

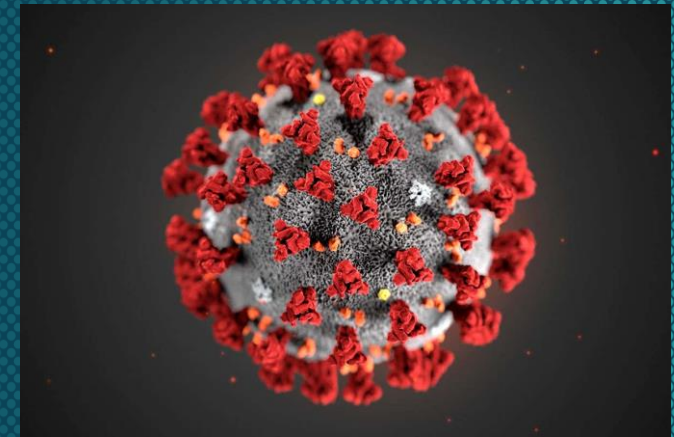


*University of Washington
Public Health Capacity Building Center*

COVID-19 Clinical Update

I-TECH Videoconference October 18, 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: October 18, 2021



I-TECH

International Training and Education Center for Health

Overview

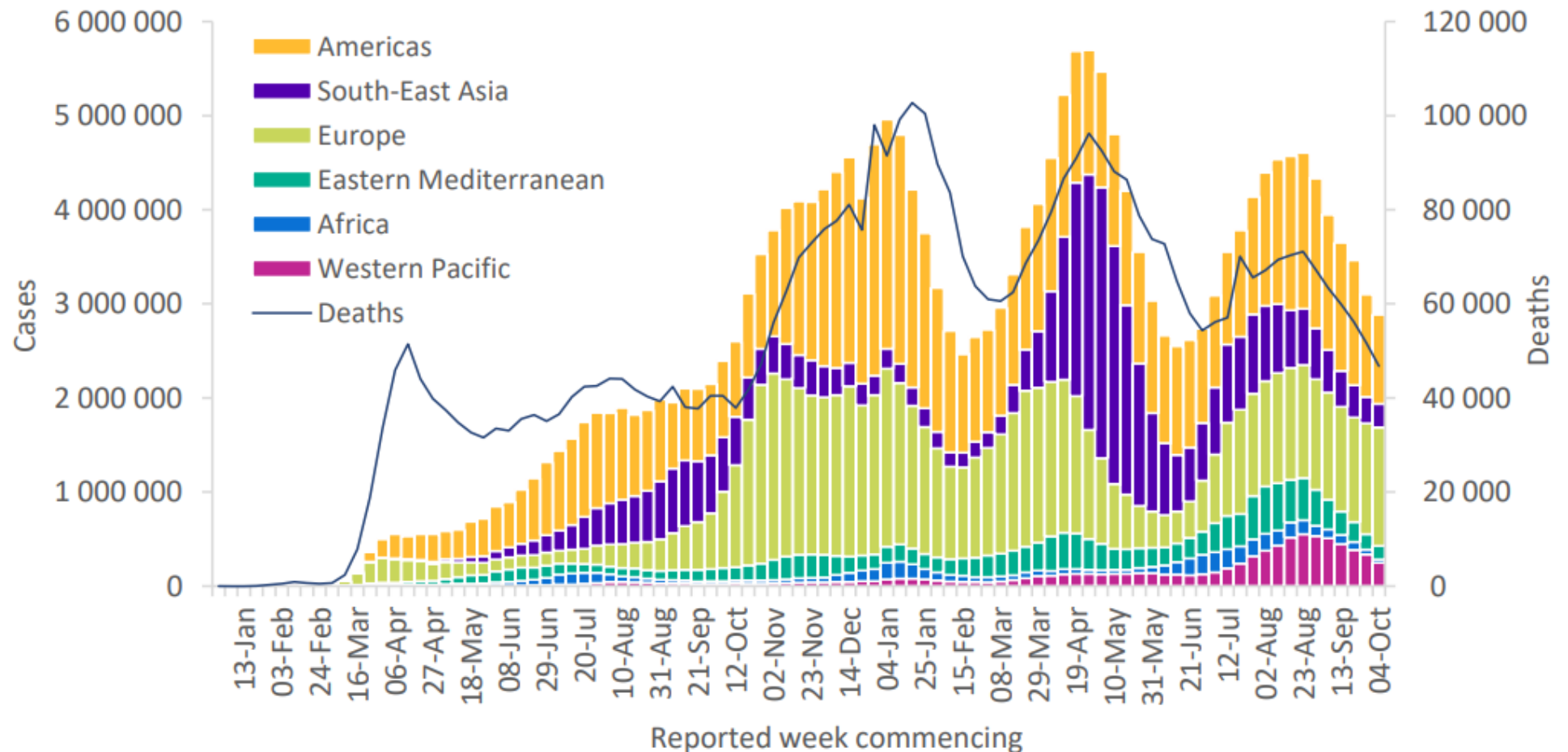
- Epidemiology & new data on HIV and COVID
- Vaccines –
 - More data on waning immunity
 - Boosters
- Molnupiravir

Global Trends in COVID-19 Diagnoses & Deaths

>237 Million Confirmed Cases
2.8 million cases/week

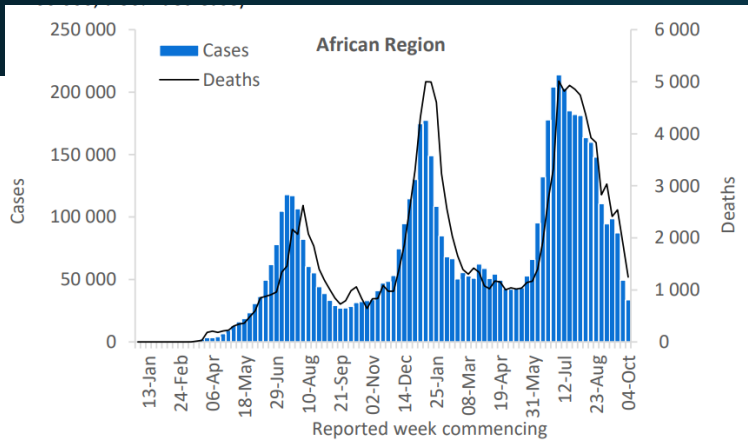
~4.8 Million Confirmed Deaths
46,000 deaths/week

Figure 1. COVID-19 cases reported weekly by WHO Region, and global deaths, as of 10 October 2021**

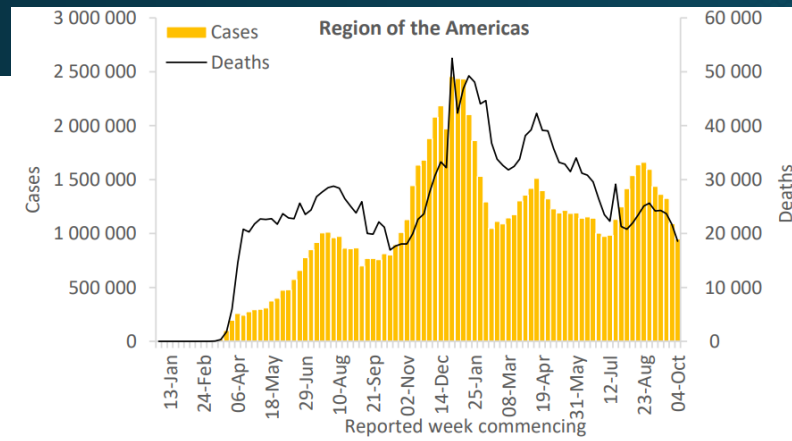


Declines in new cases and deaths globally since late August – Europe is an exception

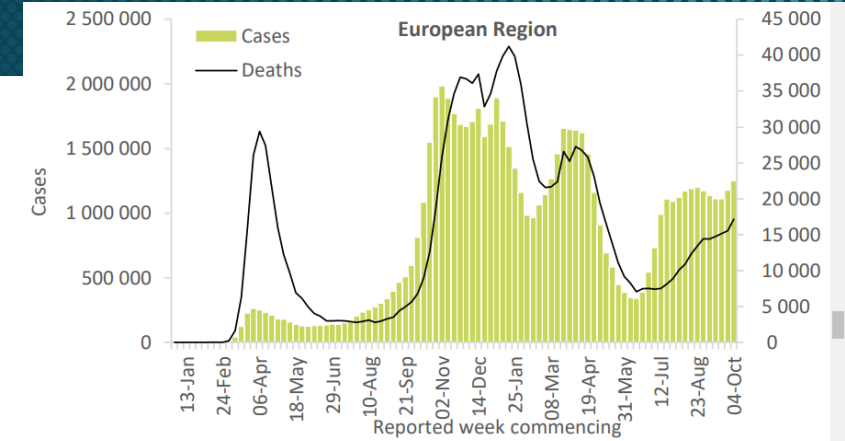
Global Trends in COVID-19 Diagnoses & Deaths



