Episode 225 : Update on drugs, immunology and virology

Dear colleague,

This episode will reiterate on some recent papers on immune-virology (my favored topic), based on the many suggestions by Dr. Patrick Smits and with a contribution from Dr. Pharm Suzy Huijgebaert on the relation between stress, immunity and respiratory infections

But first, I would like to come back on the drug chapter

DRUGS

1) A reaction by colleague **Barbara Michiels** on **how she treats patients in general practice**:

I have used **Colchicine in three patients** in my general practice. Whenever the dyspnea came to the fore and the first lung abnormalities were heard on lung auscultation.

- Two of these patients had improvement in their oxygen saturation and dyspnea symptoms after three days.
- One patient (he had also received a first vaccine) went to the emergency room on his own initiative because of insufficient improvement after two days: he had been in intensive care for three weeks and had to be given a ventilator. I still wonder if this could have been avoided if I could have given him Colchicine a few days earlier.

I also take **aspirin** earlier in the course of the disease and more frequently in patients who are lingering in their infection: if they continue to have a fever (more than a week) and are generally limp with persistent muscle aches. My experience is that they clear up with Aspegic 500mg 3x1 per day after one day. Evidence also exists about acetylsalicylic acid

Of course I realize the anecdotal nature of these cases. There is also the problem of timing (when to start correctly) and the problem of dose and duration of treatment.

I am also wary of very expensive new drugs (aspirin and colchicine are cheap with known side effects).

As a general practitioner we can do more than was previously assumed!

2) Herewith I add the **instructions for use of the recently FDA approved drugs** that I discussed in the previous episodes.

Ep 225-1: A = Molnupiravir; B = Paxlovid; C = Tocilizumab; D = Baricitinib ; E = Sotrovimab; F = Evusheld (Astra-Zeenca mAbs).

As a reminder for Remdesivir https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/remdesivir/ and Ep 225-1 G: Combination of Remdesivir and Baricinitib

IMMUNOLOGY

Before omicron

Ep225-2: Phetsouphanh in Nature Immunology Jan 2022 provides evidence of sustained inflammation in subjects with “long COVID” (by definition fatigue, dyspnea and/or chest pain) at 4 and 8 months after acute mild-to-moderate symptomatic infection with the following markers:

- Increased type 1 and type 3 **IFN**, **Interleukin-6 and pentraxin 3** (PTX3) (both IL-6 and PTX3 are also increased in acute COVID and associated with increased mortality; anti-IL6 is now used as a treatment -see Ep 224)
- Increased **"activation" markers** (HLA-DR and CD38) on **CD8 T cells, monocytes and plasmacytoid dendritic cells** as well increased **"exhaustion" marker PD-1 on CD8 T cells**.

Study well done: comparison not only with healthy controls, but also symptomatic COVID patients, who completely recovered and subjects with past "common" coronavirus

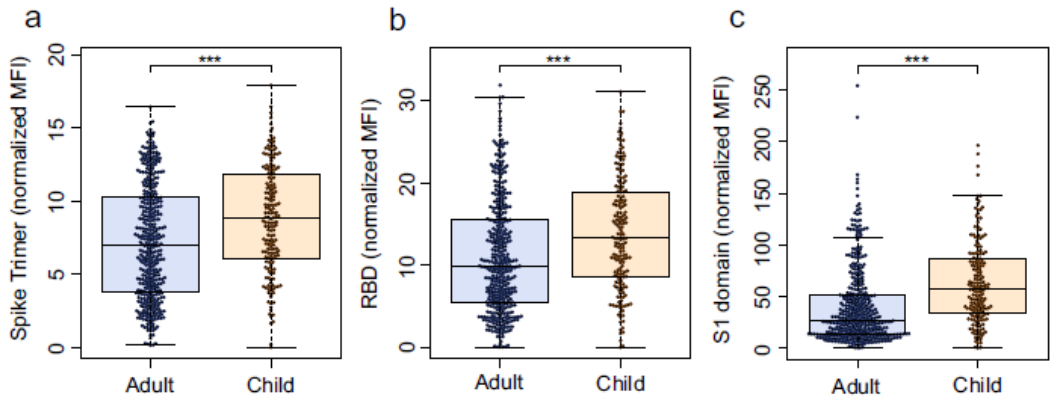
What are the drivers of this objective increased "immune activation"? Persistence of antigen, autoimmunity driven by antigenic cross-reactivity or a reflection of damage repair?

