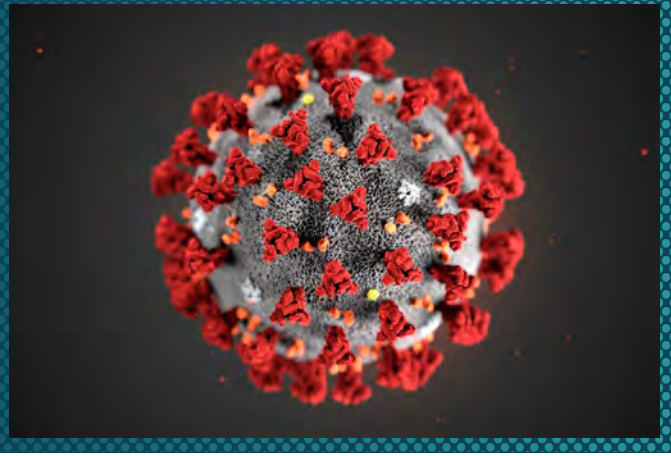
University of Washington
Public Health Capacity Building Center

COVID-19 Clinical Update

I-TECH Videoconference February 14, 2021

Matthew Golden, MD, MPH
Professor of Medicine, University of Washington
Director, PHSKC HIV/STD Program
Director, UW Center for AIDS and STD



Last Updated: February 14, 2022

I-TECH
International Training and Education Center for Health

Overview

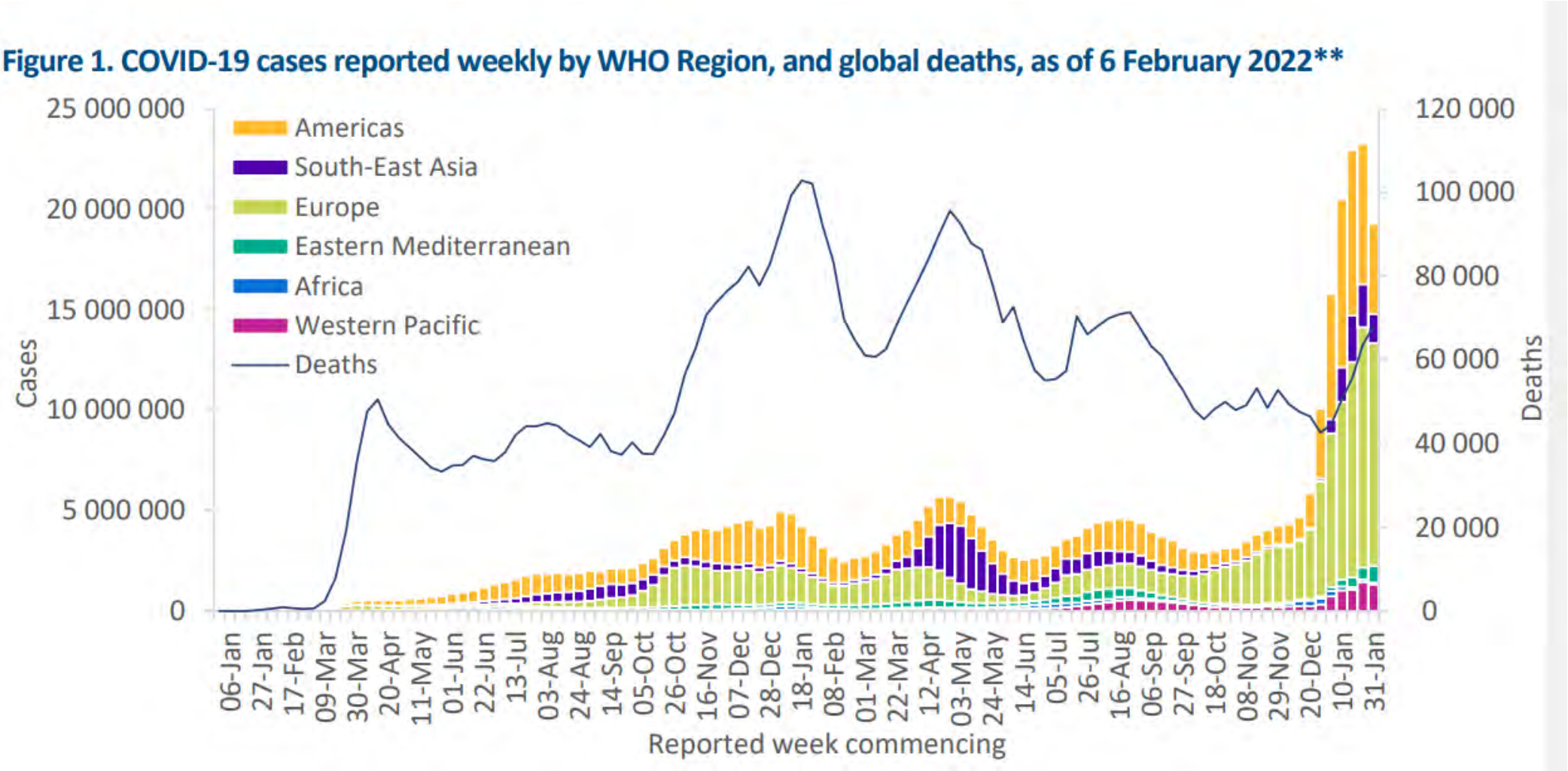
- Epidemiology
  - Trends
  - Omicron – new subvariants
- Treatment – Remdesivir
- Natural Immunity & Vaccines
  - Boosters and Omicron
- Long COVID

Global Trends in COVID-19 Diagnoses & Deaths

>392 Million Confirmed Cases
>19 million cases/week

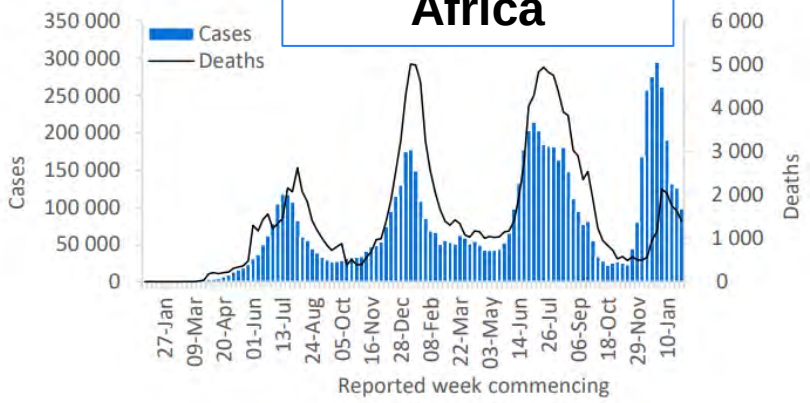
~5.7 Million Confirmed Deaths
~68,000 deaths/week

Decrease in new cases with increase in number of deaths over the last week



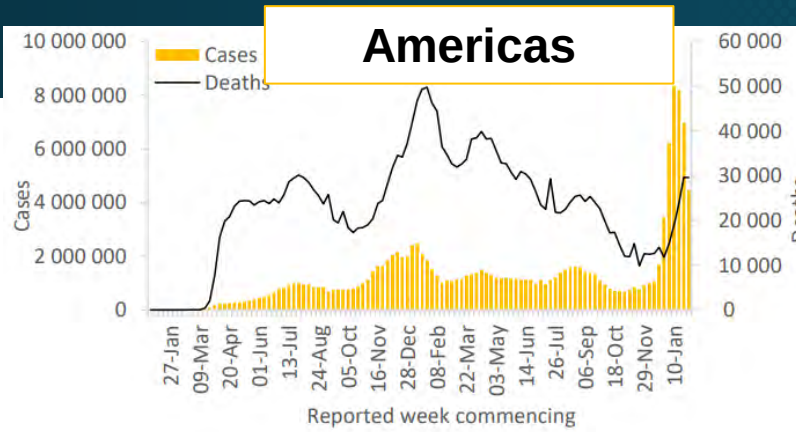
Global Trends in COVID-19 Diagnoses & Deaths

Africa



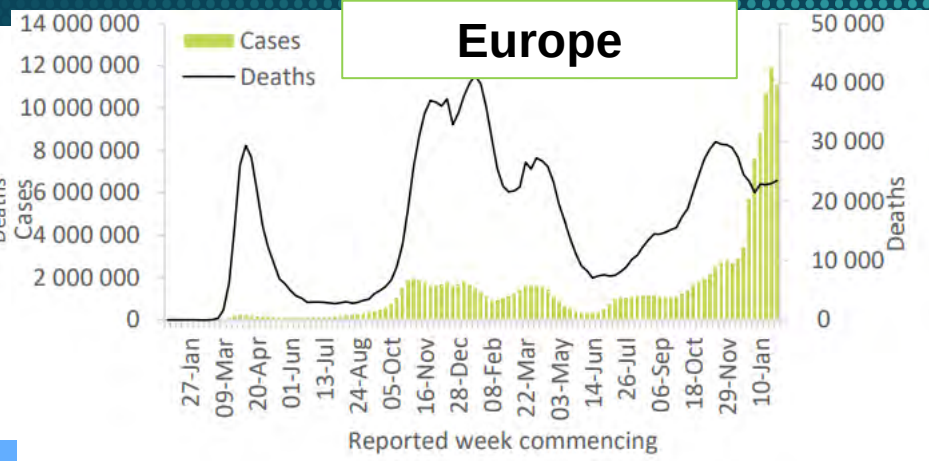
↓ Cases and Deaths most places

Americas



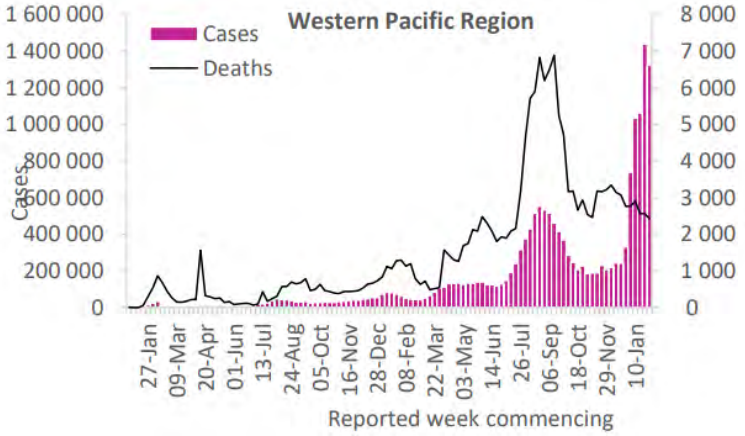
↓Cases overall, but highly variable – stable in Brazil – Death no change overall – increase in Mexico, Brazil

