

Covid-19 vaccines

A lifetime in Waves

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Learning Objectives

- To describe the safety and efficacy of Covid-19 vaccines used in the US
- To describe the effectiveness of Covid-19 in preventing specific Covid-19 outcomes

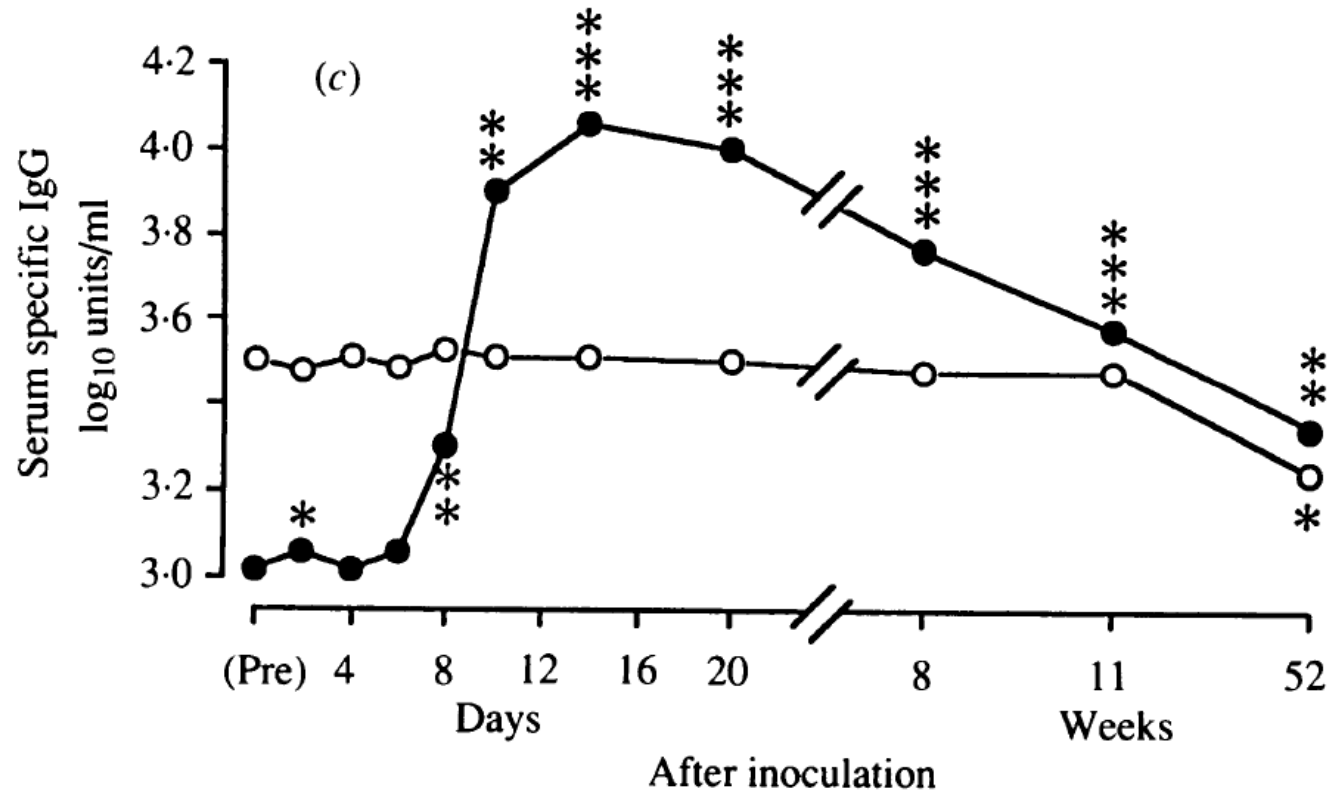
COVID-19 vaccines: any lessons from animals?

Coronaviruses (CoVs) are single stranded, positive sense RNA viruses
Largest known viral RNA: ~30 KB

Virus	Genus	Host	Tropism	
IBV	<i>Gammacoronavirus</i>	chicken	respiratory, kidney, reproductive tract	
TGEV	<i>Alphacoronavirus</i>	pig	enteric	
PRCV	<i>Alphacoronavirus</i>	pig	respiratory	
BCoV	<i>Betacoronavirus</i>	cattle	respiratory, enteric	
FCoV/FIPV	<i>Alphacoronavirus</i>	cat	enteric (FCoV) systemic (FIP)	
MHV	<i>Betacoronavirus</i>	mouse	strain dependent (enteric, hepatic, respiratory, CNS)	

1. Vaccination protects from disease and not infection
2. Immunity is not lifelong

COVID-19 vaccines: any lessons from Controlled Human Infections-229E?



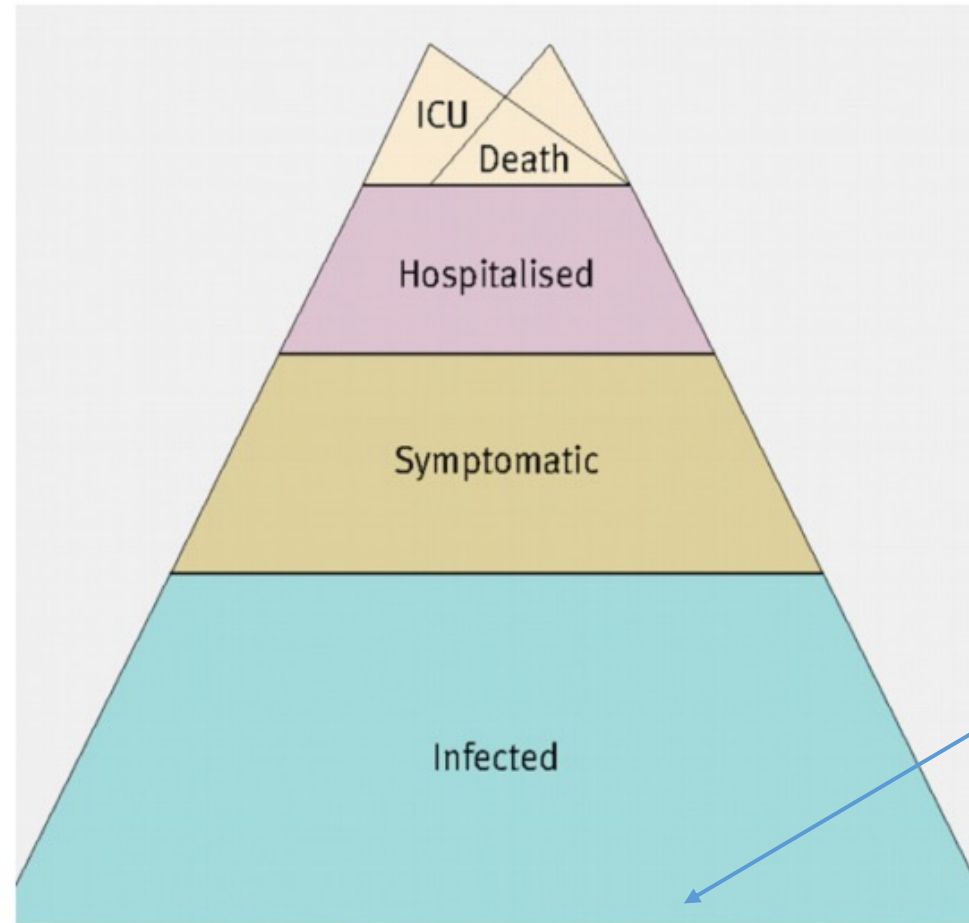
- 10/15 volunteers infected post inoculation (viral shedding)
- IgG and IgA in uninfected >infected
- At 1 year titers in both groups declined
- At 1 year: 6 / 9 from previously infected and 5/5 previously uninfected became infected upon inoculation.

