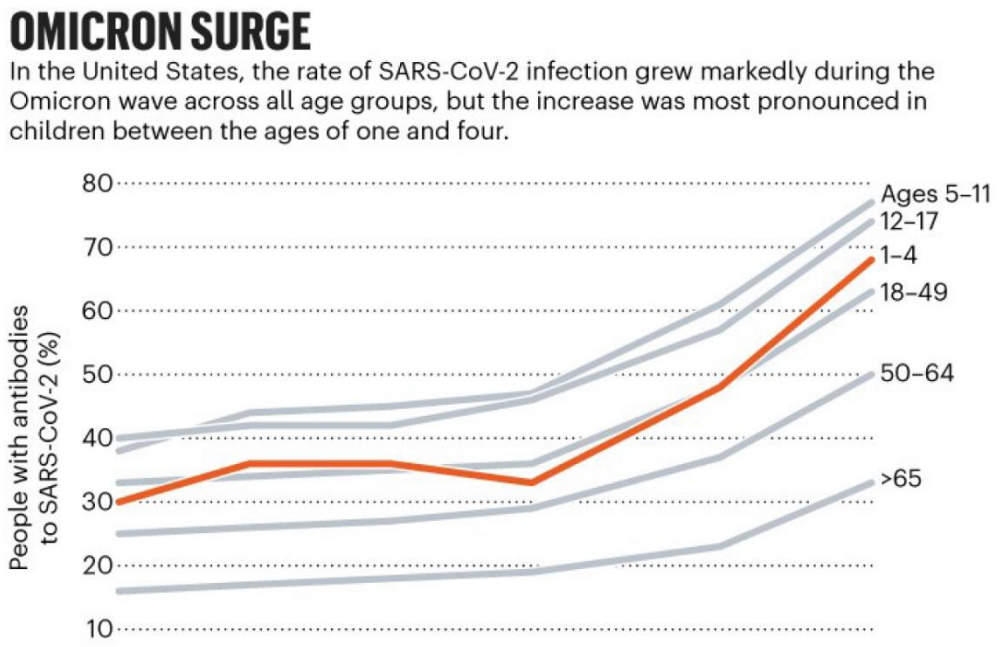
Episode 261: Perspectives on omicron subvariants and treatment

Dear colleagues,

This episode will contain less data and more reflections than usual.

Omicron and beyond

Ep 261-1: Based on specific antibodies, the **Omicron surge in US has resulted in the infection of over 2/3 of the children, with most pronounced rise in the less than 5 years**, a population that is not yet eligible for vaccination.

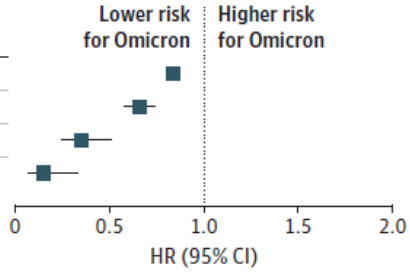


This has led to a peak in hospitalizations of children, which was 5 times the peak of the Delta wave and also 3.5 times more admission to intensive care than during Delta. Hence the impression that Omicron is not that innocent for children.

Ep 261-2: Lindsey Wang in JAMA Ped. carefully matched almost 50,000 children under five infected with either delta or omicron and found that the **incidence rate of SARS-CoV-2 infection with Omicron variant was 6 to 8 times that of Delta** variant but **severe clinical outcomes were less frequent than with Delta variant.**

A Omicron vs Delta cohorts

Outcome	Matched Omicron cohort, No. (%)	Matched Delta cohort, No. (%)	HR (95% CI)
ED visits	4637 (20.36)	5602 (24.60)	0.84 (0.80-0.87)
Hospitalizations	401 (1.76)	741 (3.25)	0.66 (0.58-0.74)
ICU admissions	38 (0.17)	115 (0.51)	0.35 (0.25-0.51)
Mechanical ventilation	10 (0.04)	51 (0.22)	0.15 (0.07-0.33)



Ep 261-3 A and B: Remarkably, at the same time, a communication by Reuters in A: **Omicron is as severe as other COVID variants in a-large U.S. study**

In fact in Ep 261-3 B Zachary Strasser et al. in Res Square investigated over 130,000 patients in Massachusetts over the course of 4 periods and they find