Europe



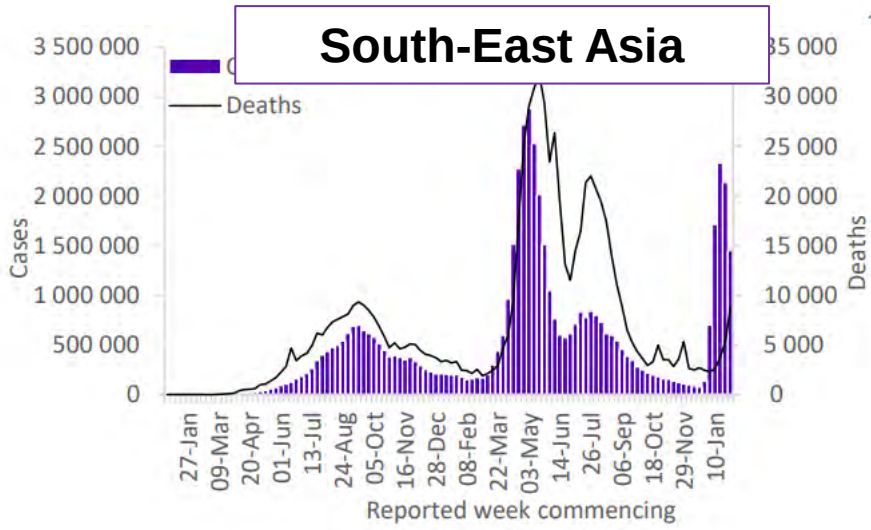
Plateau at high level – Very high in Russia