Phase III Clinical Trials

First, know your disease....

COVID 19 Clinical presentation

- **Mild** (no or mild pneumonia) reported in about **80 percent**.
- **Severe disease** (e.g., with dyspnea, hypoxia, or >50 percent lung involvement on imaging within 24 to 48 hours) reported in about **15 percent**.
- **Critical disease** (e.g., with respiratory failure, shock, or multiorgan dysfunction) reported in **5 percent** (these complications **mainly in elderly and those with other health problems**)



How big is this pool?

Unvaccinated,
Low seroprevalence
scenario

Phase 3 clinical Trial Primary Endpoint: What are the options?

- Infection
- Disease
- Severe Disease

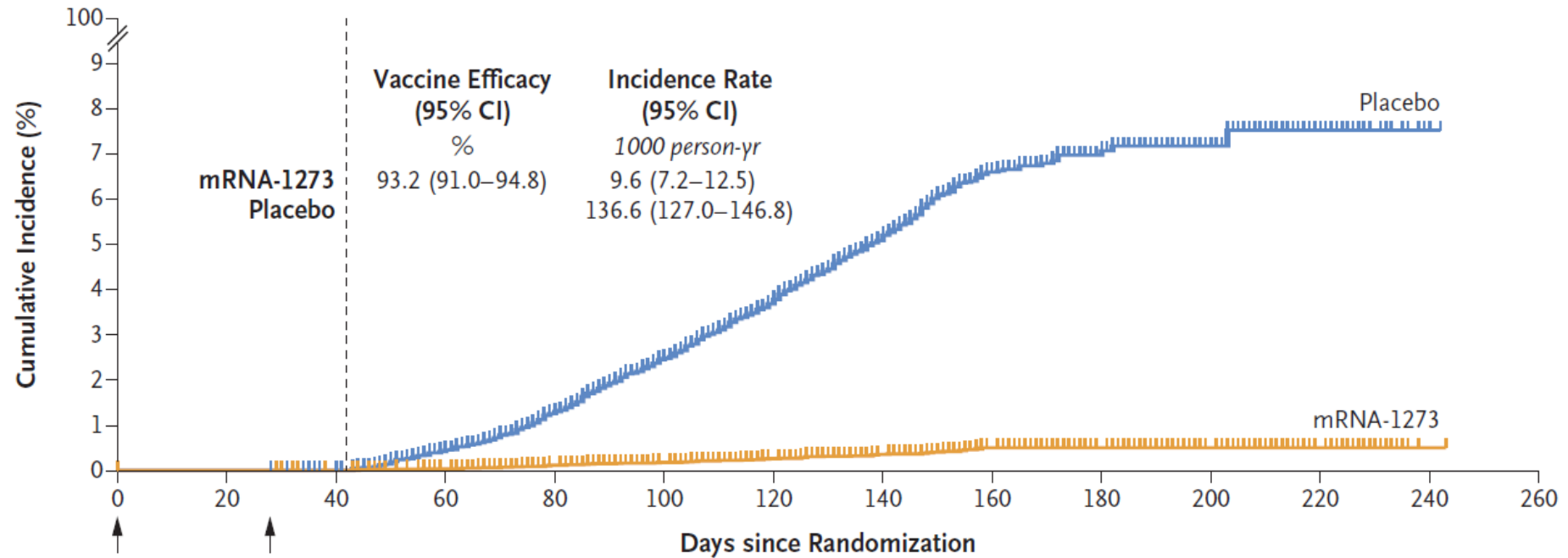
A study with a primary endpoint that captures all the endpoints of public health importance is likely not feasible

mRNA-1273 Vaccine Phase 3 Efficacy Trial

- **30,351 healthy subjects \geq 18 years of age**
 - **Stable chronic disease**
 - **Stable HIV**
 - **Exclude immunocompromised**
 - **41.5% \geq 65 years of age or with risk factor for severe disease**
- **Randomized 1:1 to vaccine or placebo**
- **Two doses 28 days apart**
- **Primary efficacy analysis starting 14 days after second dose**
 - **Incidence of COVID-19 in persons without prior evidence of SARS CoV-2 infection**