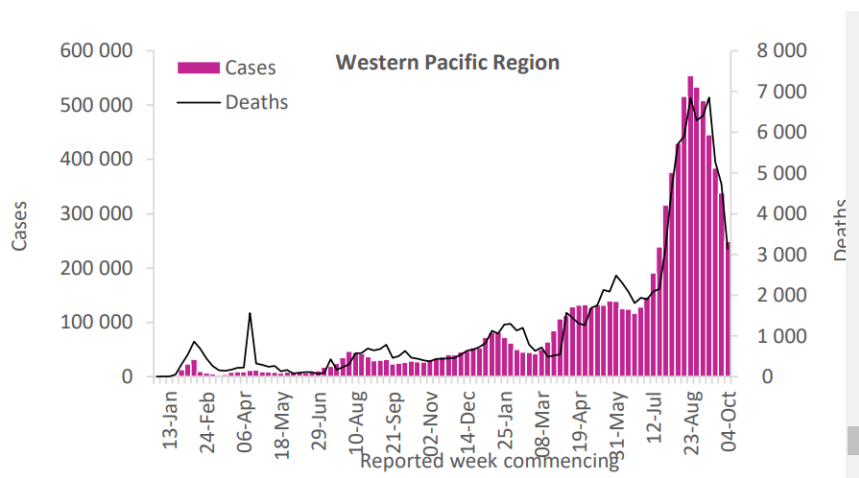
34%↓ Deaths – Exceptions in North Africa where numbers ↑



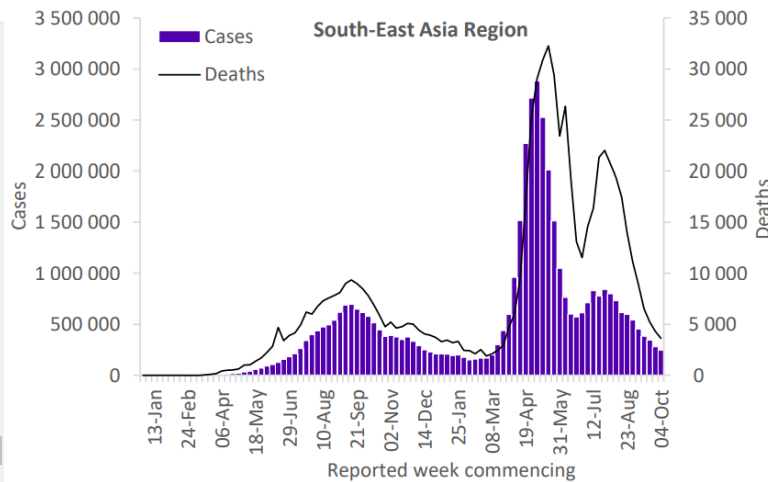
13%↓ Deaths – Exceptions in parts of Caribbean



