University of Washington
Public Health Capacity Building Center

COVID-19 Clinical Update

I-TECH Videoconference July 12, 2021

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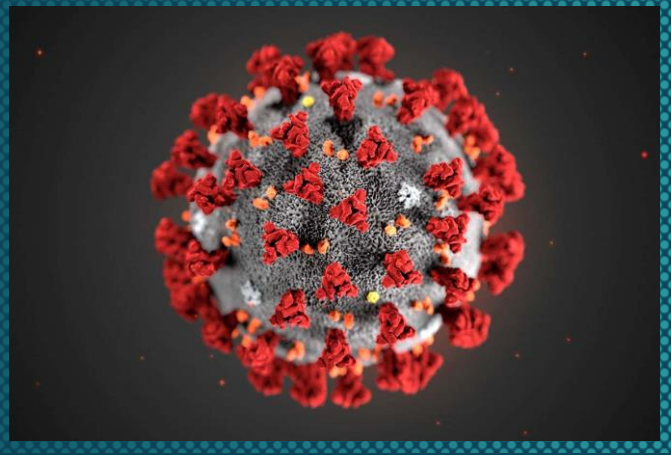


Last Updated: July 12, 2021

I-TECH
International Training and Education Center for Health

Overview

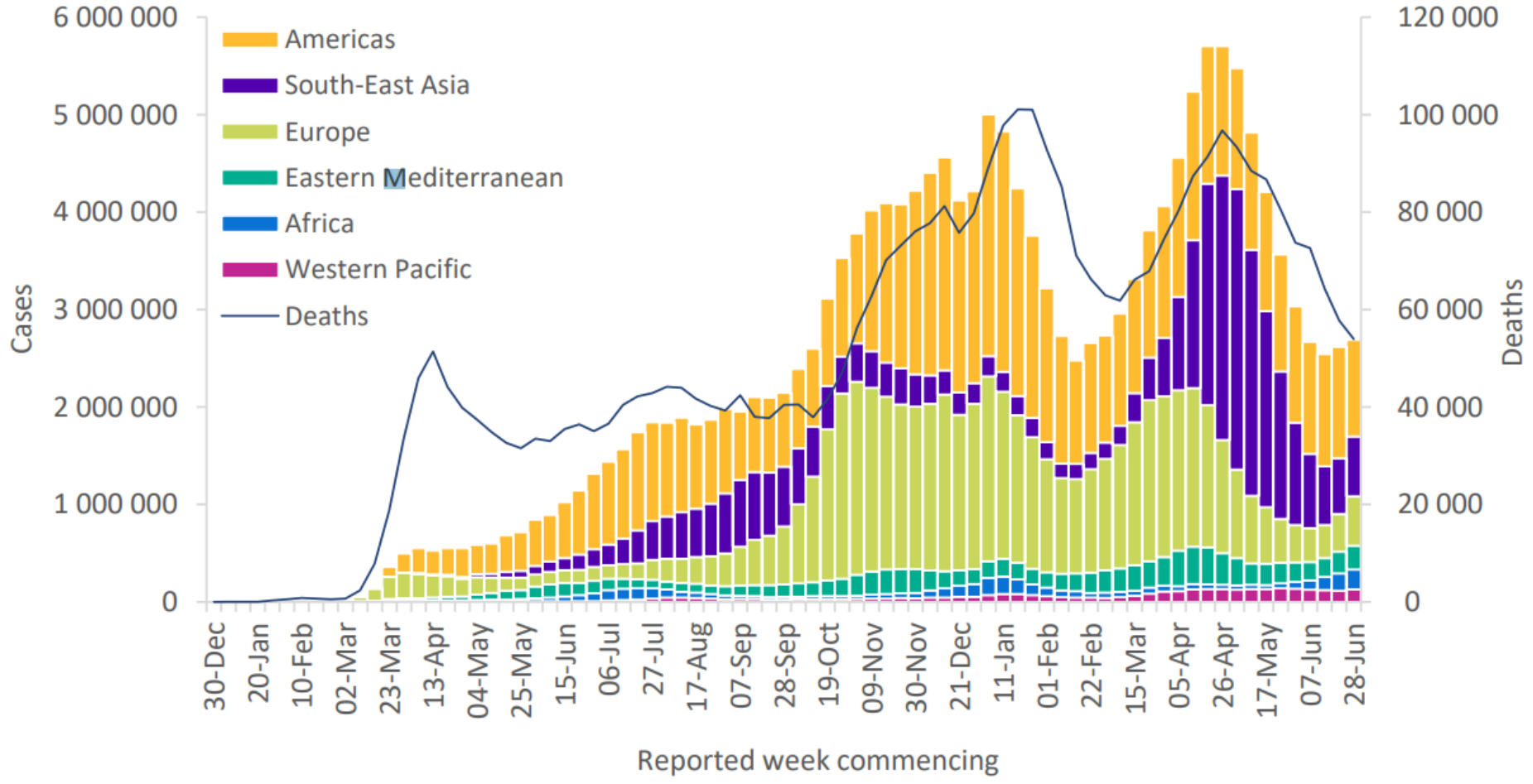
- Epidemiology
- SARS-CoV-2 Variants
- Vaccines
  - New vaccines (or new data)
  - Vaccine effectiveness against variants - delta

Global Trends in COVID-19 Diagnoses & Deaths

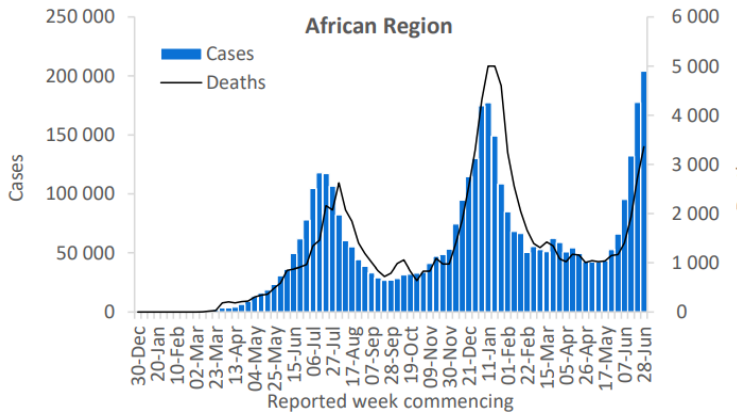
>183 Million Confirmed Cases
2.6 million cases/week

~4 Million Confirmed Deaths
54,000 deaths/week

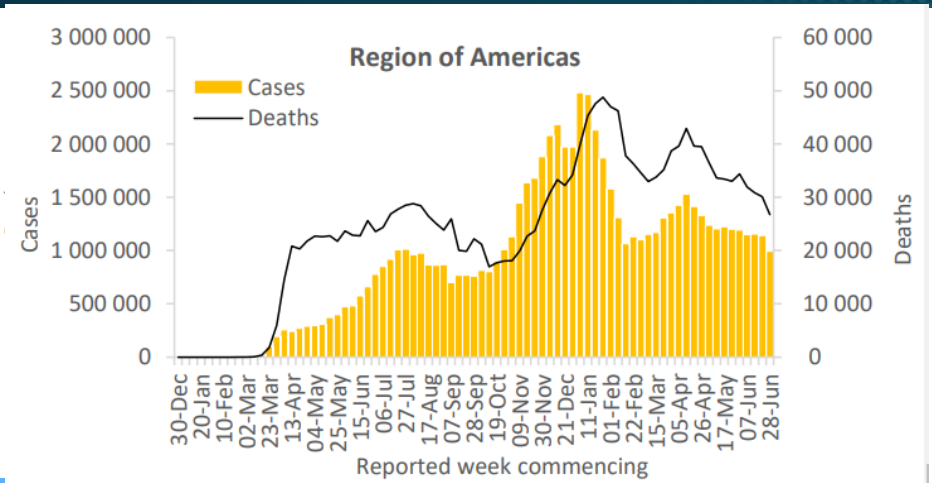
Figure 1. COVID-19 cases reported weekly by WHO Region, and global deaths, as of 4 July 2021**



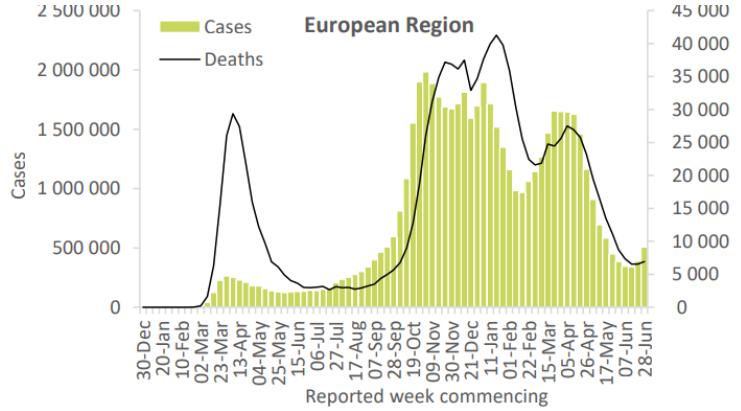
Global Trends in COVID-19 Diagnoses & Deaths