Phase 3 mRNA-1273 Vaccine Trial

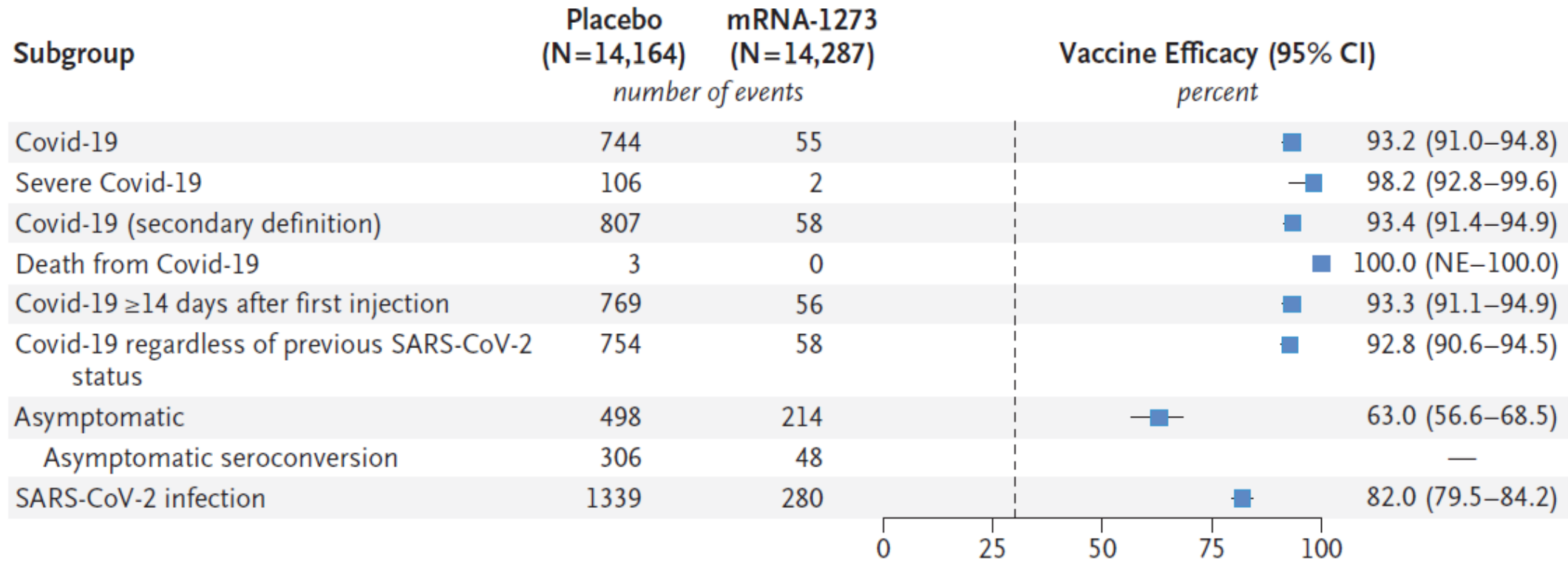
A Covid-19 Events, Per-Protocol Analysis



No. at Risk

Placebo	14,164	14,164	14,134	13,030	13,733	12,970	11,199	7783	3323	953	336	64	5	0
mRNA-1273	14,287	14,287	14,281	14,246	14,096	13,584	12,196	9031	4252	1375	473	49	2	0

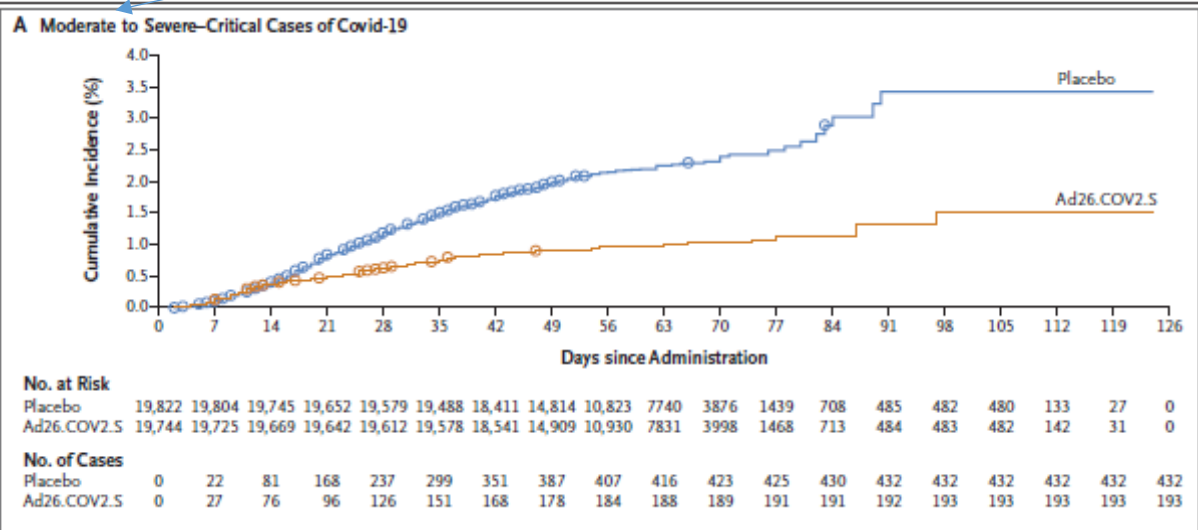
Phase 3 mRNA-1273 Vaccine Trial



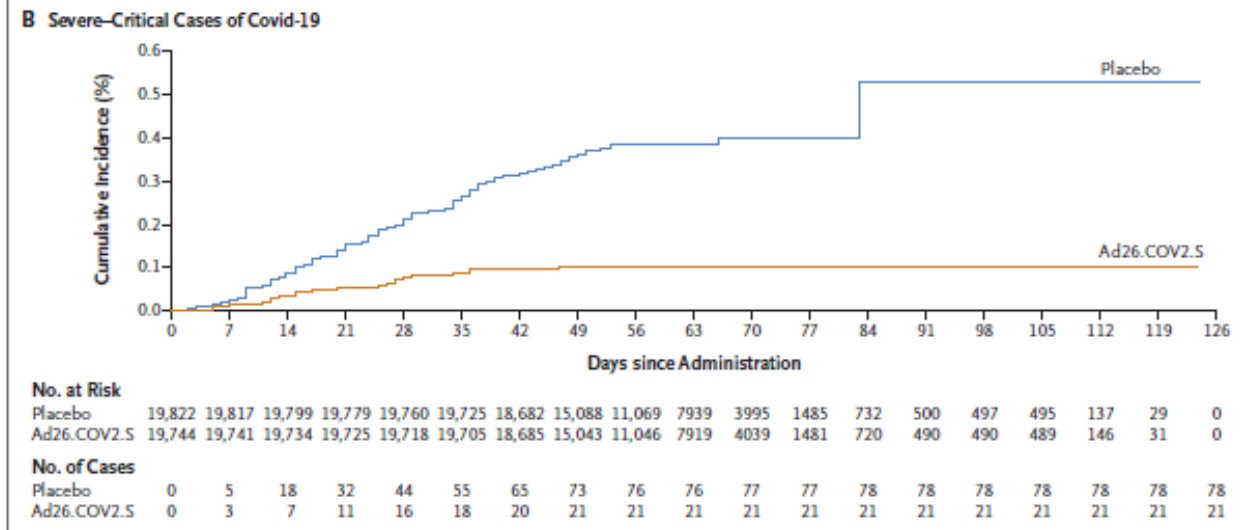
Vaccine Efficacy for Primary and Secondary End Points