Western Pacific



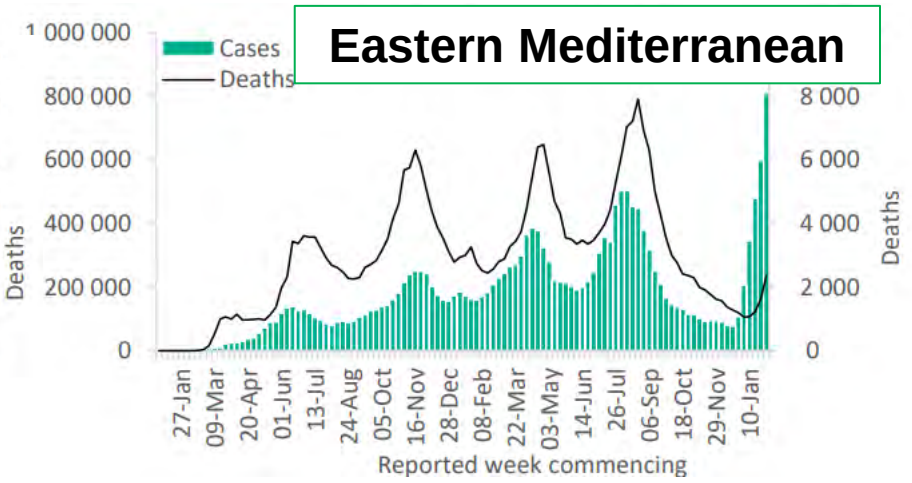
Cases plateauing at high level

South-East Asia



↓ Cases ↑ Deaths

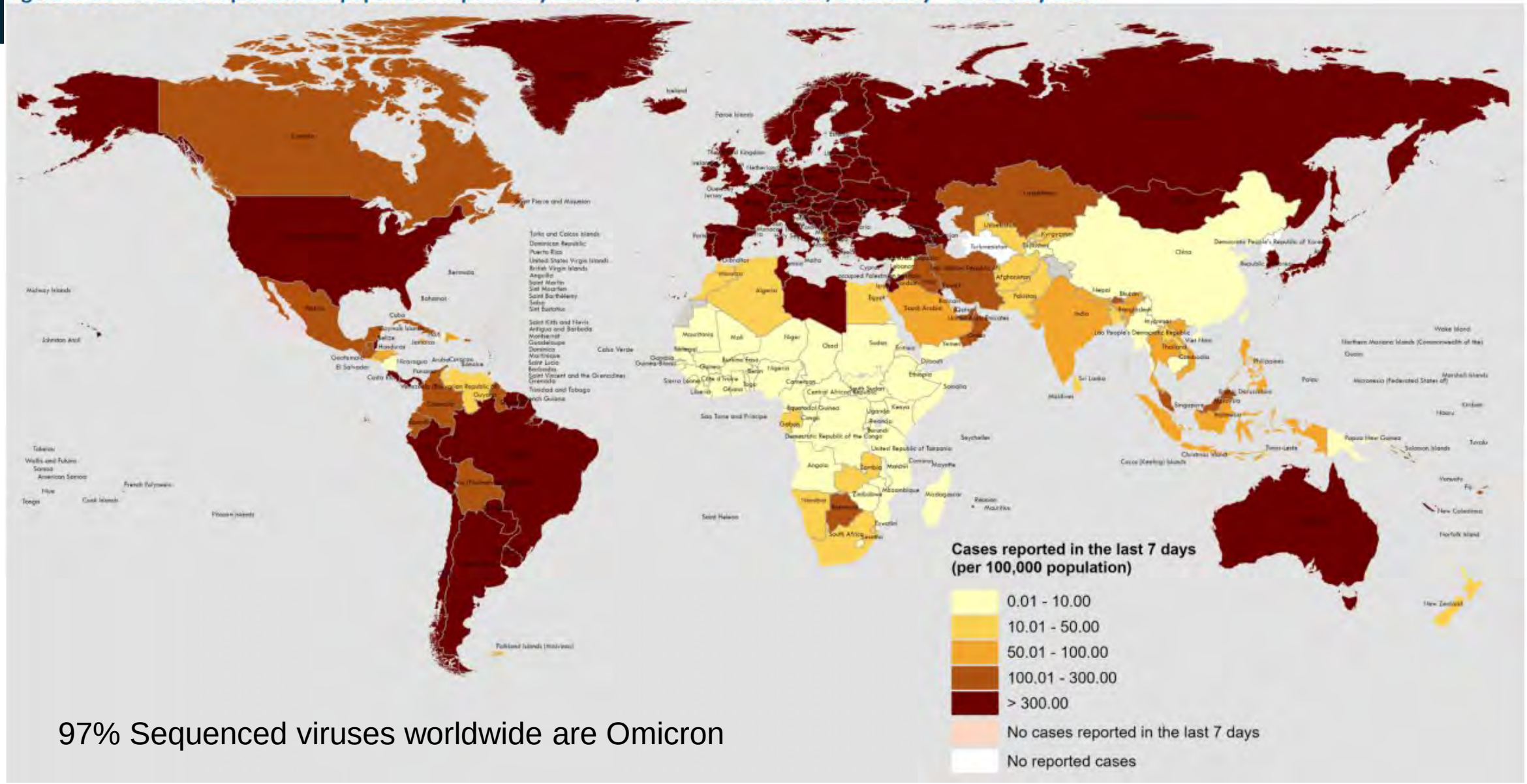
Eastern Mediterranean



↑ Cases and Deaths

COVID-19 cases/100,000 population, January 31-February 6, 2022

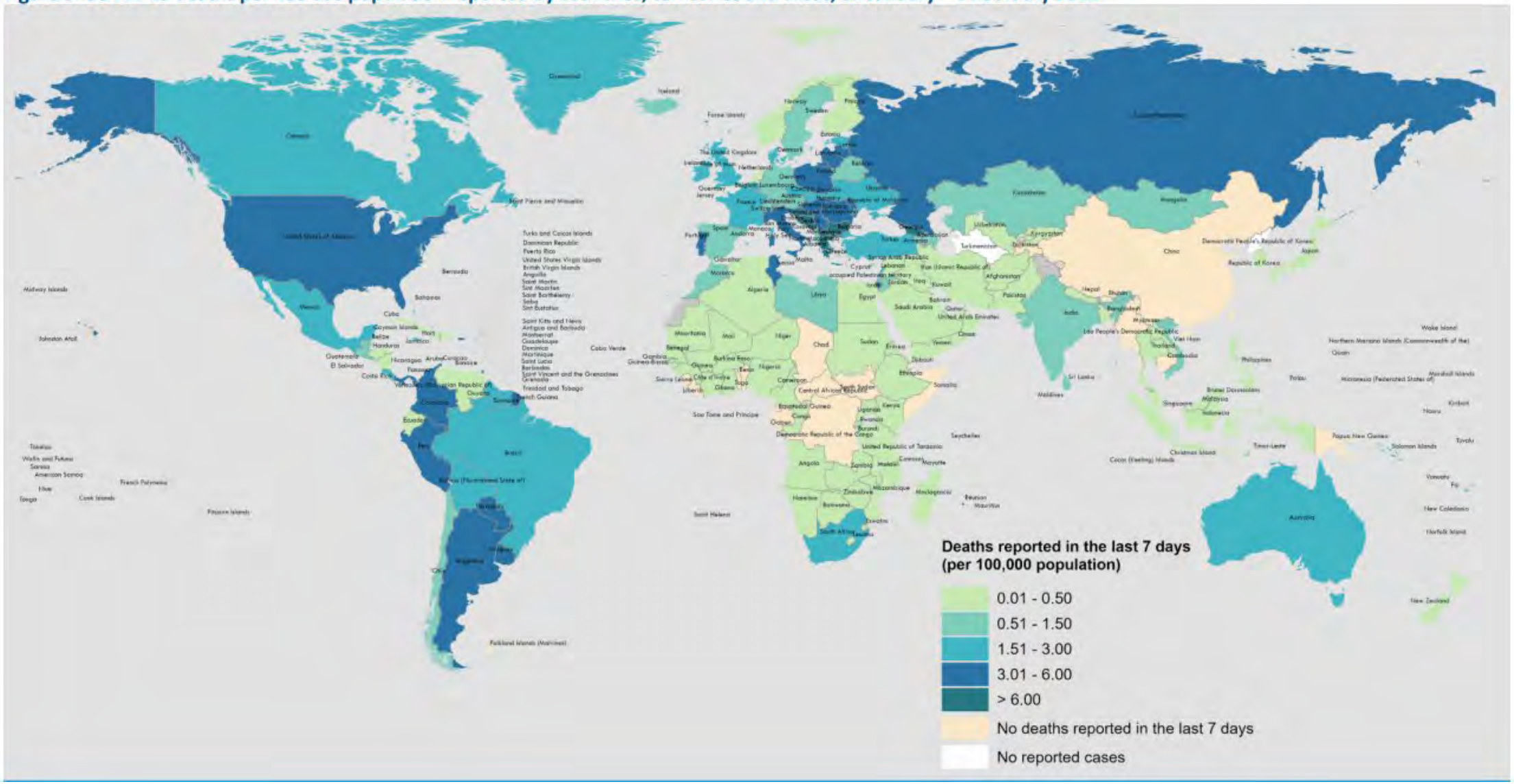
Figure 2. COVID-19 cases per 100 000 population reported by countries, territories and areas, 31 January – 6 February 2022**



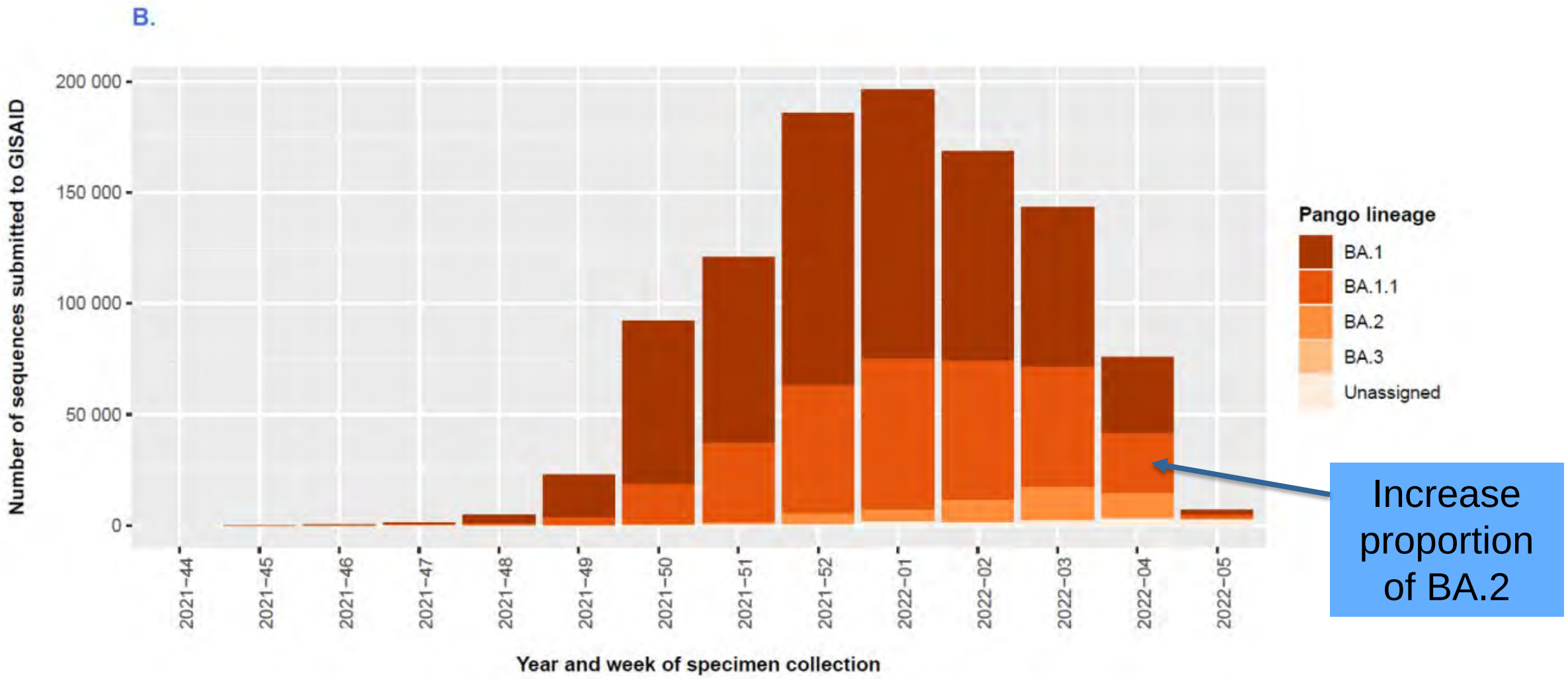
97% Sequenced viruses worldwide are Omicron

COVID-19 deaths/100,000 population, January 31-February 6, 2022

Figure 3. COVID-19 deaths per 100 000 population reported by countries, territories and areas, 31 January – 6 February 2022**



Omicron Evolution: Trends in Omicron Pango Lineage



Increase proportion of BA.2

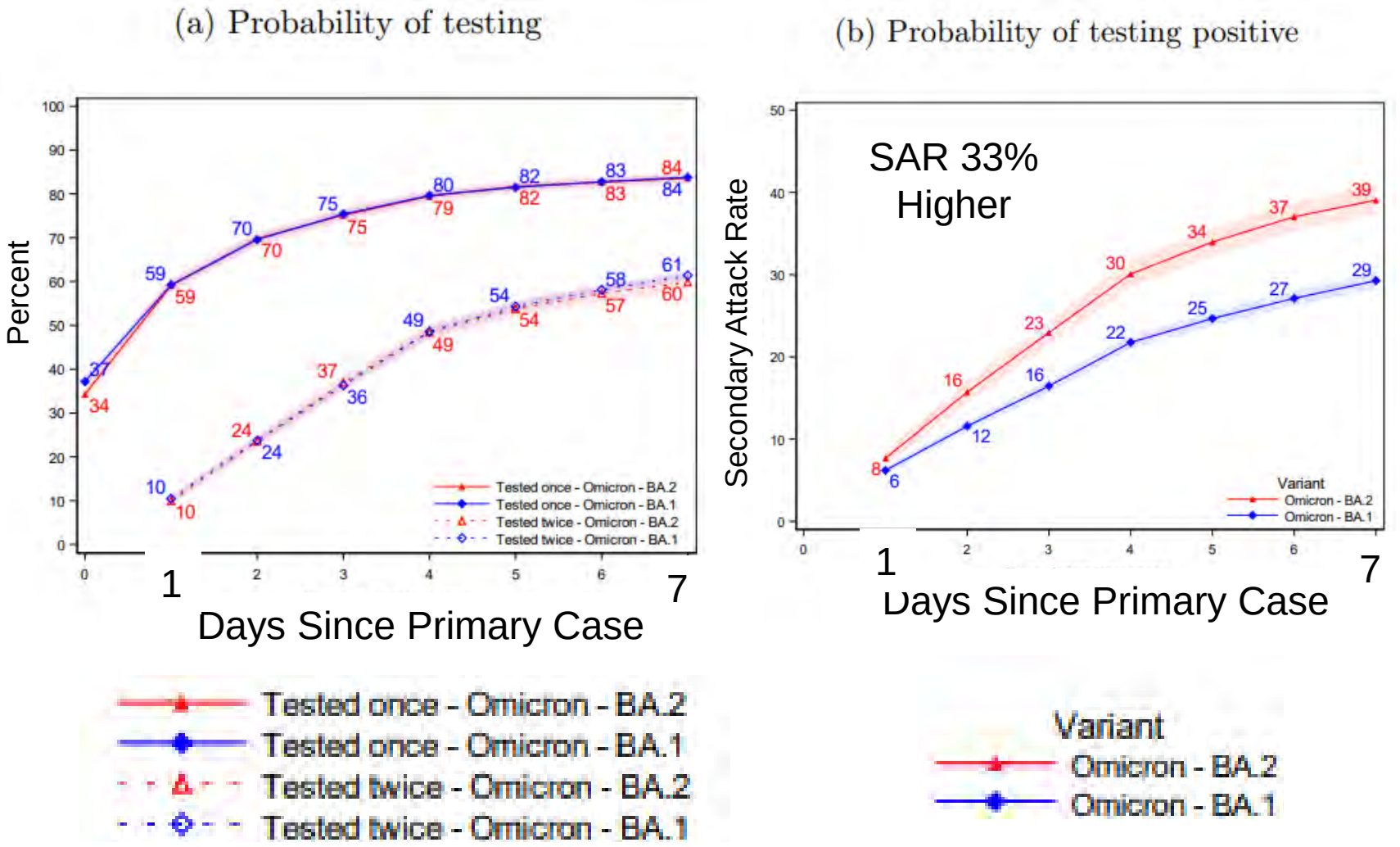
Omicron Evolution: BA2 in Denmark
Secondary Attack Rate (SAR)

Background: BA.2 differs from BA.1 by ~40 mutations. Little is known about its transmissibility or ability to evade vaccine-induced immunity.

