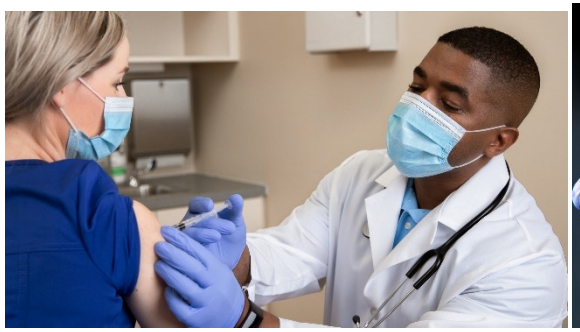
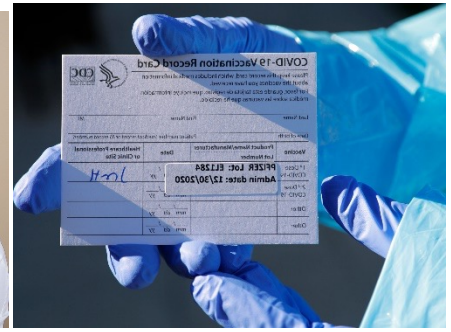
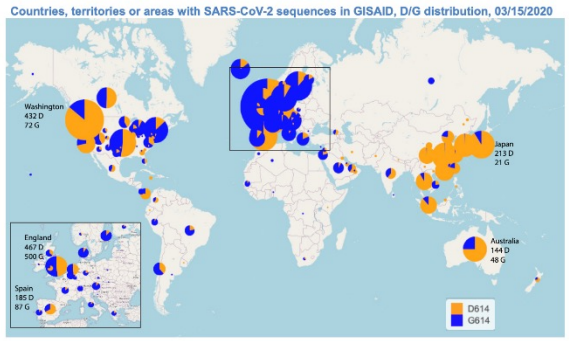
Vaccine versus variants: the battle rages

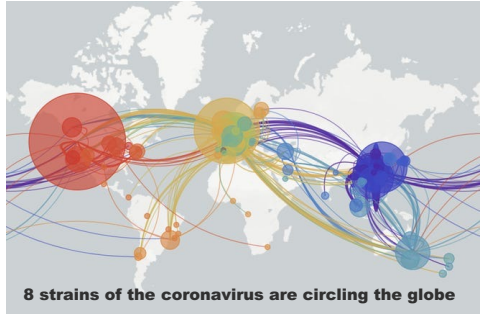
JOSEPH MCCORMICK, MD
SUSAN FISHER-HOCH, MD

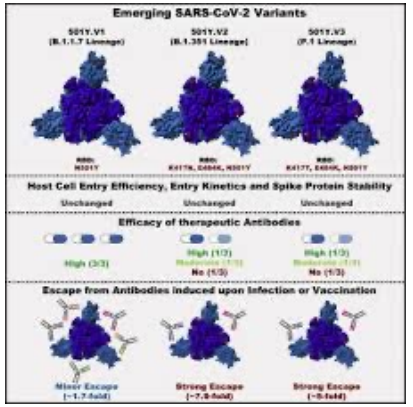
Professors of Epidemiology
Brownsville Campus, UTHealth School of Public Health











CORONAVIRINAE

- **Widespread among mammals in which it causes only mild respiratory or enteric disease**
- **Over 60 coronaviruses (CoVs) have been isolated from bats (BtCov)**
- **Bat reservoirs are large and highly mobile, and each species has its own unique BtCoV**

- **2002 saw the first outbreak in humans of a BtCoV, this was Severe Acute Respiratory Syndrome (SARS) due to a new BtCoV (SARS-CoV-1)**
- **In 2014 a second distinct BtCoV was isolated in an outbreak of severe respiratory disease in humans in the Middle East (MERS-CoV)**

In 2020, COVID-19 was the third leading cause of death in the U.S.*

PROVISIONAL 2020 DEATHS

1

Heart Disease

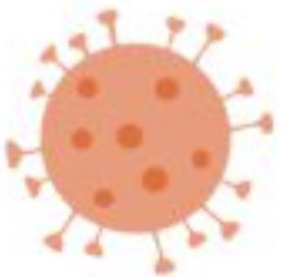
690K

2

Cancer

598K

3



COVID-19

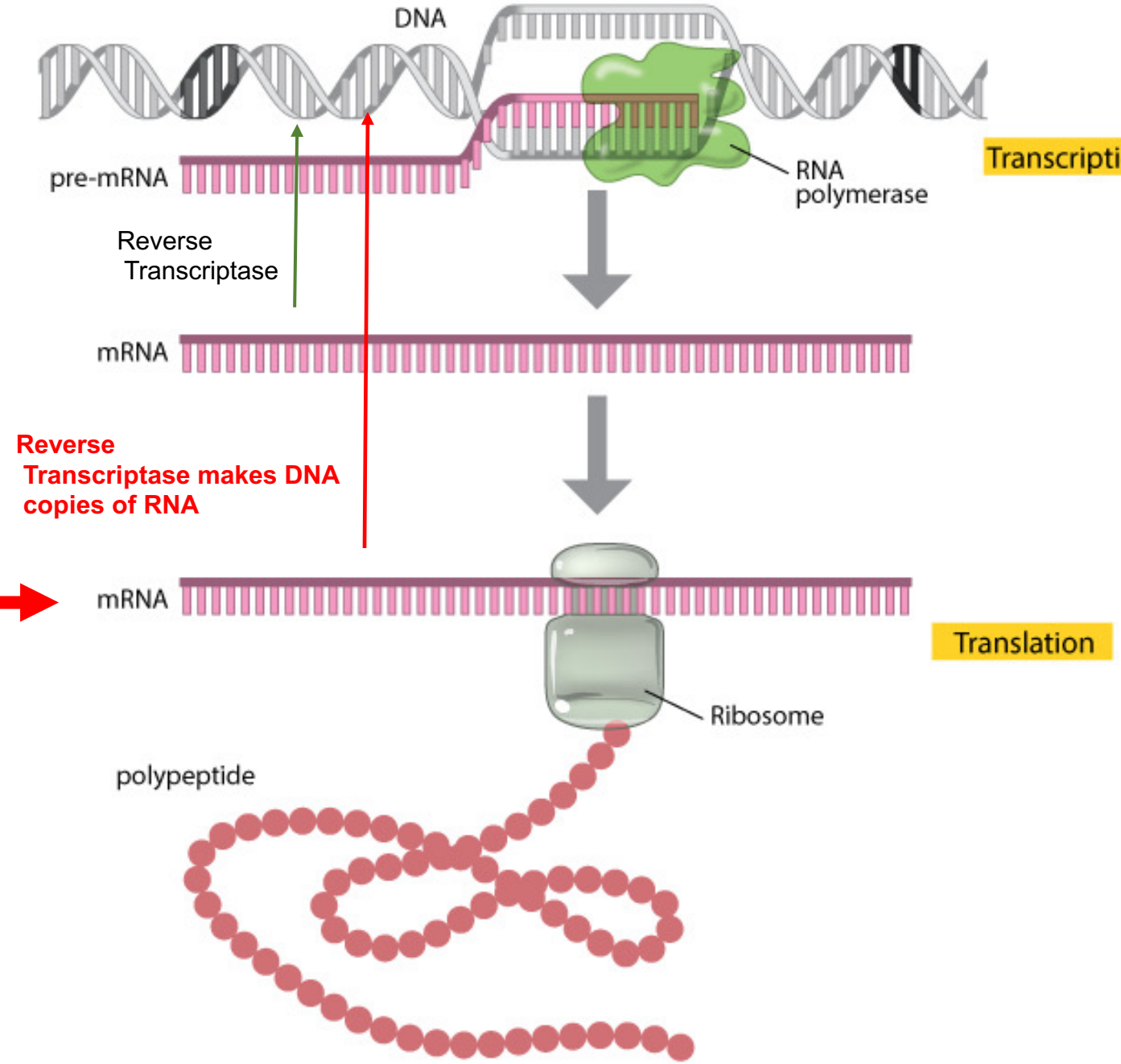
345K

* Provisional National Vital Statistics System (NVSS) death certificate data on underlying causes of death among U.S. residents in the United States during January-December 2020

DNA viruses: Herpes, CMV, smallpox, adenoviruses, chickenpox

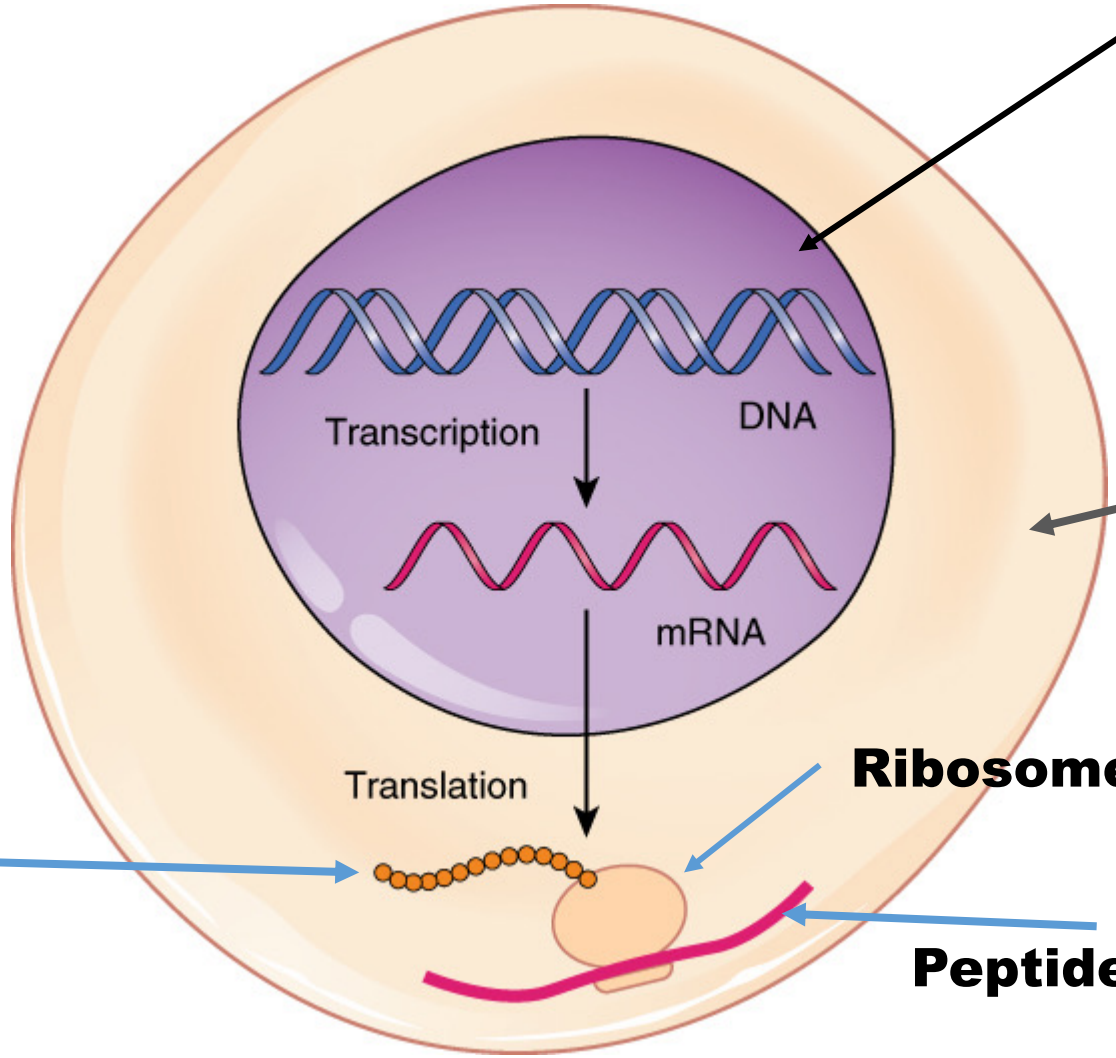
Negative Strand RNA viruses: HIV, Polio, Influenza, Ebola, measles, mumps,

