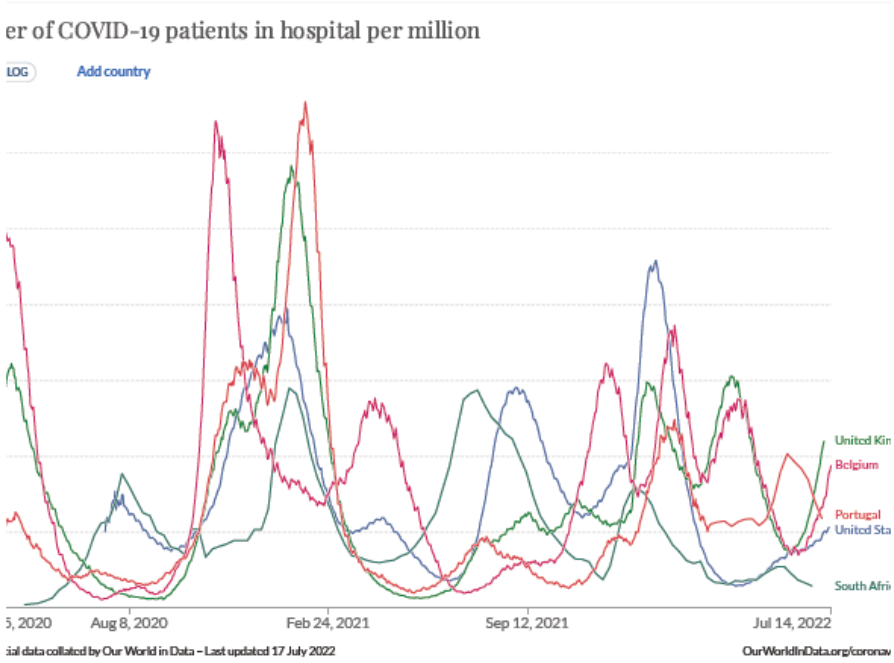
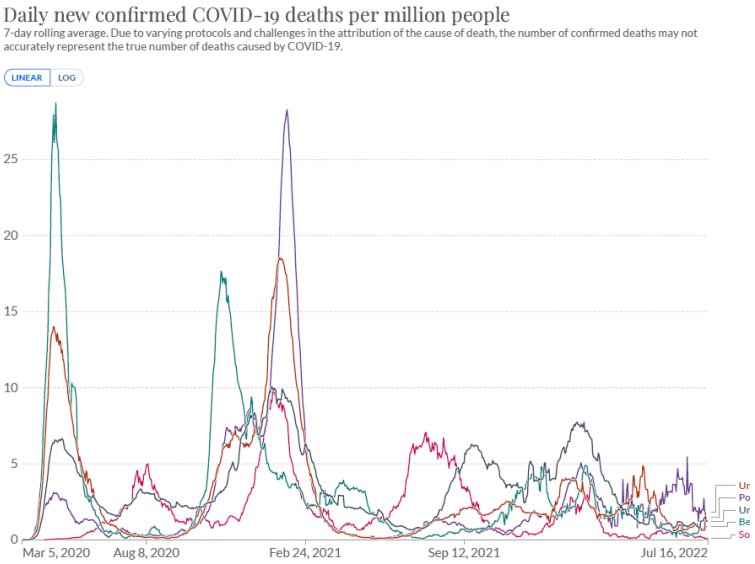
Episode 274: The BA.5 story continued and some news on various vaccines.

Par 1 BA.5





Ep 274.1: Ad Yong in The Atlantic 12 July 2022 on BA.4/.5

BA.5's impact on society will differ greatly around the world

- *Both South Africa and the U.K. have experienced only small rises in hospitalizations and deaths despite surging BA.5 cases, showing that "protection from vaccines against severe disease and death is still really strong,".*
- *Portugal hasn't been so lucky, with deaths climbing to levels that approach those of the first Omicron surge.*

*These differences should be expected. On top of their **demographic differences**, countries are now **complicated patchworks of immunity;** citizens vary in how many times they've been infected or vaccinated, which vaccines they've gotten, and which variants they've encountered.*