AD26.COVS.2.S Phase 3 Clinical Trial

Not according to the methods



VE: 66.9% at 14D+
VE: 66.1% at 28D+



VE: 76.7% at 14D+
VE: 85.4% at 28D+

Cumulative Incidence of COVID-19 and Vaccine Efficacy over Time

COVID-19 under EUA

Safety

AD26.COVS.2.S Ph3 trial

- Imbalance in cases of thromboembolic events (15 vs 10)

POST MARKETING

- Vaccine Induced Thrombosis with Thrombocytopenia (1 in 100,000)
- Guillain-Barré syndrome (1 in 100,000)
- Immune-mediated thrombocytopenia purpura (Obs/Exp~3)

mRNA Vaccines Ph3 Trials

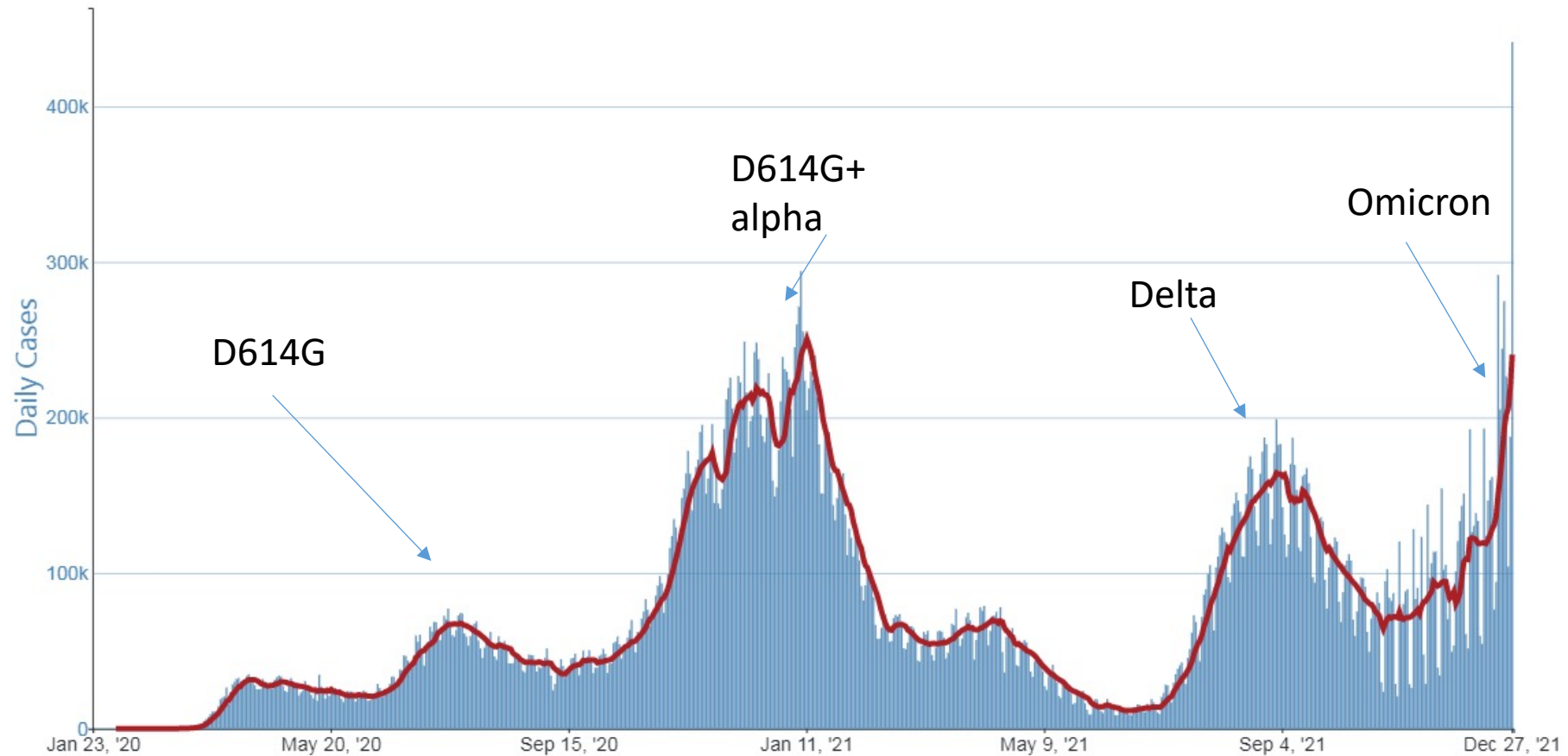
- Imbalance in Bell's Palsy (3 vs 1)

POST MARKETING

- Bell's Palsy fell out (comparable to background)
- Anaphylaxis (2.5-4.7 per million)
- Myocarditis/Pericarditis (~12 per million, age/sex dependent)