Ep 225-3: Renk in Nature Comm Jan 2022 reports on **more durable humoral responses after SARS-CoV-2 infection in children** than adults within the same households, even after asymptomatic infection.

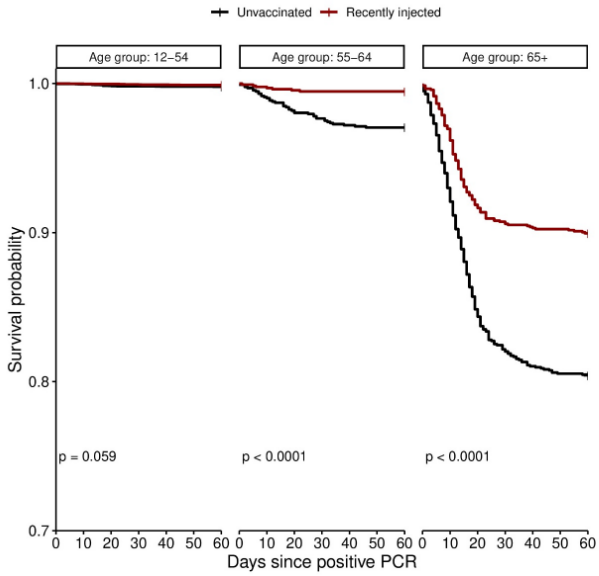
Children:
- **Five times more likely to be asymptomatic,**
- **Higher specific antibody levels which persist longer** (96.2% versus 82.9% still seropositive 11–12 months post infection).
- **Neutralization responses** of children and adults are similar, although neutralization is reduced for both against the Delta VOC.

Of note,
- Symptomatic and asymptomatic infections induce **similar humoral responses** in all age groups.
- SARS-CoV-2 infection occurs independent of HCoV serostatus.

Fig. 1 Children have a significantly higher humoral response to SARS-CoV-2 than adults.



Ep 225-4: Shmuelian in medRxiv 8 Jan Real world evidence that **Pfizer vaccine acts as post-exposure prophylaxis** between Oct 20 2020 and Dec 7th 2021 (alpha and delta wave): protection against death in those who were PCR(+) at the day of vaccination or during 5 days after vaccination:



Legend: Kaplan–Meier curves for survival of three combined age groups, starting from the day of the positive PCR.

CONCLUSIONS

1) **Long COVID** is not just subjective: there is evidence of **chronic immune activation/inflammation.**
2) **Kids** have **more durable humoral responses after SARS-CoV-2 infection** than adults. Obviously, this observation does NOT imply that vaccination is not useful to prevent infection-association complications such as MISC.
3) **mRNA vaccines** can (accidently) act as **post-exposure prophylaxis,** <u>especially in older subjects.</u>

<u>During omicron</u>

<u>Ep 225-5</u>: Rossler in NEJM 12 Jan is another nice illustration of the (in vitro) resistance of omicron to sera from both vaccinated and convalescent patients, while more susceptible to “hybrid immunity” (vaccination + infection, irrespective of the order)