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*Still, it's possible to predict what might happen as BA.5 ascends in the U.S. by looking at its effective **reproduction number**, or Rt—the average number of people whom each infected person then infects.*
*- The original version of **Omicron, BA.1**,"came in really hot," With an initial **Rt** of between **3 and 3.5,**he estimates that it infected almost half the country in a few months, including 3 million to 4 million people a day at its peak. (These numbers are higher than the official counts, which have always been underestimates.)*
*- **BA.2 was less ferocious**: with an initial Rt of 1.6, it infected about one in 10 Americans in the spring, and peaked at roughly 500,000 daily infections.*
*- **BA.4 and BA.5** have a slightly higher Rt but should "mostly mirror the BA.2 epidemic," Bedford told me. It might not look that way on recent charts of new cases, where the close overlap between BA.4/BA.5'srise and BA.2's decline creates "the illusion of a plateau," Bedford said, but the U.S. is nonetheless experiencing its third Omicron surge. He expects BA.5 to infect 10 to 15 percent of Americans over the next few months.*
…

*Still, "**it's important not to overpromise the efficacy of Omicron-specific boosters**," Barouch said. In terms of preventing infections, clinical data suggest that they'll be modestly better than current vaccines, but not substantially so. And even if we get the long-desired shots that protect against all coronaviruses, it may be difficult to persuade Americans to get them.*
***Vaccines were never going to end the pandemic on their own**. They needed to be complemented by other protective measures such as masks, better ventilation, rapid tests, and social support like paid sick leave, which were either insufficiently deployed or rolled back. And with stalled COVID funding jeopardizing supplies of tests, treatments, and vaccines, the U.S. will continue its long streak of being underprepared for new variants.*

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***The belief that viruses inevitably evolve into milder versions is a myth:** Such futures are possible but in no way guaranteed. The coronavirus could yet evolve into more severe variants, although vaccines would still be expected to blunt their sting. It could become even more contagious, although the traits that would give it a speed boost, such as higher viral loads or tighter attachments to human cells, can't ratchet up forever. "It's already super-transmissible, and there's not much to gain there," Anne Hahn told me.*

Ep 274-2: Davies medRxiv 1 July 2022: Clinical data on confirmed BA.4/5 in Western Cape

Disease severity was similar amongst diagnosed COVID-19 cases in the BA.4/BA.5 and BA.1 periods in the context of growing immunity against SARS-CoV-2 due to prior infection and vaccination, both of which were strongly protective.

Table 1: Characteristics and outcomes of COVID-19 cases included from each infection period in the Western Cape