Temporal Trends in SARS-CoV-2 Infections in the US

Daily Trends in Number of COVID-19 Cases in The United States Reported to CDC





VACCINE EFFECTIVENESS THROUGH THE D614G and ALPHA WAVES

Vaccine Effectiveness against **infections** in healthcare workers

Data from 33 states

Dec2020 and Mar2021

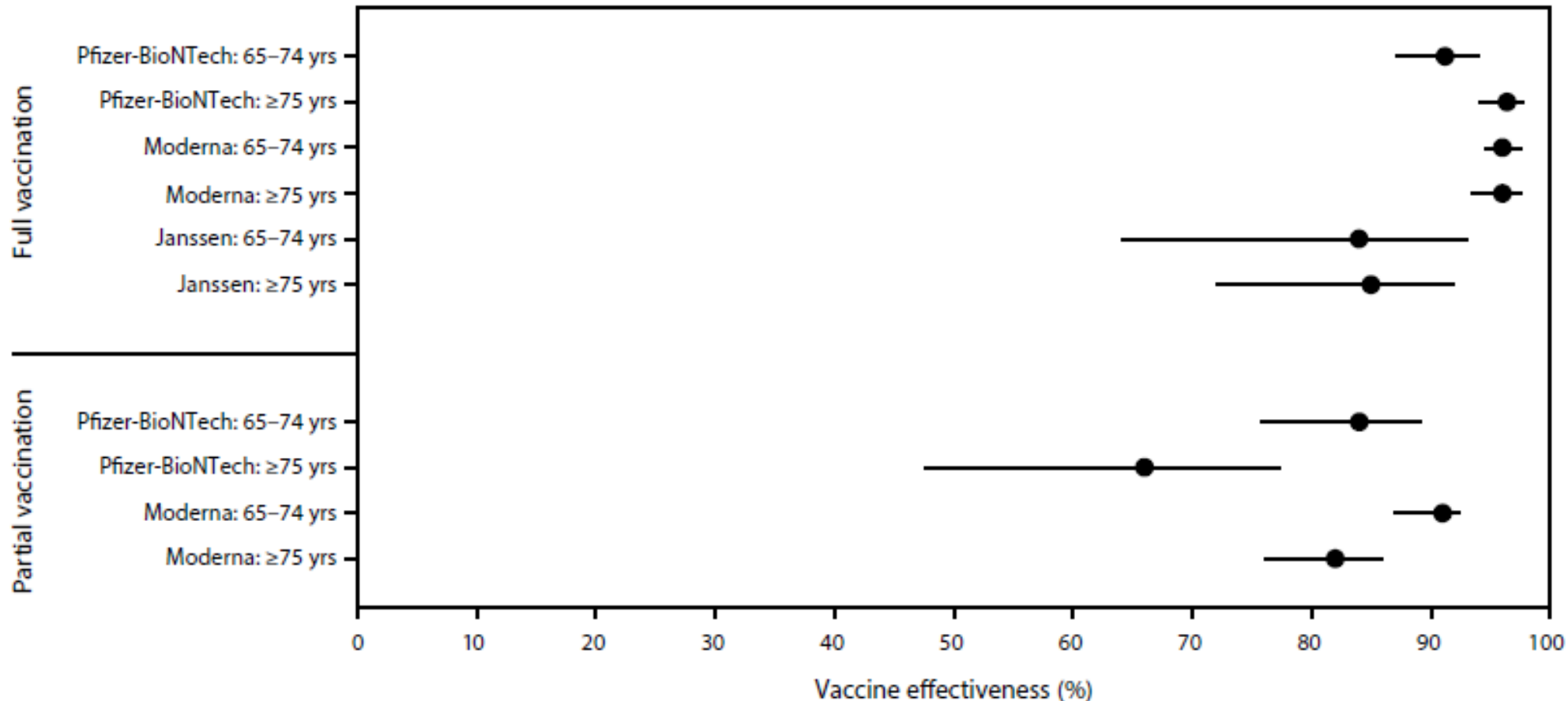
Interval from dose to test date	No. (%)		Vaccine effectiveness [†] % (95% CI)	
	Case-patients* (N = 623)	Controls* (N = 1,220)	Unadjusted	Adjusted [§]
Dose 1				
≥14 days	64 (10)	241 (20)		
Dose 2				
≤2 days	5 (<1)	109 (9)	82.2 (75.1–87.3)	81.7 (74.3–86.9)
3–6 days	16 (3)	85 (7)		
≥7 days	19 (3)	184 (15)	93.4 (86.4–96.8)	93.5 (86.5–96.9)

RWE in healthcare workers, median age of 38 yrs mirrored the efficacy in Ph3 trials

Vaccine Effectiveness against Hospitalizations

Data from 13 states

Jan-Apr2021



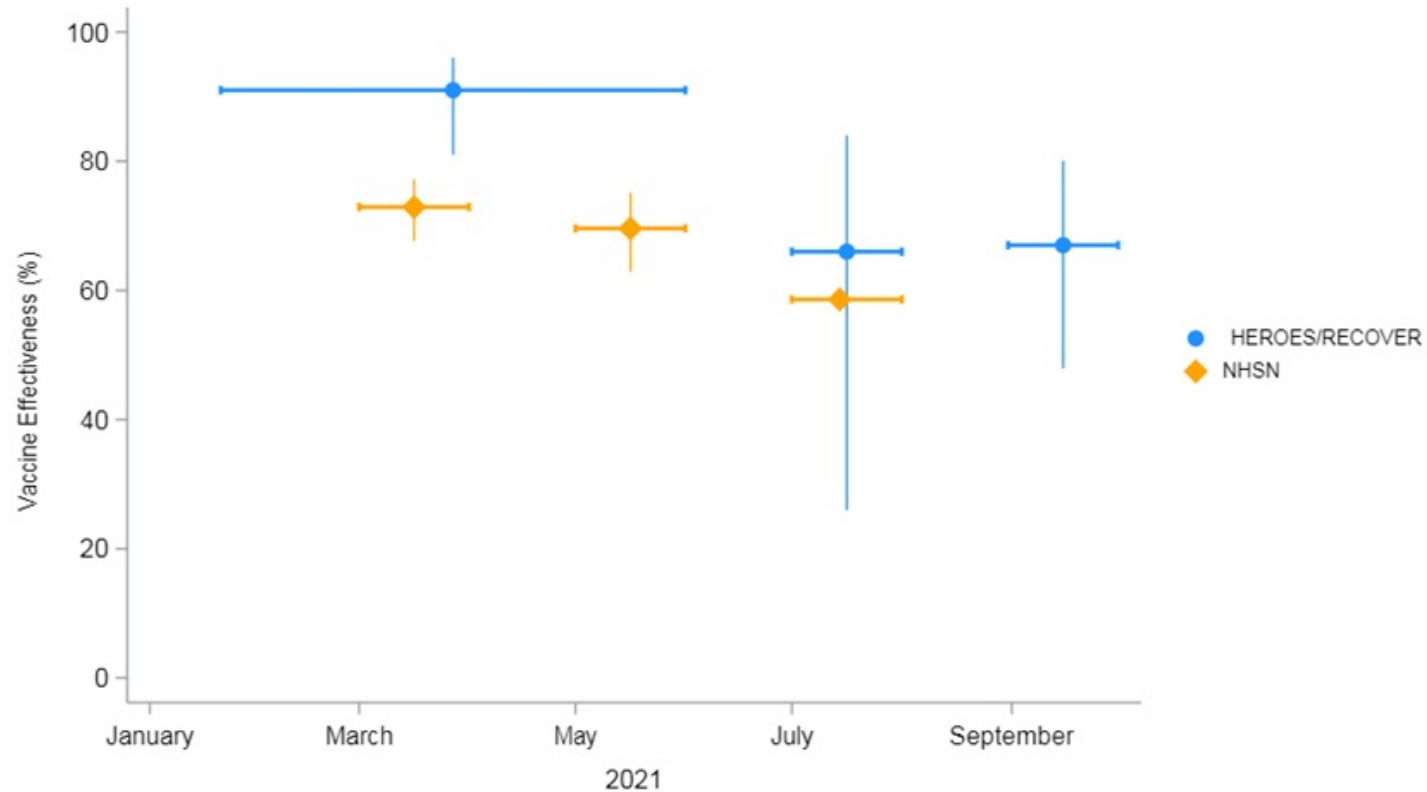
RWE in persons 65 years of age or older mirrored the efficacy in Ph3 trials