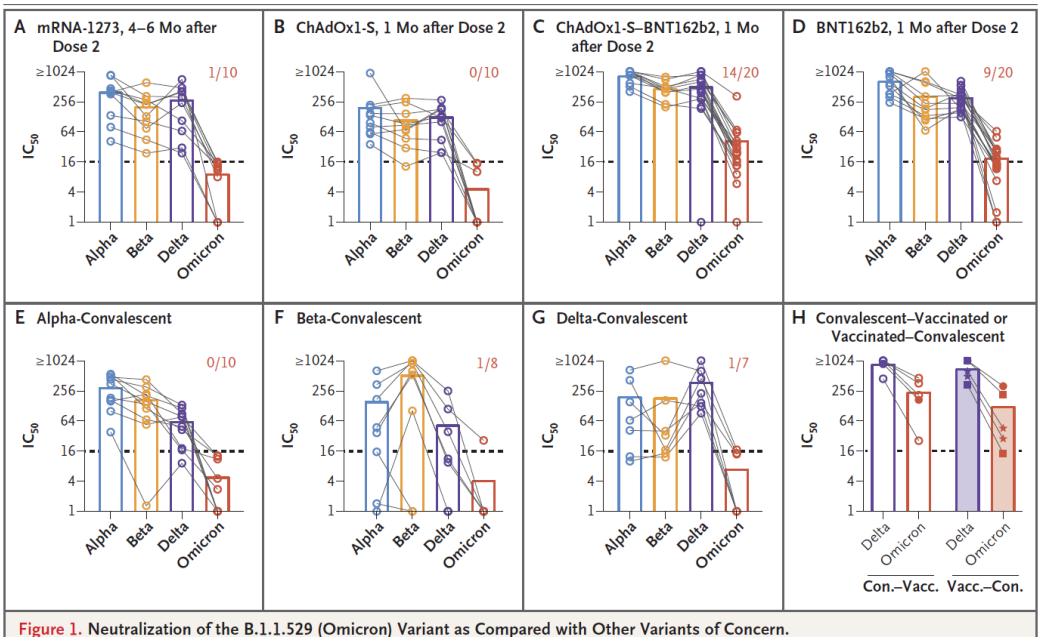


Figure 1. Neutralization of the B.1.1.529 (Omicron) Variant as Compared with Other Variants of Concern.

Ep 225-6: Elie Dolgin in Nature News 12 Jan: Inactivated vaccines have been most used in the world, but recipients of those have even less neut Ab than the ones vaccinated with mRNA or viral vectors. It is likely that at least 2 doses of mRNA will be needed for robust protection against disease.

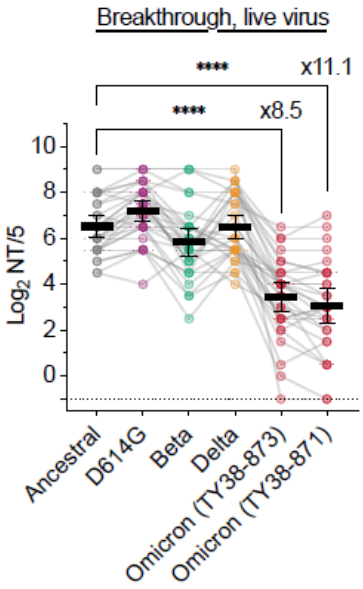
Ep 225-7: Kahn in medRxiv Dec 2021: **Omicron infection of vaccinated individuals enhances neutralizing immunity against the Delta variant**

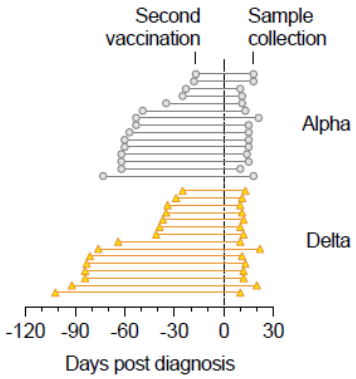
	Neut titer increase **23** days vs 5 days post omicron symptoms onset	
	In non-vaccinated	In vaccinated
Against omicron	**4.4**	**13.7**
Against delta	**2.5**	**6.6**

Clearly this "**cross-neutralisation**" against delta, induced by omicron is more pronounced in previously vaccinated subjects
→ Will this be enough to prevent new infections or disease by delta or a new variant to come?

Ep 225-8 A: Miyamoto medRxiv 1 Jan 2022: For "**hybrid immunity**" against omicron, **a longer time interval** between vaccination and breakthrough infection by Alpha or Delta is **favorable for neutralization of omicron.**