	Ancestral wave 25 Apr to 22 Jul 2020[a] (n=40,204)	Beta wave 3 Nov 2020 to 22 Jan 2021[a] (n=54,268)	Delta wave 30 May to 10 Sep 2021[a] (n=68,750)	BA.1 wave 27 Nov 2021 to 12 Jan 2022[a] (n=27,614)	BA.4/BA.5 wave 1 May to 21 May 2022[a] (n=3,793)
Male sex	13,380 (33.3%)	19,083 (35.2%)	25,948 (37.7%)	9,630 (34.9%)	1,327 (35.0%)
Age					
20-39 years	18,720 (46.6%)	21,839 (40.2%)	29,720 (43.2%)	13,944 (50.5%)	1,783 (47.0%)
40-49 years	8,280 (20.6%)	10,594 (19.5%)	14,163 (20.6%)	4,905 (17.8%)	767 (20.2%)
50-59 years	6,982 (17.4%)	10,493 (19.3%)	13,294 (19.3%)	4,216 (15.3%)	623 (16.4%)
60-69 years	3,733 (9.3%)	6,929 (12.8%)	6,780 (9.9%)	2,554 (9.3%)	333 (8.8%)
≥70 years	2,489 (6.2%)	4,413 (8.1%)	4,793 (7.0%)	1,995 (7.2%)	287 (7.6%)
Non-communicable diseases					
diabetes	8,265 (20.6%)	11,509 (21.1%)	11,581 (16.9%)	3,627 (13.1%)	406 (10.7%)
hypertension	13,065 (32.5%)	19,070 (35.1%)	21,170 (30.8%)	7,063 (25.6%)	842 (22.2%)
chronic kidney disease	2,013 (5.0%)	2,778 (5.2%)	3,018 (4.4%)	958 (3.5%)	124 (3.3%)
chronic pulmonary disease / asthma	3,099 (7.7%)	4,661 (8.6%)	6,434 (9.4%)	3,040 (11.0%)	411 (10.8%)
Tuberculosis					
previous tuberculosis	2,777 (6.9%)	3,450 (6.4%)	4,850 (7.1%)	2,229 (8.1%)	232 (6.1%)
current tuberculosis	513 (1.3%)	555 (1.0%)	803 (1.2%)	578 (2.1%)	76 (2.0%)
HIV positive	6,203 (15.4%)	5,512 (10.2%)	5,925 (8.6%)	3,298 (11.9%)	307 (8.1%)
Prior diagnosed SARS-CoV-2 infection	0 (0%)	618 (1.1%)	1,798 (2.6%)	3,179 (11.5%)	715 (18.9%)
Vaccination[b]					
none	N/A	N/A	63,644 (92.6%)	14,471 (52.4%)	1,535 (40.5%)
single dose Ad26.COV2.S	N/A	N/A	2,501 (3.6%)	4,069 (14.7%)	488 (12.9%)
single dose BNT162b2	N/A	N/A	2,289 (3.3%)	1,144 (4.1%)	147 (3.9%)
2 doses Ad26.COV2.S	N/A	N/A	30 (0.04%)	1,127 (4.1%)	298 (7.9%)
2 doses BNT162b2	N/A	N/A	286 (0.4%)	6,763 (24.5%)	1,067 (28.1%)
2 doses Ad26.COV2.S + BNT162b2	N/A	N/A	N/A	N/A	5 (0.1%)
≥3 doses Ad26.COV2.S	N/A	N/A	N/A	36 (0.1%)	38 (1.0%)
≥3 doses BNT162b2	N/A	N/A	N/A	4 (0.01%)	192 (5.1%)
≥3 doses Ad26.COV2.S + BNT162b2	N/A	N/A	N/A	N/A	23 (0.6%)
Outcomes within 21 days of diagnosis					
severe admission (not deceased)[c]	N/A[c]	1,916 (3.5%)	2,066 (3.0%)	481 (1.7%)	61 (1.6%)
death	2,147 (5.3%)	3,717 (6.9%)	4368 (6.4%)	699 (2.5%)	70 (1.9%)

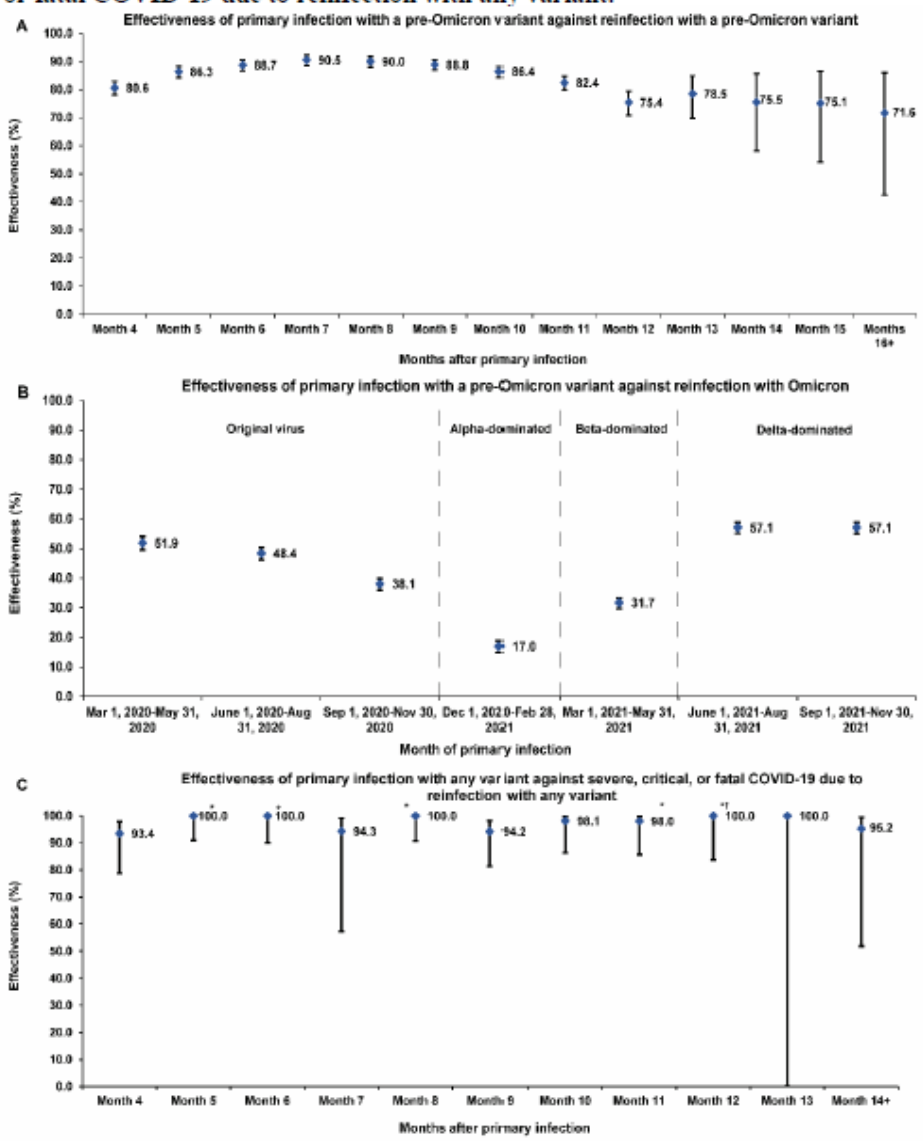
[a]Date of diagnoses for cases included in each wave. We included cases diagnosed from 7 days prior to the "wave start" to the date of wave end (deemed to occur when 7 day moving average of daily new public sector admissions exceeded 5/million (start) and dropped below 12/million (end) respectively). [b]Vaccination is summarized as vaccine type and number of doses provided diagnosis was ≥28 days after first dose, ≥14 days after second dose, and ≥7 days after third dose; [c]Admission to an intensive care unit, mechanical ventilation or prescription of oral or intravenous steroids; not reported for wave 1 as steroids not widely used until after 16 June 2020. N/A = not applicable