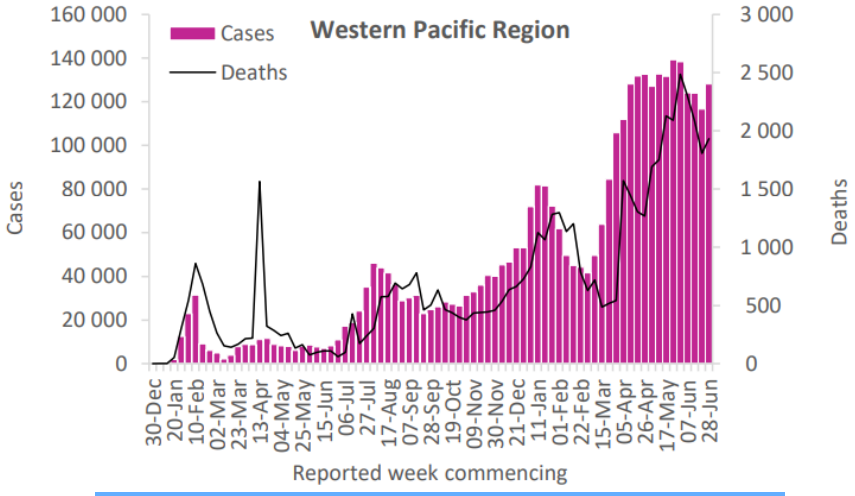
15% & 23% ↑ Cases and Deaths



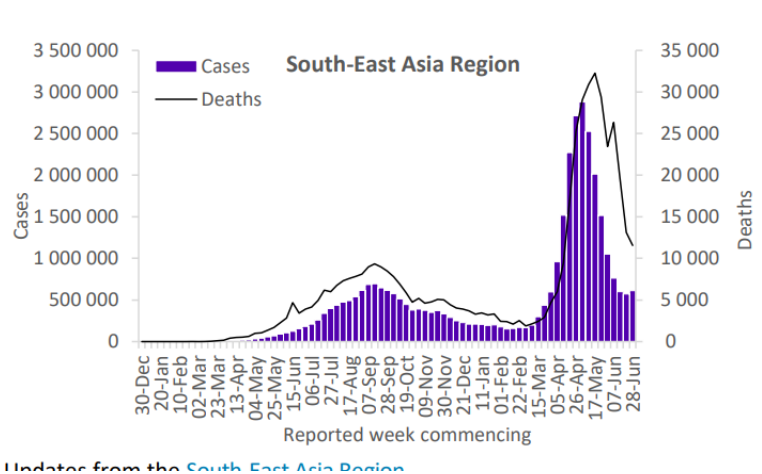
Lots heterogeneity - Brazil (still high)