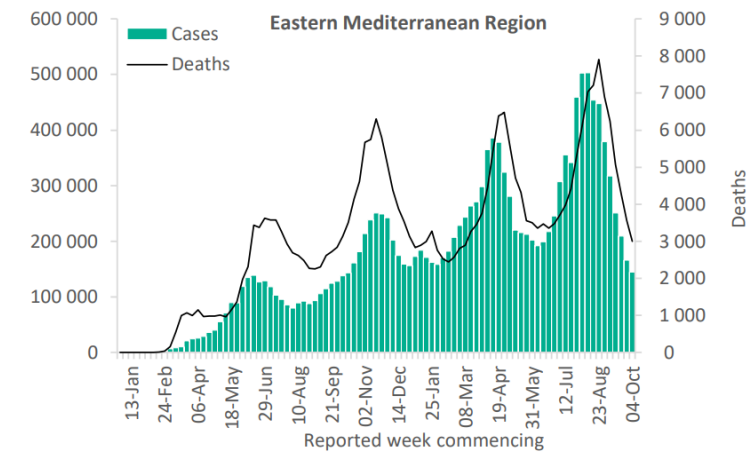
11%↑ Deaths – High in Eastern Europe



34%↓ Deaths



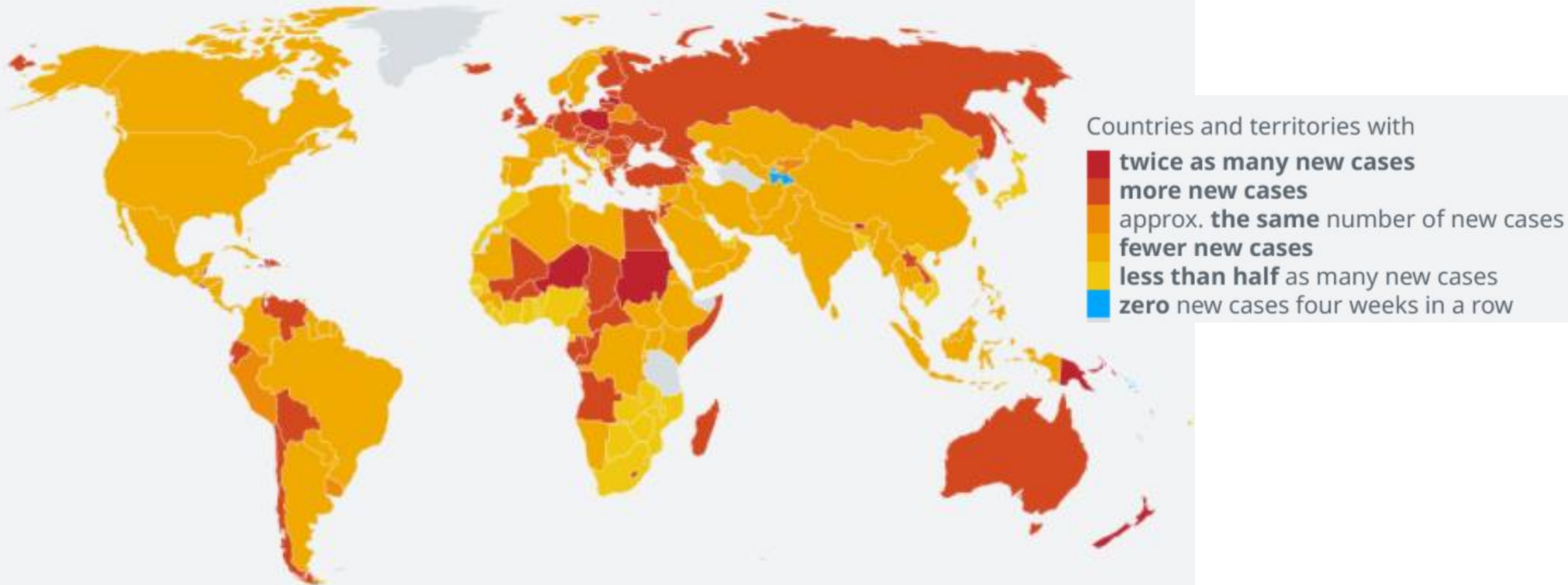
16%↓ Deaths



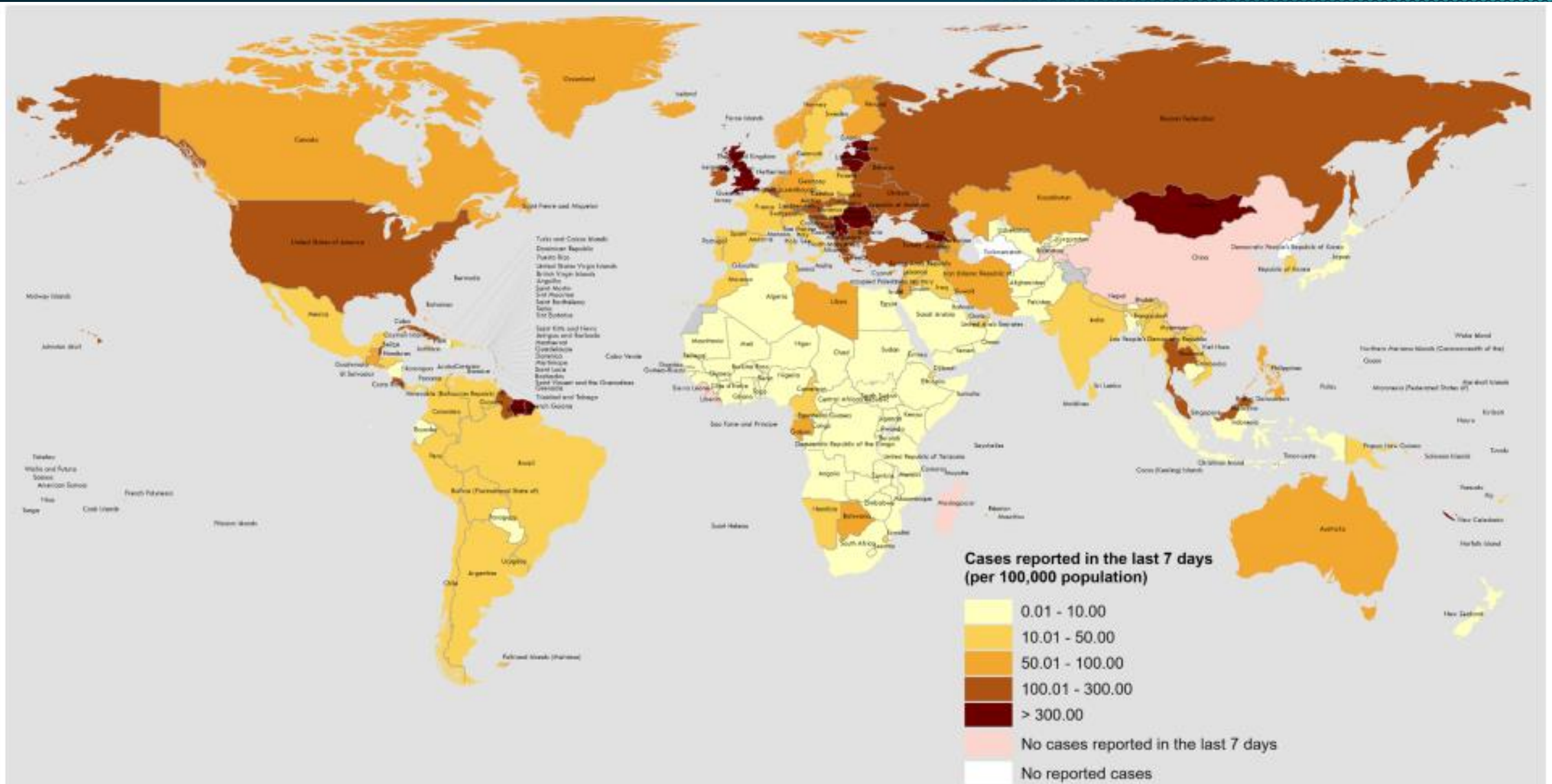
16%↓ Deaths – Rates very high in Iran and Iraq

Global Trends by Country (October 15, 2021)