Design: Analysis of national surveillance data Denmark

Population: Persons testing SARS-CoV-2 positive by PCR in Denmark 12/20/21-1/11/22 – 2,122 households with BA.2 and 6,419 BA.1

Outcome: Secondary attack rate (SAR) in household members & vaccine efficacy



Source: Lyngse FP. MedRxIV 2022

Omicron Evolution: BA2 in Denmark
Effect of Vaccination

- Comparing vaccinated vs. unvaccinated - Both susceptibility and transmissibility were lower in people who had received boosters
  - Vaccines still provided some protection

Table 2: Effect of Vaccination

Susceptibility | Transmissibility

	Omicron BA.2 households	Omicron BA.1 households	Omicron BA.2 households	Omicron BA.1 households
Unvaccinated	1.10 (0.92-1.32)	1.23 (1.09-1.40)	1.21 (0.97-1.50)	0.93 (0.80-1.08)
Fully vaccinated	ref (.)	ref (.)	ref (.)	ref (.)
Booster vaccinated	0.80 (0.67-0.94)	0.65 (0.58-0.73)	0.79 (0.64-0.98)	0.77 (0.70-0.88)
Number of observations	17,945	17,945	17,945	17,945
Number of households	8.541	8.541	8.541	8.541

Source: Lyngse FP. MedRxIV 2022

Omicron Evolution: BA2 in Denmark

- BA.2 associated with greater susceptibility to infection regardless of vaccine status
  - Relative effect of BA.2 greater in vaccinated - ↓Vaccine effectiveness
- BA.2 associated with great transmissibility than BA.1 if initial case was unvaccinated but lower transmissibility than BA.1 if the initial case was vaccinated
  - Unvaccinated cases had lower PCR Ct values – c/w higher viral loads

Table 3: Relative effect of Omicron VOC BA.2 vs. BA.1

	Susceptibility			Transmissibility		
	Unvaccinated	Fully vaccinated	Booster vaccinated	Unvaccinated	Fully vaccinated	Booster vaccinated
Omicron BA.2 households	2.19 (1.58-3.04)	2.45 (1.77-3.40)	2.99 (2.11-4.24)	2.62 (1.96-3.52)	0.60 (0.42-0.85)	0.62 (0.42-0.91)
Omicron BA.1 households	ref (.)	ref (.)	ref (.)	ref (.)	ref (.)	ref (.)
Number of observations	17,945	17,945	17,945	17,945	17,945	17,945
Number of households	8,541	8,541	8,541	8,541	8,541	8,541

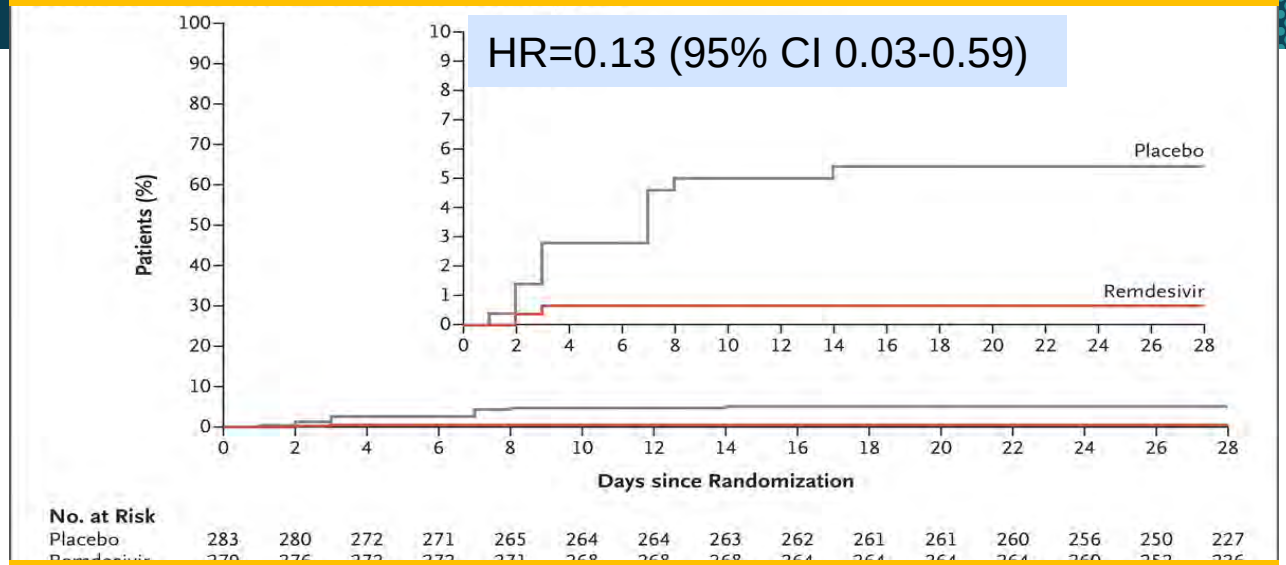
Source: Lyngse FP. MedRxIV 2022

Remdesivir: PINETREE Trial

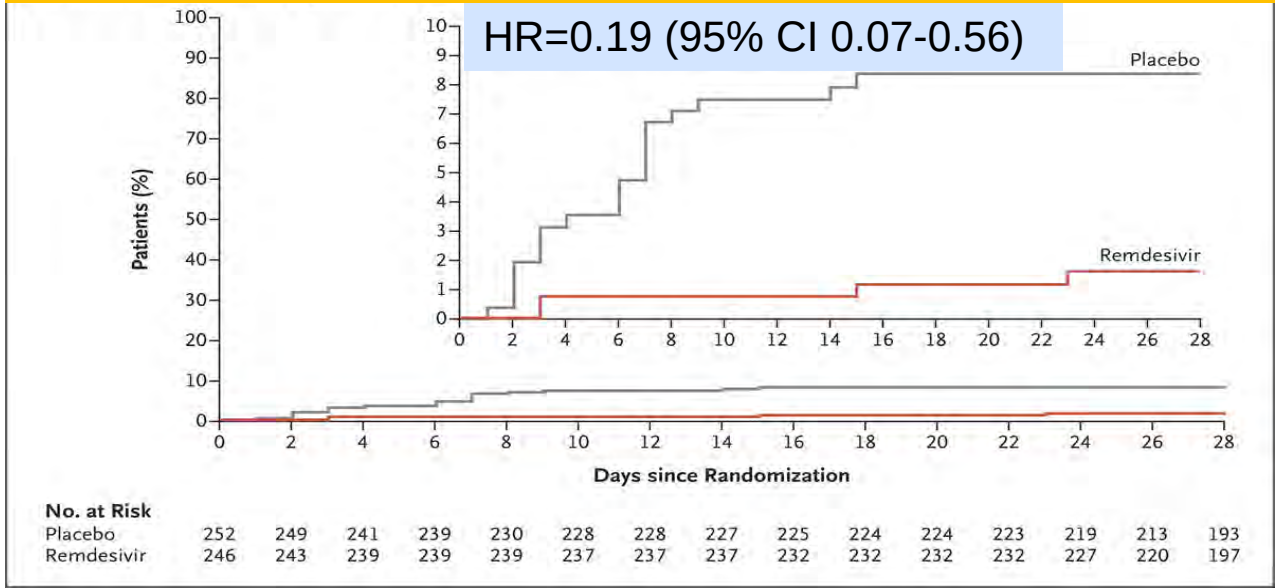
Background: Remdesivir previously shown to improve outcomes in hospitalized patients in one RCT, but not in a 2nd trial.
Design: Randomized double-blind placebo-controlled trial
Intervention: 3 days IV Remdesivir
Population: 562 people with COVID-10 and symptoms <7 days with risk for severe disease (DM, HTN, obesity)
Outcome: Hospitalization or death

