Episode 240 : Follow-up on diagnostic and clinical aspects. Boosting effect of Omicron infection or vaccination

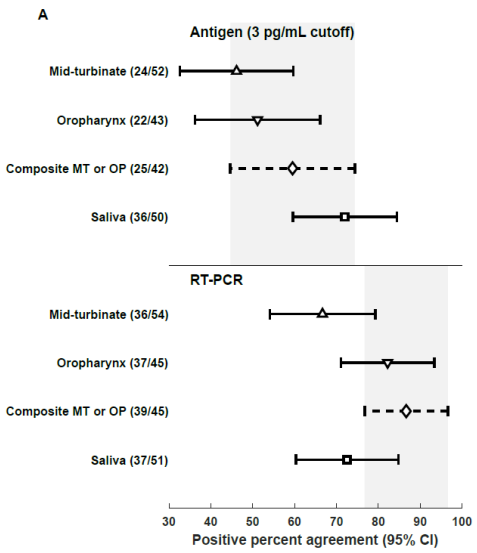
1) DIAGNOSTIC ASSAYS

Ep 240-1 : Priscilla Yueng medRxiv 8 Feb 2022 presents a very nice two steps multiplex RT-PCR that can distinguish all major VOC (and also most other variants), including omicron, based on the well-known specific mutations below. According to their data, there is more than 95 % agreement with whole genome sequencing.

Spike Mutations		WGS pos	WGS neg	PPA (95% CI)	NPA (95% CI)
Del69-70	**RT-qPCR pos**	43	0	100% (92-100%)	100% (99-100%)
	RT-qPCR neg	0	459		
K417N	**RT-qPCR pos**	27	0	96% (82-100%)	100% (99-100%)
	RT-qPCR neg	1[a]	474		
L452R	**RT-qPCR pos**	403	5[b]	100% (99-100%)	95% (89-98%)
	RT-qPCR neg	0	94		
T478K	**RT-qPCR pos**	379	0	100% (99-100%)	100% (97-100%)
	RT-qPCR neg	0	123		
E484K	**RT-qPCR pos**	35	3[c]	100% (90-100%)	99% (98-100%)
	RT-qPCR neg	0	464		
N501Y	**RT-qPCR pos**	70	0	100% (95-100%)	100% (99-100%)
	RT-qPCR neg	0	432		

RT-qPCR, reverse transcription quantitative polymerase chain reaction; WGS, whole-genome sequencing; PPA, positive percent agreement; NPA, negative percent agreement; CI, confidence interval

Ep 240-2 : Jessica Lin medRxiv 8 Feb: **Where is omicron?** Comparison of RT-PCR and rapid N antigen test Quickvue for qualitative and Quanterix for quantitative results in symptomatic individuals from a family cohort.



The figure shows the positive predictive value of either antigen test or RT-PCR of different anatomical locations if at least one sample was positive in PCR. The authors conclude that the diagnostic yield is "similar" in the midturbinate (MT), oropharynx (OP) and saliva compartment. Nevertheless, the antigen test shows a lower sensitivity….

Ep 240-3: Iftner medRxiv 13 Feb: Specificity and accuracy of 4 rapid antigen tests. This test was done in over 1000 asymptomatic RT-PCR negative individuals, performing nasal self-sampling and afterwards checked by a HCW.

As can be seen, there were many problems with false positive, invalid and unclear results…..

Conclusions

- There are several reliable assays now to distinguish variants without whole genome sequencing (see also Ep 238)
- I remain very disappointed about the use of rapid antigen tests: not only limited sensitivity, but also several other problems on accuracy, interpretation etc. I fail to understand why b these tests have ever been approved for widespread use, without much needed validation. I

2) CHILDREN AND ADOLESCENTS

Ep 240-4: da Silva 15 Feb 2022: Role of COVID-19 vaccinal status in admitted children during OMICRON variant circulation in Rio de Janeiro

A comparison between children admitted in 2020-21 and Jan 2022

	2020/2021 N=240	2022 N=60	P value
Gender			
-Female	104 (43.3)	30 (50)	0.352
-Male	136 (56.7)	30 (50)	
Age			
0-2 years	80 (33.3)	32 (53.4)	**0.015**
2-5 YEARS	52 (21.7)	6 (10)	
5-11 years	70 (29.2)	17 (28,3)	
12-18 years	38 (15.8)	5 (8.3)	
Lengh of stay (MEDIAN in days)	6 (1-164)	5 (1-19)	**0.036**
Outcome after 7 days*			
- Discharged	234 (97.5)	53 (88.3)	0.777
- Death	6 (2.5)	1 (1.7)	

*6 patients still hospitalized in 2022

Of five patients older than 12 years, that were admitted in 2022, 2 received two-dose, 2 received one-dose and 1 patient recieved zero-dose. All patients admitted in 2020 and 2021 year were not fully immunizated.