Positive Strand RNA viruses: SARS-CoV-2, Dengue, west Nile, Zika, rhinoviruses, rubella



How cells make protein from DNA

Key to virus replication



Cell Nucleus

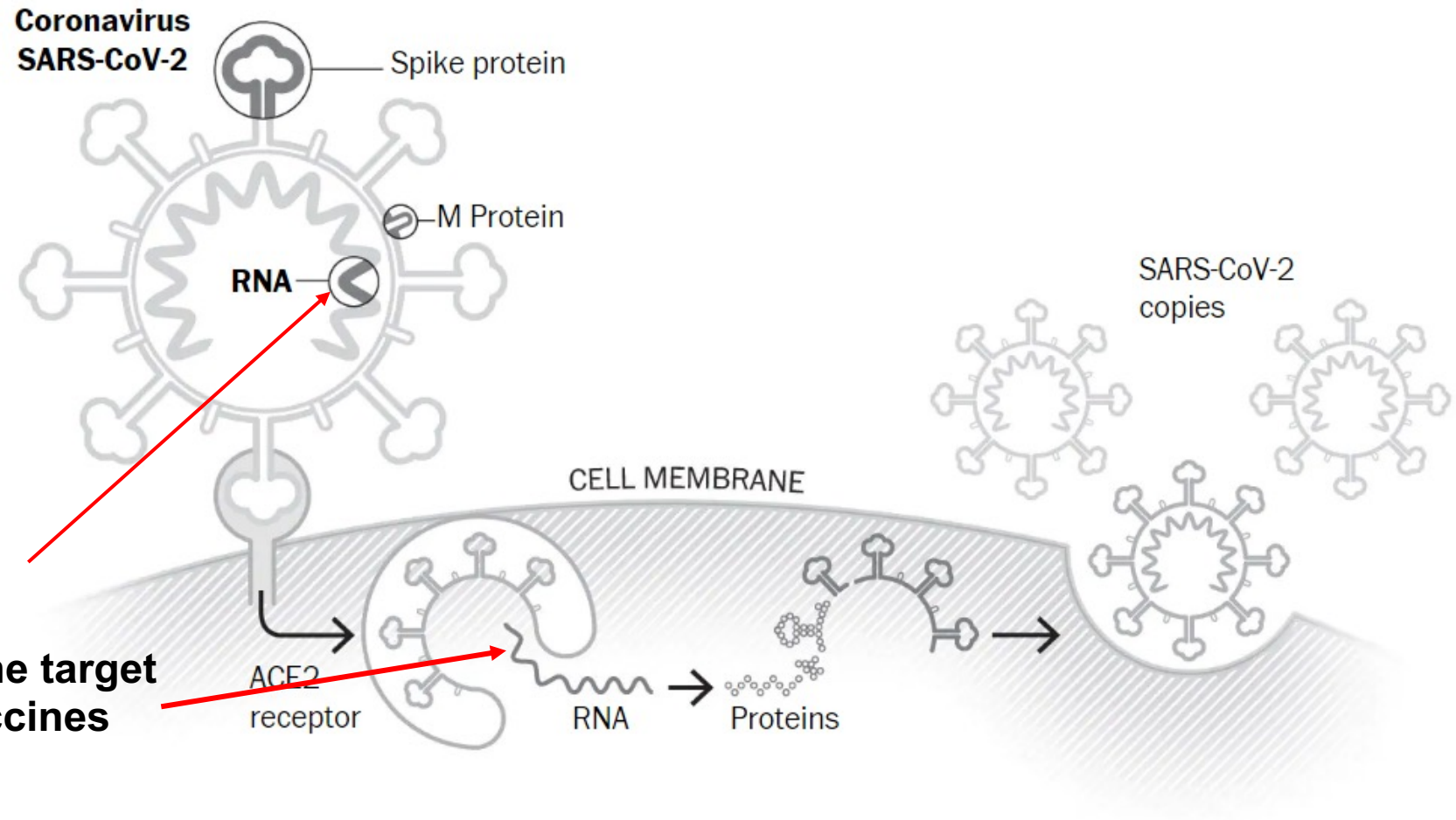
Cell Cytoplasm

Ribosome

mRNA from Nucleus

Peptide from translation of mRNA

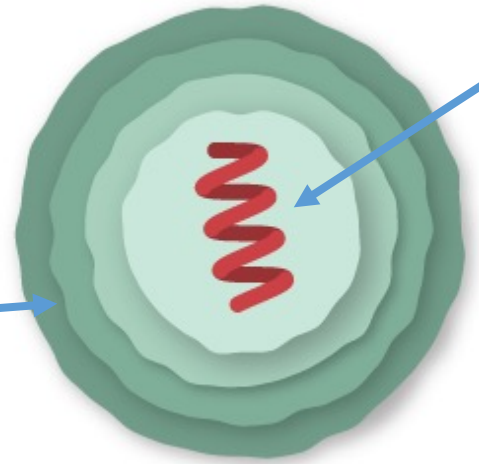
Virus Targets for Vaccine development



RNA Of the Viral spike Protein is the target Of most vaccines

Washington Post august 13 2020

Basis of Moderna and Pfizer-BioNtech vaccine

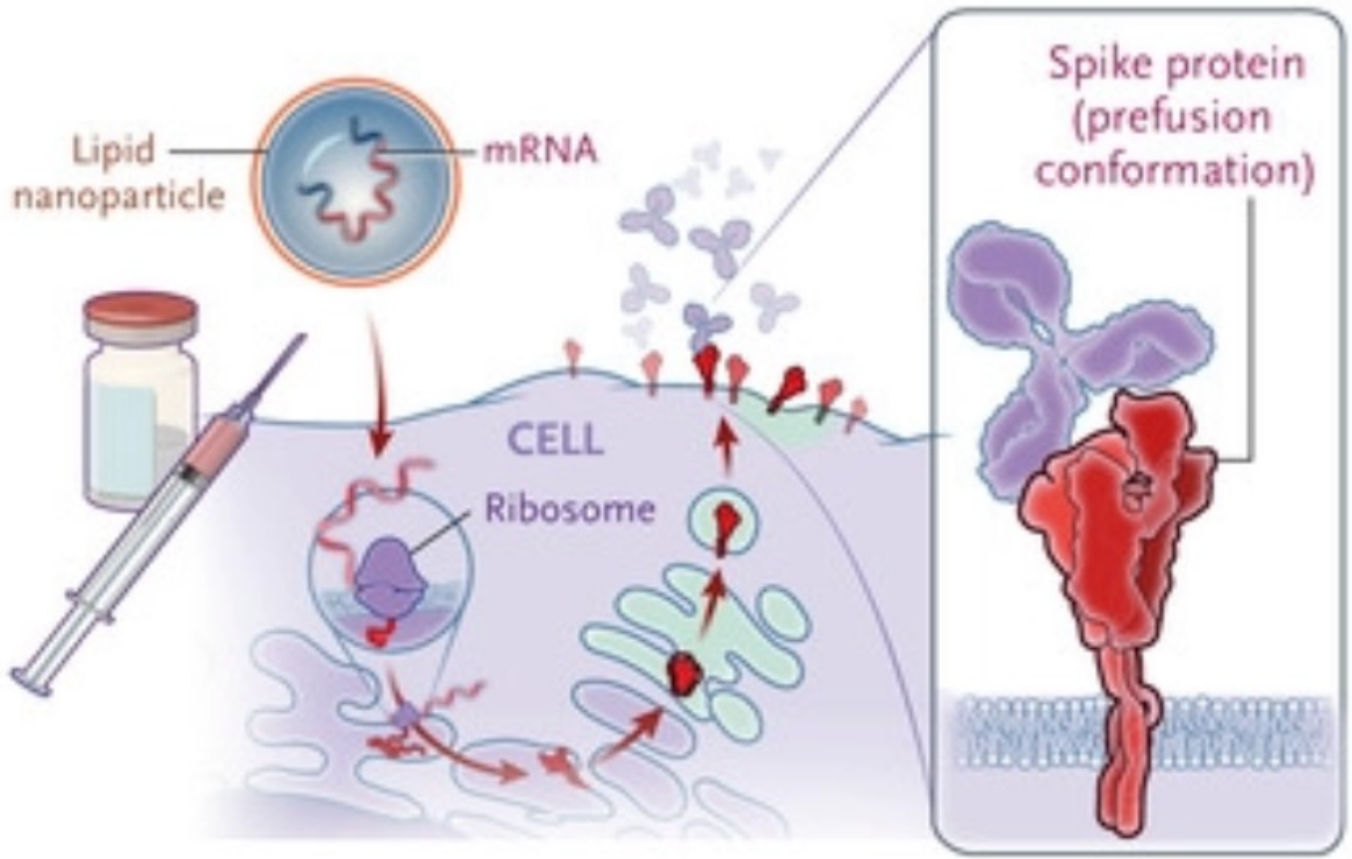


Spike Protein Gene

Lipid (fat) nano particles

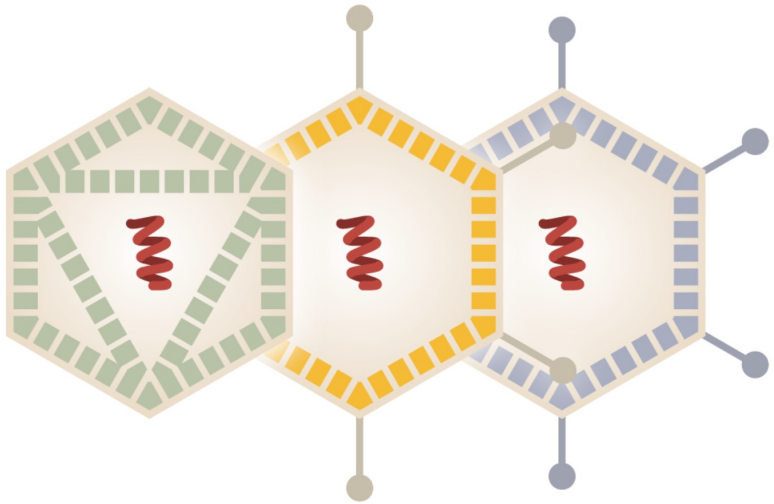
Moderna's vaccine will need to be refrigerated, and should be stable for up to six months when shipped and stored at –4°F (–20°C)
The Pfizer vaccine requires storage at -80°C

NY Times


Lipid nanoparticle
mRNA
CELL
Ribosome
Spike protein (prefusion conformation)

Viral Vector Vaccines

Vaccines that contain viruses engineered to carry coronavirus genes. Some viral vector vaccines enter cells and cause them to make viral proteins. Other viral vectors slowly replicate, carrying coronavirus proteins on their surface.