Difficult to administer an IV medication to large number of outpatients

COVID-19 Hospitalization or Death



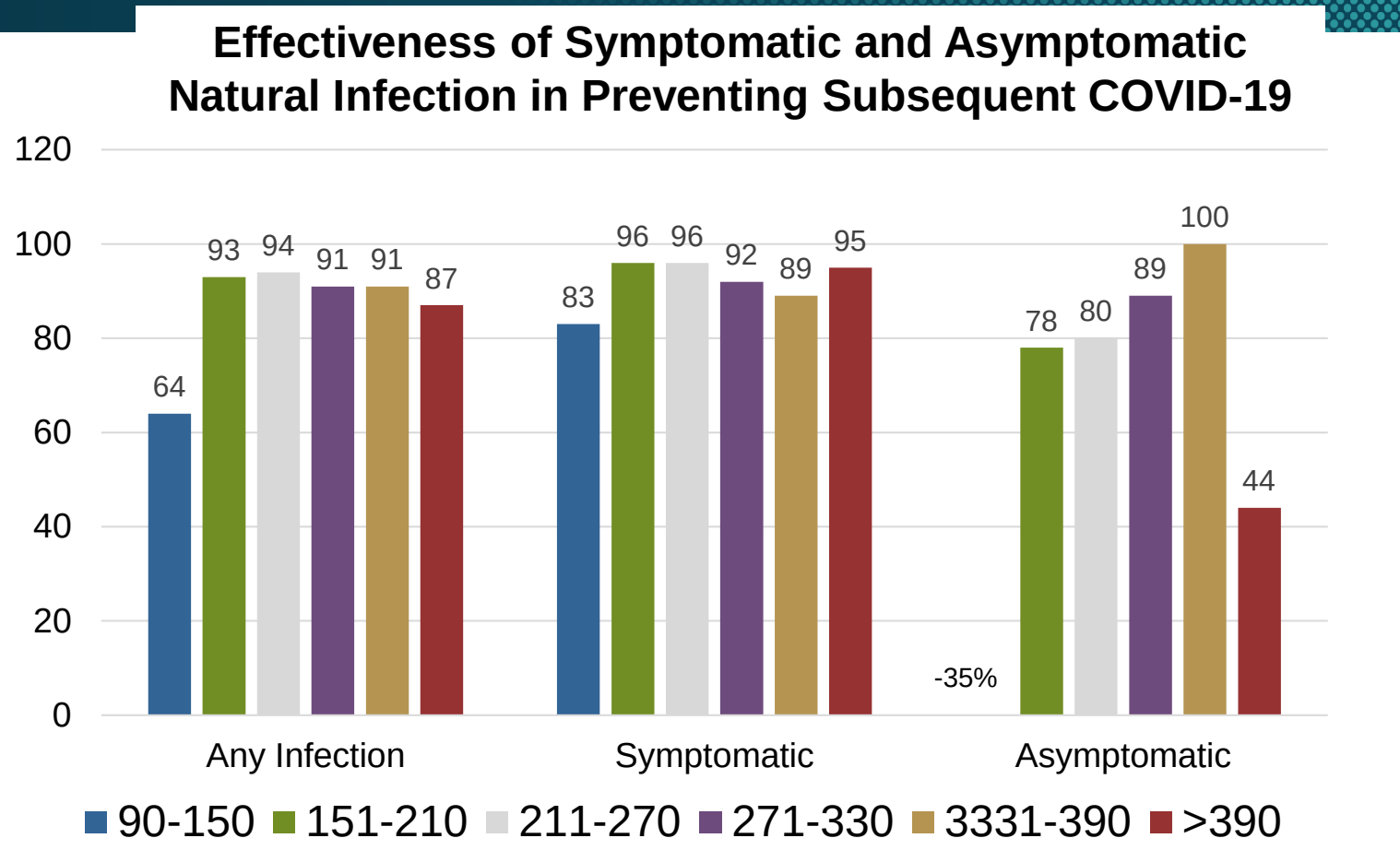
Medically Attended Visit or Death



Source: Gottlieb RL NEJM 2021

Natural Immunity

Background: The effectiveness and duration of immunity induced by COVID-19 infection is uncertain beyond 5-6 months.
Design: Retrospective cohort study
Population: 52,656 persons tested 3/20-8/20 with subsequent testing through 9/21 in Cleveland Clinic System (pre-omicron)
Outcome: Reinfection >90 days after initial infection



- Durable protection against symptomatic infection
  - Less protection asymptomatic infection (92% vs. 52%)
- Protection lower for those ≥65 than <65 (76% vs 89%)

Source: Kim P. CID 2022 (epub ahead of print)

Natural Immunity

Background: The effectiveness and duration of immunity induced by COVID-19 infection is uncertain.
Design: Test negative case-control design
Population: Analysis of national data from Qatar that includes all vaccine, hospitalization and PCR data
Outcome: Effectiveness against symptomatic infection and severe COVID-19

- **Effect variants**

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	
					percent
Effectiveness against symptoma					
Primary analysis‡					
Alpha			94	1548	90.2 (60.2 to 97.6)
Beta	14	1322	450	6084	85.7 (75.8 to 91.7)
Delta	23	2153	1154	8782	92.0 (87.9 to 94.7)
Omicron	412	5284	1620	9053	56.0 (50.6 to 60.9)
Primary analysis after adjustment for vaccination status‡					
Alpha	2	334	94	1548	90.3 (60.4 to 97.6)
Beta	14	1322	450	6084	85.1 (74.5 to 91.3)
Delta	23	2153	1154	8782	91.9 (87.8 to 94.7)
Omicron	412	5284	1620	9053	55.9 (50.5 to 60.8)
Effectiveness against severe, critical, or fatal Covid-19¶					
Alpha			5	199	69.4 (−143.6 to 96.2)
Beta			6	824	88.0 (50.7 to 97.1)
Delta			6	528	100 (43.3 to 100)‖
Omicron			9	167	87.8 (47.5 to 97.1)

Natural Immunity Against Symptomatic Infection less for Omicron

Natural Immunity Against Severe Disease Consistently High

Source: Altarawneh HN; NEJM 2022

Natural Immunity

Table S4. Effectiveness of SARS-CoV-2 prior infection against reinfection with Alpha, Beta, Delta, or Omicron variant, adjusting for time between prior infection and PCR test.

	Cases* (PCR-positive)		Controls* (PCR-negative)		Effectiveness in % (95% CI)†
	Prior infection	No prior infection	Prior infection	No prior infection	
Alpha					
3-8 months	1	334	43	1,548	89.4 (22.6 to 98.5)
9-14 months	1	334	51	1,548	91.0 (34.5 to 98.8)
≥15 months	--	--	--	--	--
Beta					
3-8 months	3	1,322		6,084	92.6 (76.7 to 97.6)
9-14 months	11	1,322		6,084	81.2 (65.5 to 89.8)
≥15 months	--	--	--	--	--
Delta					
3-8 months	10	2,153	602	8,782	93.4 (87.6 to 96.5)
9-14 months	10	2,153	454	8,782	91.1 (83.3 to 95.3)
≥15 months	3	2,153	98	8,782	87.1 (59.4 to 95.9)
Omicron					
3-8 months	94	5,284	460	9,053	64.0 (54.7-71.4)
9-14 months	191	5,284	630	9,053	47.2 (37.5-55.4)
≥15 months	127	5,284	530	9,053	59.6 (50.7-67.0)

No consistent pattern of Waning Natural Immunity

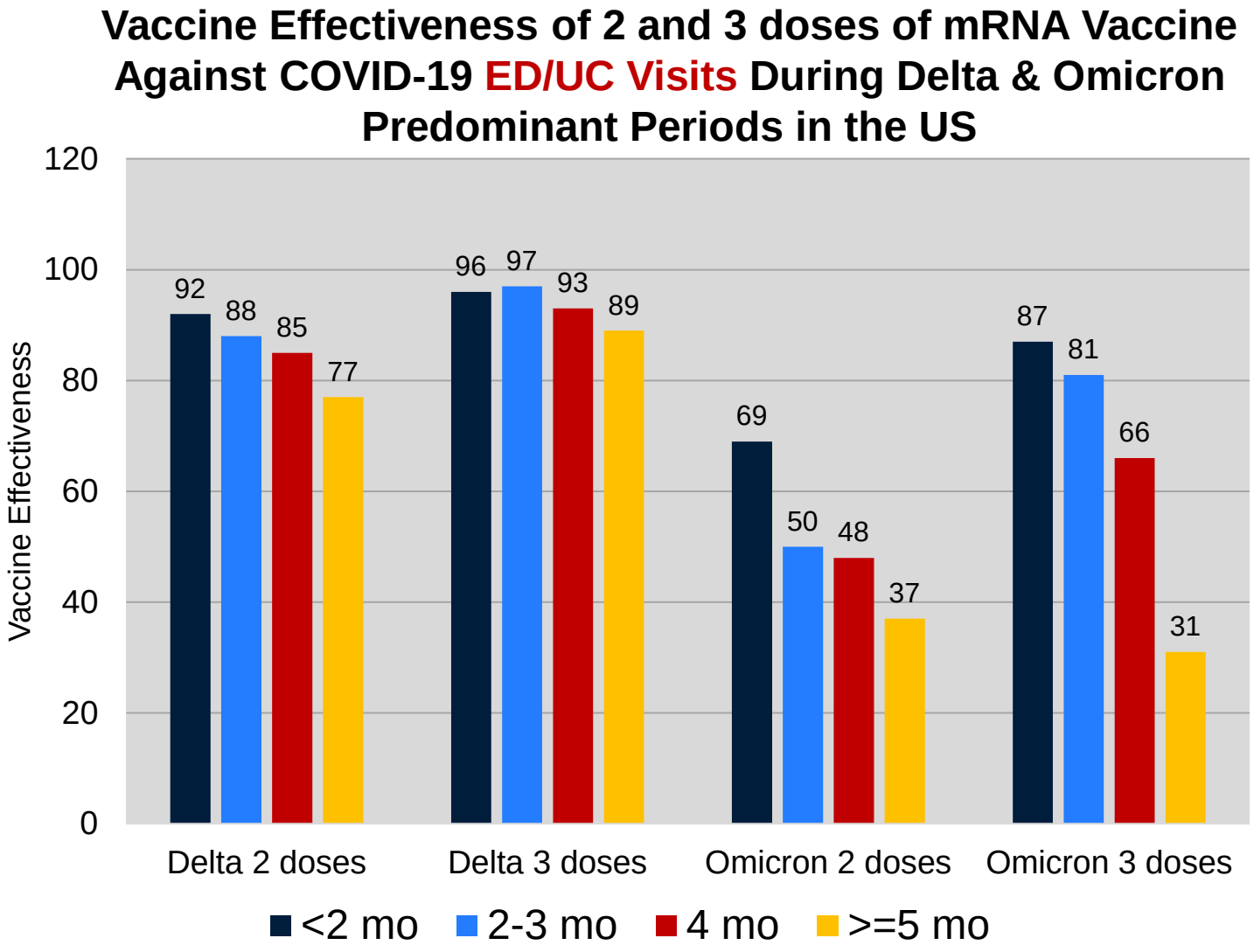
*Cases and controls were exact matched one-to-five by sex, 10-year age group, nationality, and calendar week of PCR test in the Alpha, Beta, and Delta analyses (March 23-November 18, 2021; Figure S1), and one-to-three by sex, 10-year age group, nationality, and PCR test date in the Omicron analysis (December 23, 2021- Jan 2, 2022; Figure S2).