Ep 274-3: Studies from Qatar on "natural" (in the sense of infection-induced) immunity

Ep 274-3 A: Chemaitelly medRxiv 7 July 2022 Duration of immune protection of SARS-CoV-2 natural infection against reinfection in Qatar

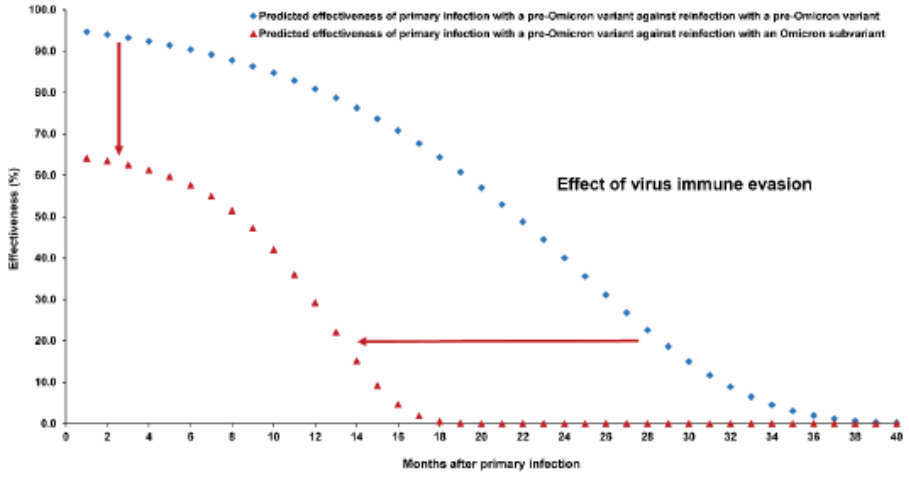
- Protection by infection against reinfection wanes and may diminish within a few years.
- Viral immune evasion accelerates this waning: this is evident in LOWER protection, induced by omicron, as compared to pre-omicron.
- Protection against severe reinfection remains very strong, with no evidence for waning, irrespective of variant, for over 14 months after primary infection.

Figure 2. A) Effectiveness of pre-Omicron primary infection against pre-Omicron reinfection. B) Effectiveness of pre-Omicron primary infection against Omicron reinfection. C) Effectiveness of primary infection with any variant against severe, critical, or fatal COVID-19 due to reinfection with any variant.