CanSinoBIO

VACCINE NAME: Convidecia (also known as Ad5-nC

EFFICACY: 65.28%

DOSE: Single dose

TYPE: Muscle injection

STORAGE: Refrigerated

Johnson & Johnson

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

VACCINE NAME: Ad26.COV2.S

EFFICACY: 72% in United States, 64% in South Africa, 61% in Latin America

DOSE: 1 dose

TYPE: Muscle injection

STORAGE: Up to two years frozen at –4° F (–20° C), and up to three months refrigerated at 36–46° F (2–8° C).

UNIVERSITY OF OXFORD AstraZeneca

VACCINE NAME: AZD1222 (also known as Covishield in India)

EFFICACY: 82.4% for doses separated by 12 weeks.

DOSE: 2 doses

TYPE: Muscle injection

STORAGE: Stable in refrigerator for at least 6 months

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

VACCINE NAME: Sputnik V (also known as Gam-Covid-Vac)

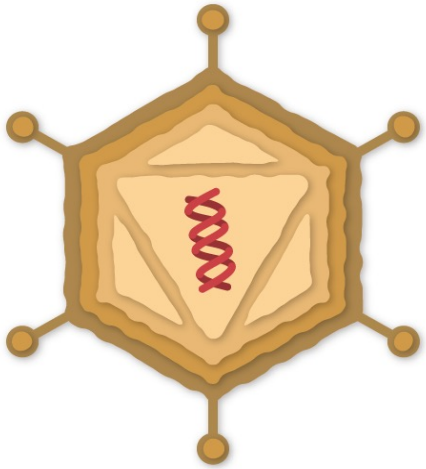
EFFICACY: 91.6%

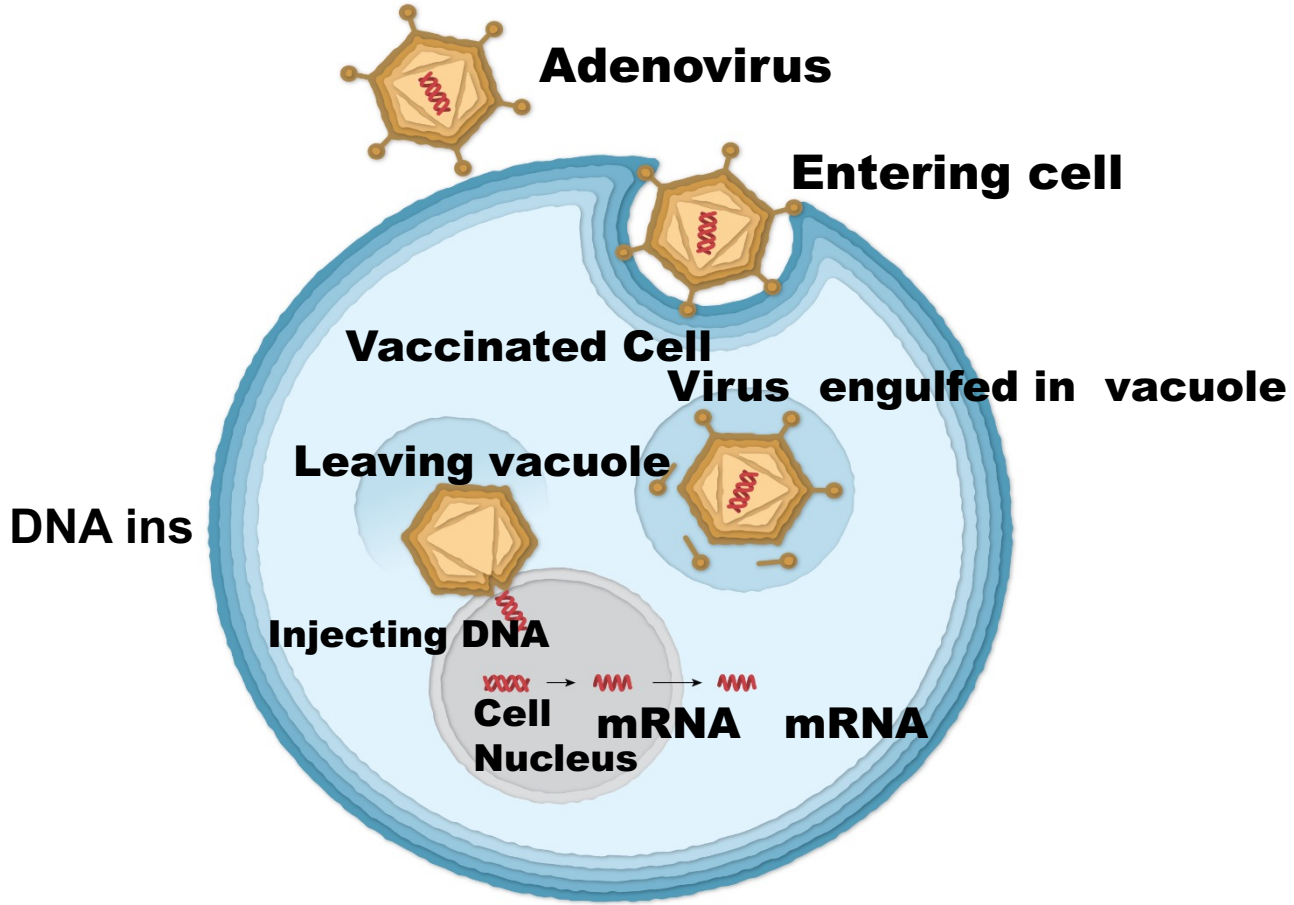
DOSE: 2 doses, 3 weeks apart

TYPE: Muscle injection

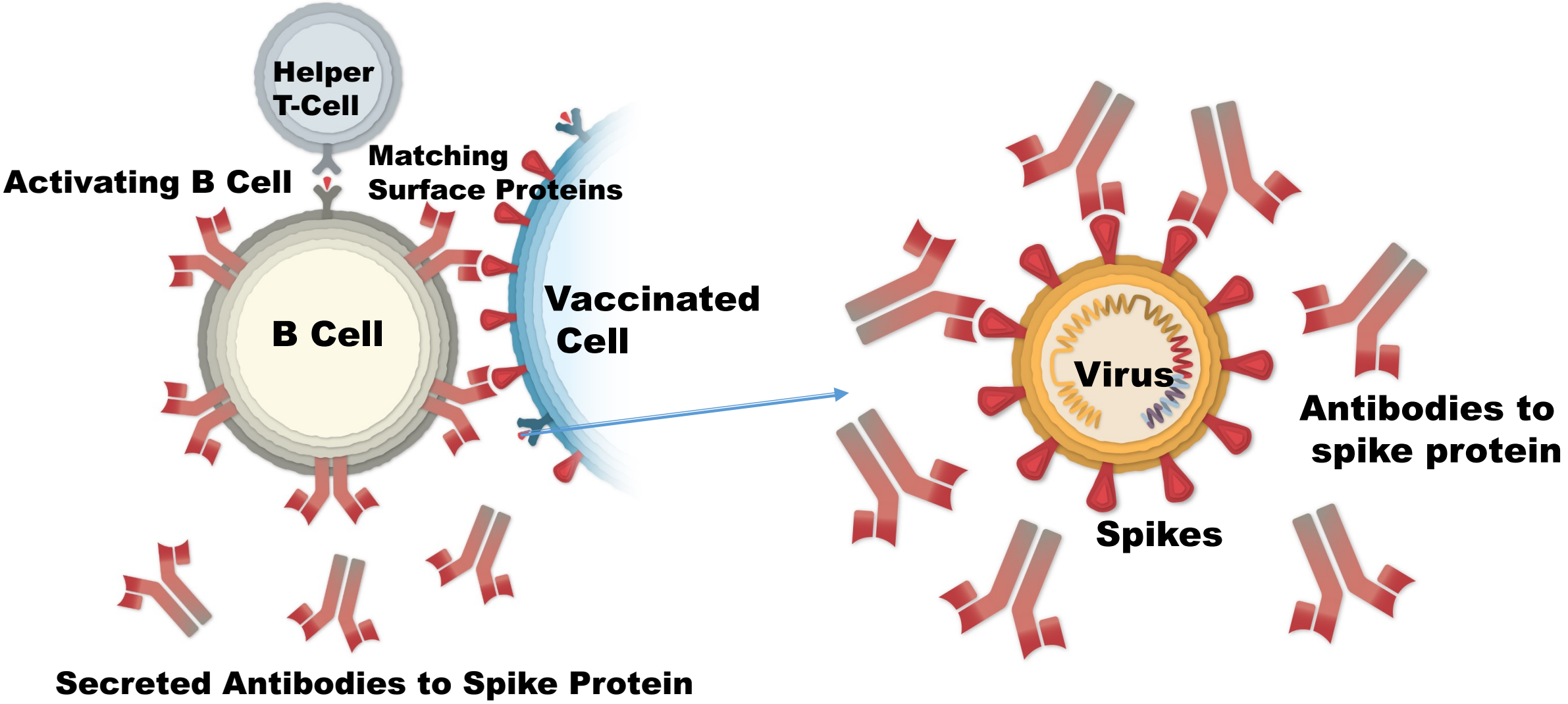
STORAGE: Freezer storage. Developing an alternative formulation that can be refrigerated.

- **The gene for the coronavirus spike protein put into another virus called Adenovirus 26.**
- **Adenoviruses are common viruses that typically cause colds or flu-like symptoms.**
- **The modified adenovirus can enter cells but can't replicate inside them or cause illness**
- **J&J vaccine comes out of decades of research on adenovirus-based vaccines.**
- **In July, the first one was approved for Ebola vaccine.**
- **DNA is not as fragile as RNA, and the adenovirus's tough protein coat helps protect the genetic material inside.**
- **It can be stored at 36-46° F so much easier to distribute**
- **It is a one dose vaccine.**