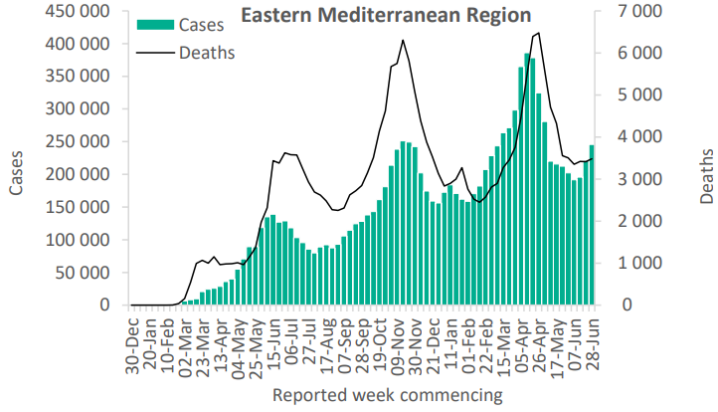
↑ Turkey – Very high Poland



Very high Mongolia, Malaysia

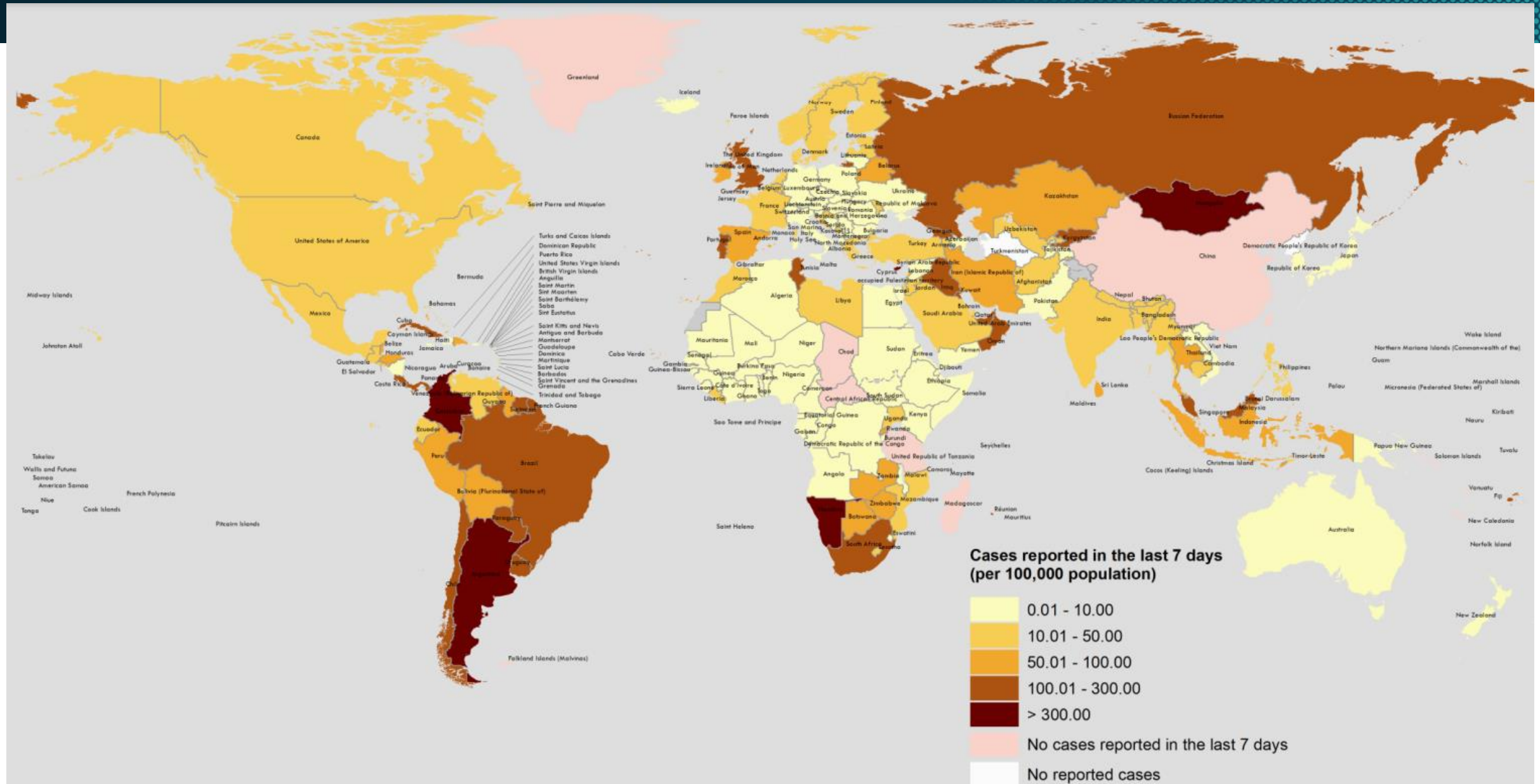


↓ India, ↑ Thailand, Indonesia, Myanmar

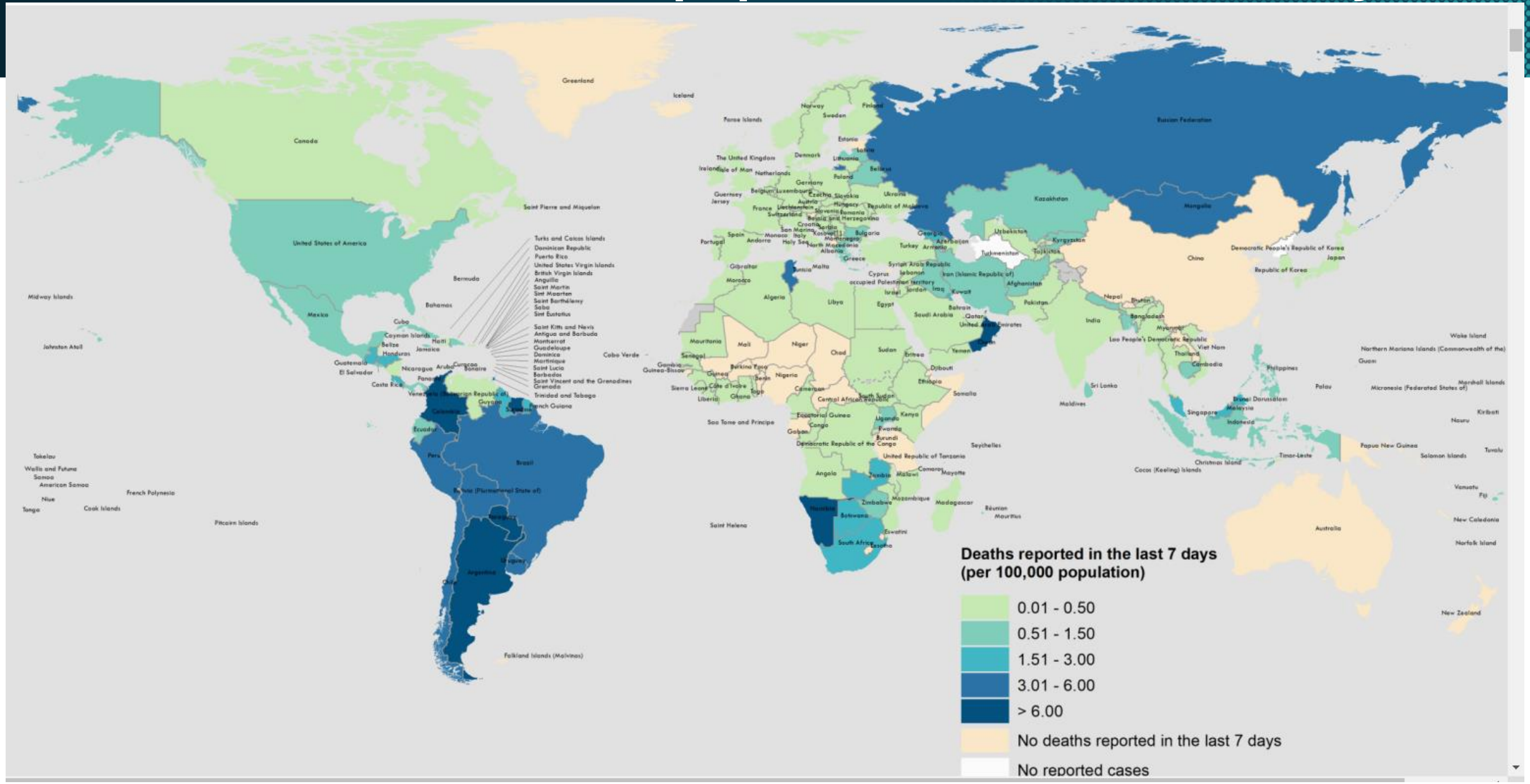


High Iran, Tunisia, Iraq

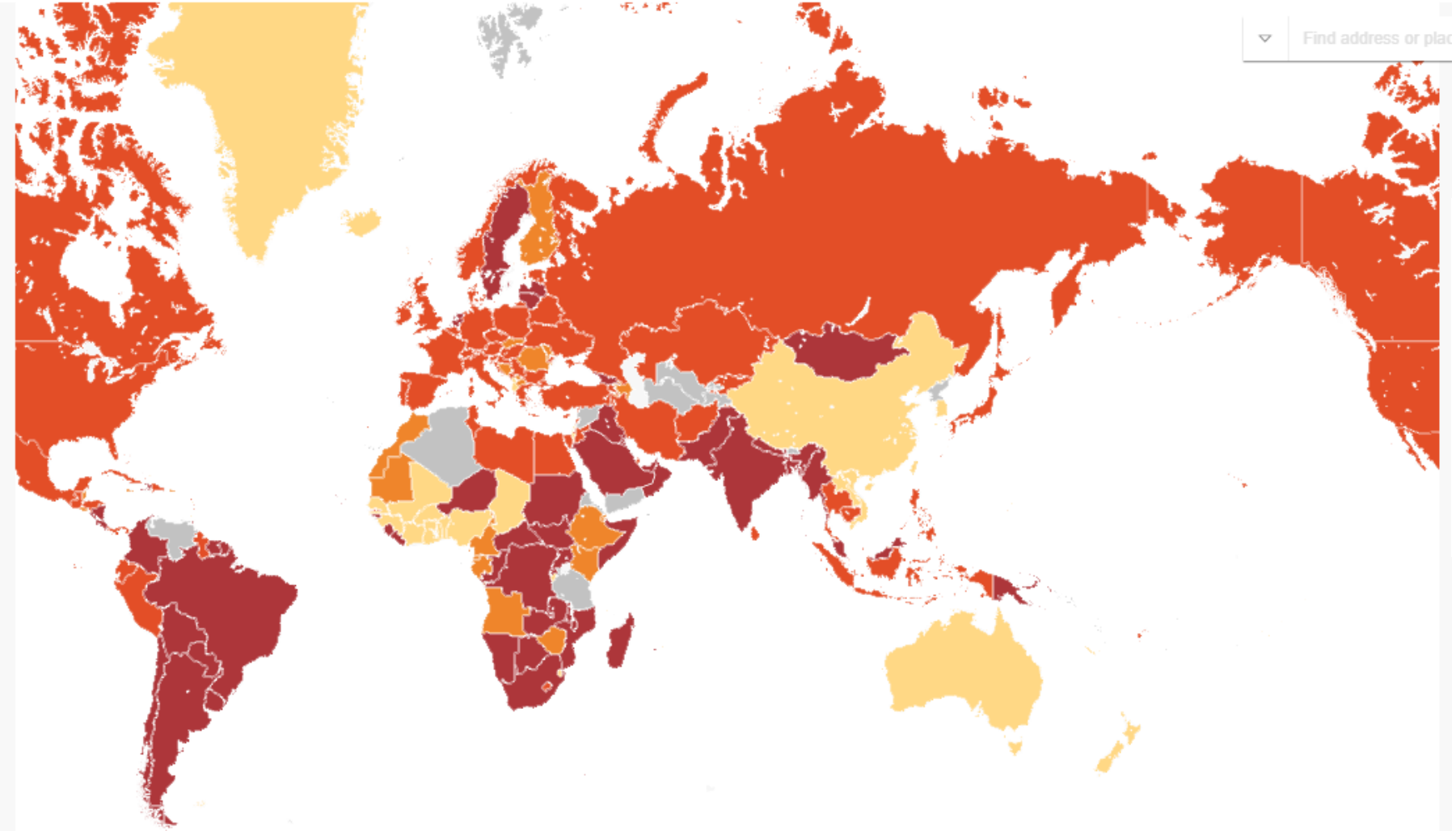
COVID-19 cases/100 000 population, 28 June – 4 July 2021



COVID-19 deaths/100 000 population, 28 June – 4 July 2021



CDC COVID-19 Risk Assessment



Level 4: COVID-19 Very High

Level 3: COVID-19 High

Level 2: COVID-19 Moderate

Level 1: COVID-19 Low

Level Unknown: COVID-19 Unknown

New CDC Variant Classification System

- **New WHO naming system – May 31, 2021** – Greek alphabet

- **Classification**
  - **Variant of interest** – Significant community transmission AND **genetic markers** associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.

  - **Variant of concern** - **A variant for which there is evidence of an increase in transmissibility, more severe disease (increased hospitalizations or deaths), or decreased effectiveness of public health control means (e.g., diagnostics, vaccines, treatment, social distancing)**.

  - **CDC - Variant of high consequence -** A variant of high consequence has **clear evidence that prevention measures or medical countermeasures (MCMs) have significantly reduced effectiveness** relative to previously circulating variants.

https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

WHO Variant of Concern and Interest

		Initial identification	Genetic changes	↑ Transmission	↑ Virulence	↓ mAb Effect	↓ Sera Neutralization
VOC	Alpha – B.1.1.7	UK – Sept 2020	E484K (some)	50%	↑30% mortality ♀	-	-
	Beta - B.1.351	South Africa – May 2020	E484K, K417N, N501Y	50%	Mixed data	+	+
	Gamma – P1	Brazil – Nov 2020	E484K, K417N, N501Y		Unconfirmed effect	+	+
	Delta – B.1.617.2	India - Oct 2020	L452R	97% vs. non-VOC 50% vs. alpha	Unconfirmed effect	+	+
VOI	Eta – B.1.525	Mult Counties – Dec 2020	E484K				
	Iota – B.1.526	USA – Nov 2020	L452R, E484K (some)				
	Kappa – B.1.617.1	India – Oct 2020	L452R				
	Lambda – C.37	Peru – Dec 2020					

Many additional "alerts for further monitoring" – red - variants have been downgraded

B1.427 & 429 (USA), P2 (Brazil), P3 (Philippines), R1 & 2 (mult counties), B.1.466.2 (Indonesia), B.1.621 (Columbia), AV.1 (UK), B.1.1.318 (Mult), B.1.1.519 (Mult), AT.1 (Russia), C.36.3 (Mult), B.1.214.2 (mult)

WHO Variants of Concern: Key Mutations & Potential Phenotypic Impact

Table 2. Key Spike Protein Mutations in Five SARS-CoV-2 Variants.