*Confidence interval could not be estimated using Cox regression because of zero events and was approximated using the confidence interval for the incidence rate ratio.
†The negative lower bound for the confidence interval was truncated because the confidence interval was too wide.

Figure 3. Extrapolated effectiveness of pre-Omicron primary infection against pre-Omicron reinfection, and extrapolated effectiveness of pre-Omicron primary infection against Omicron reinfection.



Ep 274-3 B: Altarawneh medRxiv 12 July Protection of SARS-CoV-2 natural infection against reinfection with the Omicron BA.4 or BA.5 subvariants

Protection against reinfection with BA.4 or BA.5

Previous infection	Effectiveness against	
	Sympt infection	Any infection
Pre-omicron	15 %	28 %
Omicron BA.1 or BA.2	76 %	80 %

Ep 274-3 C: Altarawneh NEJM Feb 2022 Comparison with effectiveness against early omicron(BA.1)

Table 1. Effectiveness of Previous Infection with SARS-CoV-2 against Symptomatic Reinfection, According to Variant.*

Type of Analysis and Variant	Cases (PCR-Positive)		Controls (PCR-Negative)		Effectiveness (95% CI)†
	Previous Infection	No Previous Infection	Previous Infection	No Previous Infection	
	number of patients				*percent*
Effectiveness against symptomatic infection					
Primary analysis after exclusion of vaccinated patients‡§					
Alpha	1	285	94	1294	95.3 (66.0 to 99.3)
Beta	10	1084	312	4976	85.4 (72.4 to 92.2)
Delta	11	1026	400	3966	90.2 (81.9 to 94.6)
Omicron	60	1031	258	1738	61.9 (48.2 to 72.0)
Effectiveness against severe, critical, or fatal Covid-19¶					
Alpha	1	44	15	199	69.4 (−143.6 to 96.2)
Beta	2	186	76	824	88.0 (50.7 to 97.1)
Delta	0	135	56	528	100 (43.3 to 100)‖
Omicron	2	70	39	167	87.8 (47.5 to 97.1)

In this paper, the previous infection could be any variant against reinfection with the indicated variant

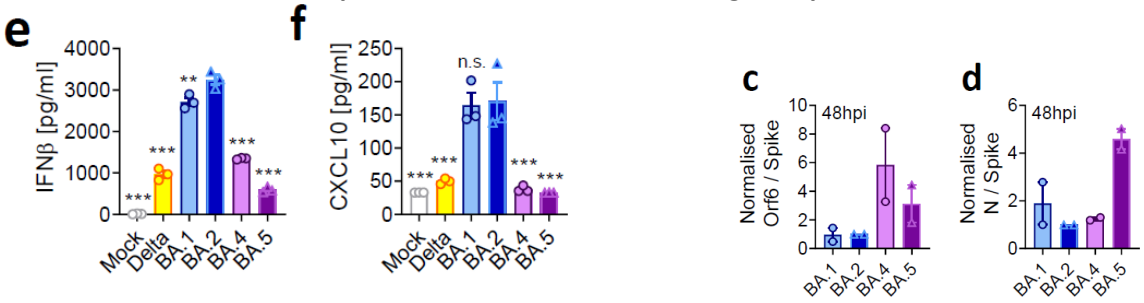
Conclusion: At first view, omicron escapes of infection-induced immunity more than previous variants and this effect is more pronounced for BA.4/5 than for the early omicron (presumably BA.1). However, there is a confounder of time since previous infection, which is not taken into account in Ep 274-3 B, as the previous infection by pre-omicron was clearly longer ago than with omicron.

As you know, I'm disturbed by the imprecise use of the term "natural immunity", which in the previous papers refers to "infection-induced immunity".

The next paper uses the term in the original meaning of "innate immunity"

Episode 274-4: Reuschl bioRxiv 12 July **Enhanced innate immune suppression by SARS-CoV-2 Omicron subvariants BA.4 and BA.5.**

- BA.4/5 show **reduced activation of epithelial innate immune responses** (in case Interferon-beta and the interferon-dependent CXCL-10 or IP-10) compared to earlier BA.1 and BA.2 subvariants, but similar to delta.
- BA.4/5 **enhanced expression of innate immune antagonist proteins Orf6 and N**, similar to Alpha



Ep 274-5: Nordstrom Lancet Reg Health July 2022: Confirmation that fourth dose is useful in "oldest olds" in long-term care facilities in Norway during omicron era (Jan 2022 onwards).