VACCINE EFFECTIVENESS THROUGH THE DELTA WAVE

Real World Effectiveness Data

Infection

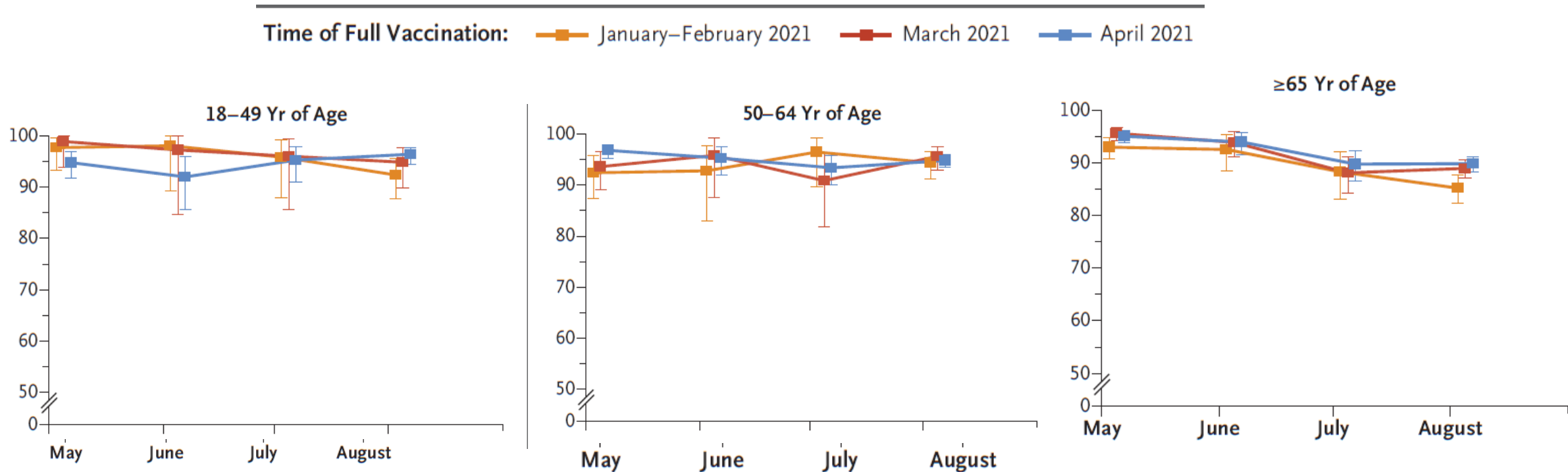


When the delta became the predominant strain in the US, the (mRNA) vaccine effectiveness at preventing infections was ~40-70%

Real World Effectiveness

Hospitalization-BNT162b2 and mRNA1273

NY State



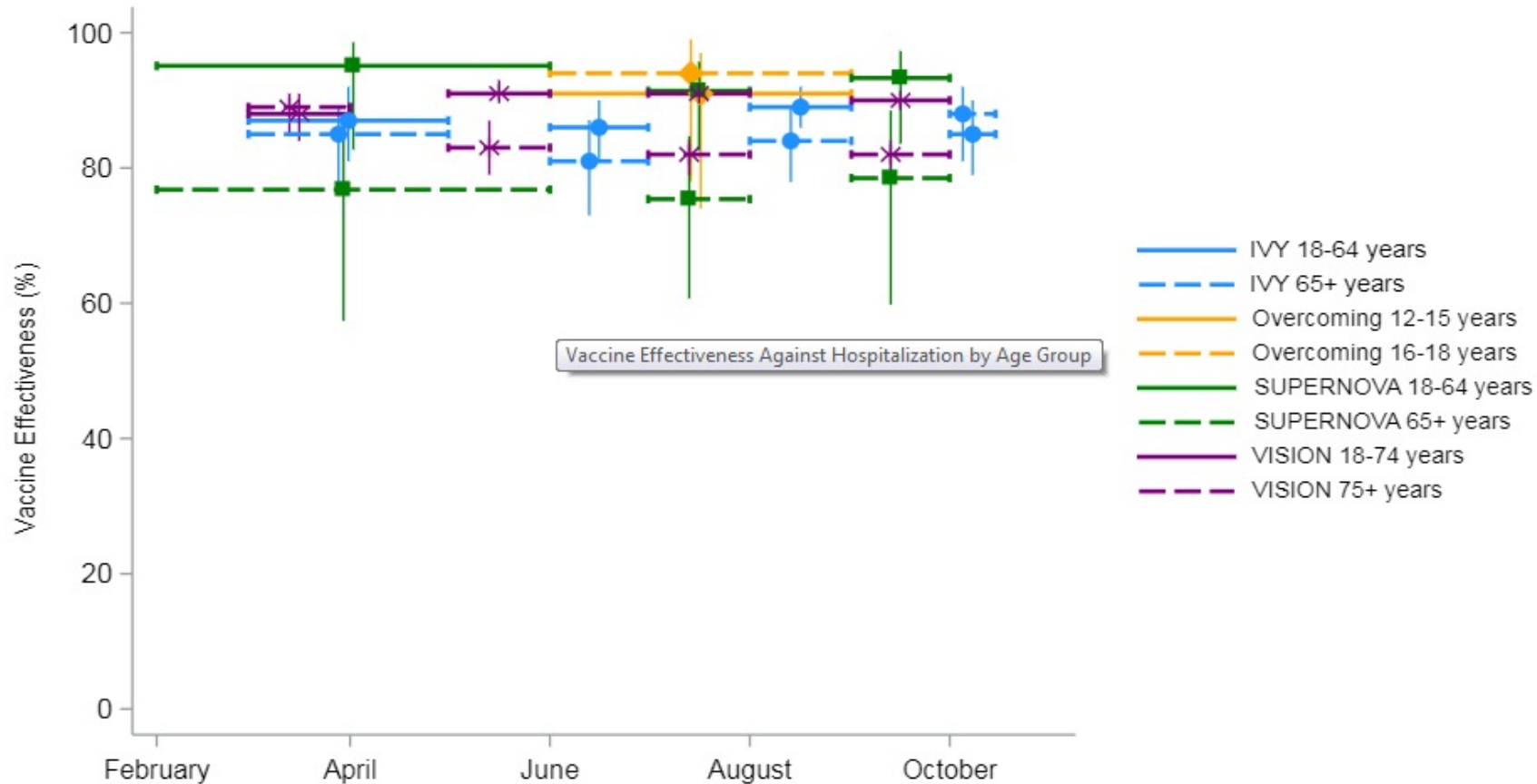
Based on 150,865 cases and 14,477 Hospitalizations