Interactions of vaccinated cells and the virus



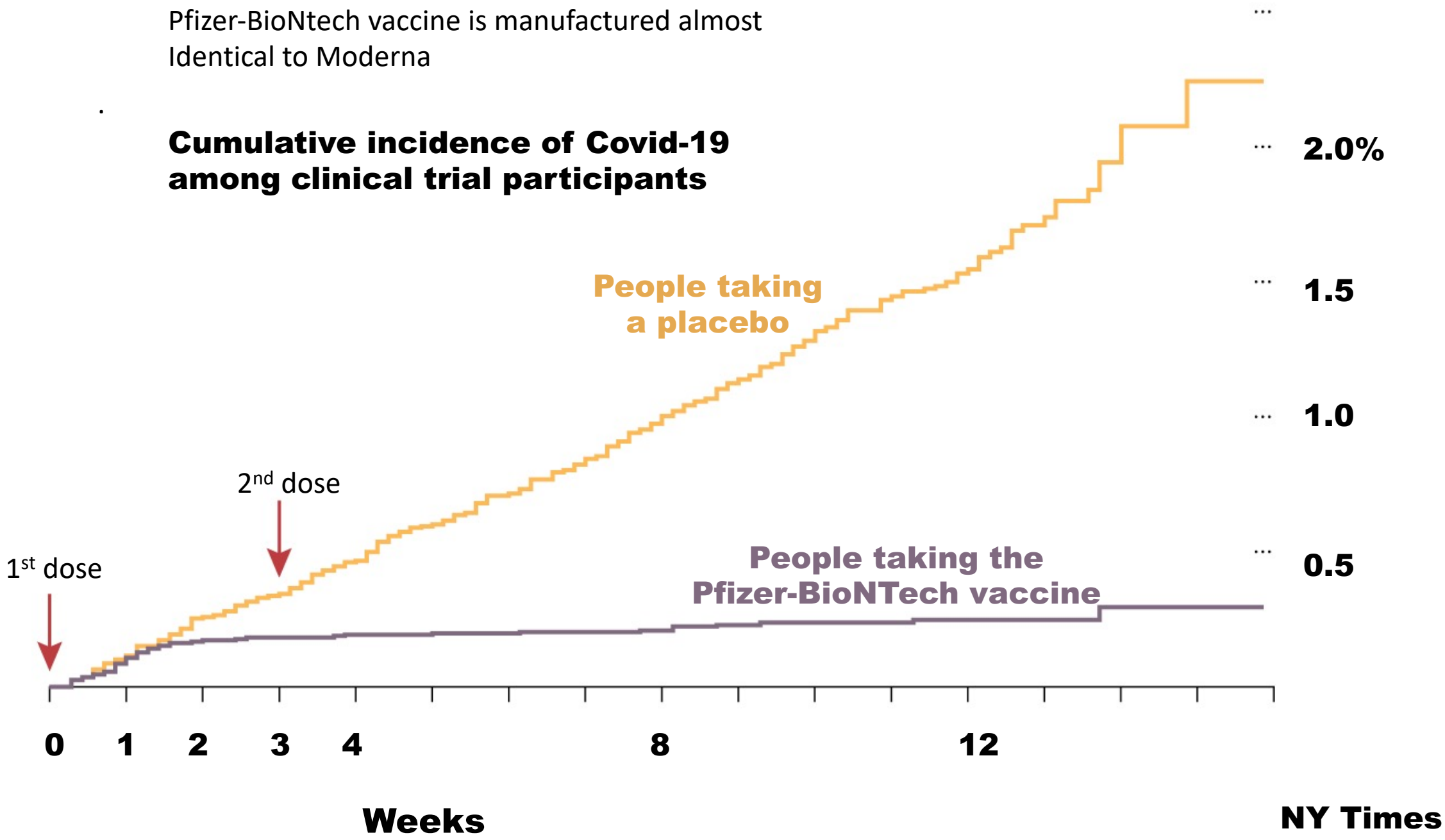
NY Times

Moderna, Pfizer, Johnson and Johnson and AstraZeneca vaccines now in full phase 4 application

Novavax protein vaccine in phase 3 trials

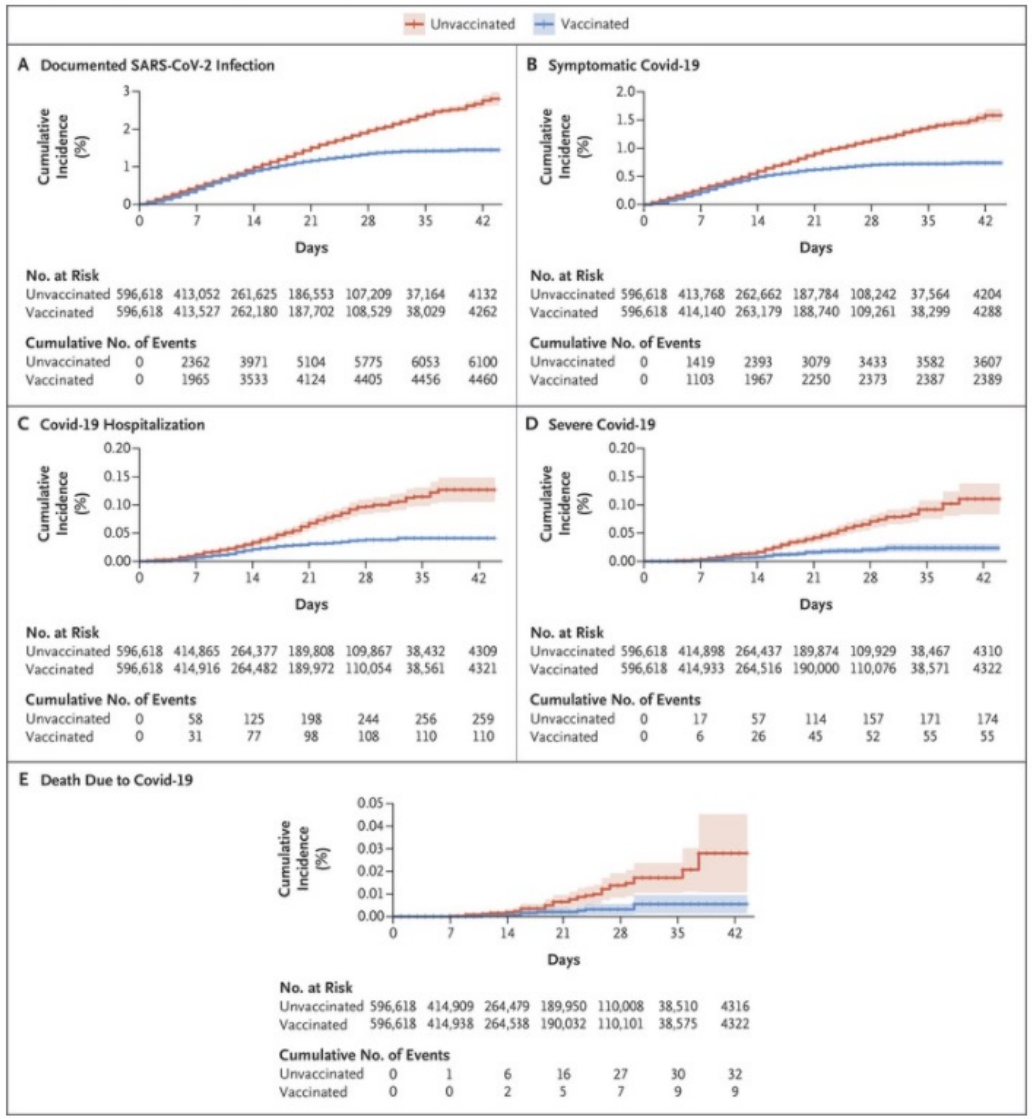
Inactivated whole virus vaccines from China and India are in Phase 4

Pfizer-BioNtech vaccine is manufactured almost
Identical to Moderna



Pfizer Vaccine in Israel NEJM Feb 25

Figure 2. Cumulative Incidence of the Five Outcomes.



Cumulative incidence curves (1 minus the Kaplan–Meier risk) for the various outcomes are shown, starting from the day of administration of the first dose of vaccine. Shaded areas represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events are also shown for each outcome. Graphs in which all data are shown with a y axis scale from 0 to 100 (along with the data shown, as here, on an expanded y axis) are provided in Figure S8 in the Supplementary Appendix.

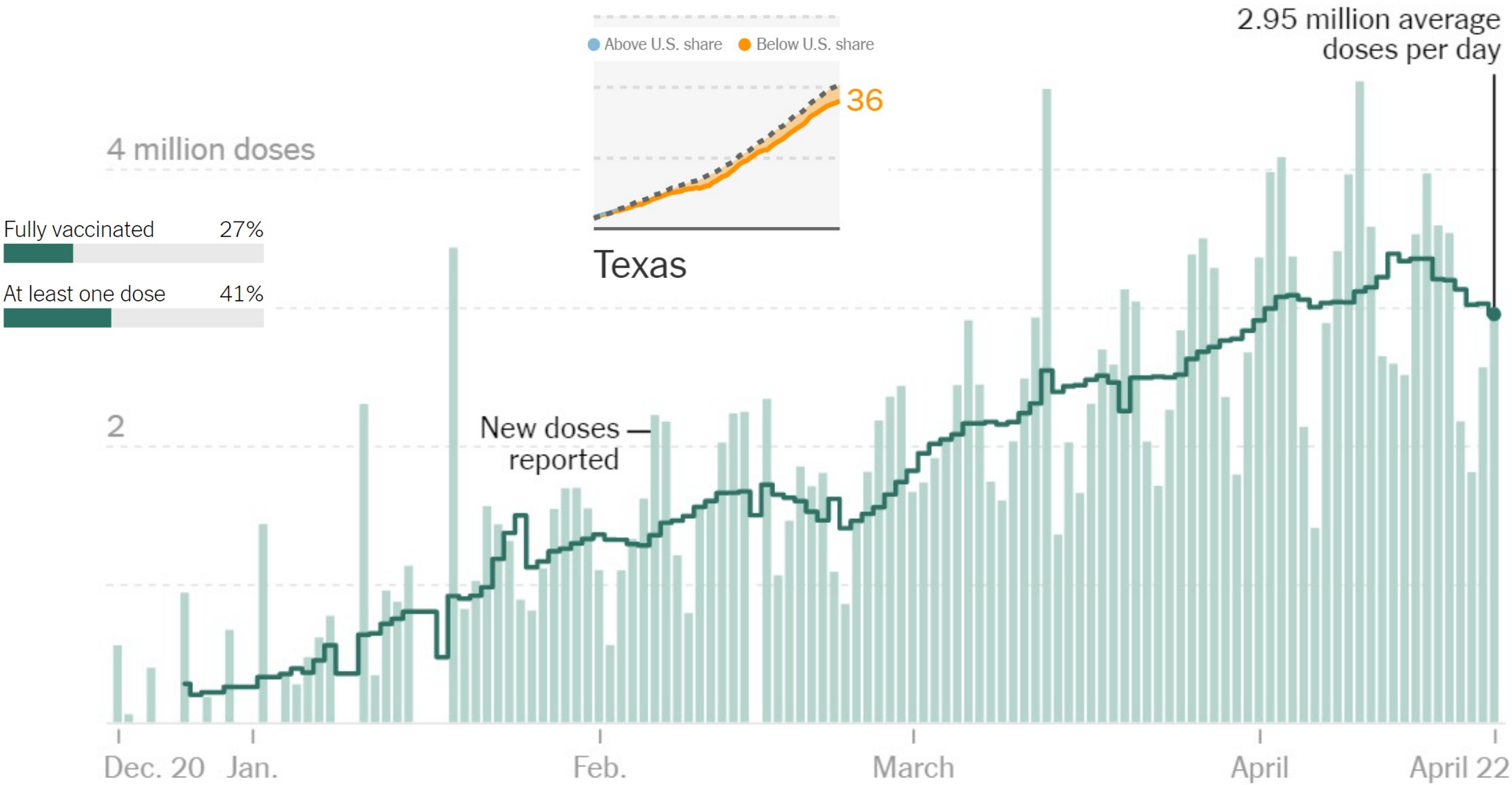
Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