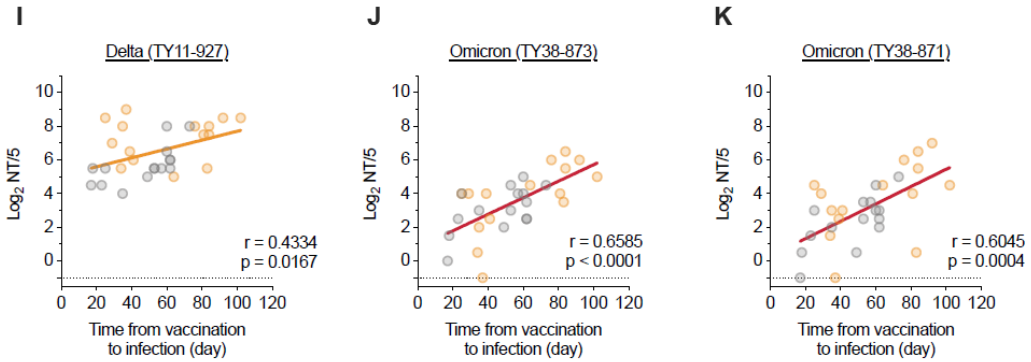
Lower neutralization to omicron after vaccination + breakthrough infection, but large variation





Timing of breakthrough infection

Variation is positively correlated with time interval between vaccination and breakthrough infection



Ep 225-8 B: Sidik in Nature News 7 Jan

Possible explanation of Miyamoto's findings: maturation of memory B cells responses with broadening towards other variants is better when longer interval between vaccination and infection

Implication: "Does the amount of time between your first two doses, and then your booster, impact how many cross-reactive antibodies you have?"

Ep 225-9: Jergovic medRxiv 16 Jan 2022 on "resilient" T cell responses to Omicron.

While neut Ab responses against omicron vs Wuhan (WA1/2020) are rather weaker, even after repeated vaccination, T cells are more "resilient":

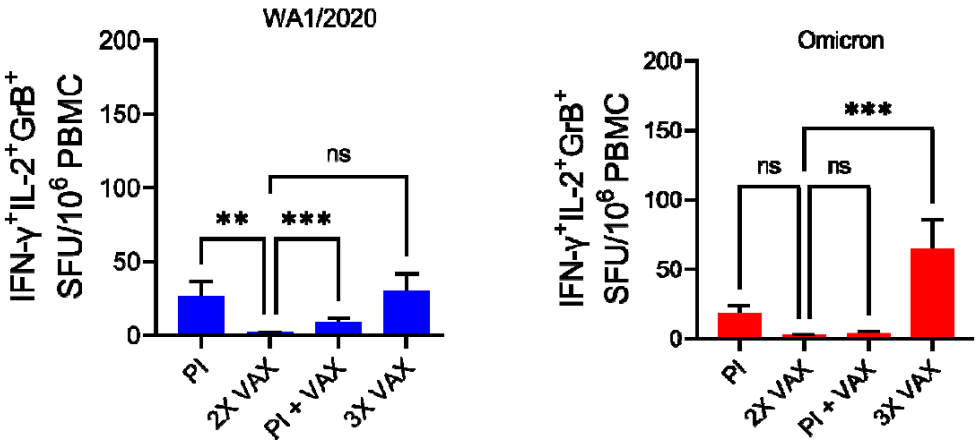
Three-dose vaccinated participants had

- **similar responses** to Omicron relative to convalescent or convalescent plus two-dose vaccinated groups
- **significantly higher** than those receiving two mRNA vaccine doses.

These results provide further evidence that a **three-dose vaccine regimen benefits the induction of optimal functional T cell immune memory.**

Example: polyfunctional (IL-2, IFN-g and Granzyme B) T cell response upon Spike peptide stimulation

D.



CONCLUSIONS

Neutralizing antibodies: more evidence for **superiority of "hybrid immunity"** over (repeated) vaccination only:

- Also protective against Delta?
- More pronounced if time between vaccination and breakthrough infection is longer

T cells are more **"resilient"**:

- Optimally induced after 3 mRNA vaccinations

→ T cells could certainly have a role in **better persistence of protection against disease** than against infection in the presence of waning antibody-mediated immunity.

VIROLOGY

1) **Viral dynamics**

Remember Ep 223-13:

Ep 223-13: Interesting study, comparing viral dynamics of delta and omicron.