-No time trend for those younger than 64 yo

-Decline in effectiveness from 94.8 to 88.6% (BNT162b2) and 97.1 to 93.7% (mRNA1273) in elders

Real World Effectiveness Data

Hospitalization



The RWE of vaccines against Hospitalization was (consistently) modestly lower in elders through 2 waves

Severe Outcomes after full vaccination

- Where: 465 US healthcare facilities from urban and rural regions
- Who: 1,228,664 persons who completed a primary series of Ad26, mRNA1273 or BNT162b2 ≥ 14 days prior to their Covid-19 illness
- What: severe outcomes of acute respiratory failure, noninvasive ventilation, admission to ICU, or hospice discharge/death
- When: December 2020–October 2021

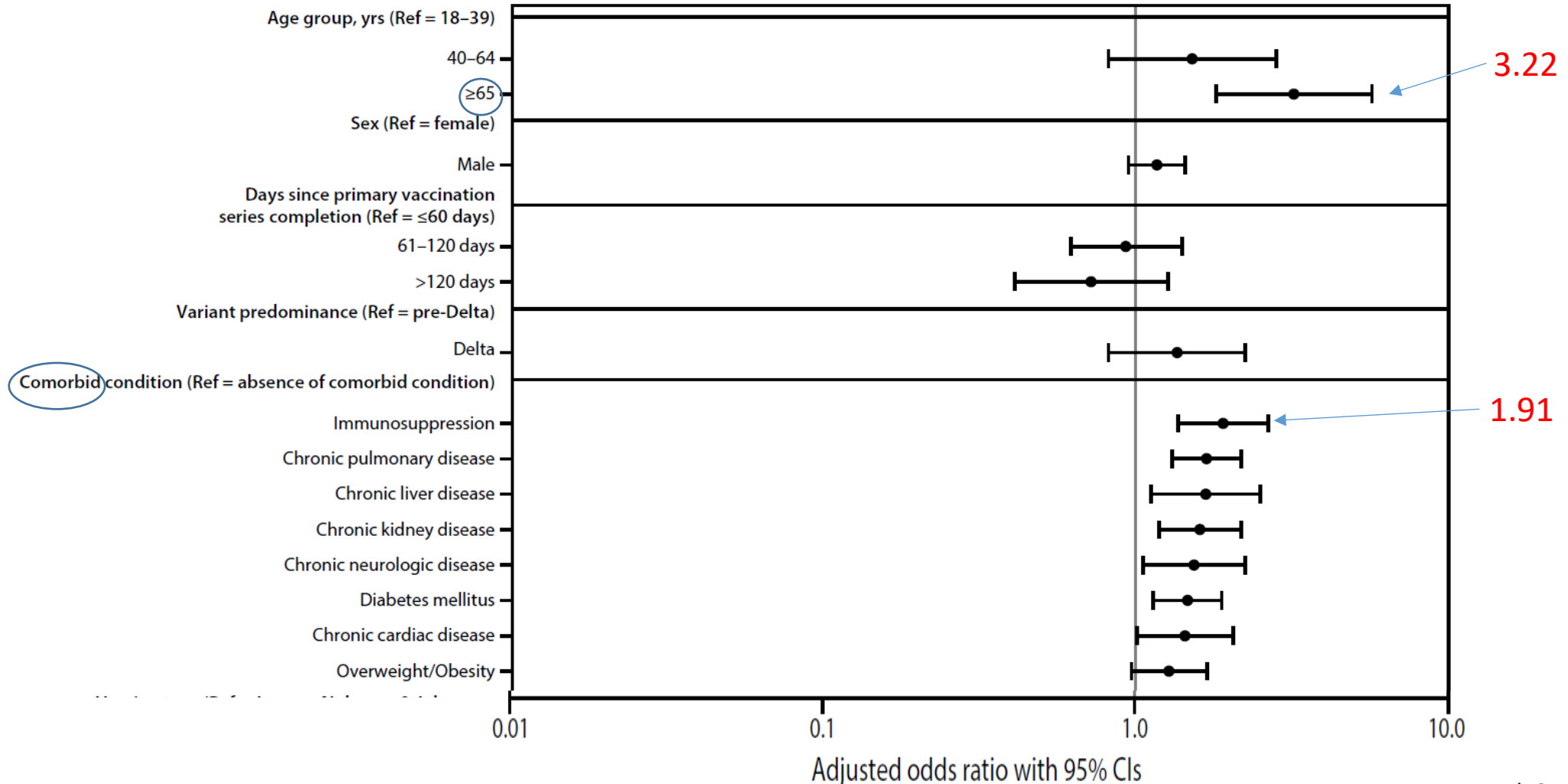
2,246 (18.0 per 10,000 vaccinated persons) developed COVID-19