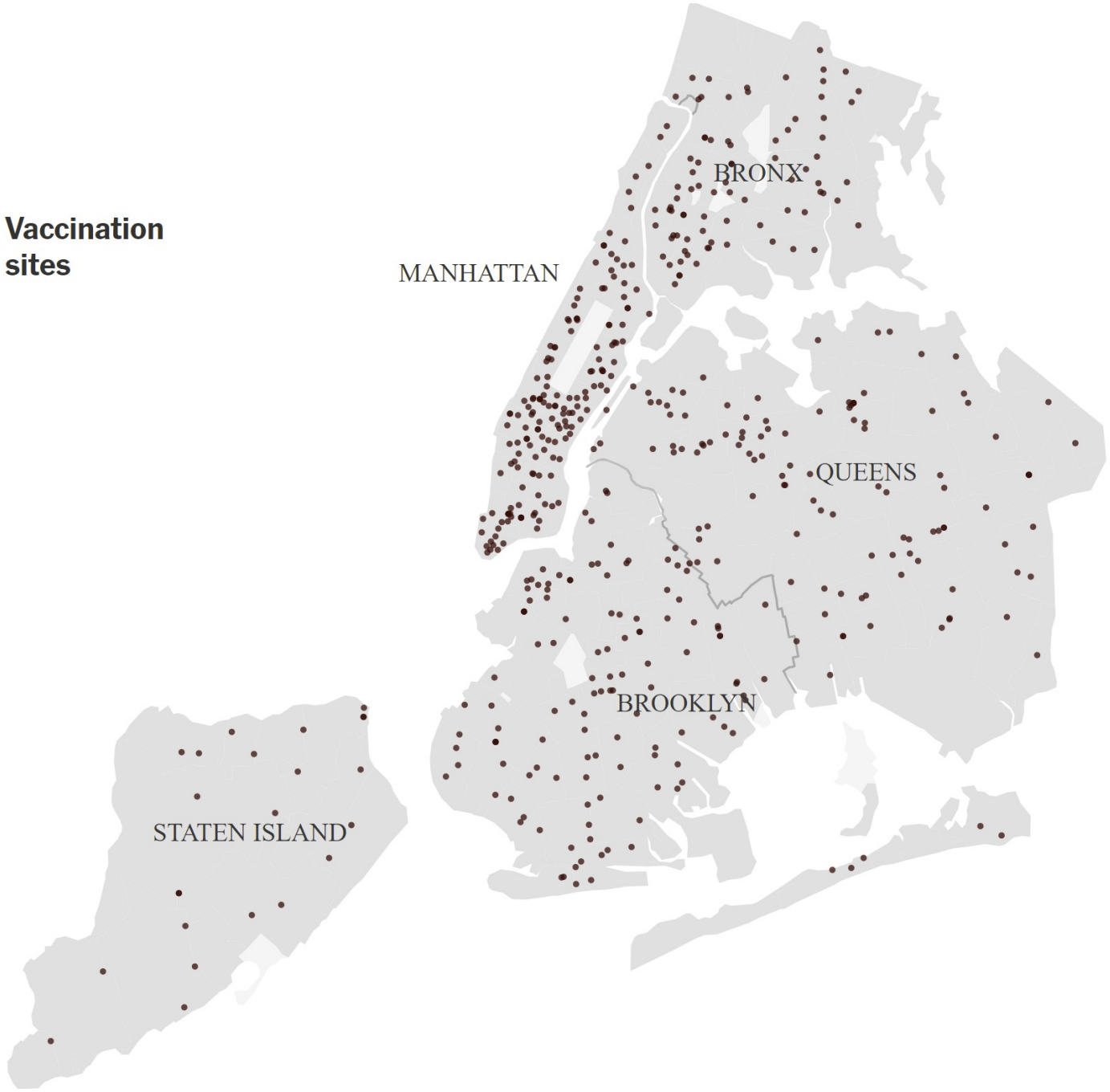
* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.
§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

New reported doses administered by day

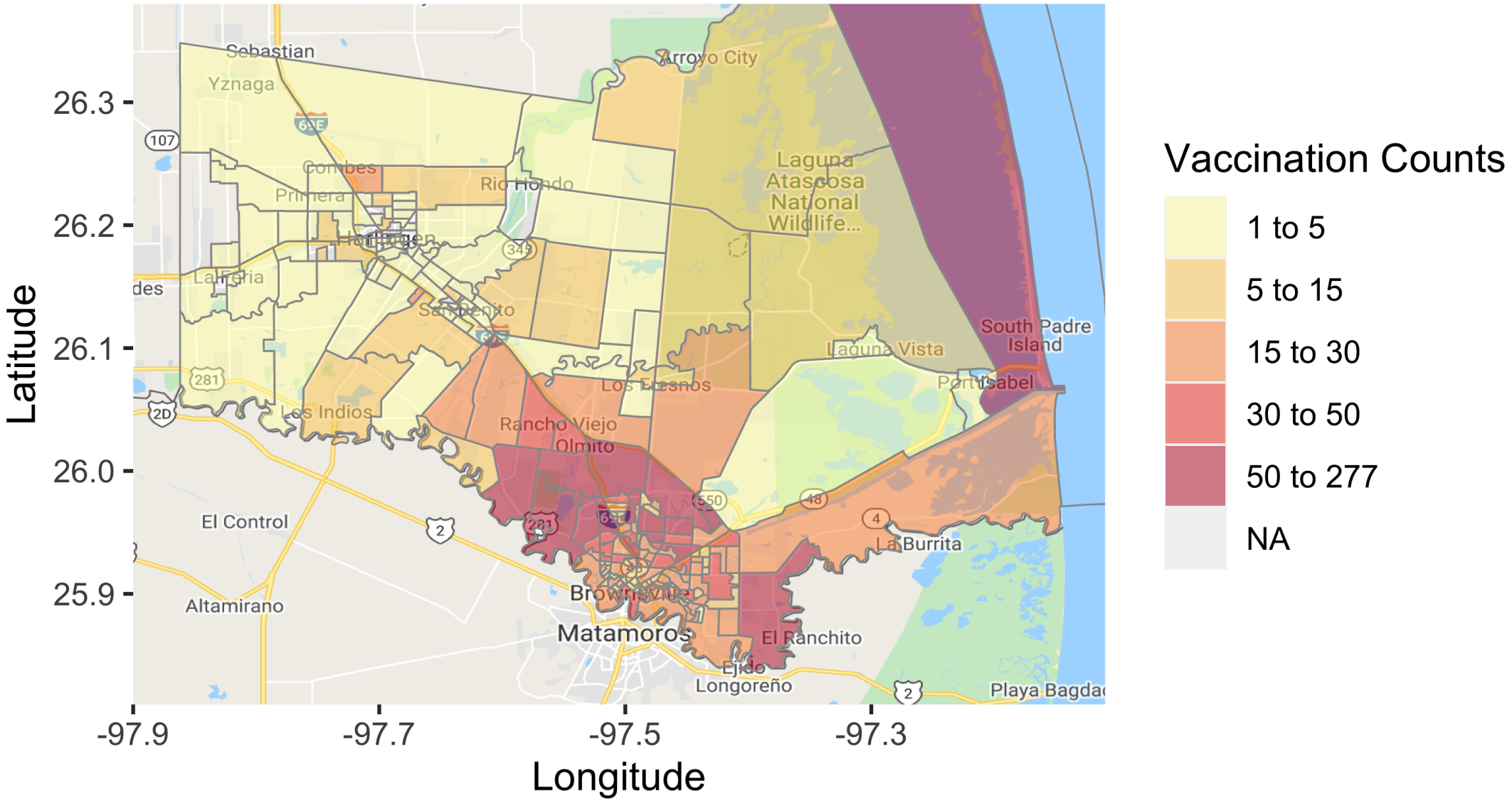


Source: Centers for Disease Control and Prevention | Note: Line shows a seven-day average. Data not updated on some weekends and holidays. Includes the Johnson & Johnson vaccine as of March 5.

Distribution of vaccine in New York City

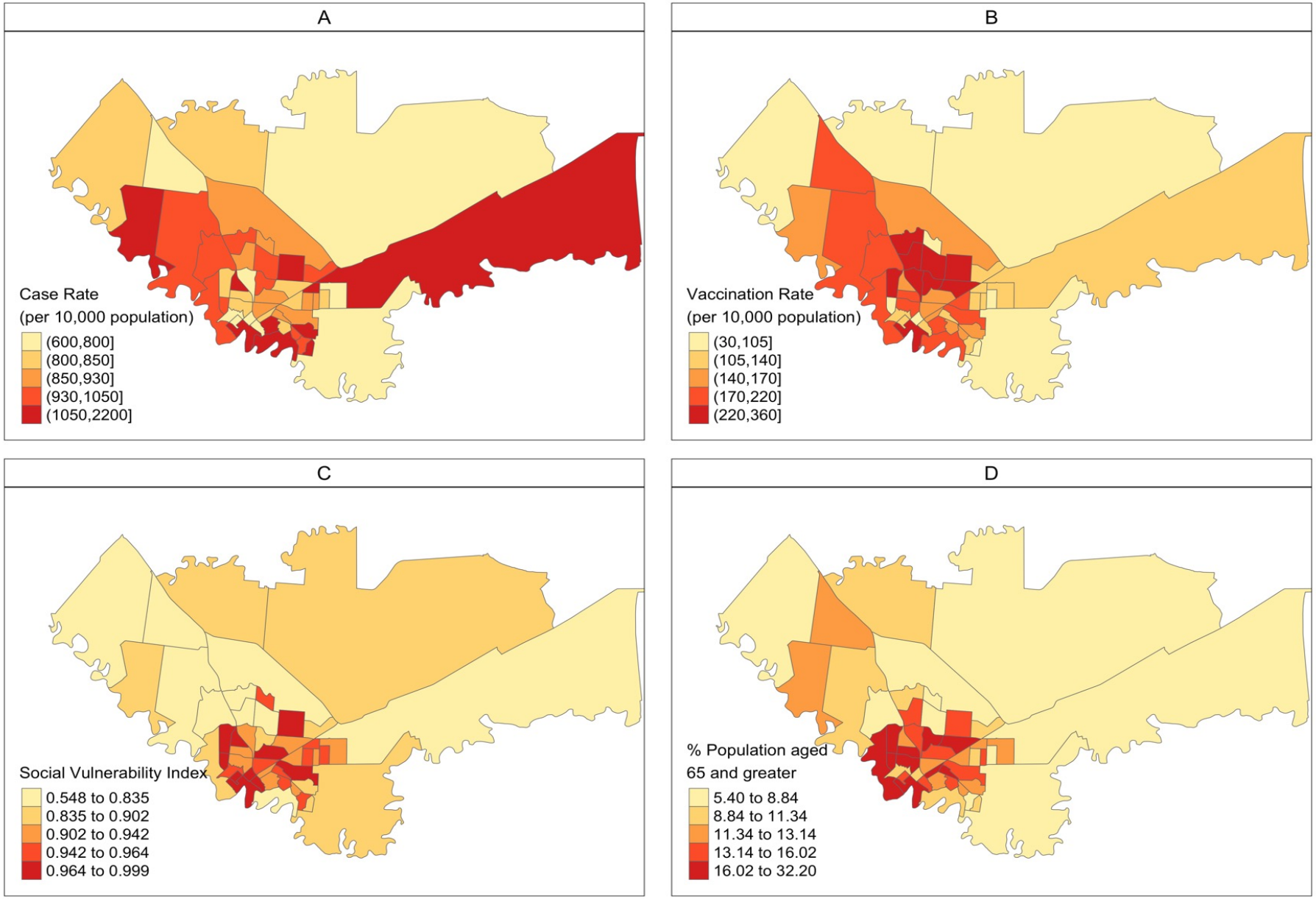


Mapping of vaccination counts at census block group level



The map of vaccination counts per 10,000 population at census block group level
4080 people were included in this initial analysis but work is continuing

Maps of the census-tract cumulative COVID-19 case between March 8th and December 12th, 2020 (panel A), vaccination rate (by March 13th, 2021) (panel B), social vulnerability index (panel C) and percentage of population with 65 years old and over (panel D).