As compared with a third dose, a fourth dose of mRNA COVID-19 vaccine, administered during the Omicron era, was associated with reduced risk of death from all causes in residents of LTCFs and in the oldest old in the general population *during the first two months, after which the protection became slightly lower.*

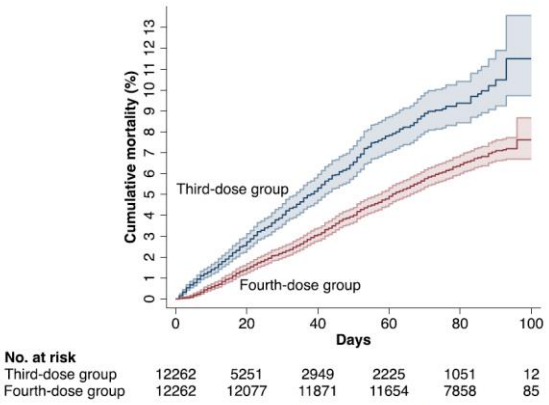


Figure 2. Cumulative risk of death in the fourth-dose group and the third-dose group during the first 100 days of follow-up in the cohort of long-term care facility residents.

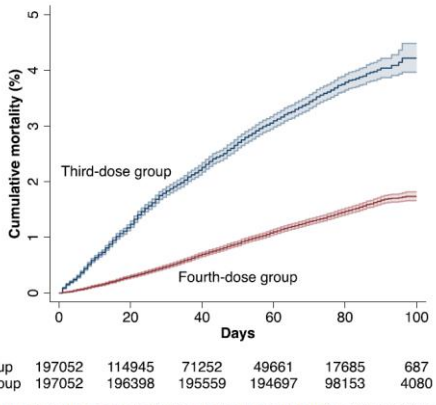


Figure 3. Cumulative risk of death in the fourth-dose group and the third-dose group during the first 100 days of follow-up in the cohort including all individuals aged 80 years and older.

Note: long-term care residents (left graph) are more frail and have higher mortality than all subjects in the oldest (80+) population (right graph).

Par 2 News on vaccines

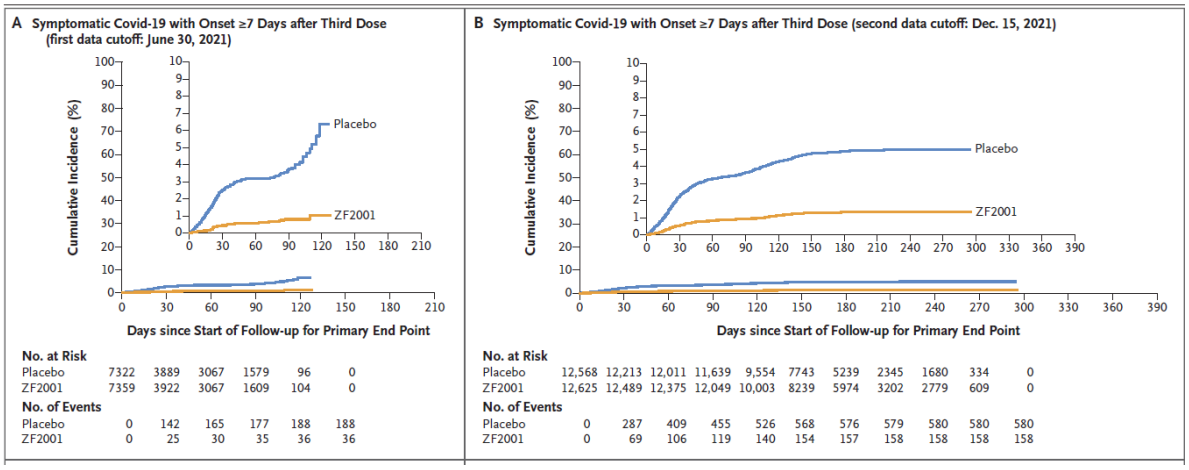
The Chinese vaccines

Ep 274-6: L. Dai NEJM 4 May 2022: ZF2001 (Zifivax®) phase 3

ZF2001 is a protein vaccine; it contains 25 µg of Wuhan-1 dimeric form of receptor-binding domain (RBD) with 0.25 mg of aluminum hydroxide. It is given in three doses, once a month. The trial was done in Uzbekistan, Pakistan, Indonesia and Ecuador during 2021 (mostly alpha, delta and kappa VOC). Over 25,000 individuals were randomized to ZF2001 or placebo.