189 (1.5 per 10,000) had a severe outcome

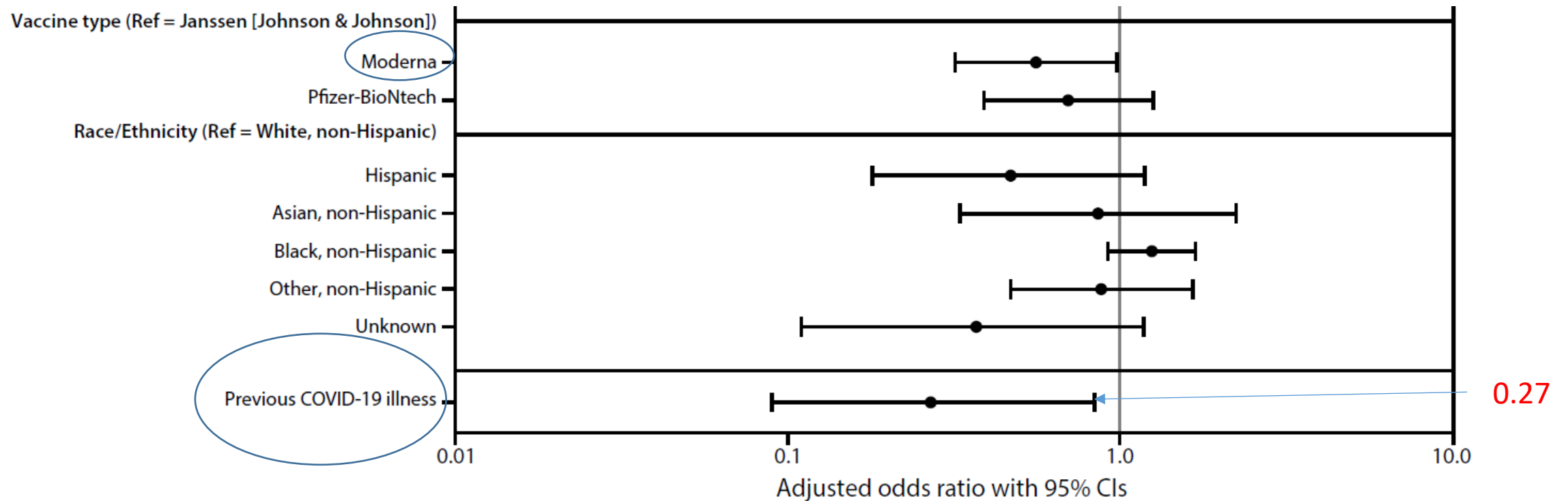
36 died (0.3 deaths per 10,000)

15 had
DNR PTA

Multivariate Model for Risk factors of severe outcomes post vaccination



Multivariate Model for Risk factors of severe outcomes post vaccination



All 189 who had severe outcomes had at least 1 risk factor identified as significant in this model



VACCINE EFFECTIVENESS THROUGH THE OMICRON WAVE

Relative Vaccine Effectiveness Against Omicron Infections

- 30NOV-01JAN; Kaiser Permanente South California.
- 52,297 cases with Omicron and 16,982 cases with Delta
- All indices point to milder disease in Omicron wave than delta wave: Admissions (OR 0.47), ICU Admission (OR 0.26), Death (0.09), Duration of Hospitalization 3.4d shorter

Characteristic	Number of cases (%)		Odds ratio (95% CI)	
	No SGTF	SGTF	Unadjusted	Adjusted
Prior SARS-CoV-2 infection ³				
No documented previous infection	16,886 (99.7)	51,625 (99.0)	ref.	ref.
Documented previous infection	43 (0.3)	508 (1.0)	3.86 (2.83, 5.28)	4.45 (3.24, 6.12)
COVID-19 vaccination				
Unvaccinated	8,419 (49.7)	13,848 (26.6)	ref.	ref.
Ad.26.COV2.S—1 dose	582 (3.4)	1,782 (3.4)	1.86 (1.69, 2.05)	1.93 (1.74, 2.13)
Ad.26.COV2.S—with any booster dose	85 (0.5)	498 (1.0)	3.56 (2.83, 4.49)	3.76 (2.97, 4.76)
BNT162b2 or mRNA-1973—1 dose	486 (2.9)	1,454 (2.8)	1.82 (1.64, 2.02)	1.73 (1.55, 1.93)
BNT162b2 or mRNA-1973—2 doses	6,573 (38.8)	27,570 (52.9)	2.55 (2.45, 2.65)	2.43 (2.33, 2.54)
BNT162b2 or mRNA-1973—3 doses	784 (4.6)	6,981 (13.4)	5.41 (5.00, 5.86)	6.31 (5.79, 6.87)

Vaccine Effectiveness Against Omicron (Maybe) Hospitalizations

- The number of patients with SARS-CoV-2-positive PCR admitted for non-Covid-19 is high during the Omicron (ratio 1:1 to 8:1 non-covid-19:covid-19)
- Analyzing and cleaning the data might take a little more time for reliable evaluations of the VE
- Early read out from South Africa:

Per authors:
unvaccinated status
not verifiable????

Variable	Vaccine Effectiveness (95% CI)	
	Comparator Period	Proxy Omicron Period
		%
Overall estimate	93 (90–94)	70 (62–76)
Sensitivity analyses of PCR results		
Patients with S-gene target failure	—	69 (48–81)
Patients in Gauteng province	—	70 (59–78)
Patients with Covid-19 symptoms	—	50 (35–62)

CONCLUSIONS

- Covid-19 vaccines are effective at preventing the severe outcomes of Covid-19 through waves by different strains
- Prevention of infection or mild disease is short-lived using the current tools
- Future Research Goals for Vaccine Development:
 1. Understanding the risk factors for vaccine failure (as measured by meaningful outcomes): host, vs vaccine, vs strain factors
 2. Developing novel vaccine strategies or products to answer item 1 above...

QUESTIONS?

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