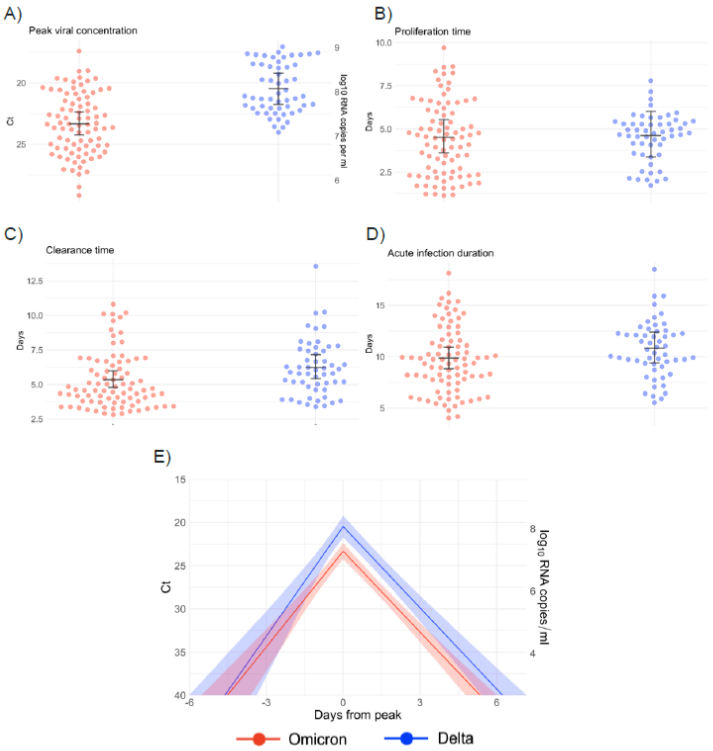
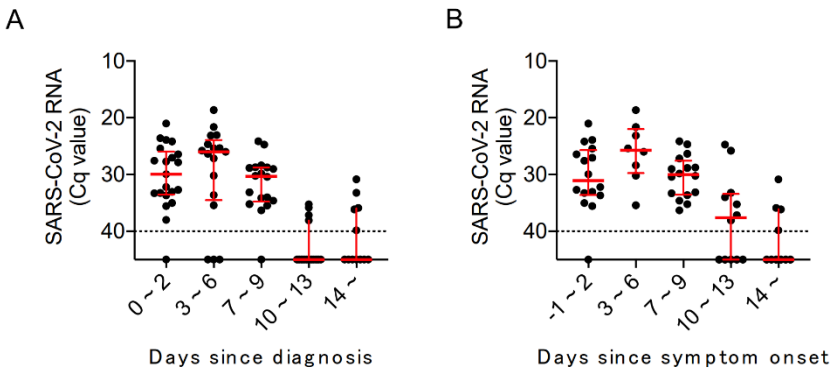


Figure 2. Inferred viral dynamics of SARS-CoV-2 variants Omicron and Delta. (A) Peak viral RNA concentration, (B) proliferation time, (C) clearance time, and (D) acute infection duration for omicron (red) and delta (blue) infections. Points depict the individual-level posterior mean values. Hatched lines depict the population mean and 95% credible intervals. (E) Mean posterior viral trajectories for Omicron (red) and Delta (blue) infections. Lines depict the mean values and shaded regions depict 95% credible envelopes.

Conclusion:

- Peak viral concentration tends to be higher in delta,
- but clearance somewhat faster in omicron infections

Ep 225-9 A: Data from Nat Inst Infect Dis Japan, however suggest that *The amount of viral RNA was **highest on 3-6 days after diagnosis or 3-6 days after symptom onset**, and then gradually decreased over time, with a marked decrease after 10 days since diagnosis or symptom onset*



Ep 225-9 B: Comment in BMJ: **these Japanese observations cast doubt on the now widely adopted shortening of the isolation period from 10 to 7 days.**
*Previous studies suggest that the peak transmission period with other variants was between 2 days before symptoms and 3 days afterward, with virus **shedding peaking on or before symptom onset.***
*The Japanese study suggests that **with omicron, the peak shedding may be two or three days later***

And then comes a remarkable argument: *One factor in favor of shortening the isolation period is that testing is "missing" about two thirds of infections anyway*.
Previously just under half of covid-19 cases were detected by testing, but since omicron emerged this figure had dropped to under a third, (because the rapid tests are clearly less sensitive to omicron).