So, clearly, in Jan 2022 (omicron) a lot of children were hospitalized in a short time. They tended to be younger (> 50 % 0-2 yrs), but stayed shorted.

The remark on vaccination is difficult to interpret, as the campaign has just started and therefore it is difficult to conclude whether or not vaccination is protective against hospitalization….

Ep 240-5: Powell 11 Feb 2022: **Vaccine effectiveness against symptomatic infection by delta and omicron** in 12-15 and 16-17 years old in England.

b) 16-17-year-olds

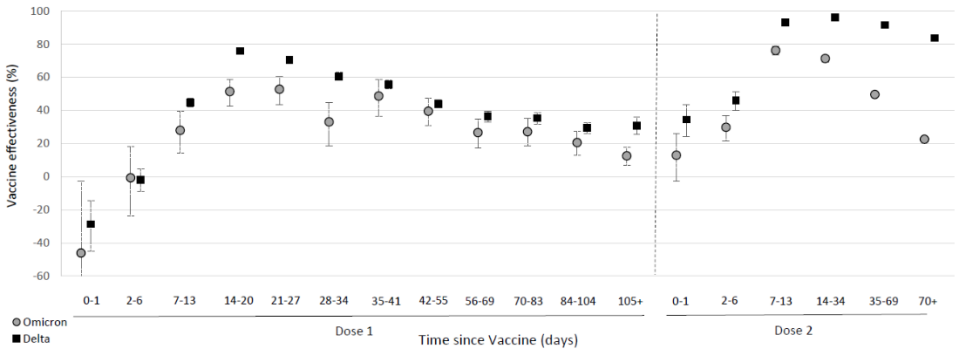
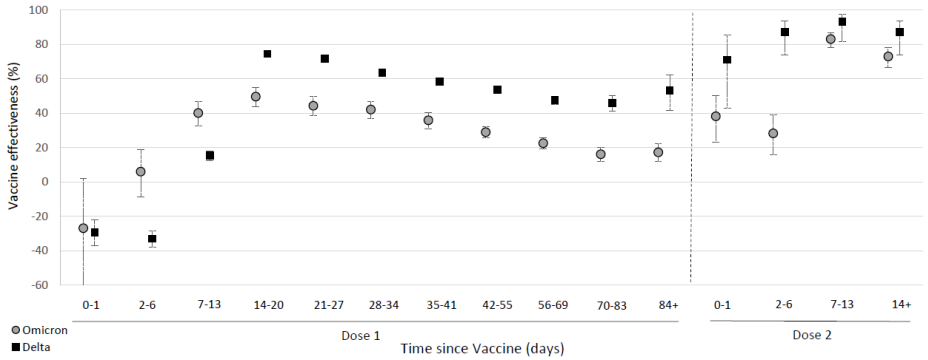


Figure 1. Vaccine effectiveness with 95% confidence intervals against symptomatic, PCR-confirmed COVID-19 with the Delta and Omicron variants among adolescents after one and two doses of BNT162b2 (Comirnaty, Pfizer-BioNTech) in England.