MMWR: March 29 2021

TABLE 2. Person-days, SARS-CoV-2 infections, and vaccine effectiveness among health care personnel, first responders, and other essential and frontline workers, by messenger RNA immunization status — eight U.S. locations, December 14, 2020–March 13, 2021

COVID-19 immunization status	Person-days	SARS-CoV-2 infections		Unadjusted vaccine effectiveness*	Adjusted vaccine effectiveness*,†
		No.	Incidence rate per 1,000 person-days	% (95% CI)	% (95% CI)
Unvaccinated	116,657	161	1.38	N/A	N/A
Partially immunized	41,856	8	0.19	82 (62–91)	80 (59–90)
≥14 days after receiving first dose only§	15,868	5	0.32		
≥14 days after first dose through receipt of second dose	25,988	3	0.12		
Fully immunized					
≥14 days after second dose	78,902	3	0.04	91 (73–97)	90 (68–97)

Abbreviations: CI = confidence interval; N/A = not applicable.

* Vaccine effectiveness was estimated using a Cox proportional hazards model accounting for time-varying immunization status.

† Hazard ratio is adjusted for study site.

§ Participants received first dose but had not received second dose by the end of the study period.

Surveillance and detection of SARS-CoV-2 variants

- **Globally the approach has been sporadic and unplanned**
- **Has depended mostly on resources and scientist initiative**
- **This is the pattern in the USA where discovery up to the end of last year is DESCRIBED AS SERENDIPITOUS**

- **ONLY IN THE UK WAS THE APPROACH SYSTEMATIC.**
- **Hence the identification of the B.1.1.7 in September associated with a cluster in Kent,**

SARS-CoV-2 variants

Variants of concern

Lineage	Variant name	Status
B.1.1.7	Variant of Concern 202012/01, or 501Y.V1	Emerged in Britain in December and is roughly 50 percent more infectious. Now detected in over 70 countries and 33 states.
B.1.351	501Y.V2	Emerged in South Africa in December. Reduces the effectiveness of some vaccines.
P.1	501Y.V3	Emerged in Brazil in late 2020. Has mutations similar to B.1.351.

Mutations that may help the coronavirus spread

Lineage	Mutation	Status
B.1	D614G	Appeared in early 2020 and spread around the world.
Several	N501Y	A defining mutation in several lineages, including B.1.1.7, B.1.351 and P.1. Helps the virus bind more tightly to human cells.
Several	E484K	Appears in several lineages. May help the virus avoid some kinds of antibodies.
Several	L452R	Increasingly common in California, but not yet shown to be more infectious.

Lineage	Variant name	Status
B.1.427, B.1.429	CAL.20C	Carries the L452R mutation. Common in California, but not yet shown to be more infectious.

KEY MUTATIONS IN B.1.1.7

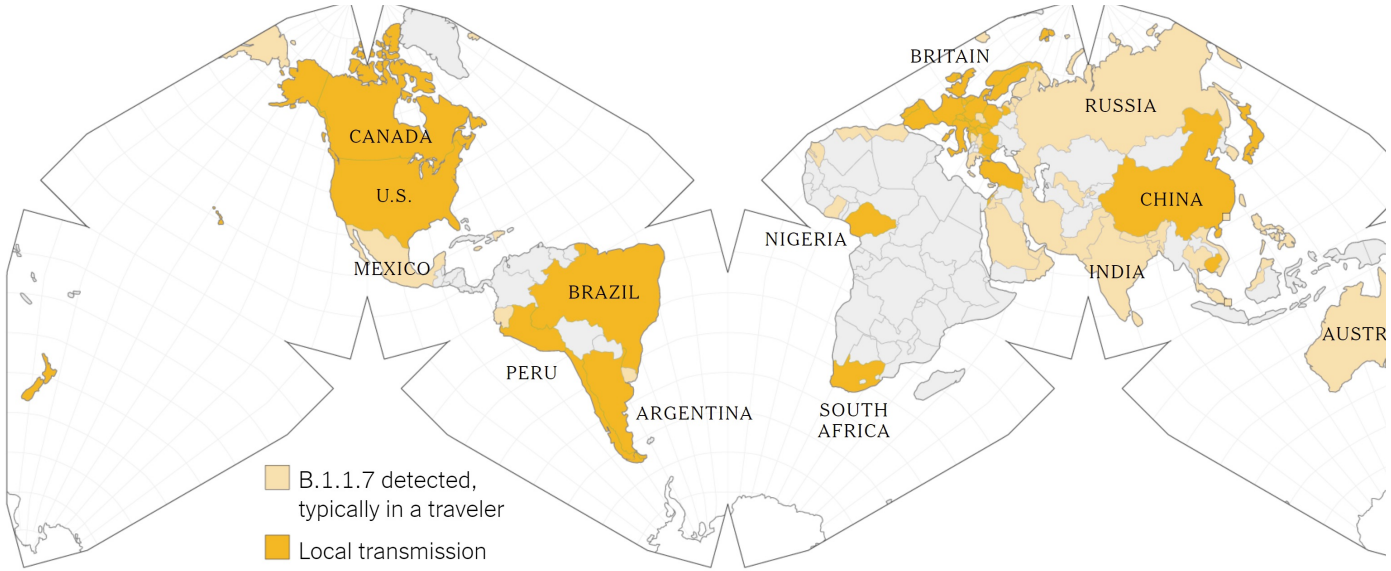
B.1.1.7

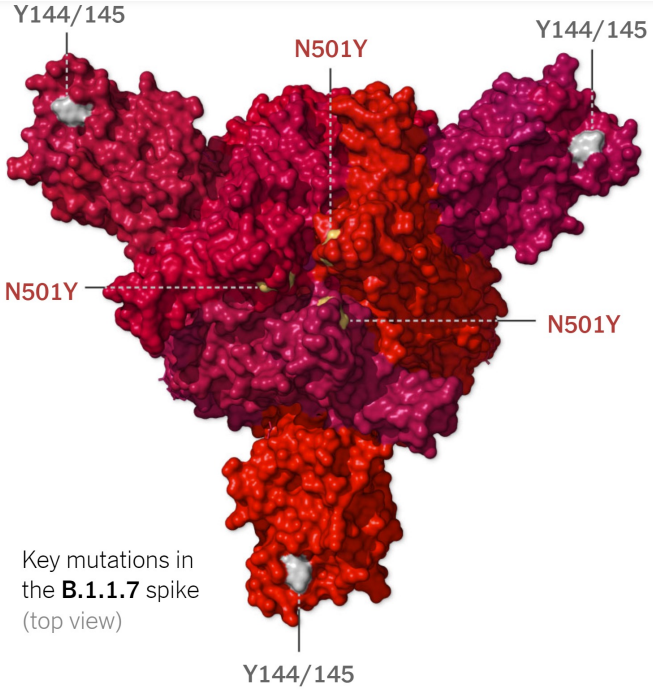
Mutations in the spike protein include:

— **N501Y**, which helps the virus latch on more tightly to human cells. But the mutation is not likely to help the virus evade current vaccines.

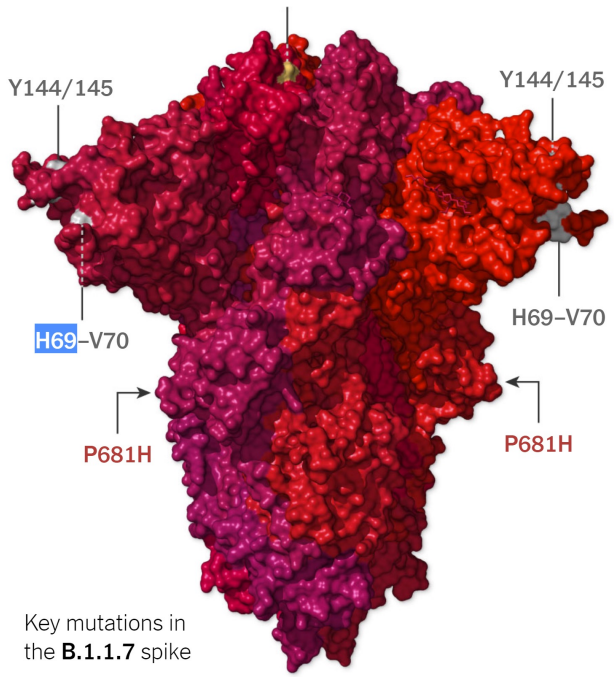
— **P681H**, which may help infected cells create new spike proteins more efficiently.

— The **H69–V70** and **Y144/145** deletions, which alter the shape of the spike and may help it evade some antibodies.





Key mutations in the **B.1.1.7** spike (top view)