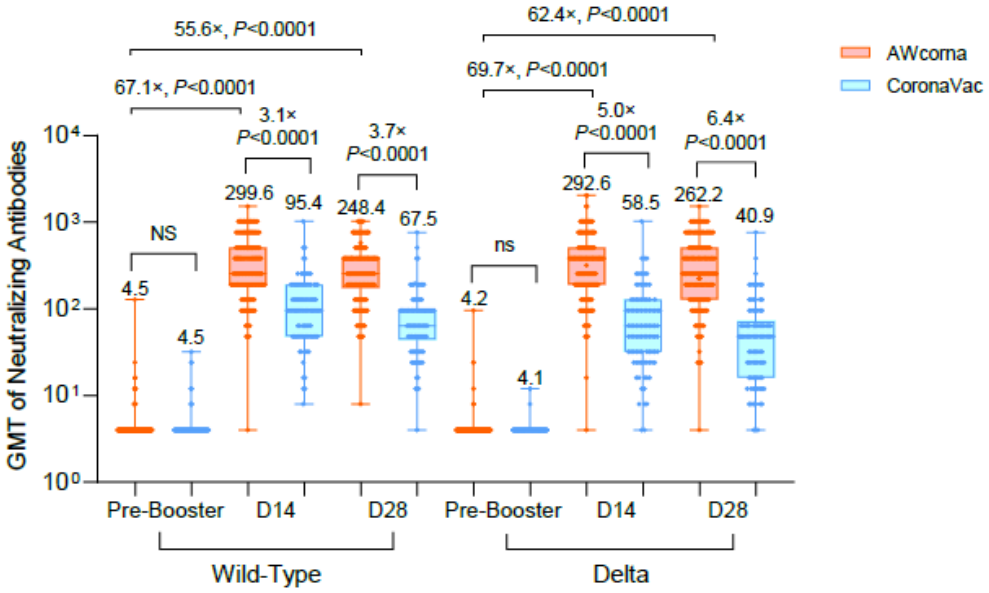
VE after 6 months:

- Primary endpoint (symptomatic COVID): 158 vs 580 = 75 % VE
- Severe-critical COVID: 6 vs 43 = 87.6 %
- Death: 2 vs 12 = 86.5 %



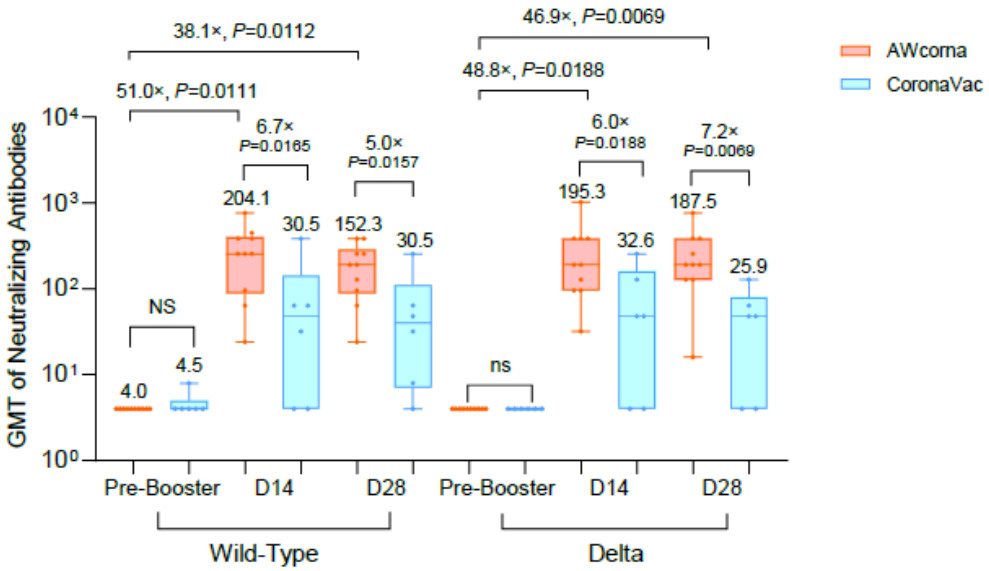
Ep 274-7: Xiaoqiang Liu medRxiv 31 May 2022 RBD-based SARS-CoV-2 mRNA (AWcorna or ArCoV®) as a booster (3rd dose) as compared to inactivated vaccine Coronavac (after 2 doses of Coronavac about 6 months earlier)