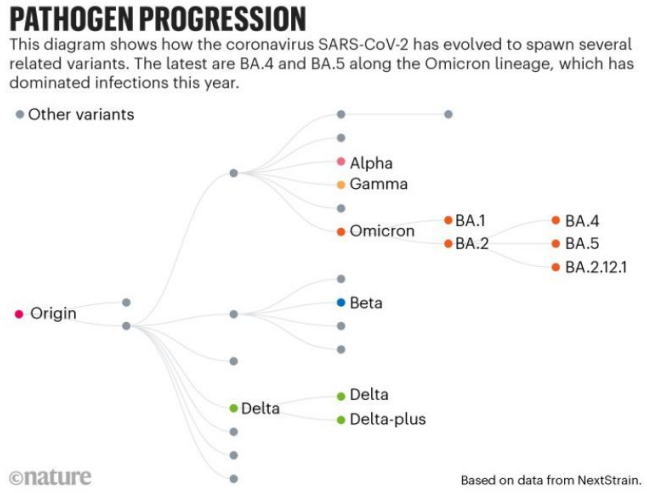
- *The **unadjusted** rates of hospital admission and mortality appeared to be higher in previous waves compared to the Omicron period,*
- *After **adjusting** for confounders including various **demographics, Charlson comorbidity index scores, and vaccination status**, the risks of hospitalization and mortality were nearly identical between periods.*

Table 2: Severity outcome across four temporal waves of SARS-CoV-2

	Infected	Hospital Admissions n (%)	OR[b] (95% CI)	Adjusted[c] OR[b] (95% CI)	Mortality[a] n (%)	OR[b] (95% CI)	Adjusted[c] OR[b] (95% CI)
12/2020 - 2/2021 (Winter 20' - 21')	36,682	5,732 (15.6)	1.24 (1.19 - 1.29)	0.92 (0.88 - 0.96)	303 (0.83)	1.85 (1.57 - 2.18)	1.00 (.99 - 1.00)
3/2021 - 6/2021 (Spring 21')	10,281	1,622 (15.8)	1.26 (1.19 - 1.33)	1.09 (0.99 - 1.21)	64 (0.62)	1.40 (1.05 - 1.85)	1.01(1.00 - 1.01)
7/2021 - 11/2021 (Delta)	18,894	2,683 (14.2)	1.11 (1.06 - 1.17)	1.00 (0.99 - 1.01)	134 (0.71)	1.60 (1.29 - 1.97)	1.01 (0.99 - 1.02)
12/2021 - 2/2022 (Omicron)	65,317	8,322 (12.7)	-	-	313 (0.48)	-	-

[a] in-hospital, 30-day mortality
[b] compared to Omicron [95% CI]
[c] adjusted refers to covariates weighted to balance for confounding bias and the model controlling for the covariates.

Ep 261-4: Ellen Callaway in Nature Briefing 10 May 2022 has talked with several experts and cautiously proposes a model where SARS-CoV-2 becomes more "predictable" (and endemic) **IF** the pattern with consecutive immune-escaping omicron subvariants continues. This could lead to a more "flu-like scenario" with relatively mild disease in a population with a decent level of immunity, but, of course, the sudden emergence of "completely new" variants cannot be excluded….



Ep 261-5: A similar reflection by Gretchen Vogel in Science with some emphasis on the mutations in L452 op the receptor binding domain, which are present in all new BA.2 subvariants and in Delta as well. These mutations could have a role in receptor binding and immune escape.

With regard to Delta, several experts repeatedly pointed to the possibility that Delta may re-emerge (as a different subvariant of recombinant?)

Ep 261-6: Karin Yaniv in Science of Total Environment calls attention for the ***Cryptic circulation of the Delta variant during the Omicron rise*** **in wastewater** in Israel. *According to the developed model, it can be expected that the Omicron levels will decrease until eliminated, while Delta variant will maintain its cryptic circulation may result in the* ***reemergence of a Delta morbidity wave*** *or in the possible generation of a new threatening variant.*