Key mutations in the **B.1.1.7** spike

The New York Times

B.1.351

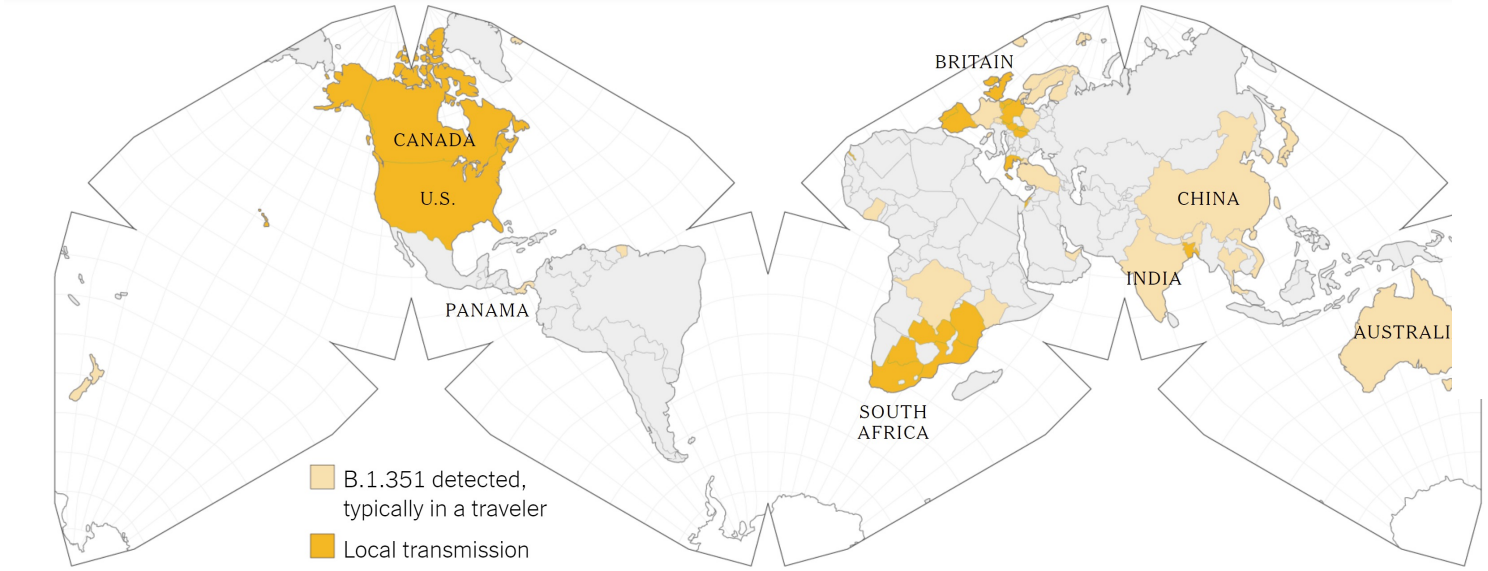
KEY MUTATIONS IN B.1.351

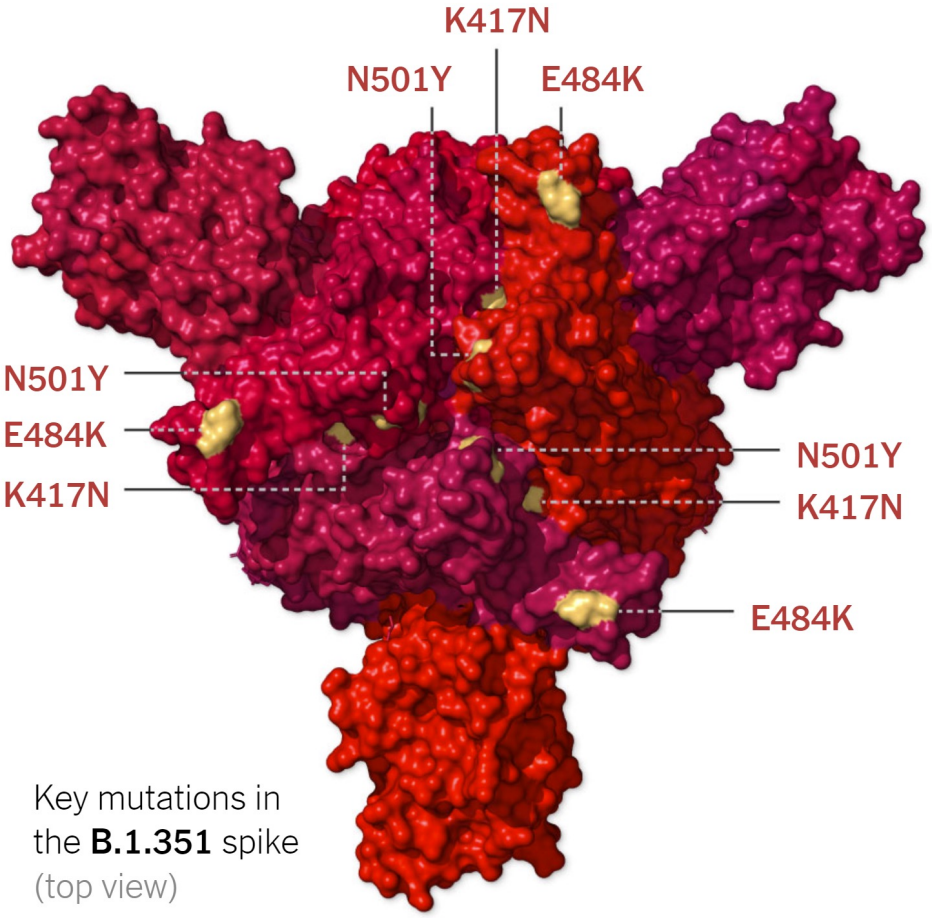
Mutations near the tip of the spike protein include:

— **N501Y**, which helps the virus latch on more tightly to human cells. This mutation also appears in the B.1.1.7 and P.1 lineages.

— **K417N**, which also helps the virus bind more tightly to human cells.

— **E484K**, which may help the virus evade some kinds of antibodies.





Key mutations in the **B.1.351** spike (top view)

The New York Times

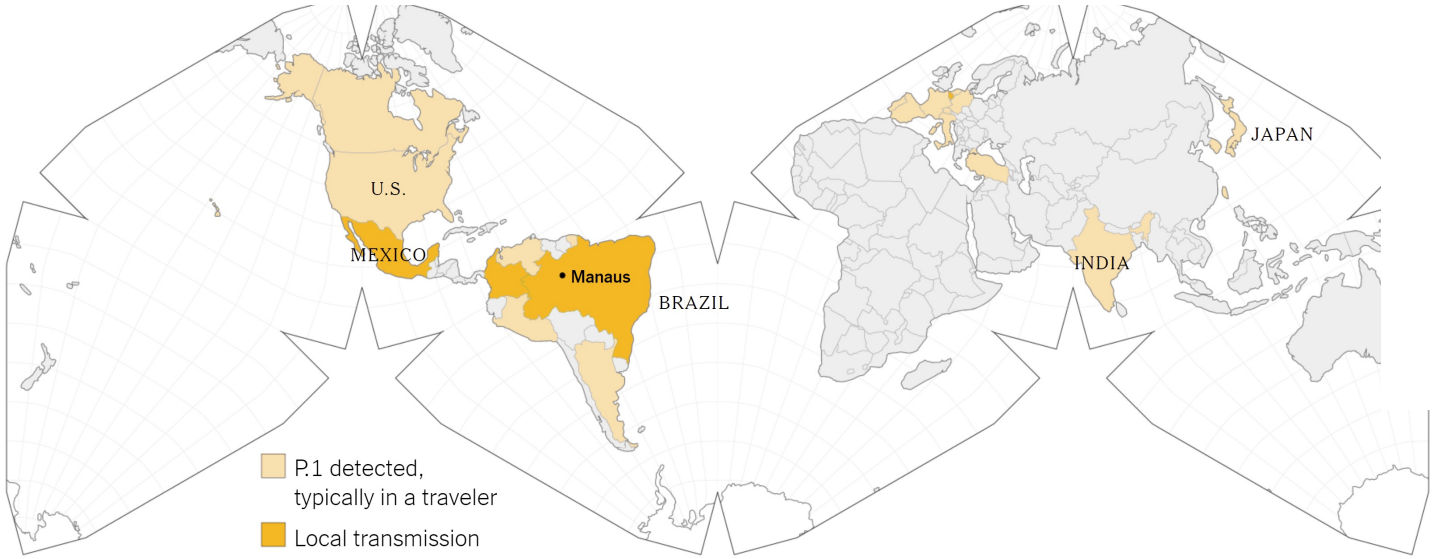
KEY MUTATIONS IN P.1

Key mutations in the spike protein are similar to those in the B.1.351 lineage, although they arose independently:

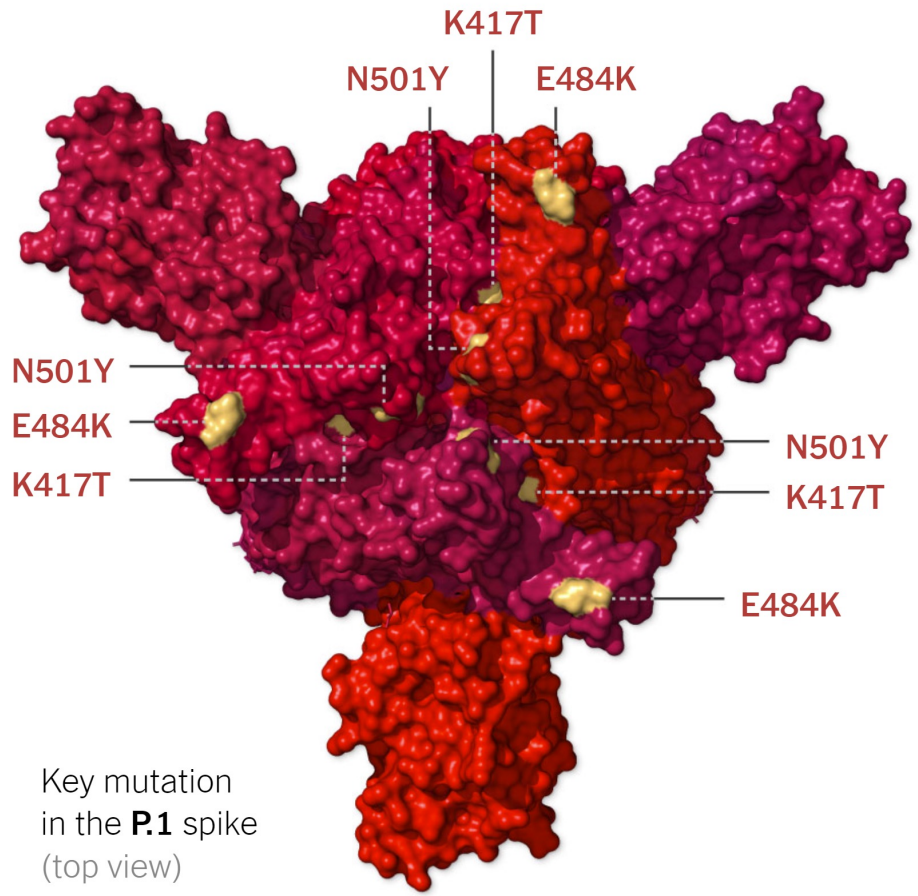
— **N501Y**, which helps the virus latch on more tightly to human cells. This mutation also appears in the B.1.1.7 and B.1.351 lineages.

— **K417T**, which is the same site as the K417N mutation in the B.1.351 lineage. It may also help the virus latch on tighter.

— **E484K**, which may help the virus evade some kinds of antibodies.



P.1

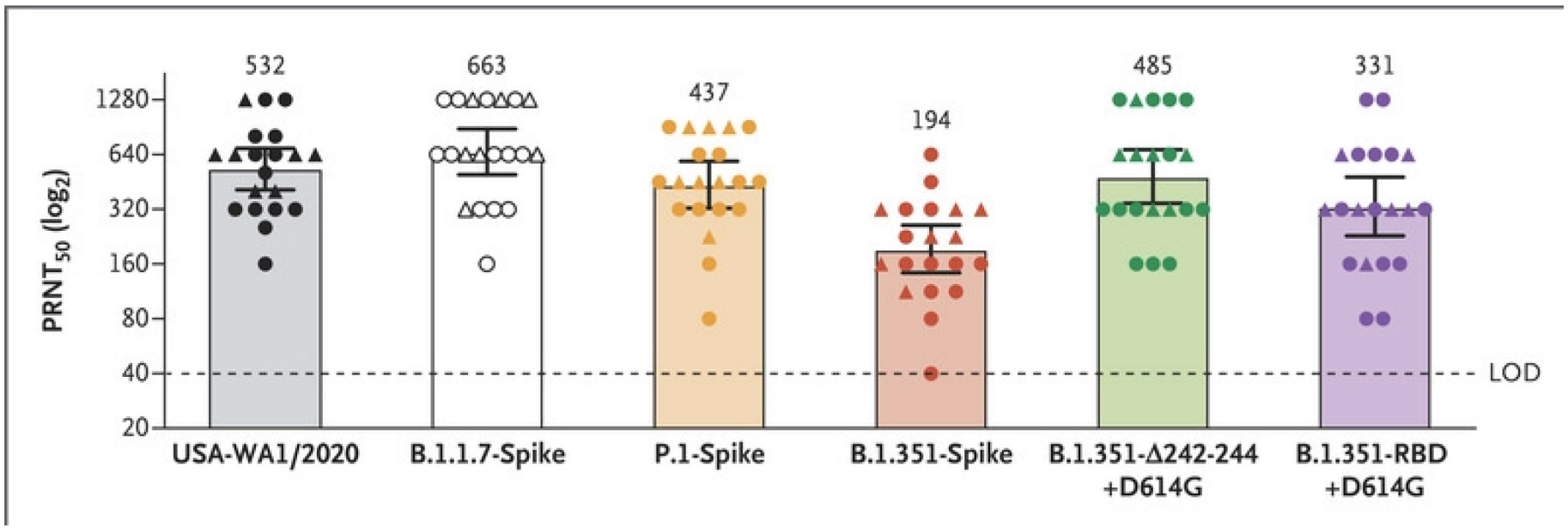


Key mutation in the **P.1** spike (top view)