2) Correlation between viral load and viral culture

Ep 225-10: Puhach medRxiv 11 Jan 2022: **Infectious viral load in unvaccinated and vaccinated patients infected with SARS-CoV-2 Wild Type, Delta and Omicron**

Infectious viral titer (IVT) and viral load (RNA) assessed during the first 5 symptomatic days:

- **unvaccinated** individuals infected with wild type (WT) (n= 118) or Delta (n= 127)
- **vaccine breakthrough** infections (BTI) with Delta (n= 121) or Omicron (n=18).

Findings:

- Correlation between RNA copy number and IVT was low, but, as expected more chance on infectious virus with high RNA copy number.
- Compare unvaccinated WT with delta: **WT higher viral RNA**, but **delta higher IVT**
- Delta: compare unvaccinated vs vaccinated BTI: similar RNA, but **vaccinated BTI lower IVT and faster clearance**
- Omicron BTI vs Delta BTI: **comparable IVT**

Interpretation:

1) **Delta clearly more infectious than WT** (with similar RNA viral load)
2) Delta: vaccination was associated with lower infectious titres and faster clearance for Delta, → **vaccination would also lower transmission risk**.
3) Omicron vaccine breakthrough infections did not show elevated IVTs compared to Delta, → **other mechanisms than increase VL contribute to the high infectiousness of Omicron**.

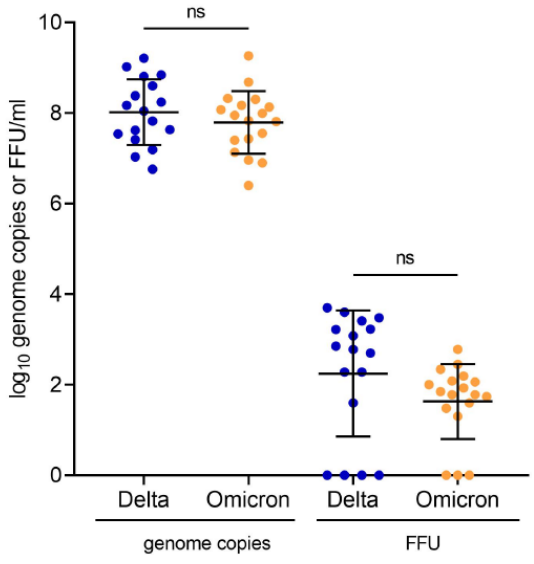


Figure 5. SARS-CoV-2 infectious viral loads in vaccine break through infections with Omicron or Delta. (A) Genome copies (left panel) and infectious virus (right panel) for vaccinated patients infected with Delta or Omicron VOC Infectious viral loads (were determined by focus-forming assay on Vero-TMPRSS cells. Significance was determined by t-test. ns: nonsignificant

CONCLUSIONS

1) Controversy over omicron viral dynamics: **virus may persist longer** than originally thought: since rapid tests are also less reliable for omicron than for other variants, the shortening of isolation and quarantine bears the risk of allowing more transmission. (These observations based on RNA viral copies)
2) Looking as infectious virus (as estimated from viral culture): **Omicron vaccine BTI doe not seem more infectious than Delta** (during first 5 days after symptoms onset)

Clearly, we need to understand the dynamics and persistence of infectious omicron virus better

STRESS, IMMUNITY and Respiratory infections (Dr Suzy Huijghebaert s.huijghebaert@gmail.com)

Although several reviews have pointed to a relationship between stress/anxiety, upper respiratory infections and immunity, the attached table has been collated as to illustrate how psychosocial stress affects lung function, upper respiratory infections and disease and immunity.

Ep 225-11: this table is not a systematic review, but just a compilation of sources to illustrate why we should not just focus on infection and its monitoring, while mongering stress and anxiety by continuous release of news over the public media may have an adverse outcome. This is because stress and anxiety affect the respiratory function and even (upper respiratory) infection rates, as well as the immune system - both acute and latent -, as well as the immune response to/after vaccination, both in children and adults.

Comments and reactions welcome !

Best wishes,

Guido