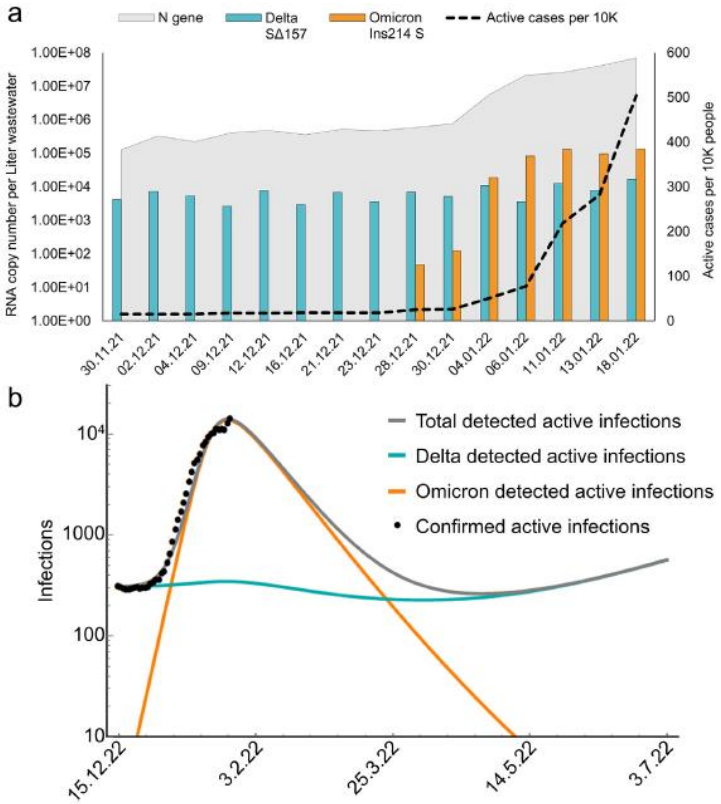


Fig. 3. SARS-CoV-2 Delta variant of concern and Omicron variant of concern dynamics. a, RT-qPCR detection of SARS-CoV-2 in the city of Beer-Sheva's wastewater during late November 2021 until late January 2022. Overall SARS-CoV-2 variants detected by N gene sets (gray area), Delta variant of concern detected by SΔ157 set (teal columns) and Omicron variant of concern detected by Ins214 S set (orange columns). Reported population's morbidity was extracted from the Ministry of Health database (black dashed line). b, Simulation results for Omicron (orange line), Delta (teal line), and total number (gray line) of detected actively infected people in the city of Beer-Sheva according to a moderately asymmetric cross-immunity, $q_{DO} = q_{OD}/4$ (see SI for the choice of parameters). Black dots represent confirmed active infections obtained from the Ministry of Health dashboard (irrespective of variants) up to January 25th, 2022. Time $t = 0$ corresponds to the date December 15th, 2021.

SOME CONCLUSIONS:

1) Omicron has increased the number of pediatric infections and hospitalizations (in the US), but is in fact less severe than Delta.
2) Remarkably, a large study in the general population of Massachusetts shows than omicron is (intrinsically) equally pathogenic, if all confounders, including vaccination, are controlled for.
3) The present viral evolution of successive omicron subvariants may suggest that we are heading towards a "flu-like" scenario.
4) Re-emergence of Delta descendants or of completely new variants remains possible.

Treatment

1) News on Paxlovid

Ep 261-7: **Paxlovid fails to prevent infection among household contacts of patients with COVID-19:** when adults who had an infected household member took the drug for either 5 or 10 days, they were 32% or 37% less likely than those on a placebo to later test positive themselves—but the differences between the groups were not statistically significant.

Ep 261-8: Practical guide for drug-drug-interactions

Step 1: *Establish the complete list with all current medications, including over-the counter drugs, herbal products, and recreational substances.*

Step 2: *Identify potential DDIs using specialized resources (e.g. www.covid19-druginteractions.org).*

Step 3: *Assess the risk/benefit of NMV/r treatment in presence of an interacting medication* ***(Table)***

The following strategies should be considered when managing DDIs with NMV/r:

- *i) pausing the comedication if it is clinically appropriate to do so;*
- *ii) monitoring or dose adjustment of the comedication*
- *iii) switch comedication;*
- *iv) patient counselling about potential DDIs with advice to withhold temporarily a comedication if feeling unwell or*
- *v) use of alternative COVID-19 therapy (sotrovimab, remdesivir, molnupiravir)*

Classification of DDI risk	Recommendation for DDI management	Examples of medications (list is not exhaustive)
Deleterious DDI	Sensitive CYP3A4 and/or P-gp drugs and/or narrow therapeutic index drugs with a long elimination half-life. DDI is not manageable →**choose alternative anti-Covid-19 drug**	Amiodarone, bepridil, bosentan, clorazepate, diazepam, pimozide
	Strong inducers are expected to reduce NMV/r efficacy. Given the persisting enzymatic induction upon discontinuation of inducer, DDI is not manageable →**choose alternative anti-Covid-19 drug**	Carbamazepine, enzulatamide, phenobarbital, phenytoin, primidone, rifampicine, rifapentine, St. John's wort
	Sensitive CYP3A4 and/or P-gp substrates and/or narrow therapeutic index drugs. NMV/r use only possible if comedication is paused. If paused, drug can be resumed 72 h after completing NMV/r treatment. TDM is advised for calcineurine inhibitors and mTOR inhibitors →**conditional use of NMV/r**	Alfuzosin, apixaban, calcineurine inhibitors (tacrolimus, cyclosporine), clopidogrel (recently stented patient), domperidone, lovastatin, midazolam, mTOR inhibitors (everolimus, sirolimus), rivaroxaban, simvastatin, ticagrelor
Potential DDI manageable by dose adjustment/monitoring (and for some medications by patient counselling)	Drugs requiring dosage adjustment and/or specific monitoring (e.g. INR, TDM,) →**evaluate risk/benefit of prescribing NMV/r**	Aripiprazole, haloperidol, risperidone, cancer drugs (CYP3A4/P-gp substrates), digoxin, warfarin
	Patient counselling about potential DDI with advice to pause temporarily the medication if feeling unwell or informed to be aware of side effects → **use of NMV/r possible**	Amlodipine, diltiazem, indapamide, verapamil zolpidem, zopiclone
DDI of weak clinical relevance	Drugs for which a weak magnitude DDI is expected or with a low risk of adverse event from DDI →**safe use of NMV/r**	Bupropion, codeine, desipramine, ezetimibe mirtazapine, methadone, mycophenolate
No expected DDI	→**safe use of NMV/r**	ß-blockers, ACE-inhibitors, lamotrigine; drugs not undergoing CYP3A4 metabolism and/or not transported by P-gp