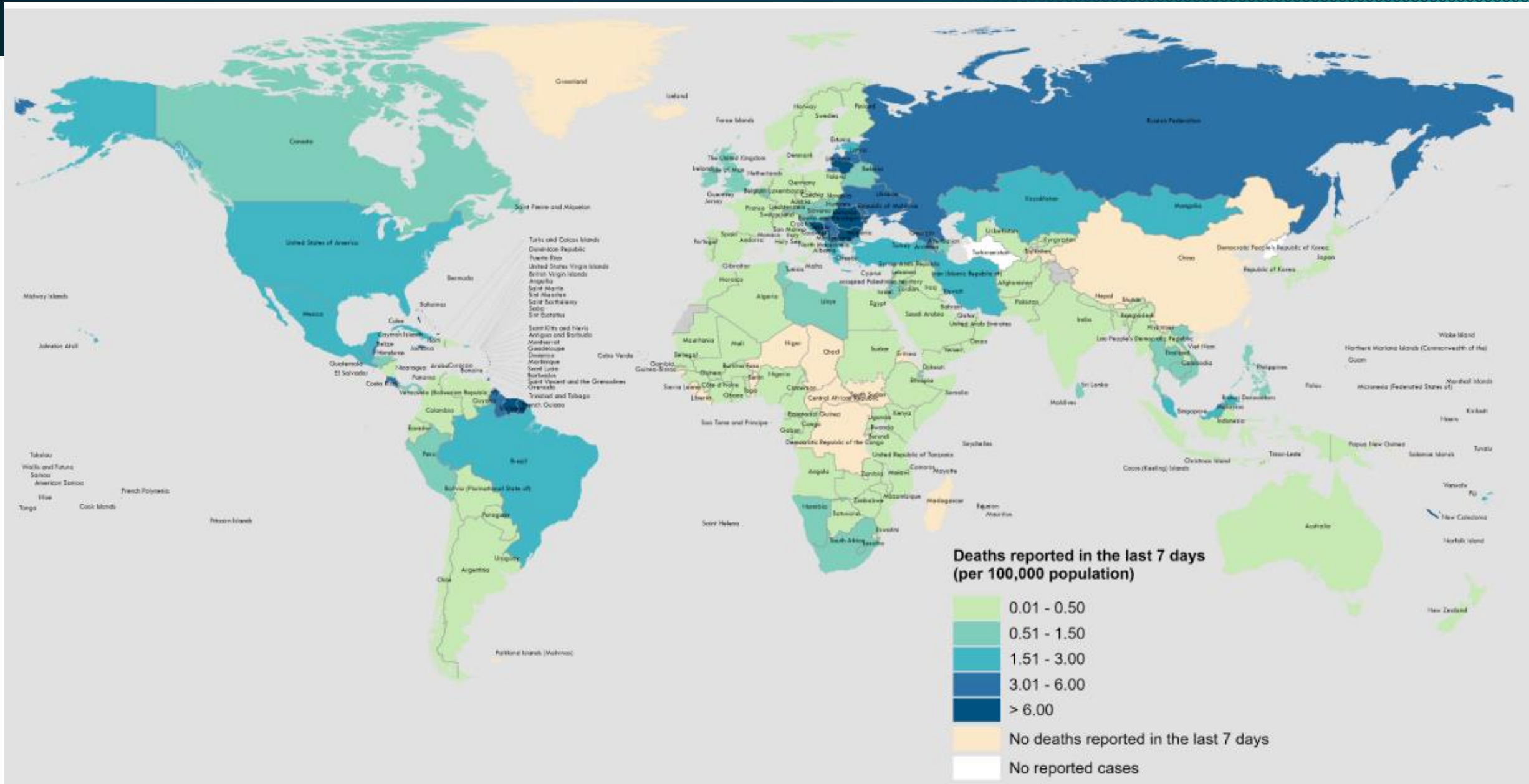
Week 41: New COVID-19 cases by country



COVID-19 cases/100,000 population, October 4-10, 2021



COVID-19 deaths/100,000 population, October 4-10, 2021



Association COVID-19 Severity & HIV

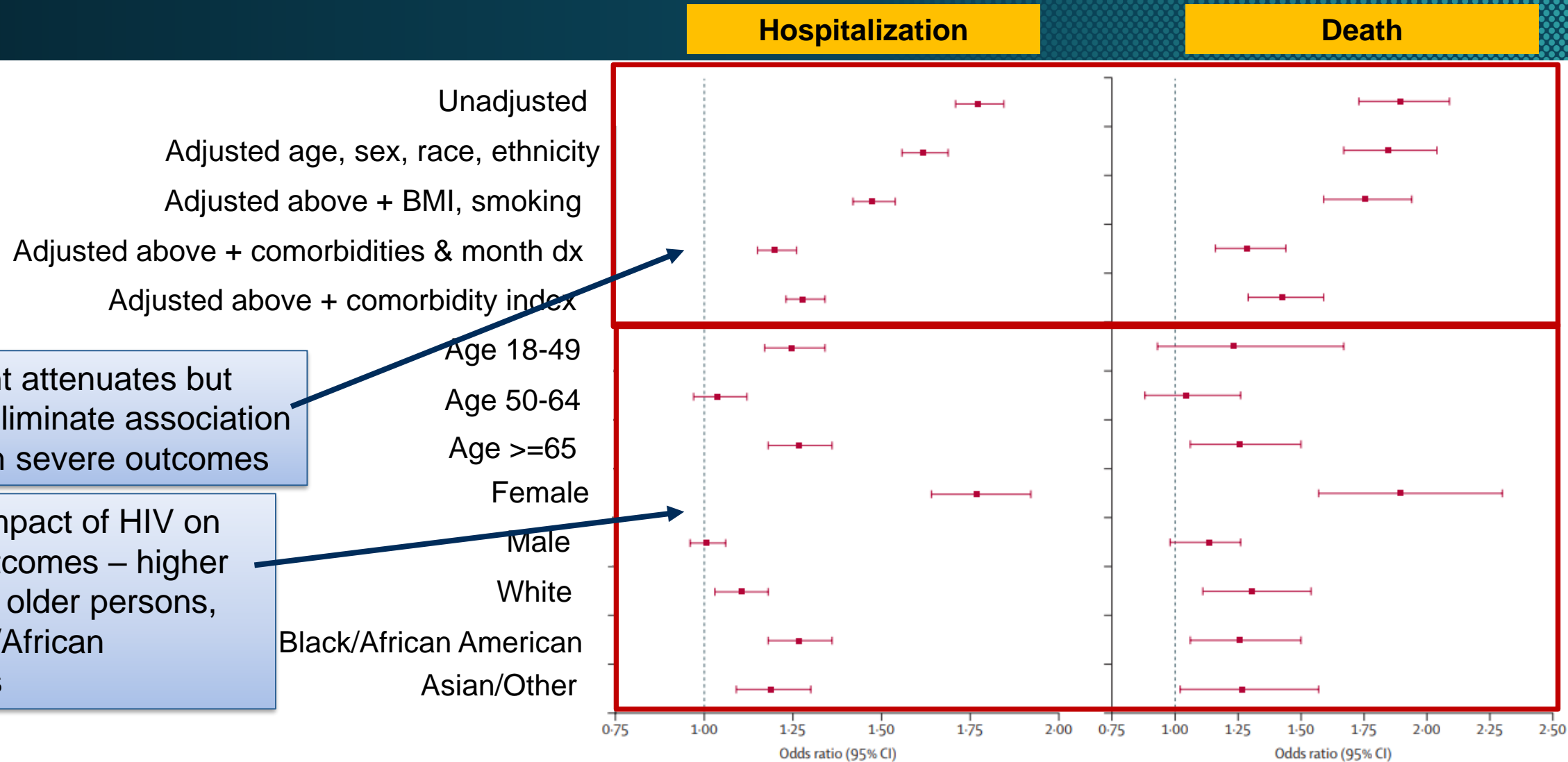
Background: Studies from the UK and South Africa have suggested increased mortality in HIV+ persons with COVID-19. Some uncertainty of relationship of HIV to COVID-19 severity persists.

Design: Analysis US National COVID Cohort Collaborative – ~1.4 million COVID19 cases, 13,170 HIV+

Outcome: Hospitalization, death, clinical severity

	Overall (n=1 436 622)	People with HIV (n=13 170)	People without HIV (n=1 423 452)	p value
(Continued from previous page)				
Clinical spectrum outcomes				
COVID-19 death	26 130 (1.82%)	445 (3.38%)	25 685 (1.80%)	<0.0001
COVID-19 hospitalisation	262 331 (18.26%)	3724 (28.28%)	258 607 (18.17%)	<0.0001
COVID-19 disease severity				
Unaffected	476 250 (33.15%)	6395 (48.56%)	469 855 (33.01%)	<0.0001
Mild† or moderate	895 491 (62.33%)	6209 (47.15%)	889 282 (62.47%)	..
Severe‡	25 054 (1.74%)	475 (3.61%)	24 579 (1.73%)	..
Unknown	39 827 (2.77%)	91 (0.69%)	39 736 (2.79%)	..

Association COVID-19 Severity & HIV



Association COVID-19 Severity & HIV

- **Severity associated with low CD4 count and lack of viral suppression**

	Death, OR (95% CI)*	Hospitalisation, OR (95% CI)*	Mild† or moderate vs unaffected, OR (95% CI)*	Severe‡ vs unaffected, OR (95% CI)*
HIV factors				
Most recent CD4 count§				
>500 cells per µL	1.00	1.00	1.00	1.00
200–500 cells per µL	1.49 (0.55–4.03)	1.28 (0.94–1.75)	1.15 (0.89–1.48)	1.62 (0.59–4.44)
<200 cells per µL	3.10 (1.06–9.13)	2.73 (1.80–4.14)	1.51 (1.04–2.21)	3.91 (1.31–11.62)
Most recent viral suppression, <200 copies per mL§	0.71 (0.27–1.89)	0.69 (0.49–0.97)	0.87 (0.64–1.17)	0.62 (0.24–1.57)

- Study is consistent with prior studies from South African and UK demonstrating that HIV, particularly with low CD4 or in the absence of viral suppression, is associated with severe COVID-19
- Large attenuation of HIV effect with adjust suggests other comorbidities are likely more important than HIV

Vaccine Effectiveness at Population-Level: King County, WA, USA

For data sources and technical notes, click on the data notes section on the top-right.

Select a time period: ☒ Past 30 Days
☐ Since 1/17/2021

Cases

People who are **not fully vaccinated** are:

9x

more likely to test positive for COVID-19

Relative Risk trend

The vaccines effectively reduce a person's risk of catching COVID-19 and spreading it to others, although they are more effective at preventing serious infections leading to hospitalization and death. Vaccinated people who do get infected tend to have mild or non-severe illness.



Hospitalizations

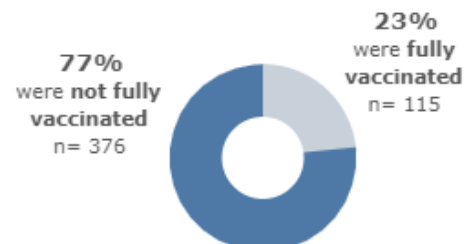
People who are **not fully vaccinated** are:

48x

more likely to be hospitalized for COVID-19

Relative Risk trend

The vaccines are highly effective at preventing severe illness from COVID-19 requiring hospitalization.



Deaths

People who are **not fully vaccinated** are:

69x

more likely to die of COVID-19 related illness

Relative Risk trend

Getting vaccinated dramatically reduces one's risk of dying from COVID-19. Deaths among the unvaccinated have tended to affect younger and healthier people than the comparatively rare deaths among vaccinated people.



Source: <https://kingcounty.gov/depts/health/covid-19/data/vaccination-outcomes.aspx>

Comparative Effectiveness of Vaccines

Background: Relative effectiveness of different vaccines is uncertain.

Design: Case-control study 3,689 immunocompetent persons hospitalized with COVID-19 in US March-August 2021 and controls were hospitalized persons without COVID. Second study looked at antibody levels in 100 persons 2-6 weeks post vaccine.

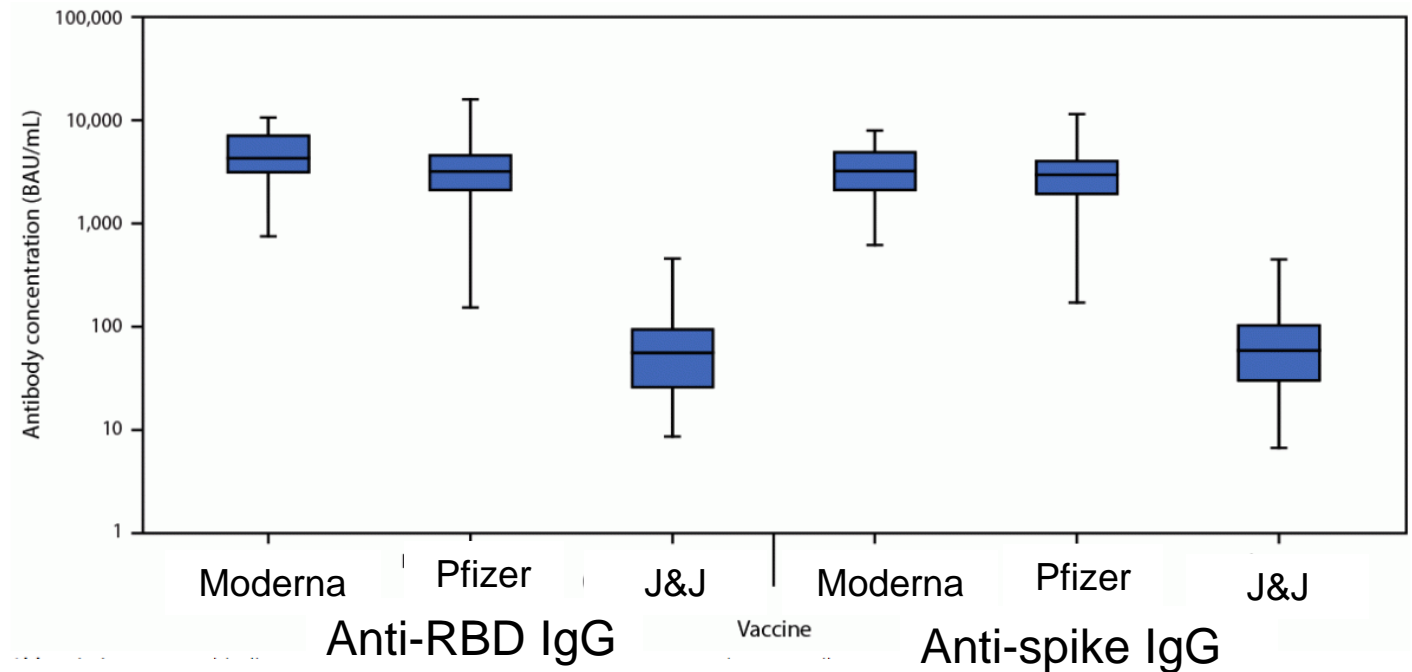
Outcome: Vaccine effectiveness comparing vaccinated and unvaccinated patients