a) 12-15-year-olds

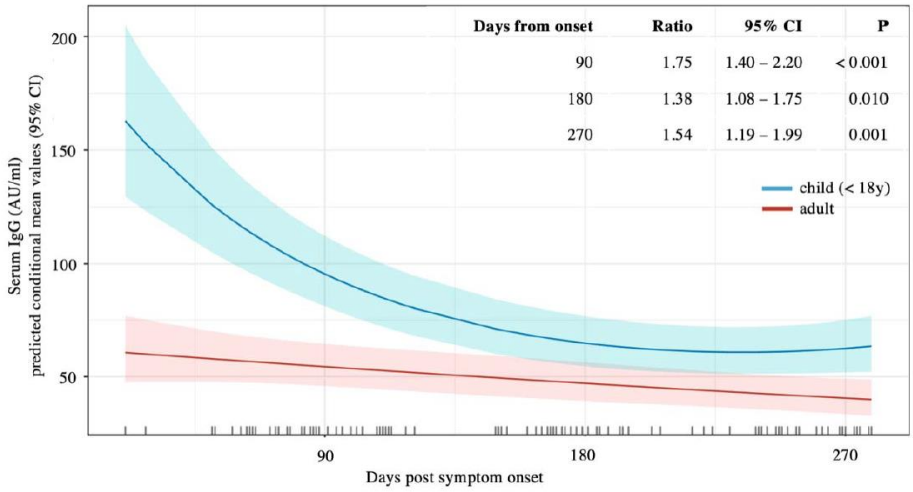


As expected, effect of first dose optimal after 14 days and slightly better against delta, but waning. A second dose increases VE , but after > 1 month waning quickly against omicron.

Conclusion of the authors*: Our data highlight the importance of the second vaccine dose for protection against symptomatic COVID-19 and raise important questions about the objectives of an adolescent immunisation programme: if prevention of infection is the primary aim, then regular COVID-19 vaccine boosters will be required*.

Ep 240-6: Dunay medRxiv 11 Feb 2022: Longitudinal follow-up of children and families infected during first lockdown (March-June 2020) in Germany.

- Only 1.44 % seropositive children.
- **Higher seroconversion rates** in families with **adult index** cases compared to pediatric index cases (OR: 1.79, P=0.047).
- **Children** showed **sustained seroconversion up to nine months** post-symptom onset and serum antibody concentrations persistently surpassed adult levels.



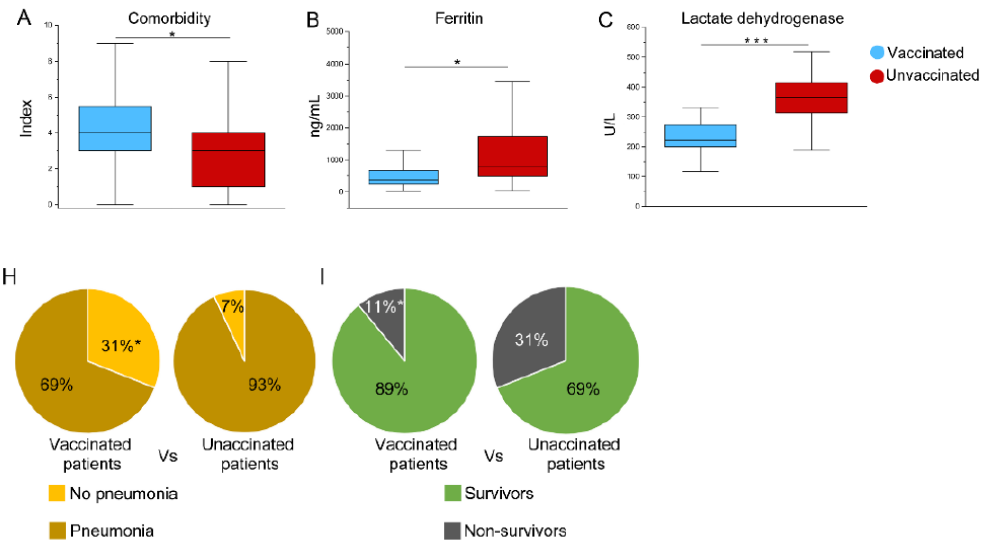
Conclusions:

- Children have superior immune responses to SARS-CoV-2
- Nevertheless, more questions than answers on boosting strategy: waning in adolesecentsd rather similar to adults, but risk/benefit of repeated boosters maybe different in children vs adults

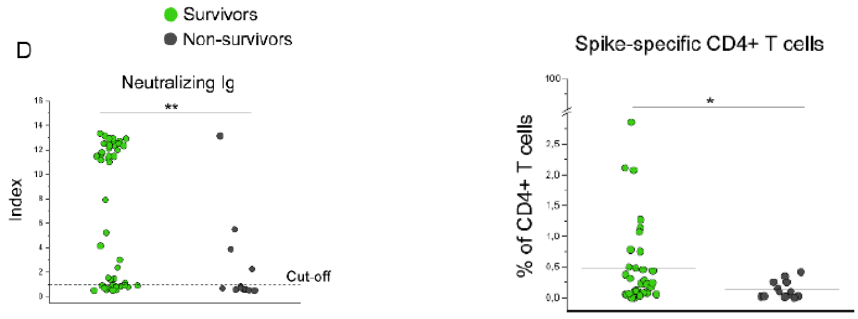
3) ADULTS AND ELDERLY

Ep 240-7: Lamacchia 15 Feb 2022 Better outcome of hospitalized vaccinated versus unvaccinated delta-infected subjects (Nov-Dec 2021).

