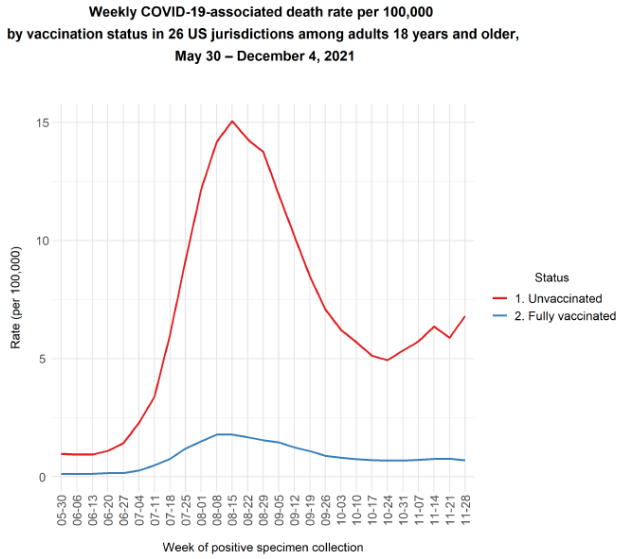
Episode 243 : Focus on various aspects of vaccinations: second, third fourth dose

CLINICAL

Ep 243-1: Katherine Jia Feb 2022: Excess COVID-19-associated deaths among the unvaccinated population >18 years old in the United States, May 30 – December 4, 2021

To calculate, they subtracted the death rate in the vaccinated from rates in the unvaccinated and multiplied this rate difference by the number of people in the unvaccinated group for each age group and each week.



Overall 135,000 extra deaths because on non-vaccination.

Ep 243-2: Paredes medRxiv 16 Feb 2022 Differential risk on hospitalization according to SARS-CoV-2 variant in Washington State

Overall (irrespective of vaccination): risk gamma> beta > delta> alpha, but omicron = ancestral strain

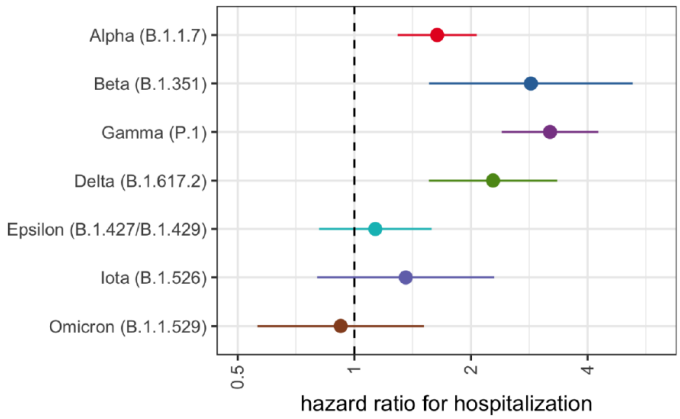


Figure 2: Relative Risk of Hospitalization by Variant Lineage. Risk of hospitalization is compared to individuals infected with an ancestral lineage. Error bars represent 95% CI. Estimates are adjusted for age, sex assigned at birth, calendar week, and vaccination status.

Taking vaccination into account: significant reduction of risk, especially for omicron.

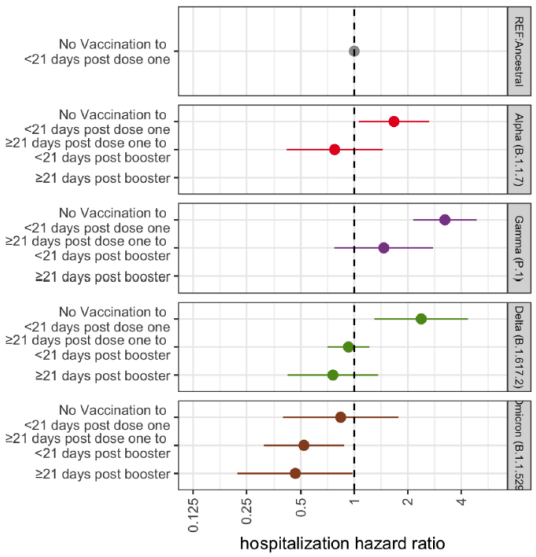


Figure 3: HR for risk of hospitalization following infection with a VOC (excluding Beta due to small sample size) stratified by vaccination status. Unvaccinated individuals infected with ancestral lineages serve as the reference category for each VOC HR. Error bars represent 95% CI. Estimates are adjusted for calendar week, age and sex assigned at birth. Categories with less than 4 hospitalizations are censored.