Vaccine Period	Case	Control	VE COVID-19 Hospitalization
Moderna			
Full period	54/1517 (3.6)	422/1221 (31.9)	93 (91-95)
14-120 days	36/1499 (2.4)	345/1244 (27.7)	93 (90-95)
>120 days	18/1481 (1.2)	77/976 (7.9)	92 (87-96)
Pfizer			
Full period	128/1591 (8)	610/1509 (40.4)	88 (85-91)
14-120 days	65/1528 (4.3)	495/1395 (35.5)	91 (88-93)
>120 days	63/1526 (4.1)	115/1014 (11.3)	77 (67-84)
J&J			
Full period	37/1500 (25)	76/975 (7.8)	71 (56-81)
>28 days	33/1496 (2.2)	59/958 (6.2)	68 (49-80)

Comparative Effectiveness of Vaccines

- Anti-receptor binding domain IgG (RBD) higher for Moderna vs. Pfizer ($p=0.03$) or J&J ($p<0.001$)
- Anti-spike higher for Moderna than J&J ($p<.001$), but not Pfizer

FIGURE. Serum anti-receptor binding domain and anti-spike immunoglobulin G levels 2–6 weeks after full vaccination among healthy adult volunteers — three hospitals in three U.S. states,*[†] April–June 2021



Waning Immunity to COVID Vaccine

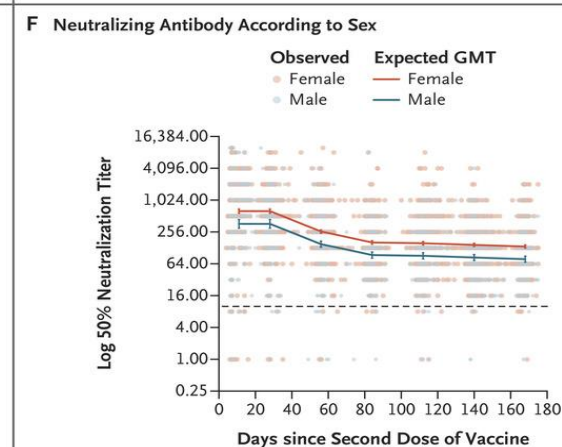
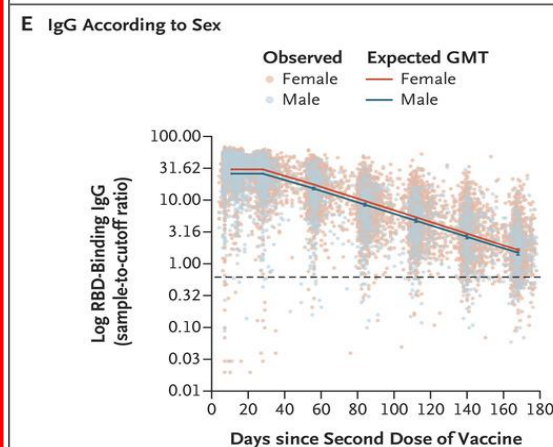
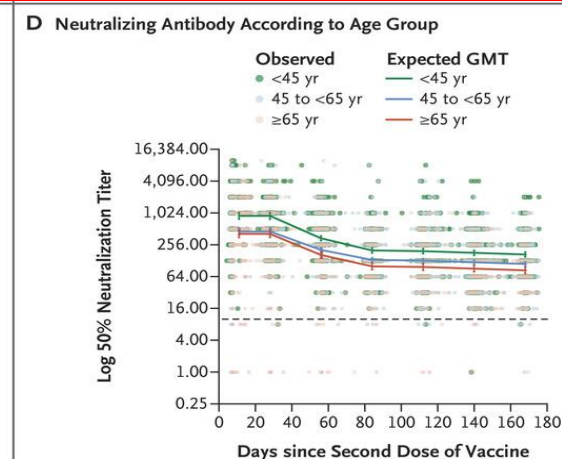
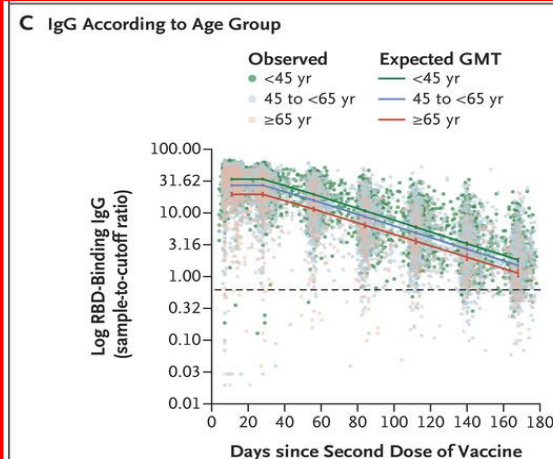
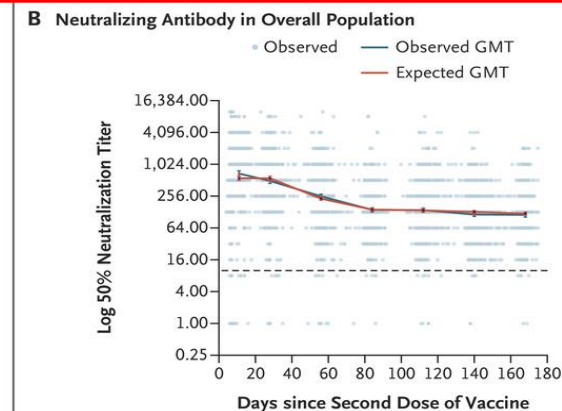
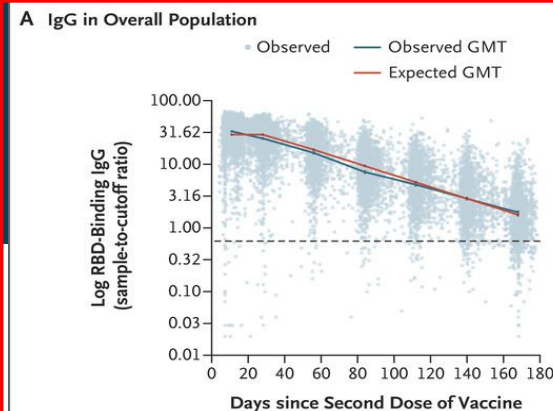
Background: Population-based observational data from Israel suggest that vaccine effectiveness wanes over time (reviewed in Sept).

Design: 6-month longitudinal prospective study of 2631 Israeli healthcare workers measuring antibody to spike protein.