a



Age 18 to 59

b



Age ⩾60

As can be seen, pre-boost there was almost no neutralizing activity in the serum.
A booster with either Coronavac or ArCov induces clear neut activity against both wild-type (Wuhan) and delta.
The mRNA ArCov is better in all cases.
However:

- No data on omicron
- No comparison with other vaccines (e.g. ZF2001)
- Only in vitro data.

Ep 274-8: Yvaine Ye Nature Briefing 30 June puts the ArCoV into perspective:

- China has not yet approved the "Western" mRNA vaccines, most probavly for "political' reasons.
- The inactivated Chinese vaccines have limited protective effect.
- The mRNA ArCoV has only finished a phase 2.
- A large part of the Chinese elderly (60 % of 60+ and 80 % in 80+) remains unvaccinated or without booster

- (The RBD protein (ZifiVax), which is highly active see Ep 247-6) , is not considered in this analysis)

→ China has to continue its "zero COVID policy"

Ep 274-9: Le Vu Nat Comm June 2022 Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines

- Increased risks of myocarditis and pericarditis during the **first week** following vaccination, and particularly after the **second dose,** with adjusted odds ratios of myocarditis of 8.1 for the BNT162b2 (Pfizer) and 30 for the mRNA-1273 (Moderna) vaccine.
- The largest associations are observed for myocarditis following mRNA-1273 vaccination in persons aged **18 to 24 years,** with a substantial burden of both myocarditis and pericarditis across other age groups and in **both males and females**.

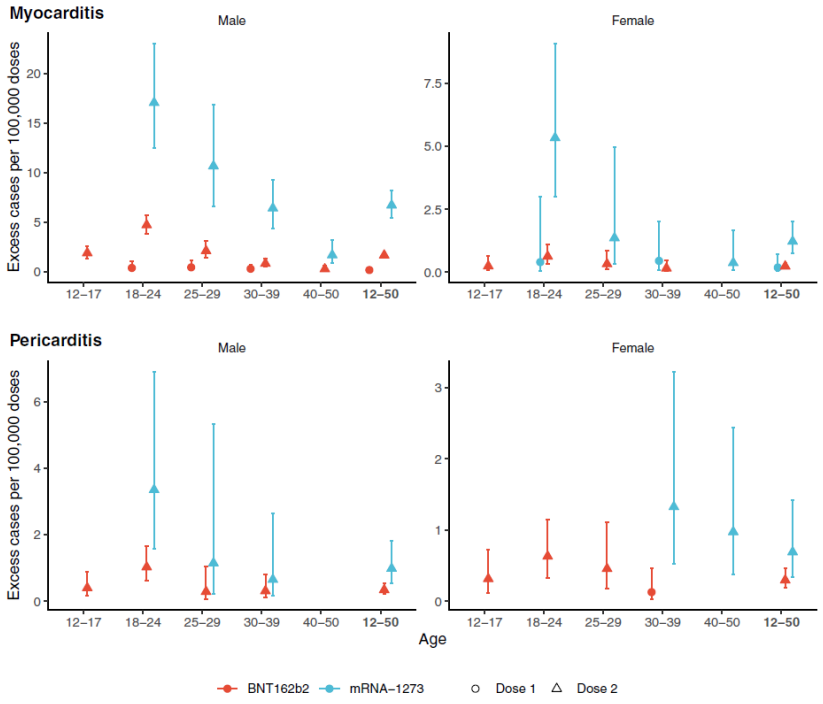


Fig. 3 Excess cases of myocarditis and pericarditis attributable to mRNA vaccines according to sex and age group, per 100,000 doses. Excess cases

Ep 274-10: Press communication on Moderna booster. Will be bivalent (Wuhan and omicron), but in US the omicron will be based on BA.4/5 and in the rest of the Western world (EU, UK, Australia) it will be based on BA.1. Pfizer is likely to follow.

Best wishes,

Guido