PREGNANCY VACCINATION FOR NEWBORNS

Ep 243-3: Halasa MMWR 15 Feb '22: 2 doses Pfizer during pregnancy protect newborns (> 6 months) against COVID -associated hospitalization.

TABLE 3. Effectiveness* of maternal 2-dose primary mRNA COVID-19 vaccination against COVID-19-associated hospitalization in infants aged <6 months, by timing of maternal vaccination during pregnancy† — 20 pediatric hospitals, 17 states,§ July 2021–January 2022

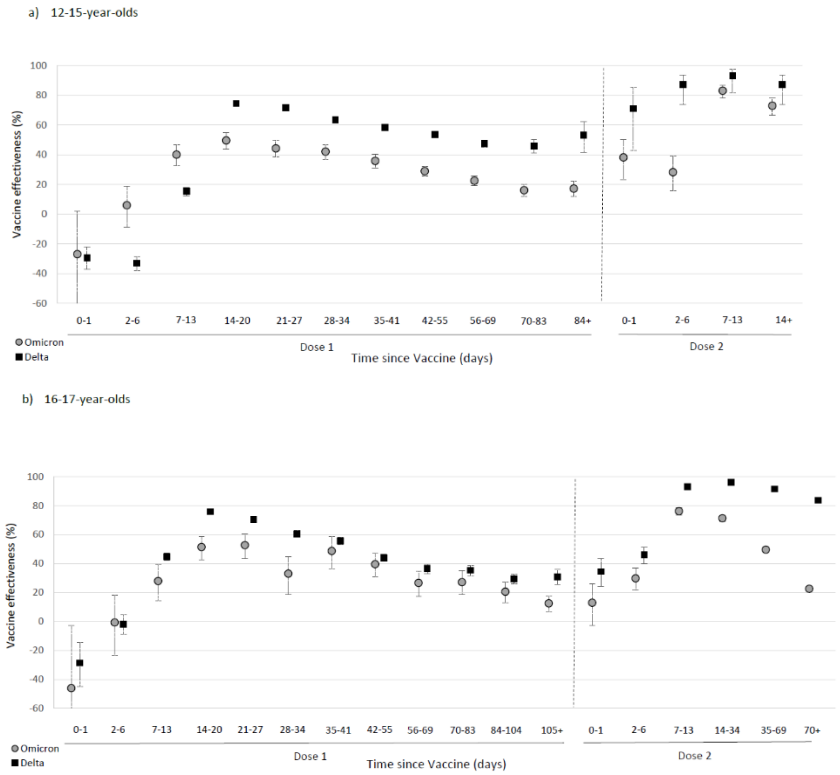
Timing of maternal vaccination during pregnancy†	No. vaccinated¶/Total (%)		Vaccine effectiveness,* % (95% CI)
	Case-infants	Control-infants	
Any time	28/176 (15.9)	65/203 (32.0)	61 (31 to 78)
Early (first 20 weeks)	17/165 (10.3)	26/164 (15.9)	32 (−43 to 68)
Late (21 weeks' gestation through 14 days before delivery)	9/157 (5.7)	38/176 (21.6)	80 (55 to 91)

WANING IMMUNE RESPONSES

1) IN ADOLESCENTS

Ep 243-4: Powell medRxiv 15 Feb '22: A second dose of Pfizer is required to keep vaccine effectiveness against delta and omicron, but VE wanes like in adults

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.



Ep 243-5: Burns medRxiv 16 Feb '22: Similar findings at the level of neutralizing antibodies in adolescents in US:

- Serum from adolescents showed that **anti-Spike antibodies wane significantly over 6 months**.
- After completion of a two-vaccine series, **cross-reactivity against Omicron**-specific receptor-binding domain (RBD) was seen.

Evidence of waning mRNA- induced vaccine immunity underscores vulnerabilities in long-term pediatric protection against SARS-CoV-2 infection, while cross-reactivity highlights the additional benefits of vaccination.