Table 1: Risk of drug-drug interactions with nirmatrelvir/ritonavir and recommended drug-drug interaction. Note that the inhibitory effect of ritonavir needs 72 h after discontinuation to resolve. The classification of the drug-drug interactions refers to the University of Liverpool COVID19 drug interaction resource: www.covid19-druginteractions.org.

2) **News on Interferon**:

Several trials with **type 1 IFN** (alpha-beta) in hospitalized mainly unvaccinated COVID patients have **failed** to provide convincing benefit. Here I will summarize the studies on **type 3 IFN** (lambda).

Ep261-9 A: Meredith Waldman in Science Insider 5 May 2022 reports on the favorable results of the most recent **large phase 3 placebo-controlled trial in Brazil,** based on a press release (Ep 261-9 B), in the context of the TOGETHER consortium, with EIGER as the sponsor.

Set-up: single injection (dose not specified) within 7 days after symptoms onset.

Population: Non-hospitalized patients who were older than 50 and/or were at higher risk of severe COVID-19 because they had conditions including diabetes, obesity, high blood pressure, and lung disease. Eighty-four percent of participants were vaccinated. Over 900 in peginterferon and placebo arm.

Findings:

- 25 of 916 patients (**2.7%**) in the treatment arm were **hospitalized** or spent more than 6 hours in an emergency room, compared with 57 of 1020 patients (**5.6%**) who received placebo.
- Risk on hospitalization was lower when treatment was given within 3 days (60 % lower) vs 3-7 days (40 % lower)
- Only one person in the treatment group died, compared with four in the placebo group.
- No data on viral load

Going back in literature, I found **two other very small phase 2 trials, each in about 60 outpatients:**

Ep 261-10: Jagannathan Nature Comm March 2021

180 µg sc injection within **3** days of symptomatic uncomplicated COVID **neither shortened the duration of SARS-CoV-2 viral shedding nor improved symptoms** (30 patients in each arm)

Ep 261-11: Feld Lancet Resp Dis March 2021

Set-up = very similar: 180 µg sc within 7 days of symptom onset or positive test in 30 treated and 30 placebo.
Finding: Peginterferon lambda **accelerated viral decline** in outpatients with COVID-19, increasing the proportion of patients with viral clearance by day 7, particularly in those with high baseline viral load.

3) Convalescent plasma

Ep 261-12: Very complex analysis by Herman in medRxiv 22 Feb 2022 on a successful clinical trial with 2 units of COVID-19 convalescent plasma (CCP) in a small cohort of early hospitalized at risk patients: there was a very significant improvement of 28 clinical severity and survival.

The main message is that two IgG functions were improved in subjects who responded favorably:

- Anti-inflammatory Fc-glycan profiles, presumably because CCP induced a different glycan profile on the Fc part of the IgG, which reduced the pro-inflammatory monocyte activation
- Persistently expanded nucleocapsid-specific humoral immunity, presumably because free nucleocapsid is pro-inflammatory and will be "neutralized" by N-specific antibodies in CCP.

Remarkably, these anti-inflammatory effects were long-lasting.

Clearly, the suggestion here is that CCP is not just "neutralizing" virus (by Spike specific Ab), but rather diminishing the hyper-inflammation.

CONCLUSIONS

1) PAXLOVID does not seem indicated as prevention of SARS-CoV-2 infection within households. For treatment, potential drug-drug interactions need to be carefully considered.
2) The TOGETHER-EIGER study suggests for the first time that systemic interferon lambda could prevent severe disease in at risk SARS-CoV-2 infected outpatients. Earlier doubtful results with interferon alpha/beta and with interferon lambda may relate to the interferon type (3 better than 1?), sample size and/or choice of "wrong" patient groups: outpatients with limited risk may mount sufficient IFN themselves, treatment of hospitalized subjectsmay be "too late" for IFN.
3) The success of CONVALESCENT PLASMA treatment may not (only) depend on the level of Spike-specific neutralizing antibodies, bur more on "immune modulatory" and anti-inflammatory effects.

Best wishes,

Guido