Outcome: Anti-spike IgG and neutralizing antibody

Antibody levels decline over time – neutralizing anti-body seems to plateau

Antibody levels decline over time – neutralizing anti-body seems to plateau



Waning Immunity to COVID Vaccine

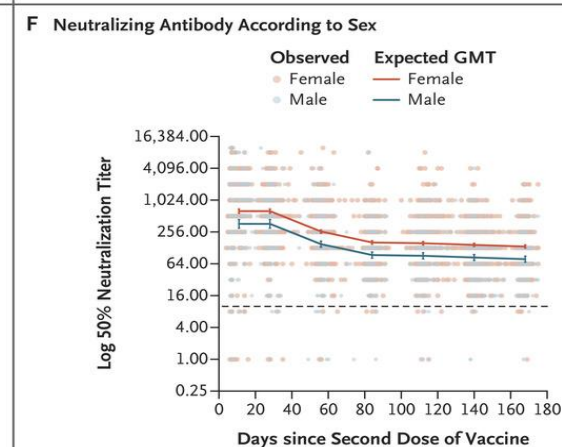
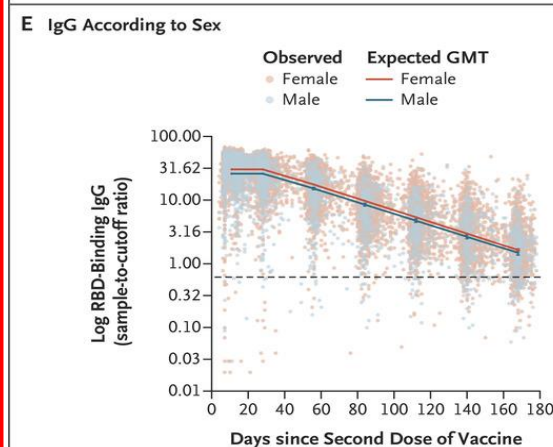
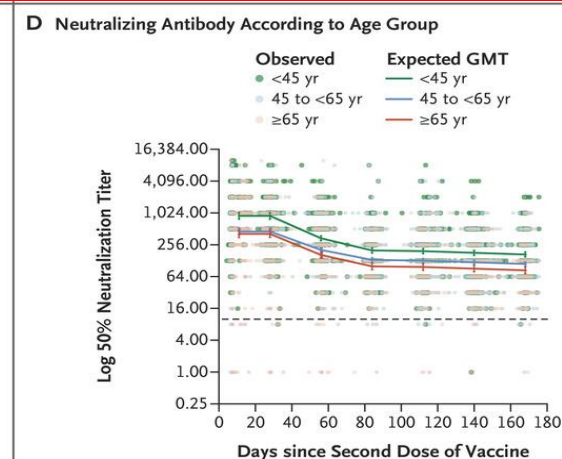
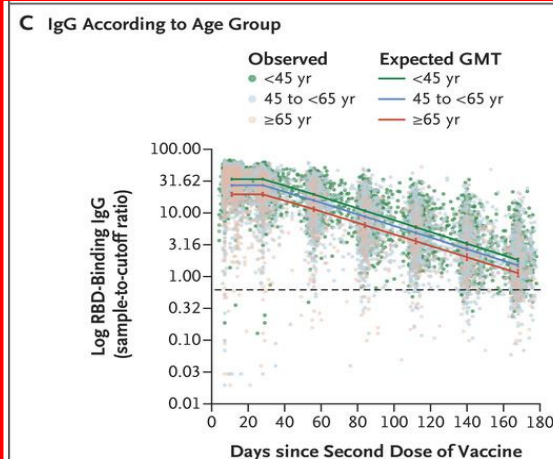
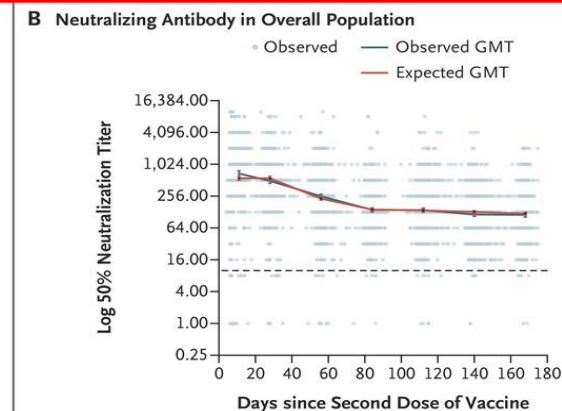
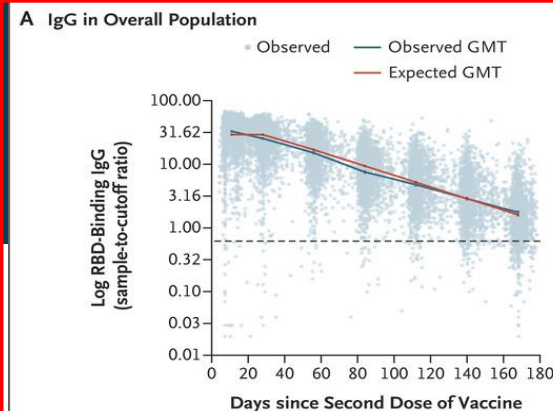
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Antibody levels decline over time – neutralizing anti-body seems to plateau



Waning Immunity to Pfizer COVID Vaccine

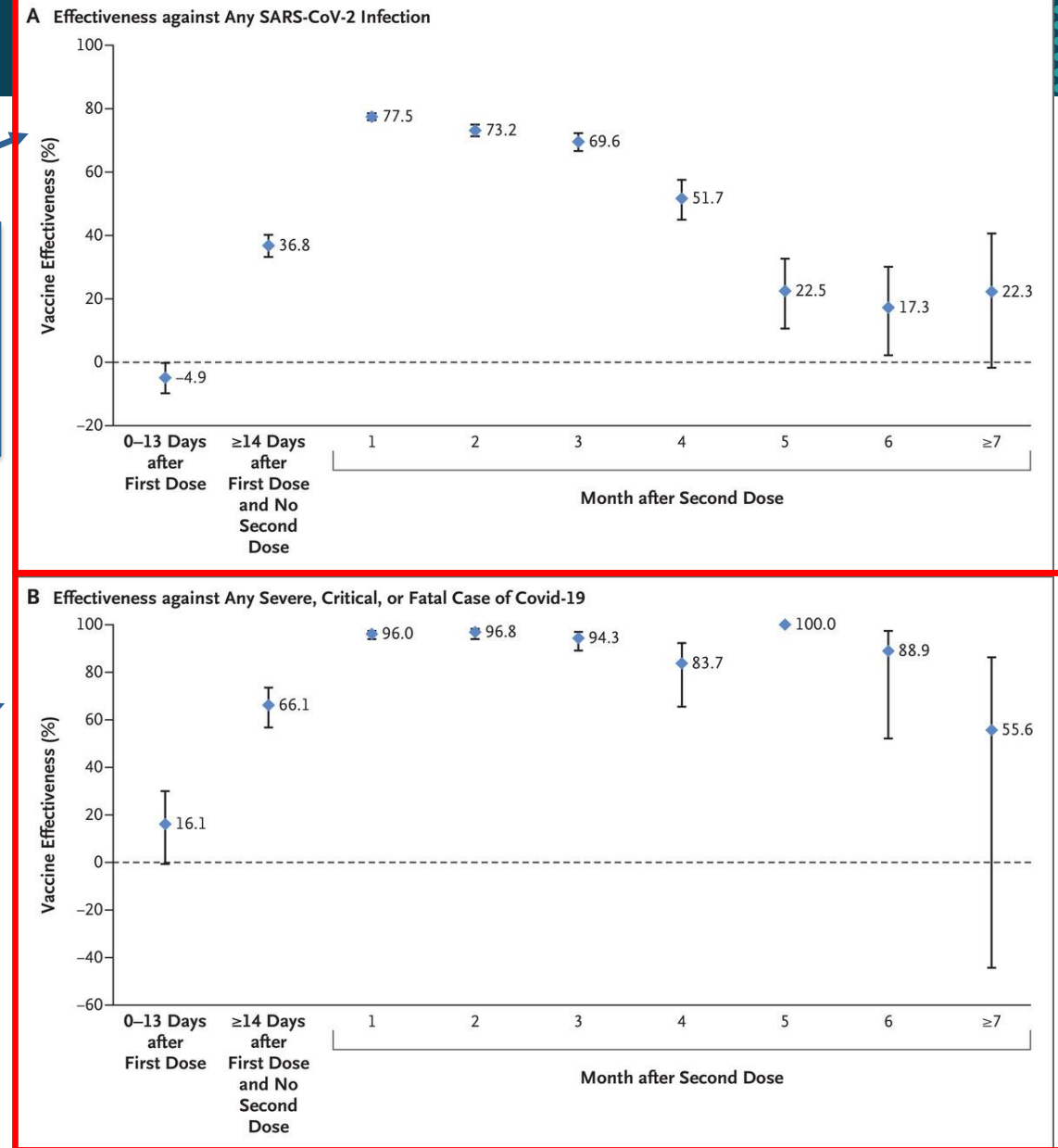
Background: Population-based observational data from Israel suggest that vaccine effectiveness wanes over time (reviewed in Sept)

Design: Matched test negative case control study Qatar using population-based data Jan-Sept 2021. 494,859 people received 2 doses of vaccine with 10,543 breakthroughs infections.

Outcome: Vaccine effectiveness against infection and against severe/critical/fatal COVID-19

Effectiveness against infection declines over time

Less clear that effectiveness against severe disease declines over time



Impact of Booster Doses in the Elderly

Background: In the face of waning immunity and Delta, Israel instituted 3rd dose boosters in the elderly in July, 2021.