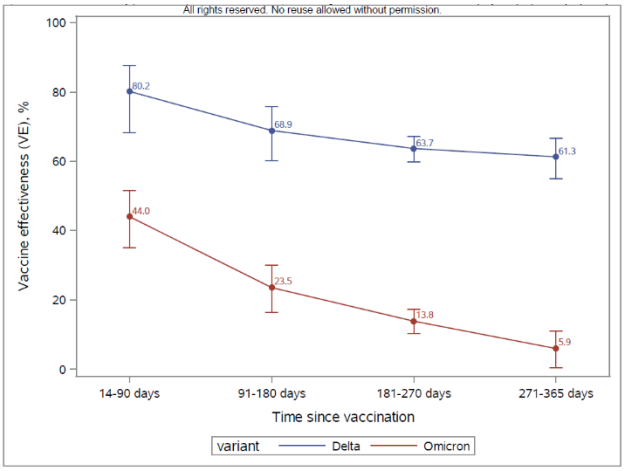
2) IN ADULTS

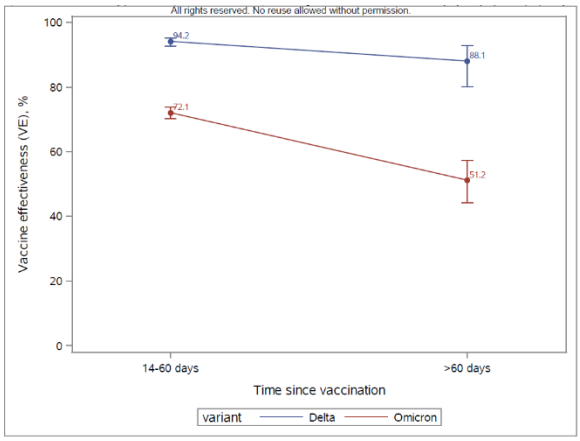
Ep 243-6: Tseng medRxiv 18 Feb 2022 Vaccine effectiveness against delta and omicron **infection** in a test-negative control study in Southern California

1) In general population

Waning after 2 doses

Waning after booster



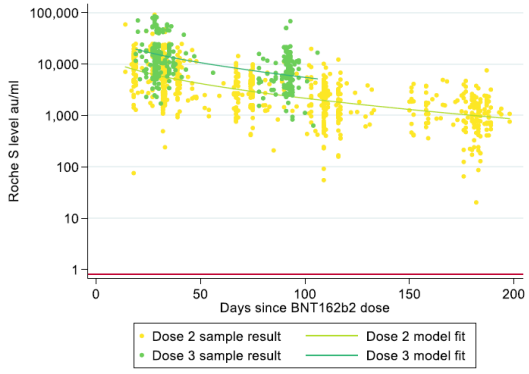


2)In immunocompromised subjects: 3-dose VE was only 29.4% (0.3–50.0%) against omicron infection in immunocompromised individuals, but 3-dose VE against hospitalization with delta or omicron was >99%.

Ep 243-7: Georgina Ireland medRxiv 18 Feb 2022: differential course of S-specific antibodies after infection and vaccination.

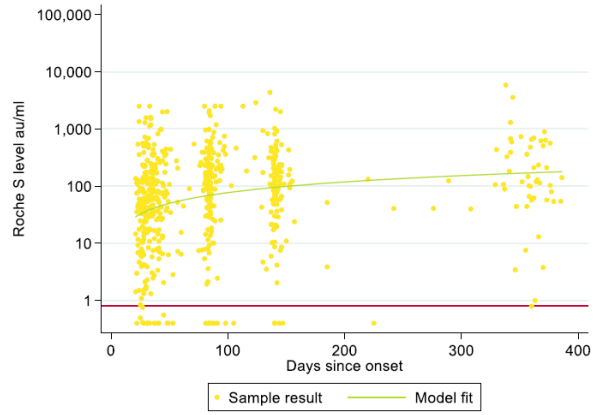
After vaccination: as expected a rapid serological response post-booster for all primary immunisation vaccines and schedules, to higher levels than observed after dose 2 of the primary schedule, but **waning was observed after 5 weeks**.

c) Infection-naïve



By contrast: in naturally infected unvaccinated subjects **very little S-antibody waning** up to 365 days

a) Convalescent serum

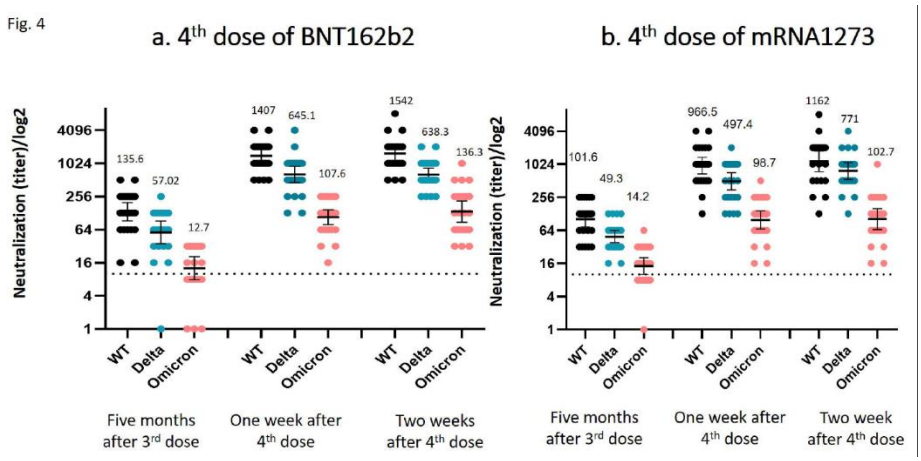


Interpretation: *The rapid waning of post-booster antibodies along the same trajectory as two primary immunisation doses indicates that a fourth dose may be required when predictions of future waves coincide with declining protection ?????*