†Effectiveness of prior infection in preventing reinfection was estimated using the test-negative, case-control study design.[3]

Source: Altarawneh HN; NEJM 2022

Boosters: Waning Immunity

Background: COVID-19 vaccine immunity wanes over time. A 3rd dose of mRNA vaccines increases VE, but the durability of that increase is unknown.
Design: Test negative control
Population: 241,204 symptomatic emergency room & 93,408 hospitalized patients tested for SARS-coV-2 in US 8/21-1/22.
Outcome: Vaccine effectiveness against ED visit infection and hospitalization

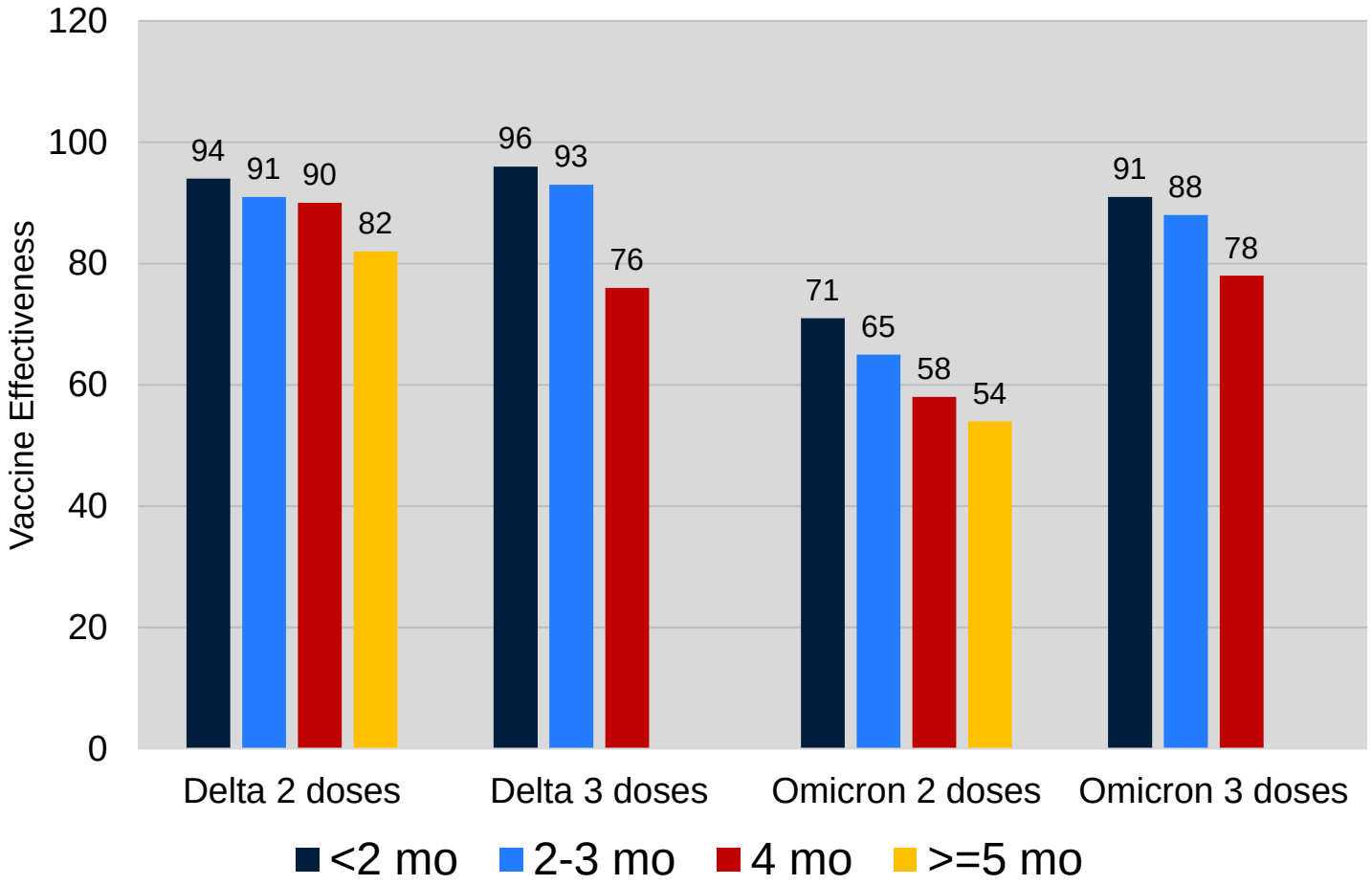


Source: Ferdinands JM; MMWR 2022

Boosters: Waning Immunity

- VE for Omicron is lower and wanes substantially within 4 months
- Boosters increase VE, but effect also wanes
- Efficacy higher against more severe disease

Vaccine Effectiveness of 2 and 3 doses of mRNA Vaccine Against COVID-19 Hospitalization During Delta & Omicron Predominant Periods in the US



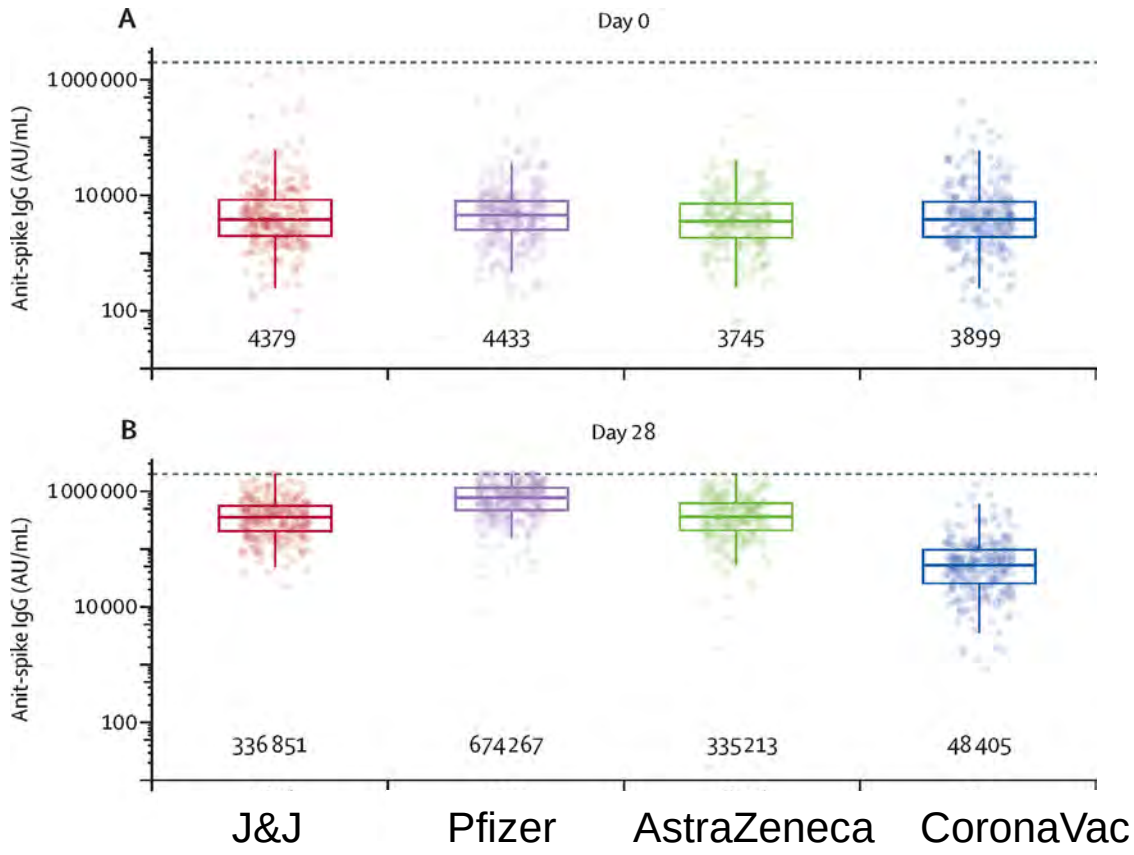
Insufficient data to estimate VE for >5 months