Design: Retrospective cohort study of population-based data comparing persons who received booster to those who had not and, among boosted elderly, 4-6 days after booster to ≥ 12 days.

Outcome: Infection rate and rate severe illness

Absolute between-group difference in the rate of severe illness was 7.5 cases per 100,000 person-days.

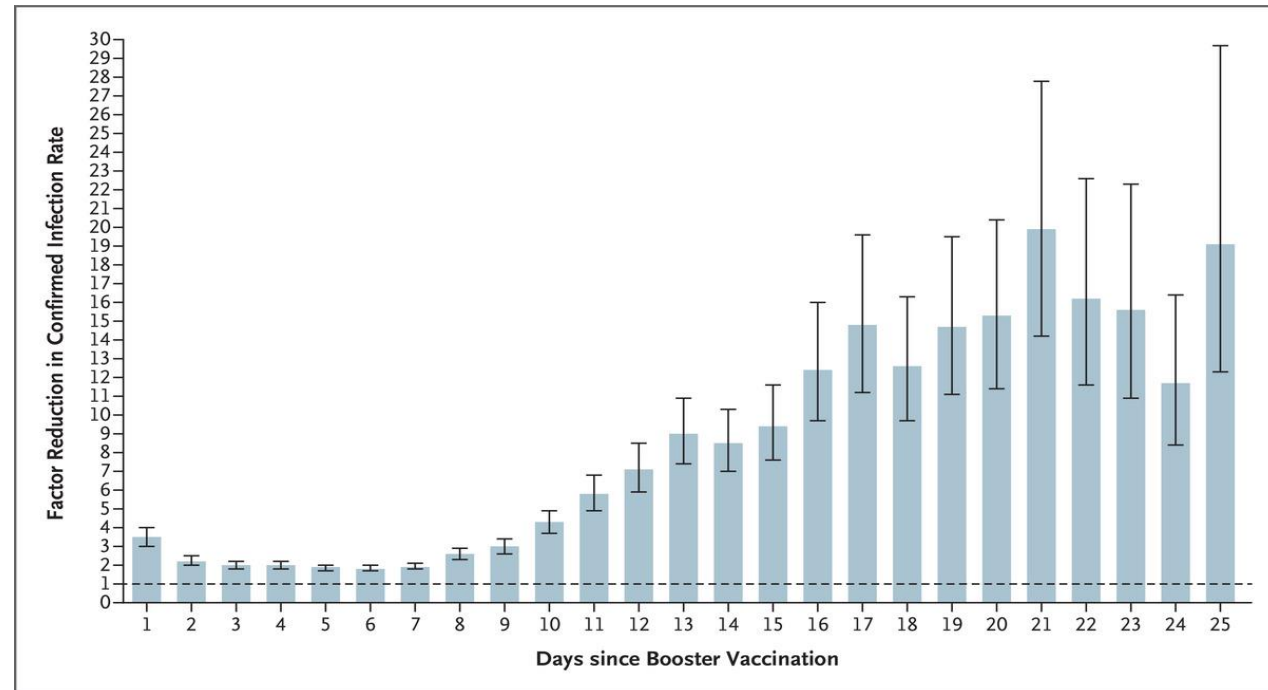
Source: Bar-on YM. NEJM 2021

Table 2. Primary Outcomes of Confirmed Infection and Severe Illness.*

Outcome	Nonbooster Group	Booster Group	Adjusted Rate Ratio (95% CI)†
Confirmed infection			11.3 (10.4 to 12.3)
No. of cases	4439	934	
No. of person-days at risk	5,193,825	10,603,410	
Severe illness			19.5 (12.9 to 29.5)
No. of cases	294	29	
No. of person-days at risk	4,574,439	6,265,361	

* Listed are the results of the Poisson regression analysis in participants who received a booster vaccine and in those who did not receive a booster. The booster group includes data that were obtained at least 12 days after receipt of the booster dose.

† The rate ratio is the estimated factor reduction in the rate in the booster group as compared with the rate in the nonbooster group.



Can We Change Vaccines When we Give Boosters?

Vaccine Mix and Match Boosters

Background: The impact of using different vaccines for boosters than original immunization for COVID-19 is

Design: Clinical trial with participants who received 1 or 3 vaccines: Moderna, Pfizer, J&J.

Outcome: Safety, immune response

- All of the boosters increased antibody and neutralizing antibody levels
- Moderna produced the highest levels

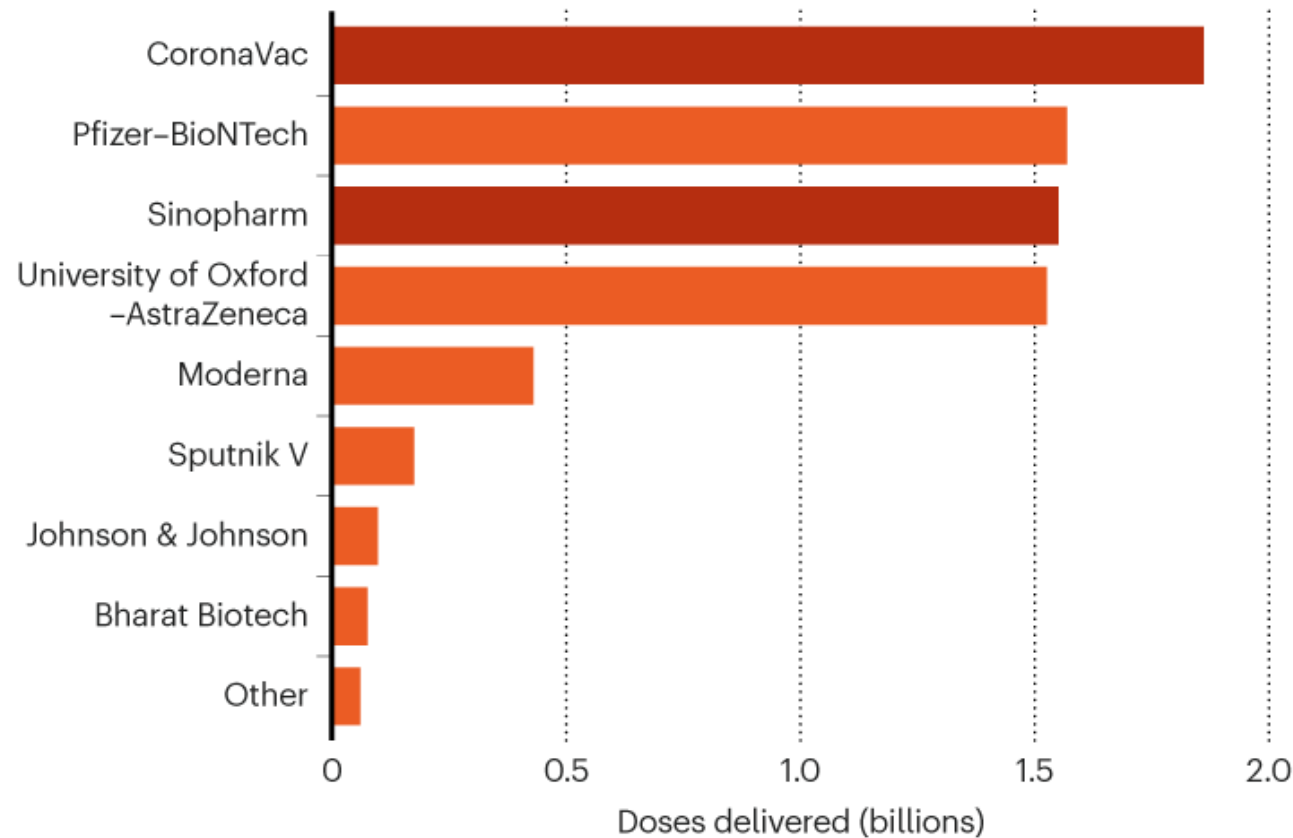
Increase was greatest for people who received J&J

	Primary Vaccine	J&J	Moderna	Pfizer	J&J	Moderna	Pfizer	J&J	Moderna	Pfizer
	Booster	Moderna			J&J			Pfizer		
IgG	Day 1 GMT	57	859	357	71	638	321	75	534	2235
	Day 15 GMT	320	6800	6155	326	3026	1904	2550	5196	3409
	Day 29 GMT	2803	5917	5170	368	4560	2600	In Process		
	Geo Mean rise	56	7.9	17	4.6	4.7	6.2	32.8	9.7	14.9
Neutralizing Ab	Day 1 GMT	8.9	89	25	7.6	62	19	9.4	58	21
	Day 15 GMT	676	902	786	31	382	216	341	678	447
	Day 29 GMT	431	700	496	In Process					
	Geo Mean	76	10	32	4.2	6.2	12.5	35	12	20

Boosters Following CoronaVac?