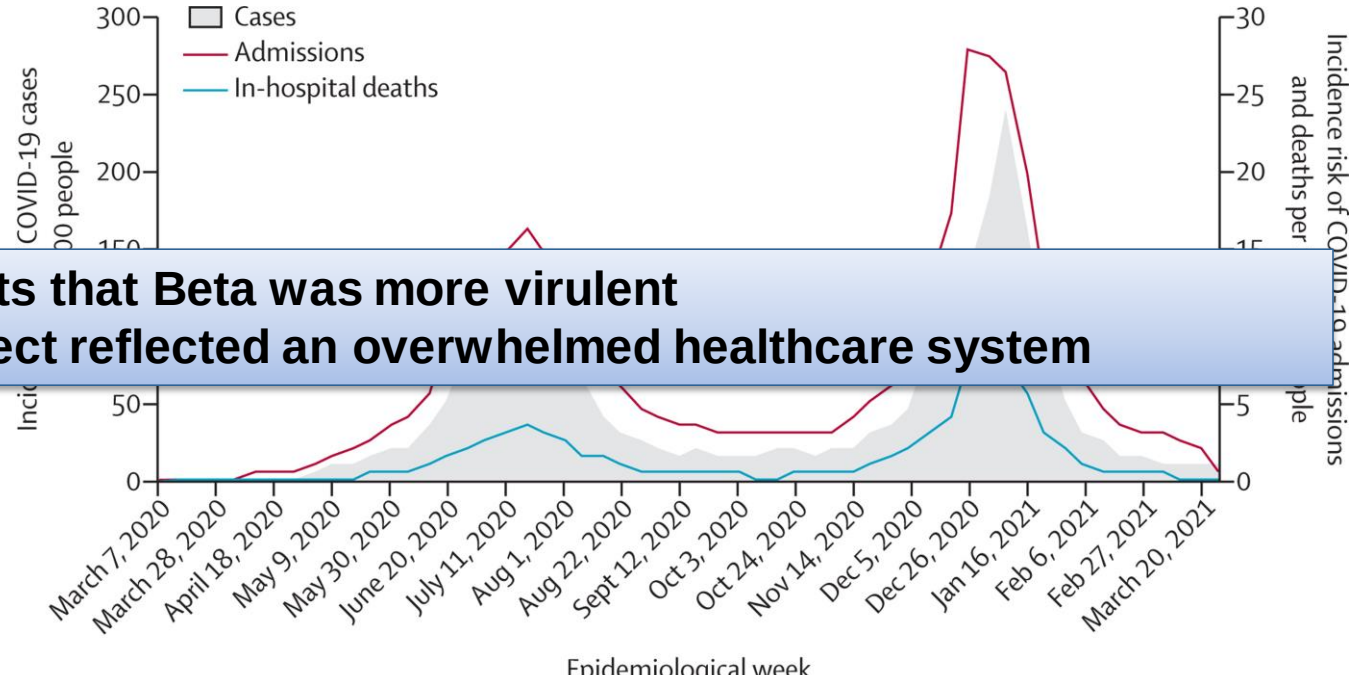
Variant	Phenotypic Change	Amino Acid Position in Prototype Virus and Proposed Effect of Changing It*						
		Δ69–70 Increase transmission	K417 Decrease neutralization	L452 Decrease neutralization	E484 Decrease neutralization	N501 Increase transmission	D614 Increase transmission	P681 Increase transmission
B.1.1.7 (or alpha)	Increase transmission	69–70 deleted			K (later change)	Y	G	H
B.1.351 (or beta)	Increase transmission and virulence		N		K	Y	G	
B.1.1.28.1 (or gamma or P.1)	Increase transmission and virulence, decrease neutralization		N/T		K	Y	G	
B.1.617.2 (or delta)	Increase transmission, decrease neutralization			R			R	R
B.1.617.1 (or kappa)	Increase transmission, decrease virulence			R	Q		G	R

* Single letter codes of amino acid changes at specified positions for the listed variants are shown.

Increased COVID-19 Mortality in the 2nd Wave in South Africa

Background: South Africa now in 3rd wave of infections. Study compares mortality in wave 1 (peak July 2020) vs wave 2 (peak January 2021) when wave had beta variant predominance. **Design:** Prospective cohort study of surveillance data from South Africa 3/5/2-3/27/21
Outcome: In hospital mortality

Suggests that Beta was more virulent
Some of the observed effect reflected an overwhelmed healthcare system

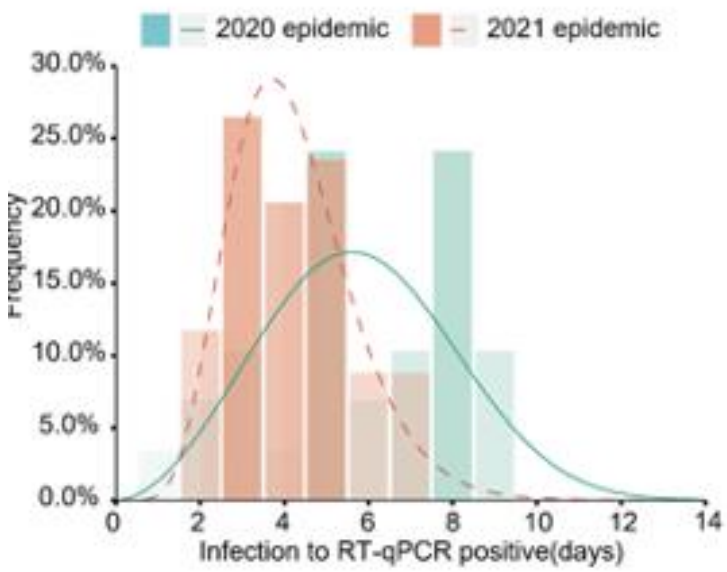


Wave period	Case-fatality risk (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Pre-wave 1	18·0% (17·2–18·7)	0·79‡ (0·75–0·84)	0·88‡ (0·83–0·93)	0·99 (0·91–1·07)
Wave 1	20·8% (20·5–21·1)	1 (ref)	1 (ref)	1 (ref)
Pre-wave 2	16·4% (16·0–16·9)	0·70‡ (0·68–0·73)	0·76‡ (0·73–0·79)	0·85‡ (0·79–0·91)
Wave 2	27·8% (27·5–28·1)	1·34‡ (1·31–1·37)	1·37‡ (1·33–1·40)	1·31‡ (1·28–1·35)
Post-wave 2	18·6% (17·9–19·2)	0·80‡ (0·76–0·84)	0·90‡ (0·85–0·95)	1·02 (0·95–1·09)

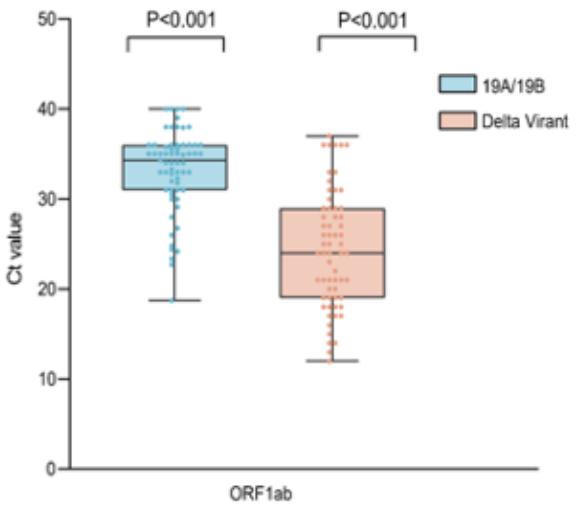
Jassat W. Lancet Global Health 2021

Delta Variant – Mechanism of Increased Infectiousness

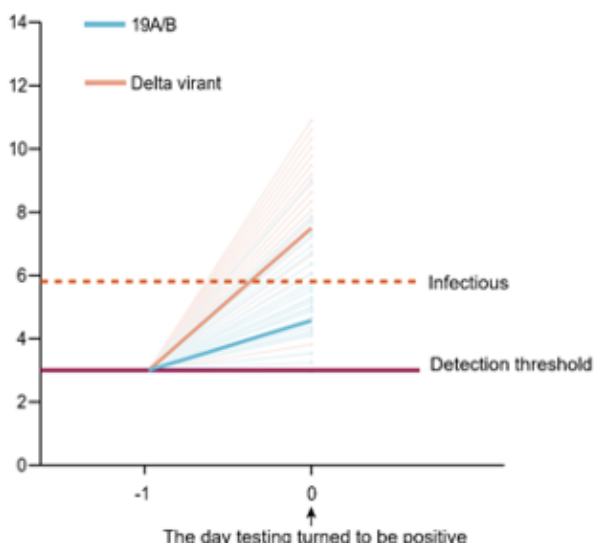
Background: Evidence suggests delta variant is more transmissible. Mechanism uncertain.
Design: Assessment of respiratory tract viral load persons in quarantine in China