Source: Ferdinands JM; MMWR 2022

Boosters in Persons Receiving CoronaVac

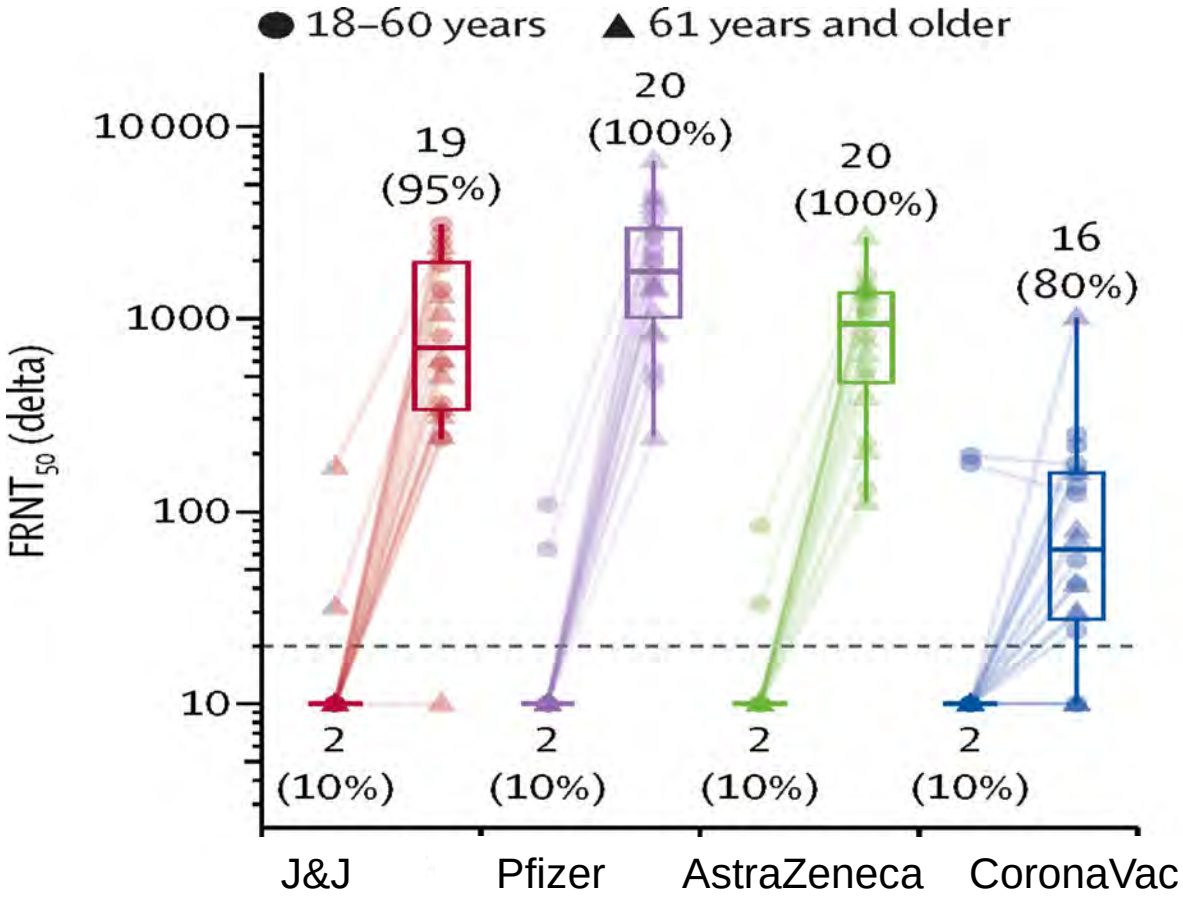
Background: Impact of COVID-19 vaccine boosters other Pfizer vaccine ill-defined.
Design: Phase 4 safe and immunogenicity study comparing 4 vaccine boosters given at ~6 months – AZ, Pfizer, J&J, and Coronavac
Population: 1240 Brazilian adults
Outcome: Anti-spike IgG antibodies 28 days after the booster dose

All heterologous boosters were significantly better than a 3rd dose of CoronaVac

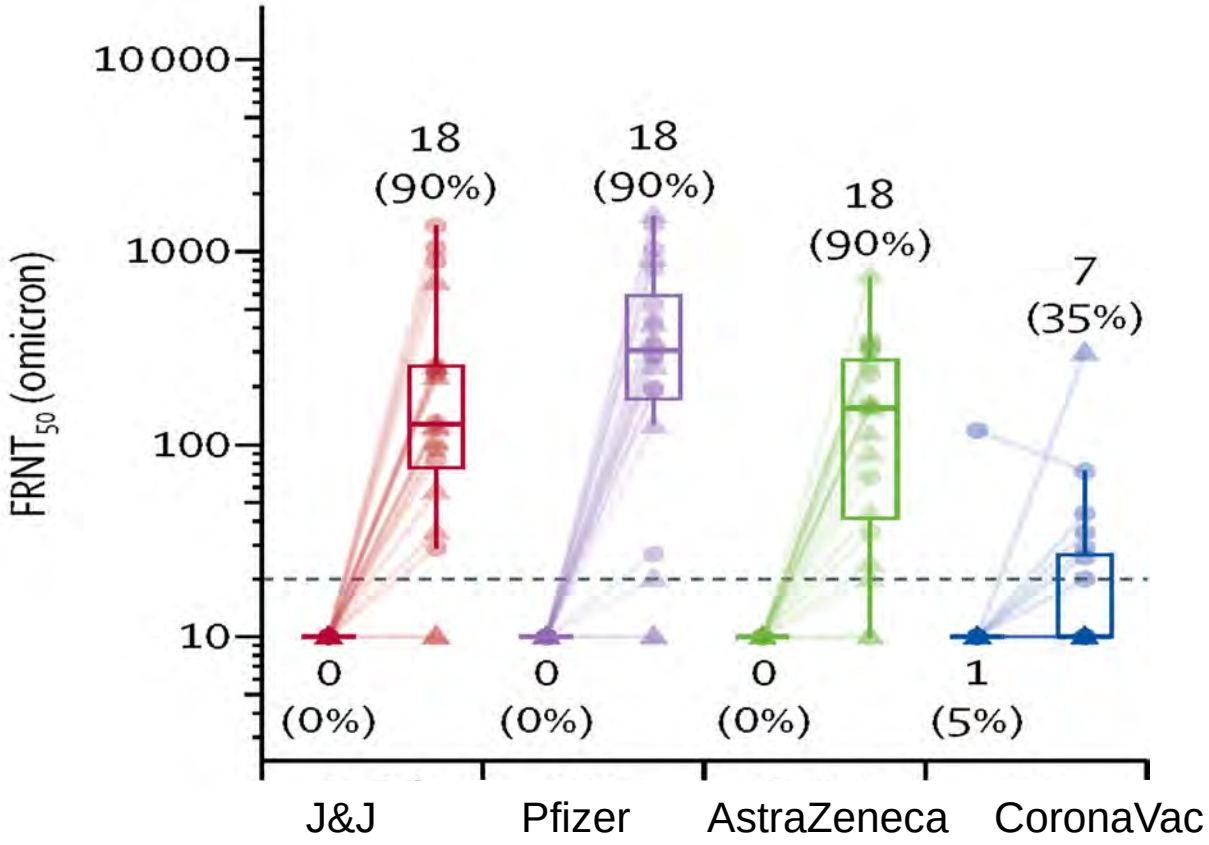


Source: Clemens SAC. Lancet 2022

Boosters in Persons Receiving CoronaVac Neutralizing Antibody Delta & Omicron



Delta



Omicron

Source: Clemens SAC. Lancet 2022

Boosters: Waning Immunity - Summary

- **Good news**
  - Natural immunity is pretty durable
  - mRNA Boosters increased VE – 54%->78% against hospitalizations at >=4 months
    - Effect greater on hospitalizations than ED visits
  - Heterologous booster for persons receiving CoronaVac increased antibody levels
  - Supports strategy of giving boosters
- **Bad news**
  - VE wanes over relatively short period of time
  - VE lower for Omicron than Delta
    - Complex issue – less virulent virus – is lower VE reflective of a more compromised population seeking care?
  - CoronaVac boasters don’t look to be effective
- Would an mRNA vaccine designed to induce immunity against more contemporary strains perform better?