THE RACE TO VACCINATE

Out of the eight vaccines that account for the vast majority of COVID-19 vaccine doses delivered globally, China's CoronaVac and Sinopharm jabs account for nearly half of all doses.



Boosters Following CoronaVac?

- Laboratory data suggest inactivated vaccines produce lower levels of antibody that wane more rapidly than mRNA vaccines (reviewed in September) – cell mediated immunity may be different
- New preliminary data from Chile reported online on boosters following CoronaVac
- 4,785,749 people immunized with CoronaVac
- 2,017,818 received a booster shot with AstraZeneca (75%), Pfizer (18%), or Sinvac (7%)
- Data supported Chile's decision to initiate a booster program

	No Booster	CoronaVac Booster	Pfizer Booster	AZ Booster
Infection	56%	80%	90%	93%
Hospitalization	84%	88%	87%	96%

CDC Guidance on Boosters

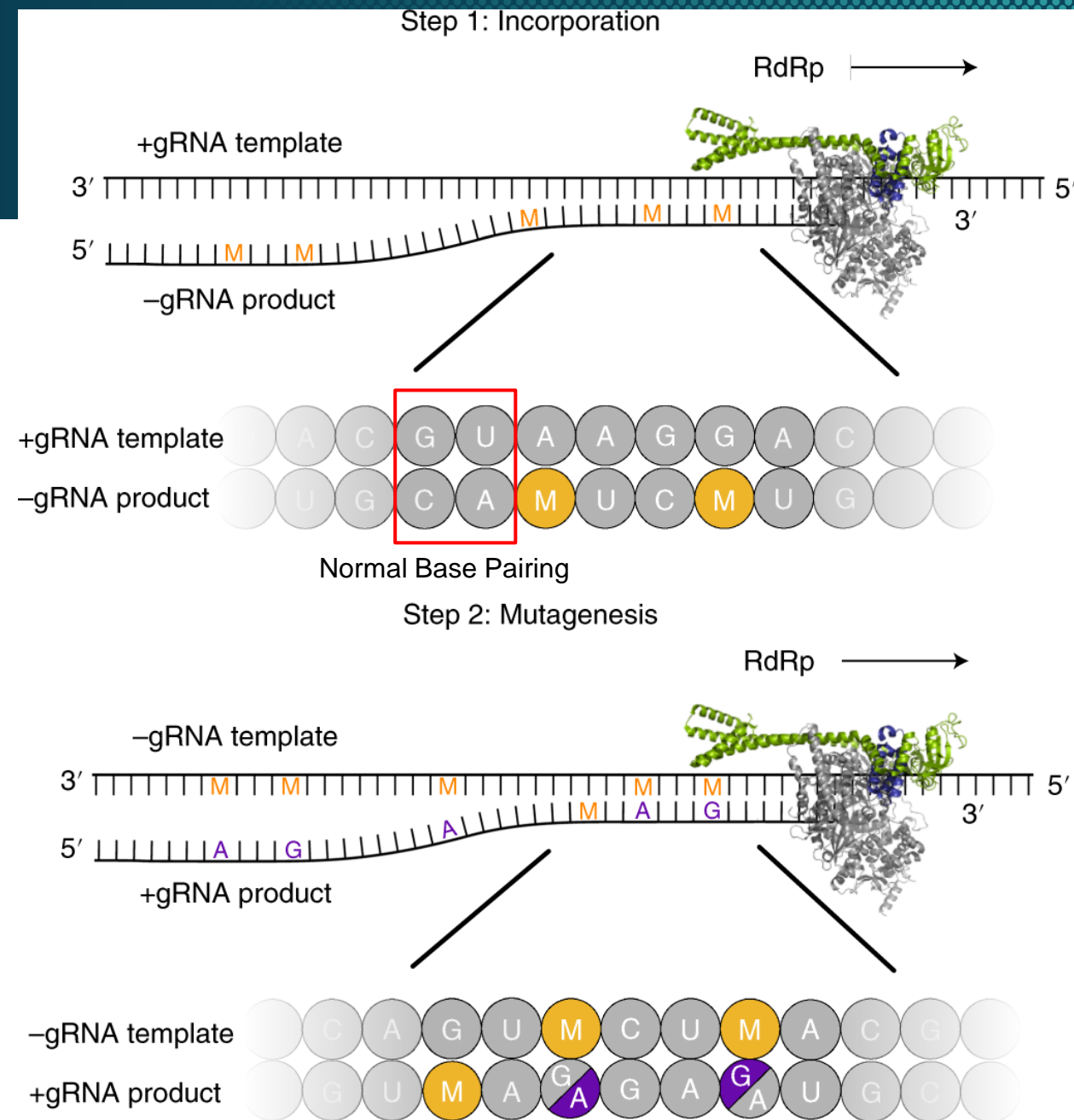
- Age 65
- 50-64 with underlying medical conditions
- Age 18-49 with underlying medical conditions – individual decision
- Employees and residents at increased risk for COVID-19 exposure because of occupational or residential exposure

Recommendation currently only for Pfizer, but Moderna will likely be recommended in next week

Medical conditions: cancer, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes, Down syndrome, dementia, HIV, heart disease, immunocompromised

Molnupiravir - A Mutagenic ribonucleoside

- β -D-*N*⁴-hydroxycytidine (NHC, ribonucleoside form = rNHC)
- Similar to ribavirin and favipiravir , but >100 fold more active
- Drug interferes with RNA synthesis through a 2 step process
 - Viral RNA-dependent RNA polymerase (RdRp) uses rNHC as a substrate instead of cytidine or uridine triphosphate
 - Mutated –gRNA strand leads to mutanized +gRNA strand
 - Resultant RNA does not support functional virus – “error catastrophe”
- Broad spectrum anti-RNA virus activity



Molnupiravir - Interim Analysis – Study Stopped Early

October 1, 2021

Background: There is a need for COVID-19 treatments, particularly orally administered drugs.

Design: RCT

Population: ~1400 unvaccinated persons at high risk for COVID-19 (obesity, age >60, DM, heart disease) within 5 days of symptom onset – interim analysis 775 through day 29

Outcome: Hospitalization or death

	Hospitalization or Death	Death
Molnupiravir	28/385 (7.3%)	0
Placebo	53/377 (14.1%)	8
	P=0.0012	

- Similar results for all variants
- Lower rate of discontinuation in Molnupiravir than placebo

<https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderate/>

Molnupiravir - Impact on Viral Shedding

Background: Impact of molnupiravir on viral shedding unknown. Decreased shedding would suggest that the drug would decrease transmission.

Design: RCT placebo, 200mg, 400mg, or 800mg bid

Population: 202 untreated patients within 7 days symptom onset

Outcome: Nasopharyngeal viral shedding day 3 and 5

	200mg	400mg	800mg	Placebo
Day 1	50%	42%	38%	47%
Day 3	18%	12%	2%*	17%
Day 5	4%	0*	0*	11%

* P<0.05 vs. placebo

Molnupiravir - Interim Analysis – Study Stopped Early

Merck is committed to providing timely access to molnupiravir globally, if it is authorized or approved, and plans to implement a **tiered pricing approach based on World Bank country income criteria** to reflect countries' relative ability to finance their health response to the pandemic.

As part of its commitment to widespread global access, Merck previously [announced](#) that the company has entered into **non-exclusive voluntary licensing agreements for molnupiravir with established generic manufacturers to accelerate availability of molnupiravir in more than 100 low- and middle-income countries (LMICs) following approvals or emergency authorization by local regulatory agencies.**

Summary

- **Epidemiology** – Declining epidemic in most of the world
- **Vaccines**
 - Moderna likely the most effective vaccine
 - Vaccine-induced immunity wanes over time – not so clear how much this is true for the most severe disease in all people
 - Boosters work – greater impact on infection than severe disease
 - Probably OK and even good to use different boosters than initial vaccine – particularly true of using mRNA boosters following inactivated vaccine
 - It would be good to see published data
- Molnupiravir looks promising
 - May be less effective than mAb treatments (50% vs. 85%), but likely much easier to deploy
 - Exciting to have a new, possibly broad spectrum anti-viral against RNA viruses
 - We need to see the data in a publication and additional safety data will be important

Questions and Comments