Exposure to 1st PCR + 2020 vs Delta 6 (peak 5.6) vs. 4 (peak 3.7) days



Lower PCR Ct value= 1260x more virus

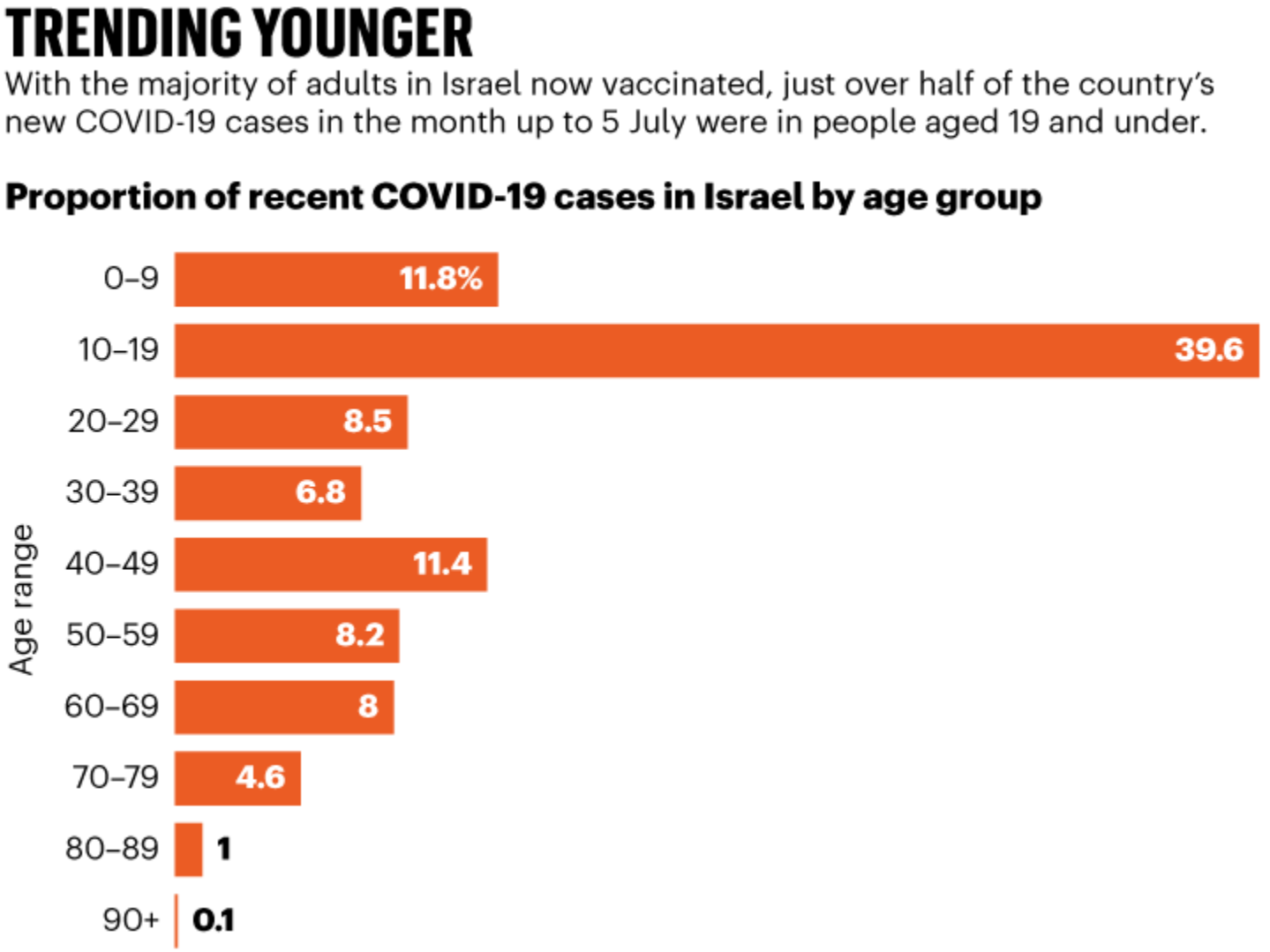


Faster onset of infectiousness – high risk early asymptomatic transmission

https://virological.org/t/viral-infection-and-transmission-in-a-large-well-traced-outbreak-caused-by-the-delta-sars-cov-2-variant/724/1

Shift to Younger Ages: Israel

- High vaccine uptake in adults (~85%)
- Increase in the proportion of cases in children, not the absolute risk in children
- Raises questions about masks and social distancing until immunization more widespread in children
- Equity issue: Will we vaccinate children in wealthy countries before elderly people in poor ones?



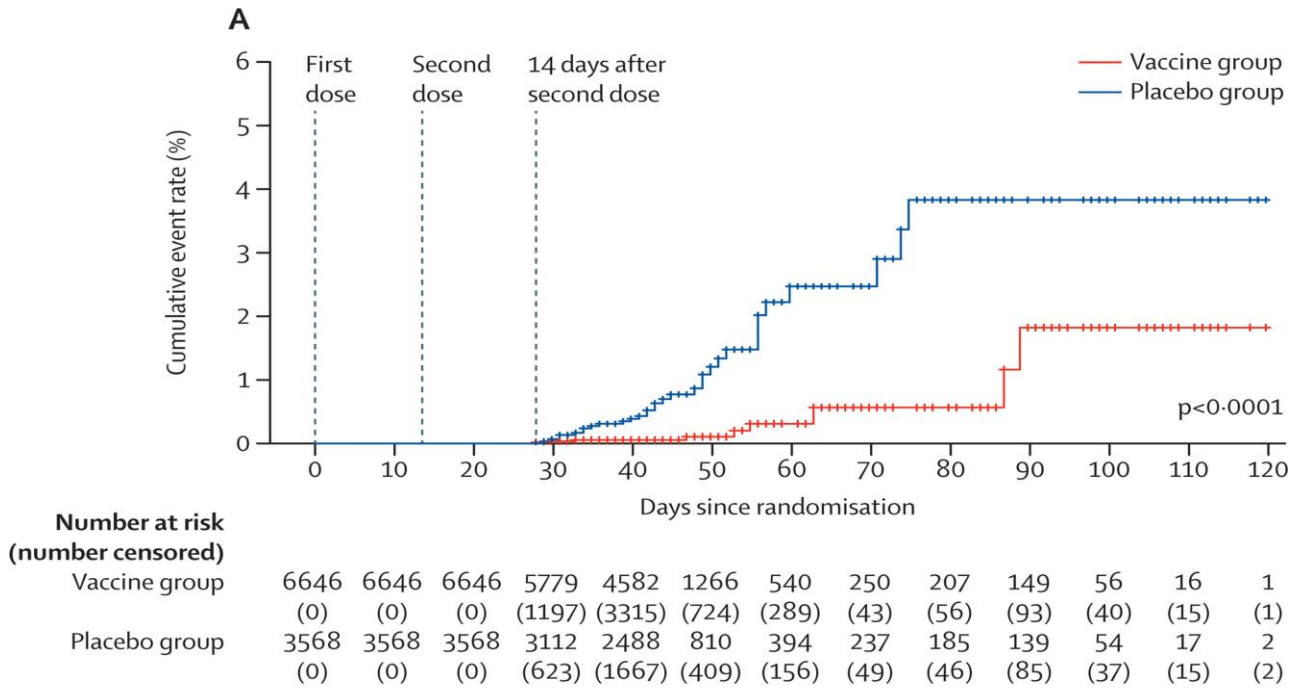
Nature News July 8, 2021

Vaccines

CoronaVac (Sinovac) Randomized Trial

VE=83.5% 95% CI 65.4-92.1

Background: CoronaVac – an inactivated virion - has been widely used in LMIC, but efficacy data from RCTs of the vaccine have not been published. Preliminary efficacy estimates vary from 50-91%.
Design: Double blind placebo-controlled trial
Population: 11,303 persons aged 18-59 in Turkey 9/20-1/21
- **Outcome**: PCR+ symptomatic COVID-19 ≥14 days after 2nd dose

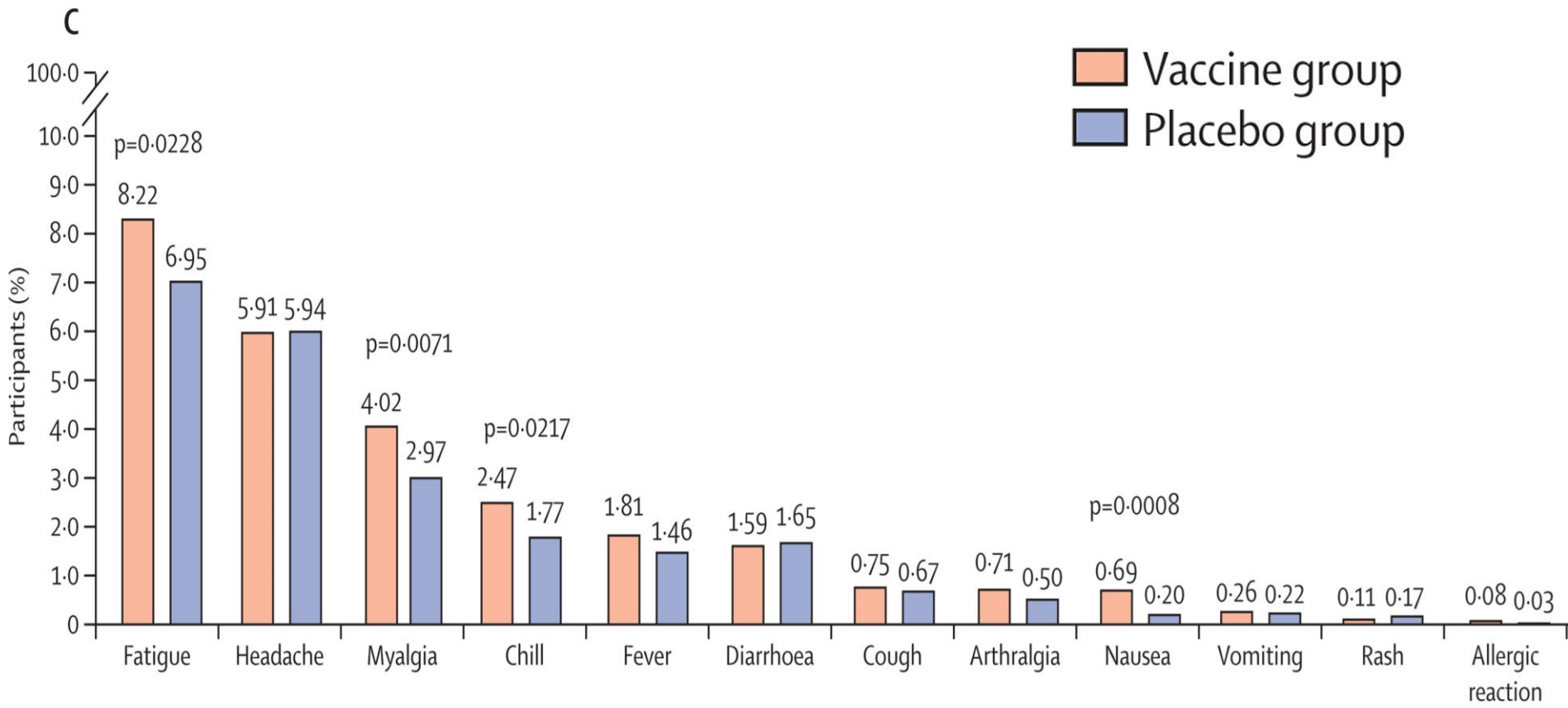


	Vaccine group (n=6646)	Placebo group (n=3568)
Between first and second dose	48	27
From second dose to 14 days after second dose	17	17
More than 14 days after second dose	9	32
Total (any time after randomisation)	74	76

Source: Tanriover D. Lancet 2021

CoronaVac (Sinovac) Randomized Trial

- **Good safety profile**



Source: Tanriover D. Lancet 2021

CoronaVac (Sinovac) Effectiveness in Chile

Background: CoronaVac has been widely used in LMIC , but efficacy data from RCT of the vaccine have not been published. Preliminary efficacy estimates vary from 50-91%.