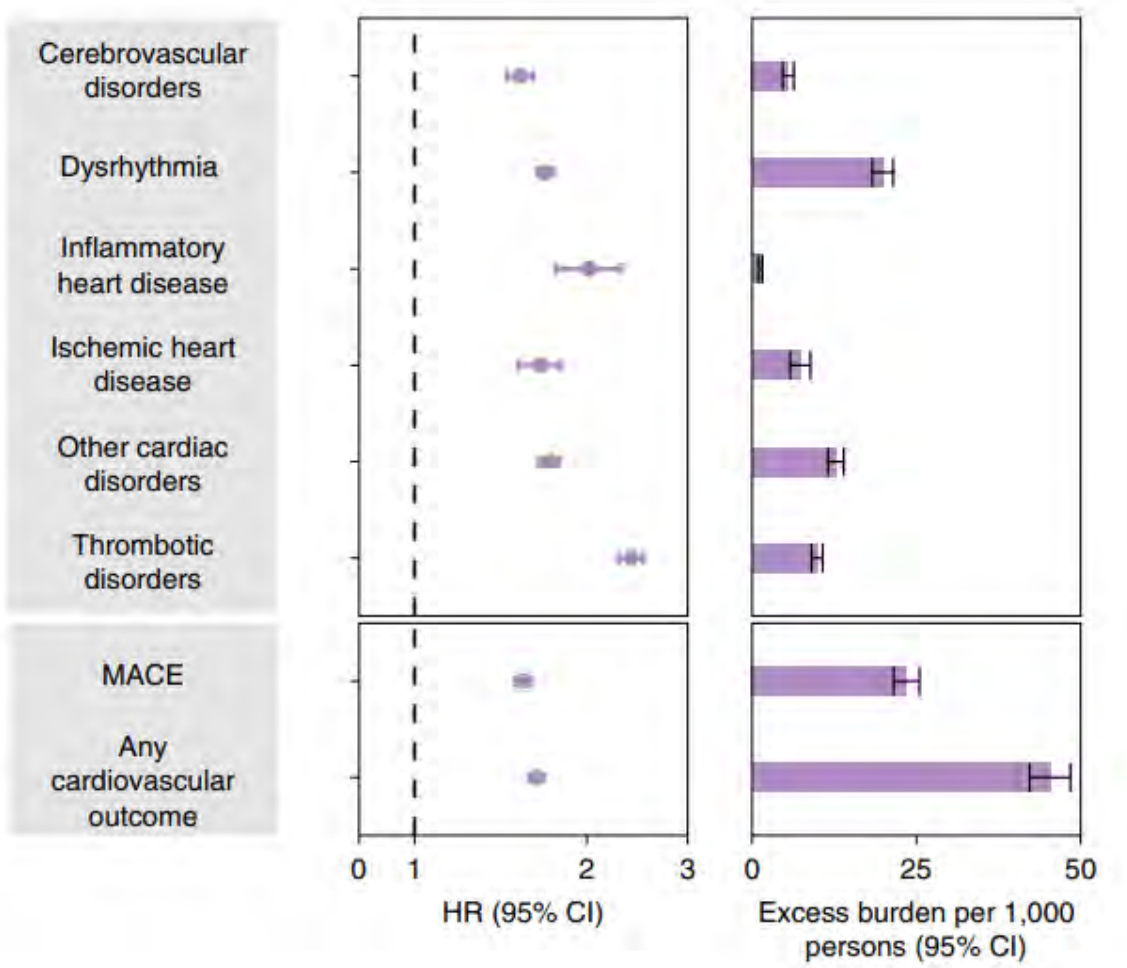
Long COVID: WHO Definition

- Post COVID-19 condition – 10-20% of patients
  - History of probable or confirmed SARS CoV-2 infection
  - Usually 3 months from the onset of COVID-19
  - Symptoms persisting ≥2 months
  - Not explained by an alternative diagnosis
- Common symptoms: fatigue, shortness of breath, cognitive dysfunction - impact on everyday functioning
  - New onset following initial recovery or persist from the initial illness
  - May fluctuate or relapse over time

Late Onset Cardiovascular Morbidity

Background: The long-term health impacts of COVID-19 are ill-defined
Design: Retrospective cohort study
Population: Veterans Affairs cohort 153,760 people with COVID, 5.6 million contemporary controls and 5.8 million historical controls
Outcome: Cardiovascular outcomes >30 days-1 year post diagnosis

Risk and 12-month burden incident post-COVID CV Outcomes vs. Contemporary Control



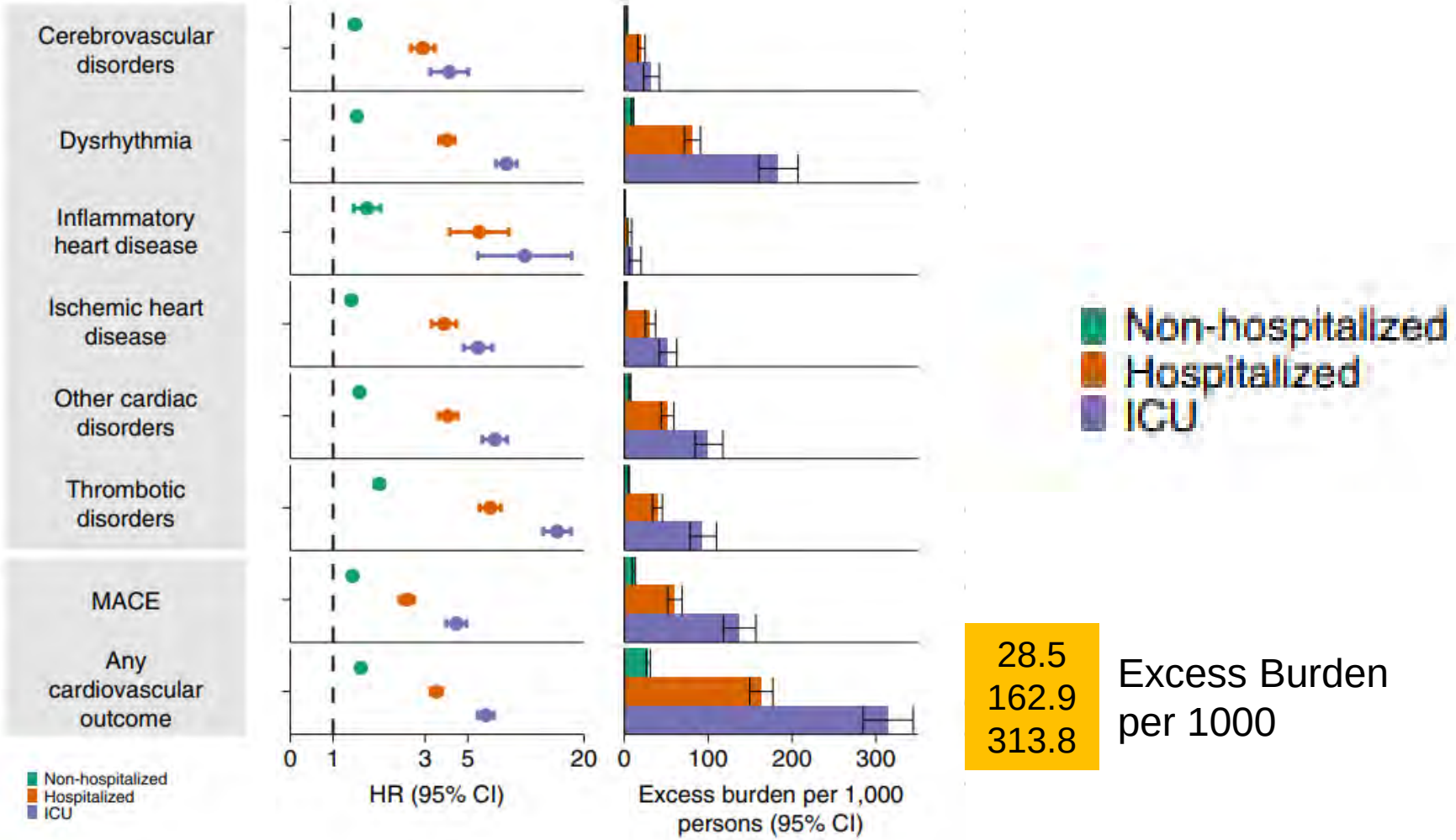
Source: Xie Y. Nature Medicine 2022

MACE= all-cause mortality, stroke & myocardial infarction

Long COVID

Risk and 12-month burden incident post-COVID CV Outcomes vs. Contemporary Control, Stratified by Acute COVID-19 Severity

- Risk highest in those with more severe disease
- Risk was elevated even in those who were not hospitalized



28.5
162.9
313.8

Excess Burden per 1000

Source: Xie Y. Nature Medicine 20

The End of COVID?

I use the term pandemic to refer to the extraordinary societal efforts over the past 2 years to respond to a new pathogen that have changed how individuals live their lives and how policy responses have developed in governments around the world.

The era of extraordinary measures by government and societies to control SARS-CoV-2 transmission will be over. After the omicron wave, COVID-19 will return but the pandemic will not.

The Seattle Times

"This framing that the pandemic is ending is really unfortunate," said Jeff Duchin, the chief health officer for Seattle and King County, and also affiliated with the UW, when I asked him about the predictions.

The thing that makes pandemics so challenging, as we all ought to know by now, is that they feature a novel, evolving pathogen.

"It's by its nature unpredictable," Duchin said. "We've just seen that evolving unpredictability, twice, since last summer" — the delta and omicron waves, which combined have killed nearly 300,000 more Americans. **The key is having some humility about it.** There's no reason to think another variant like that can't happen again."

Summary

- **Epidemiology**
  - Case numbers declining though mortality still not declining consistently
  - New Omicron variant – more transmissible with lower vaccine effectiveness
- **Treatment**
  - Remdesivir – looks good in outpatients – hard to give IV meds
- **Immunity & Vaccines**
  - Natural immunity less for Omicron, but durable for severe disease for all variants to date
  - Boosters are protective - effectiveness wanes relatively quickly, though less for severe disease
  - Heterologous boosters for CoronaVac recipients
- **Clinical**
  - Long COVID is concerning – we have a lot we don’t know about this

Questions and Comments