not seen signal of possible Pfizer COVID shot stroke link**

To be followed up (but clearly very rare).

Perspectives on COVID vaccines:

Ep 312-8/-9: FDA advice to simplify vaccination against SARS-CoV-2 in the future = based on Influenza model.

Proposed potential simplified immunization schedule

One Dose	Two Dose Series
General population (age-based*) Young children *if ≥2 doses received previously* Older children, adolescents, and all but older adults	Risked-based adjustments** Young children *if ≤1 dose received previously* Older adults Persons with comprised immunity

*Presumed to have had at least two S protein exposures, resulting in sufficient preexisting immunity such that a single dose of COVID-19 vaccine induces or restores sufficient vaccine effectiveness for a desired duration.
**Presumed to have insufficient preexisting immunity based on age and other risks (e.g., children less than 2 years of age are presumed to have had no more than one prior immunizing SARS-CoV-2 infection, adults 50 years of age and older are presumed to have higher-level risk for severe COVID-19 and death, and persons with comprised immunity are presumed to require two rather than one dose of vaccine in each COVID-19 vaccine campaign).

Hence, adaptation of vaccine composition once per year, because:

- Everybody has baseline immunity by vaccination and/or infection.
- Booster protects little against infection with the latest omicron variants but strongly against severe disease (see Ep 307, 310, 311).
- Consistent messaging is needed, because “booster fatigue”, in general population.

However, many questions need to be addressed:

- Include Wild-type, along with new variant or leave WT out (because risk on imprinting and immune deviation)?
- Which vaccine format for booster: only mRNA (because most evidence), also protein-based?
- Route: intranasal vaccine?
- What clinical evidence is needed to approve adapted vaccine?
- ….

Still much to be learned….

Best wishes,

Guido