Design: National observational cohort analysis

Population: 10.2 million persons in Chile

- **Outcome**: PCR+ infection, hospitalization, ICU admission, death

Source: Jara A. NEJM 2021

Table 2. Effectiveness of CoronaVac Vaccine in Preventing Covid-19 Outcomes in Overall Study Cohort, According to Immunization Status.*

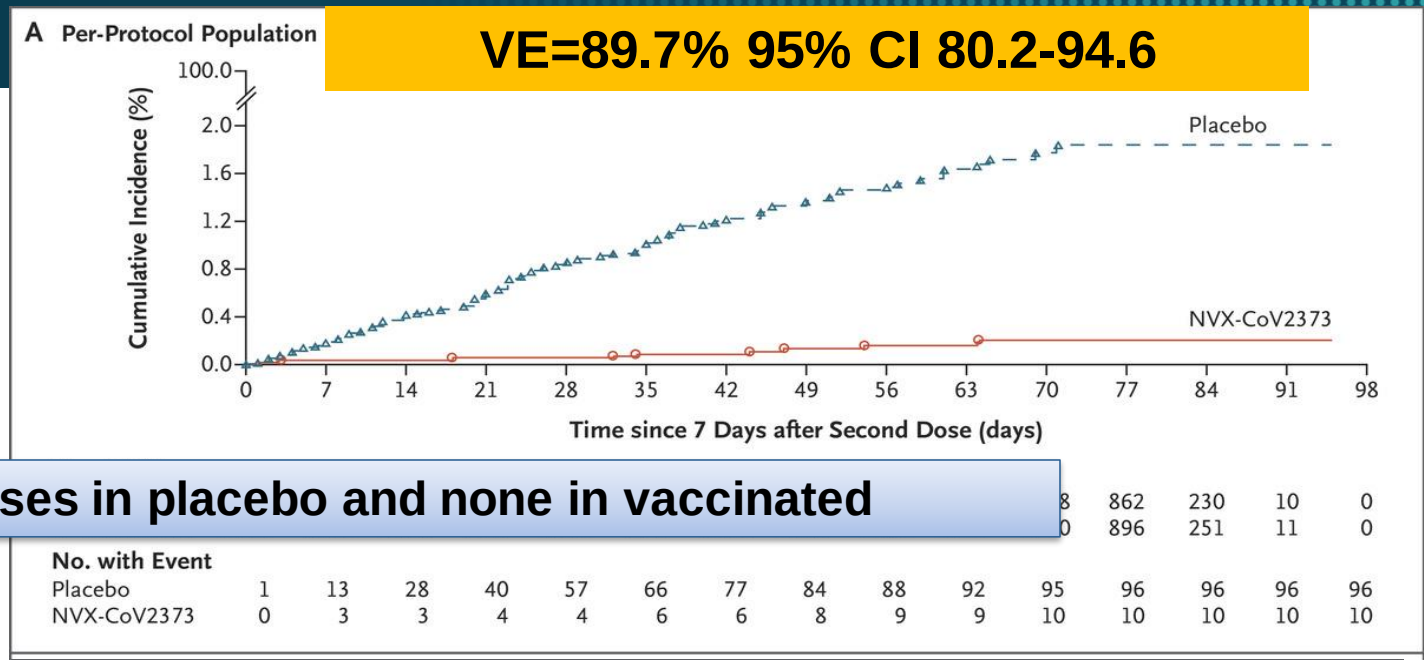
Outcome and Immunization Status	Study Cohort	Persons with Covid-19		Vaccine Effectiveness (95% CI)		
	No. of Person-Days	No. of Persons	Incidence Rate	Analysis Adjusted for Sex and Age	Analysis Adjusted for All Covariates†	Stratified Analysis‡
			no. of events/ 1000 person-days		*percent*	
Covid-19						
Unvaccinated	614,868,240	185,633	0.3019	—	—	—
Partially immunized	69,788,352	20,865	0.2990	8.0 (6.5–9.4)	15.5 (14.2–16.8)	17.2 (15.8–18.6)
Fully immunized	91,671,797	12,286	0.1340	61.2 (60.3–62.0)	65.9 (65.2–66.6)	63.7 (62.8–64.6)
Hospitalization						
Unvaccinated	620,894,706	18,034	0.0290	—	—	—
Partially immunized	70,690,796	3,370	0.0477	31.4 (28.6–34.0)	37.4 (34.9–39.9)	40.3 (37.6–42.8)
Fully immunized	92,445,333	1,462	0.0158	86.0 (85.1–86.8)	87.5 (86.7–88.2)	86.5 (85.6–87.4)
Admission to ICU						
Unvaccinated	621,226,431	6,359	0.0102	—	—	—
Partially immunized	70,836,597	1,154	0.0163	37.5 (33.1–41.5)	44.7 (40.8–48.3)	45.3 (41.2–49.2)
Fully immunized	92,622,083	360	0.0039	88.8 (87.4–90.0)	90.3 (89.1–91.4)	90.2 (88.9–91.4)
Confirmed death						
Unvaccinated	621,426,477	2,786	0.0045	—	—	—
Partially immunized	70,854,187	847	0.0120	39.8 (34.4–44.7)	45.7 (40.9–50.2)	46.0 (40.7–50.8)
Fully immunized	92,514,261	409	0.0044	84.4 (82.4–86.2)	86.3 (84.5–87.8)	86.7 (84.9–88.3)

Novavax Randomized Trial

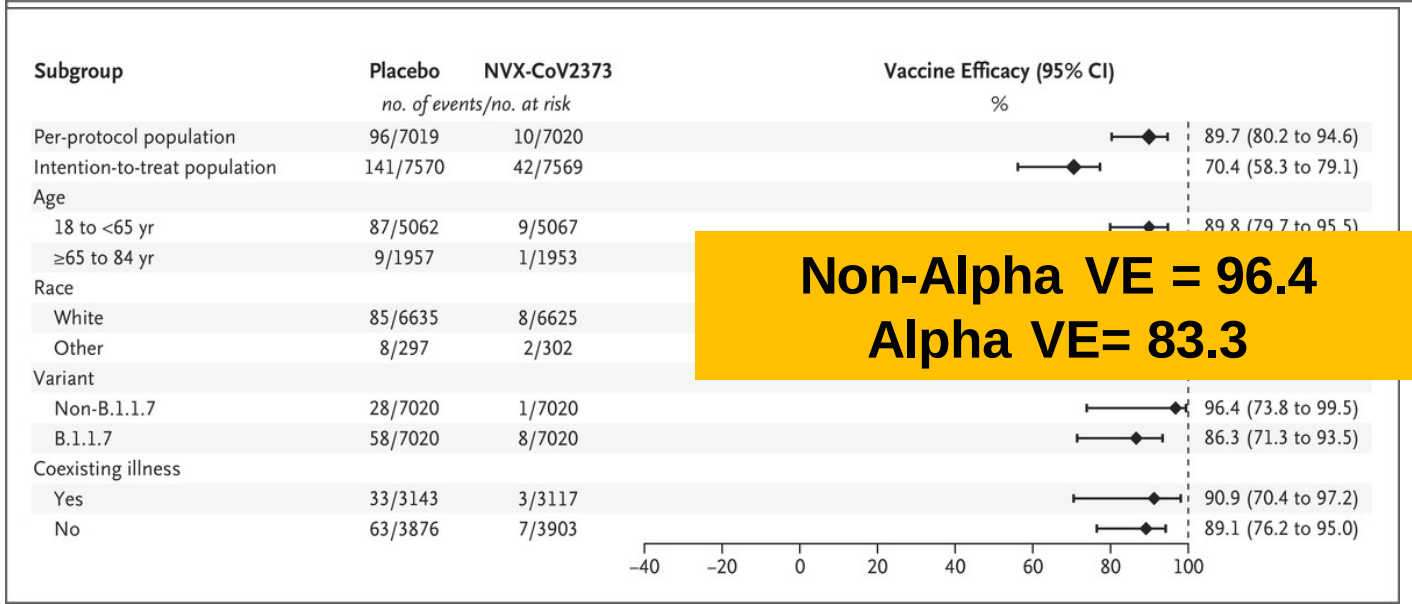
Background: Preliminary data suggest that NVX-CoV2373 (Novavax) – a recombinant nanoparticle vaccine – is immunogenic and safe.
Design: Observer blind placebo-controlled trial
Intervention: – 2 doses 21 days apart – normal refrigeration
Population: 15,187 persons aged 18-84 in UK
- **Outcome**: PCR+ symptomatic COVID-19 ≥7 days after 2nd dose