Vaccinated patients were older and with more comorbidities, nevertheless unvaccinated subjects showed higher levels of pro-inflammatory markers, more severe disease and increased mortality rate

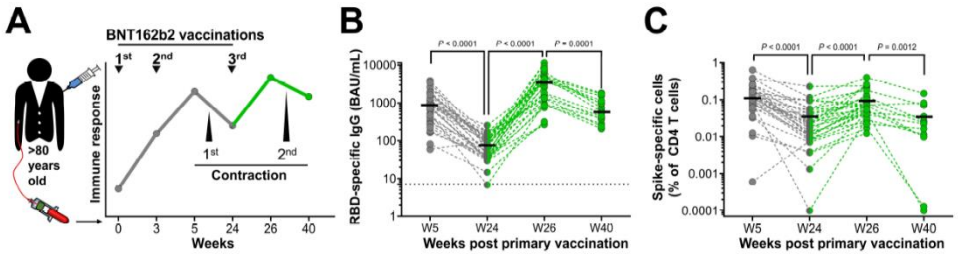


Patients with higher neutralizing Ab or Spike specific CD4 T cells: more likely to survive



6 out of 65 patients (9.2%) displayed high autoantibodies targeting IFN-α: 3 unvaccinated died, 3 vaccinated survived

Ep 240-8: Romero-Olmedo 15 Feb 2022: **Immune response to 2nd and 3rd vaccine in elderly over 80**



Strong booster effect on antibodies, but not on T cells: enhanced risk for omicron? (Since immunity to omicron may depend more on T cells than antibodies).

4) WHAT ABOUT OMICRON VACCINE?

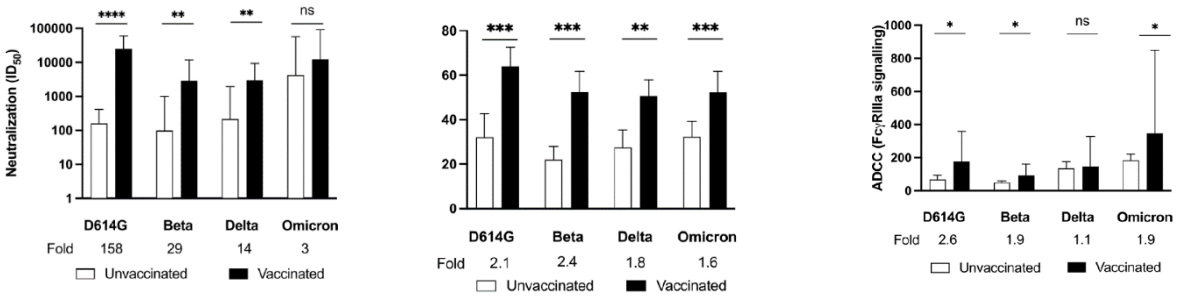
Ep 240-9: Richardson medRxiv 14 feb 2022 **SARS-CoV-2 Omicron infection triggers cross-reactive neutralization and Fc effector functions in previously vaccinated, but not unvaccinated individuals**

Fc effector functions = antibody dependent phagocytosis (ADP) and antibody-dependent cellular cytotoxicity (ADCC)

Sera from omicron-infected subjects, who were unvaccinated or vaccinated;

- Against omicron itself: similar neutralization, but lower "Fc effector functions" in unvaccinated versus previously vaccinated subjects
- Against all other variants: the sera from unvaccinated omicron-infected subjects showed much lower neutralization, ADP and ADCC

Neutralization **ADP** **ADCC**



Interpretation:

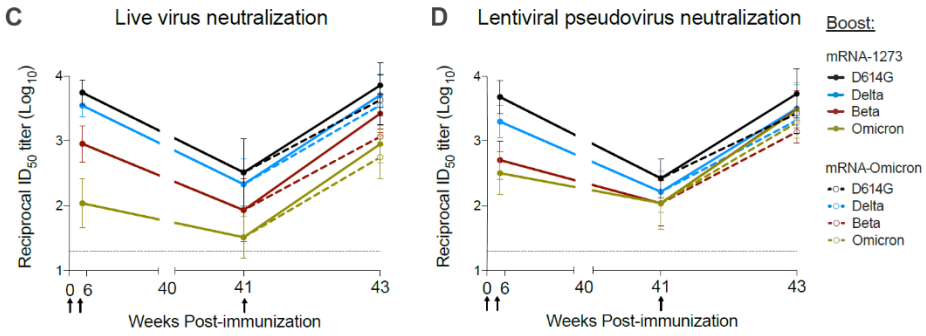
1) Unvaccinated Omicron-infected individuals may remain vulnerable to reinfection by circulating and emerging VOCs
2) Omicron-based immunogens may be adequate boosters, but they are unlikely to be superior to existing vaccines for priming in SARS-CoV-2 naïve individuals.

Ep 240-10: Gagne medRxiv 4 Feb 2022 **mRNA-1273 or mRNA-Omicron boost in vaccinated macaques elicits comparable neutralizing antibodies and protection against Omicron**

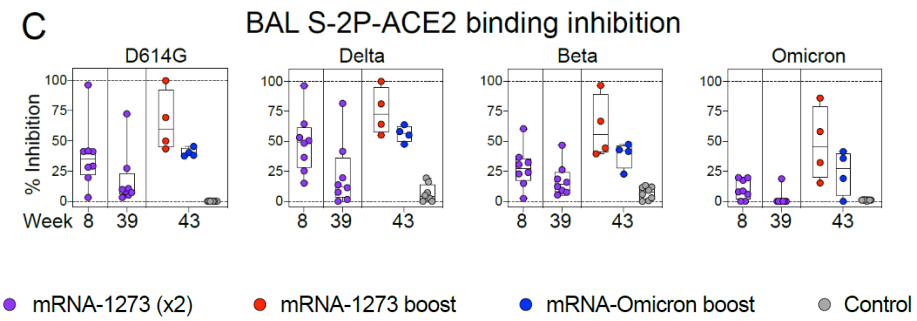
Eight NHP were vaccinated with "standard" mRNA-1273 (based on Wuhan)

- 9 months after 2nd dose 4 were boosted with the same mRNA-1273 or mRNA-omicron
- 4 weeks later challenged with omicron

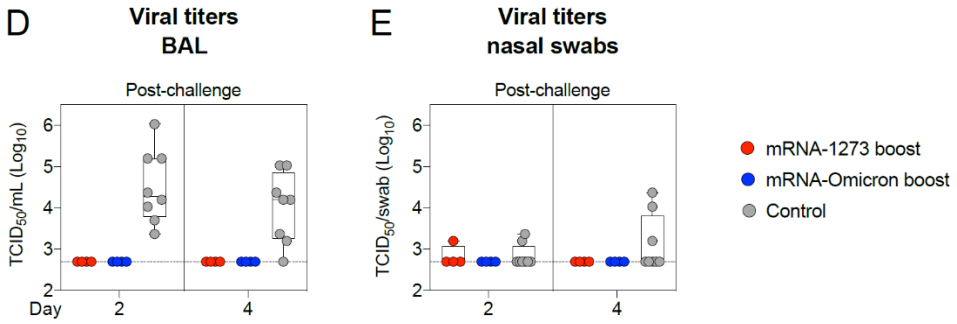
1) Similar kinetics and breath of neutralization after booster with either vaccine



2) Also similar neutralization (surrogate neut test = inhibition of Spike binding to ACE-2) in broncho-alveolar lavage (BAL)



3) Very similar protection after challenge



Conclusion:

1) *At present, boosting with **mRNA-1273** provides robust increases in neutralizing antibodies and appears to be sufficient to prevent severe disease from all known variants* (incl.omicron)
2) *Variant-matched vaccines may be preferable in the future if new variants were to emerge that were even further antigenically distant.*

But there are limitations:

- NHP not fully representative (higher neut Ab than humans)
- No control group with 2 doses (without booster) was challenged: protection due to booster or not?

Ep 240-11: Emily Walz comment in Nature 14 Feb points to similar results in mice, while human trials with omicron-adapted vaccine by both Pfizer and Moderna are awaited….

Conclusions:

- **Omicron infection** provides a strong and broad "boost" to various functions of antibodies (in vitro neutralization, ADP, ADCC) but much more in previously vaccinated subjects.
- **Omicron-specific mRNA boost** does not seem to be superior to standard Wuhan mRNA boost with regard to protection against omicron challenge

Best wishes,

Guido