FOUR DOSE REGIMEN: not so bright as we would hope!

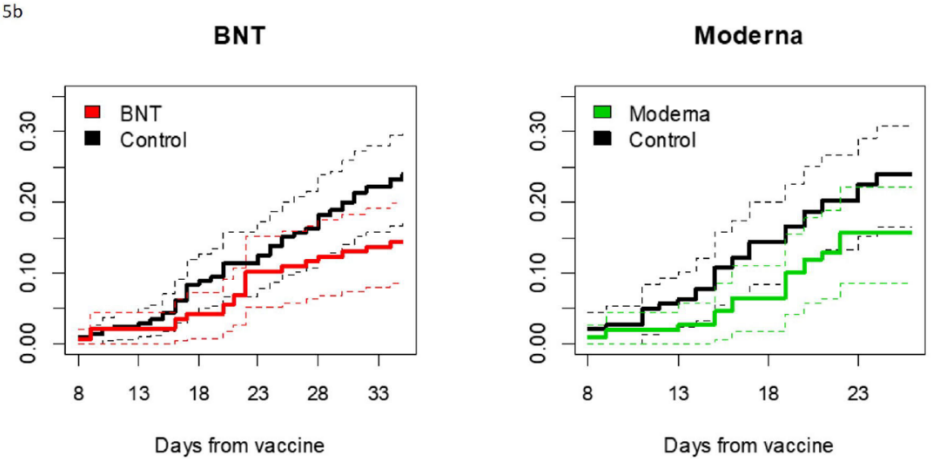
Ep 243-8: Regev-Yochay medRxiv 15 Feb 2022: **4th mRNA** (either Pfizer or Moderna) in health care workers with low IgG after 3rd vaccine

Nice restoration of neutralizing antibody titers



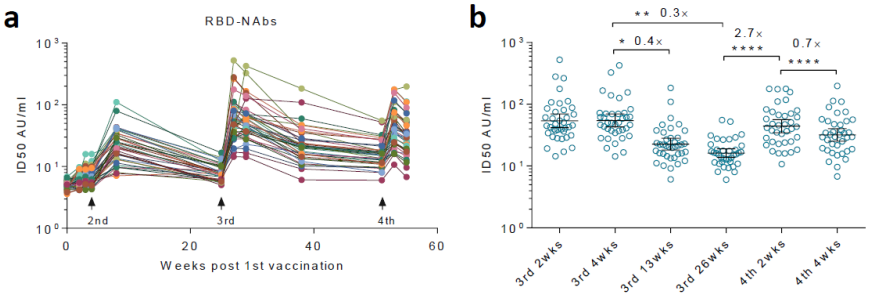
However: high incidence rate of mildly symptomatic omicron infections !!!

Fig 5b



Conclusion: *Low efficacy in preventing mild or asymptomatic Omicron infections and the infectious potential of breakthrough cases raise the urgency of next generation vaccine development.*

Ep 243-9: Wang medRxiv 18 Feb 2022: A fourth dose of the inactivated Sinopharm vaccine induced a peak Receptor Binding Domain (RBD)-Neutralizing Abs that was **inferior** to the peak of the 3rd dose. The immune system shifted responses to the nucleocapsid protein (NP) and the N-terminal domain (NTD) of the spike protein.



Interpretation: ***immune responses could not be endlessly elevated****, while suppression of heightened immune responses focusing on one subunit (RBD) together with a shift of immune responses to other subunits would occur after repeated vaccination.*

CONCLUSIONS

The presented data further underscore the importance of a two-dose regimen to protect against symptomatic severe disease in newborns (vaccination during pregnancy), adolescents and adults. Unfortunately, vaccine-induced antibodies wane quicker than those induced by natural infection. A third vaccine dose is clearly very useful to protect against delta and omicron, but the question whether a fourth dose of either an RNA or inactivated vaccine is really very useful in immunocompetent subjects remains open.

Best wishes,

Guido