Source: Heath P. NEJM 2021

VE=89.7% 95% CI 80.2-94.6



5 severe cases in placebo and none in vaccinated

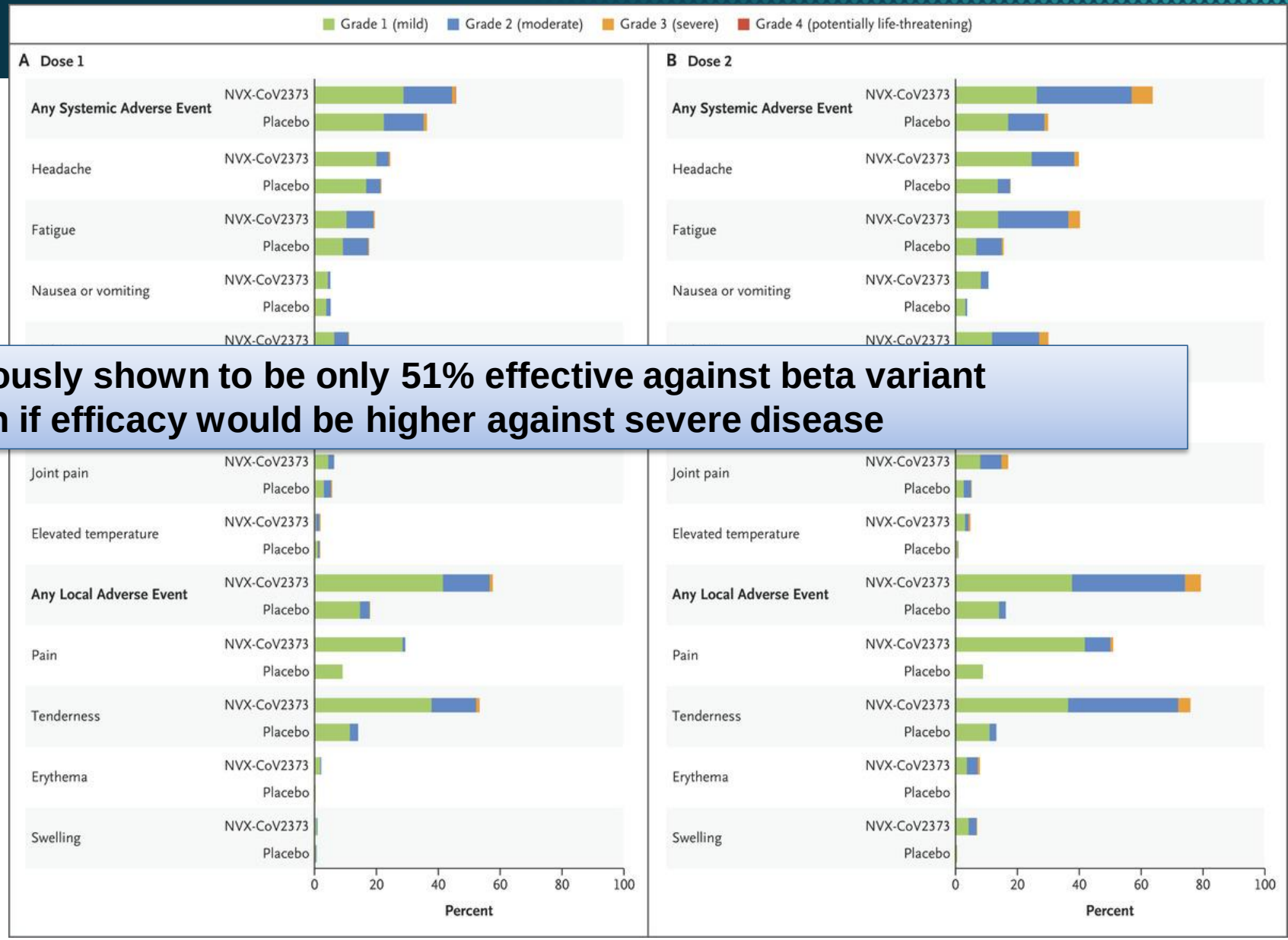


Non-Alpha VE = 96.4
Alpha VE= 83.3

Novavax Randomized Trial

- **Good**
- More dose two
- One case myocarditis – patient recovered

Novavax previously shown to be only 51% effective against beta variant
Uncertain if efficacy would be higher against severe disease



Source: Heath P. NEJM 2021

BIBP (Sinopharm) Vaccine

- Data reviewed by WHO Strategic Advisory Group of Experts
- Inactivated COVID-19 vaccine
- Phase 3 trial 2 doses administered 21 days apart
  - Efficacy 79% against symptomatic COVID-19
  - Study not powered to look at severe disease
  - No data on efficacy vs. varients

https://www.who.int/news-room/feature-stories/detail/the-sinopharm-covid-19-vaccine-what-you-need-to-know

COVAXIN (Bharat) Vaccine
July 5 Press Release

- Inactivated COVID-19 vaccine
- Phase 3 trial 2 doses administered 21 days apart – 25,798 participants
  - 130 symptomatic events – 24 in vaccine arm and 196 in placebo
  - Efficacy 77.8% overall
    - 93.4% against severe symptomatic COVID-19
    - 63.6% against asymptomatic infection
    - 65.2% against Beta and Delta variants – data not broken down by variant

https://www.pharmaceutical-technology.com/news/bharat-biotech-covaxin-efficacy/

Impact of mRNA Vaccines on Household Transmission

Background: Impact of vaccines on transmission not well defined
Design: Household transmission evaluation dataset – observational UK study that includes data persons in household. Comparison 2 attack rate when index case was vaccinated or not vaccinated
Population: 960,765 household contacts
Outcome: CoV-2 + test in unvaccinated household contacts 2-14 days after index case positive test

Table 1. Numbers of Household Contacts and Secondary Cases of Covid-19, According to Vaccination Status of Index Patient, and Adjusted Odds Ratios.*

Vaccination Status of Index Patient	Household Contacts	Secondary Cases	Adjusted Odds Ratio (95% CI)
	no.	*no. (%)*	
Not vaccinated before testing positive	960,765	96,898 (10.1)	Reference
Vaccinated with ChAdOx1 nCoV-19 vaccine ≥21 days before testing positive	3,424	196 (5.7)	0.52 (0.43–0.62)
Vaccinated with BNT162b2 vaccine ≥21 days before testing positive	5,939	371 (6.2)	0.54 (0.47–0.62)

* Odds ratios were adjusted for the age and sex of the index patient and their household contact, geographic region, calendar week of the index case, and an index of multiple deprivation and household type and size. CI denotes confidence interval, and Covid-19 coronavirus disease 2019.

93% Index Cases Only Had One Dose of Vaccine

Source: Harris R. NEJM 2021

Delta Variant: Virulence and Vaccine Effectiveness: England

Background: The delta variant is now the dominant circulating strain in many parts of the world.

Data & Population: English surveillance

Design:

1) Test negative cases control (compares symptomatic persons who test + and -). Comparison effectiveness delta vs. alpha variants.

2) Comparison % delta in vaccinated and unvaccinated

Outcome: Vaccine effectiveness.

	Alpha	Delta
Pfizer vaccine		
1 dose	49.2 (42.6-55.0)	33.5 (20.6-44.3)
2 dose	93.4 (90.4-95.5)	80.9 (70.1-87.6)
AstraZeneca		
1 dose	51.4 (47.3-55.2)	32.9 (19.3-44.3)
2 dose	66.1 (54-75)	59.8 (28.9-77.3)

- Ratio of Delta to Alpha was higher in vaccinated than unvaccinated – supports diminished vaccine efficacy
  - Higher with AstraZeneca vs. Pfizer

Vaccine efficacy lower with delta vs. alpha
2nd dose is very important
Vaccines still worked, just not as well

Bernel JP. MedRxiv 2021

Delta Variant: Virulence and Vaccine Effectiveness: Scotland

Background: The delta variant is now the dominant circulating strain in many parts of the world.
Design: Cohort study using Scottish surveillance data 4/21-6/21. Control for vaccine effectiveness tested negative.
Outcome: Hospitalization and and vaccine effectiveness.

- Delta associated with an increased risk hospitalization vs. alpha variant
  - HR 1.85 (95% CI 1.39-2.47)

	S gene negative	S gene+ (Delta)
Hospitalization	HR 0.32 (95% CI 0.22-0.46)	HR 0.38 (95% CI 0.24-0.58)
All COVID cases		
Pfizer vaccine	92% (95%CI 90-93)	78% (95%CI 74-82)
AstraZeneca	73% (95% CI 66-78)	60% (95% CI 53-66)

Risk hospitalization higher with Delta variant, and vaccine effectiveness lower, particularly with AstraZeneca.
Vaccines still worked, just not as well

Sheikh A. Lancet 2021

Delta Variant: Virulence and Vaccine Effectiveness: Canada

Background: The delta variant is now the dominant circulating strain in many parts of the world.

Data & Population: Canadian surveillance

Design:

1) Test negative cases control (compares symptomatic persons who test + and -). Comparison effectiveness different variants.

Nasreen S. MedRxiv 2021

Adjusted VE

		Non-VOC	Alpha	Beta/Gamma	Delta
Symptomatic Infection					
Pfizer	1 dose 2 dose	61 93	66 89	60 84	56 87
Moderna	1 dose 2 dose	54 89	83 92	77 -	72 -
AstraZeneca	1 dose 2 dose	67 -	64 -	48 -	67 -
Hospitalization or death					
Pfizer	1 dose 2 dose	68 96	80 95	77 95	78 -
Moderna	1 dose 2 dose	57 96	79 94	89 -	96 -
AstraZeneca	1 dose 2 dose	- -	85 -	83 -	88 -

Delta Variant: Virulence and Vaccine Effectiveness: Canada

Background: The delta variant is now the dominant circulating strain in many parts of the world.

Data & Population: Canadian surveillance

Design:

1) Test negative cases control (compares symptomatic persons who test + and -). Comparison effectiveness different variants.

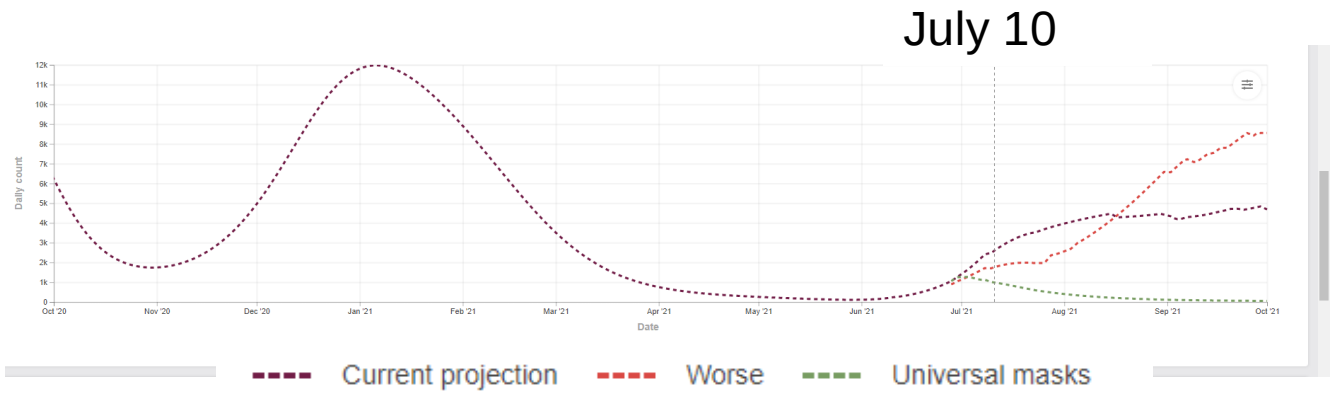
Nasreen S. MedRxiv 2021

Adjusted VE

		Non-VOC	Alpha	Beta/Gamma	Delta
Symptomatic Infection					
Pfizer	1 dose 2 dose	61 (54-68) 93 (88-96)	66 (64-68) 89 (86-91)	60 (52-67) 84 (69-92)	56 (45-64) 87 (64-95)
Moderna	1 dose 2 dose	54 (28-70) 89 (65-96)	83 (80-86) 92 (86-96)	77 (63-86) -	72 (57-83) -
AstraZeneca	1 dose 2 dose	67 (38-82) -	64 (60-68) -	48 (28-63) -	67 (44-80) -
Hospitalization or death					
Pfizer	1 dose 2 dose	68 (54-78) 96 (82-99)	80 (78-82) 95 (92-97)	77 (69-83) 95 (81-99)	78 (65-86) -
Moderna	1 dose 2 dose	57 (28-75) 96 (70-99)	79 (74-83) 94 (89-97)	89 (73-95) -	96 (72-99) -
AstraZeneca	1 dose 2 dose	- -	85 (81-88) -	83 (66-92) -	88 (60-96) -

Delta Variant: Virulence and Vaccine Effectiveness: Israel

- Press release of Israeli population-based study
- Pfizer vaccine **64% effective against delta variant infection, but 94% effective against severe illness**
  - Prior report 94% effective against infection and 97% effectiveness against severe disease
- ~85% adults immunized
- 1271 (83%) of 1528 new infections occurred in vaccinated persons
- 23 (62%) of 37 hospitalizations occurred in vaccinated persons
- 90% new infections caused by delta



- Israel reimposes indoor mask wearing requirement

Summary Vaccine Efficacy vs. SARS-CoV2 Variants

	Alpha (B.1.117)	Beta (B 1.351)	Gamma (P2)	Delta (B.1.617)
Severe disease	↔ to ↓ - Moderna, Pfizer ↓ AstraZeneca	↔ Janssen, Pfizer	No evidence	↔ AstraZeneca, Pfizer
Symptomatic disease				↔ to ↓ Pfizer Bharat-Covaxin AstraZeneca
Infection	↔ to ↓ - AstraZeneca			↓ AstraZeneca ↓↓- Pfizer

Bottom Line on Vaccines & Delta Variant

- **All of the vaccines for which we have evidence confer significant protection against disease**
  - **No data on CoronaVac or Sinopharm**
- **Some variability in activity between vaccines**
- **Second dose is important**

↓=10-<20% decrease
↓↓=20-<30% decrease
↓↓↓=>30% decrease

https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---6-july-2021

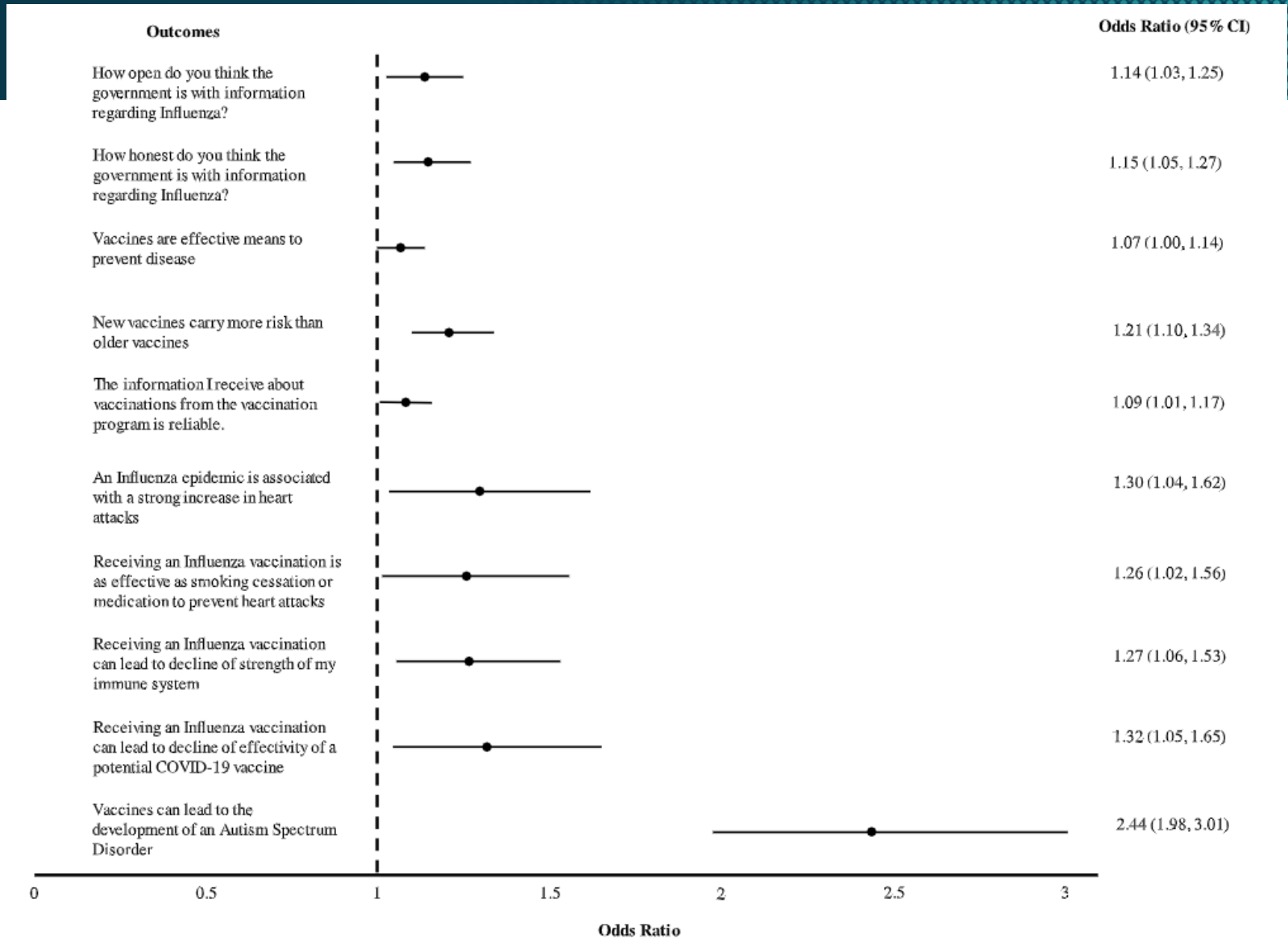
Summary

- **Epidemiology** – Divergent epidemiology based on vaccines
- **Variants** - New system for classifying variants
  - Delta variant is a big concern – much more transmissible (~300% ↑ vs. Wuhan strain)
- **Vaccines**
  - Good news
    - Vaccines with very high efficacy and good safety
    - Increasing evidence that vaccines prevent transmission
    - Diverse vaccines retain substantial efficacy against disease caused by the delta variant
  - Bad news
    - Roll out continues to be slow in much of the world due to inadequate supply and, in some places, vaccine hesitancy
    - Delta is not the last variant we will see, and we need a vaccine strategy that anticipates further evolution toward immune escape.

Questions and Comments

Confronting Vaccine Misinformation

Background: Misinformation about COVID-19 vaccines is widespread. How confront this is uncertain.
Population: 980 mostly lower income Dutch viewers of a TV show that focuses on the elderly
Design: Randomized controlled trial – video with vaccine information + social norms +/- info debunking vaccine myths
Outcome: Vaccine knowledge and awareness



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Directly confronting misinformation can be effective