The New York Times

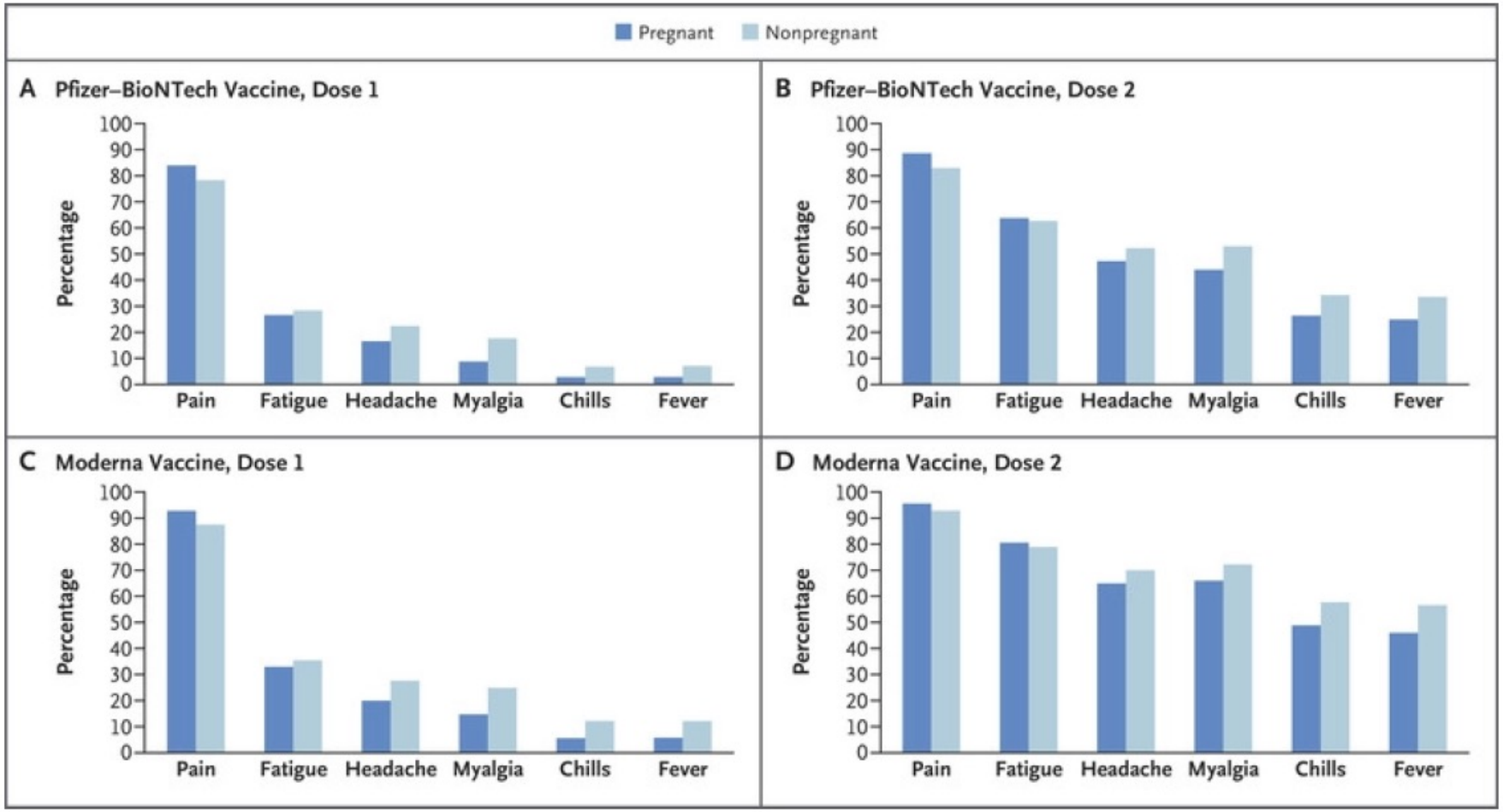
Neutralizing Activity of BNT162b2-Elicited Serum

March 8, 2021
DOI: 10.1056/NEJMc2102017



Serum Neutralization of Variant Strains of SARS-CoV-2 after the Second Dose of BNT162b2 Vaccine.

NEJM April 21, 2021. Shimabukuro et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons



Calculated proportions of adverse pregnancy and neonatal outcomes were similar in incidences to those pre CPOVID-19 pandemic

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D., Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skattør, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

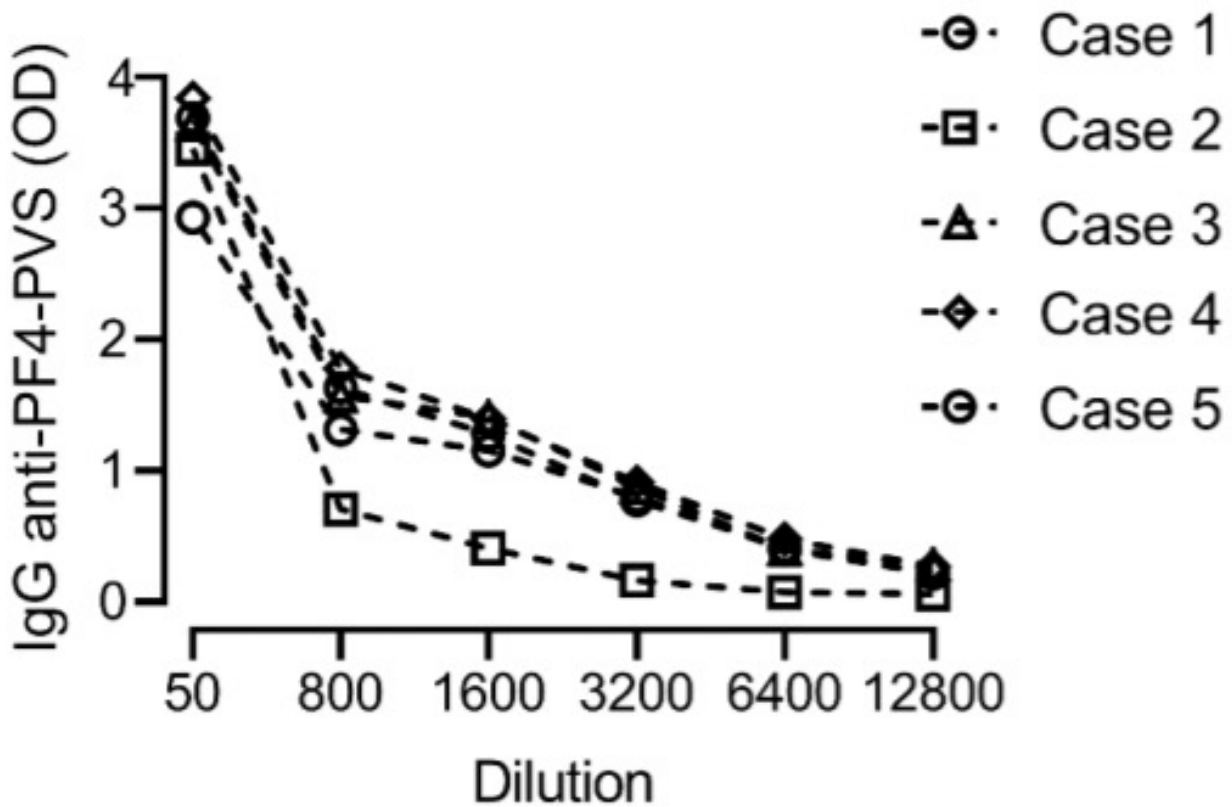


Figure S2: Serial dilution of patient sera in IgG anti-PF4/polyanion ELISA.

JAMA Pediatrics | Original Investigation

Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection

The INTERCOVID Multinational Cohort Study

Table 1. Pregnancy Complications, Perinatal Events, and Neonatal Morbidities Among Women With and Without COVID-19 Diagnosis and Their Newborns

Characteristic	No. (%)		Relative risk (95% CI)
	Women with COVID-19 diagnosis (n = 706)	Women without COVID-19 diagnosis (n = 1424)	
Maternal morbidity and mortality index[a]	225 (31.9)	296 (20.8)	1.54 (1.33 to 1.78)[b]
Vaginal bleeding	44 (6.2)	87 (6.1)	1.02 (0.72 to 1.46)
Pregnancy-induced hypertension	58 (8.2)	80 (5.6)	1.46 (1.05 to 2.02)
Preeclampsia/eclampsia/HELLP	59 (8.4)	63 (4.4)	1.76 (1.27 to 2.43)[b]
Hemoglobin level <10 g/dL at >27 wk gestation	130 (18.4)	228 (16.0)	1.15 (0.91 to 1.45)
Preterm labor	52 (7.4)	88 (6.2)	1.20 (0.86 to 1.68)
Infections requiring antibiotics	25 (3.6)	16 (1.1)	3.38 (1.63 to 7.01)
Admitted to ICU	59 (8.4)	23 (1.6)	5.04 (3.13 to 8.10)
Time in ICU, mean (SD), d	7.3 (7.8)	2.0 (1.7)	3.73 (2.37 to 5.86)[c]
Referred for higher dependency care	6 (0.9)	1 (0.1)	6.07 (1.23 to 30.01)
Maternal death	11 (1.6)	1 (0.1)	22.26 (2.88 to 172.11)
Fetal distress	87 (12.3)	120 (8.4)	1.70 (1.06 to 2.75)[b]

JAMA Pediatrics | Original Investigation

Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection

The INTERCOVID Multinational Cohort Study

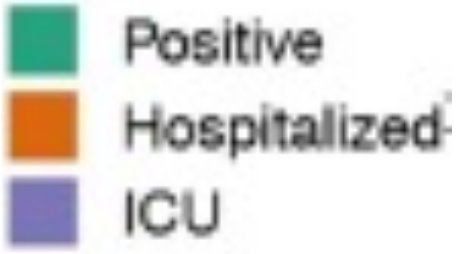
Spontaneous initiation of labor	333 (47.2)	793 (55.7)	0.85 (0.77 to 0.93)
Induced labor	157 (22.3)	320 (22.5)	0.99 (0.84 to 1.18)
Cesarean delivery	346 (49.0)	547 (38.4)	1.28 (1.16 to 1.40)[b]
Prelabor rupture of membranes	114 (16.1)	262 (18.4)	0.87 (0.71 to 1.07)
Gestational age at birth, mean (SD), wk	37.9 (3.3)	38.5 (3.1)	−0.61 (−0.90 to −0.32)[d]
Preterm birth (<37 wk gestation)	159 (22.5)	194 (13.6)	1.59 (1.30 to 1.94)[e]
Spontaneous preterm birth	27 (3.8)	66 (4.6)	0.81 (0.52 to 1.27)
Medically indicated preterm birth	133 (18.8)	127 (8.9)	1.97 (1.56 to 2.51)[e]
Birth weight, mean (SD), kg	2.96 (0.70)	3.07 (0.68)	−0.11 (−0.18 to −0.04)[d]
Male	353 (50.0)	749 (52.6)	0.95 (0.87 to 1.04)
Female	353 (50.0)	675 (47.6)	1.06 (0.96 to 1.16)
Low birth weight (<2500 g)	145 (20.5)	181 (12.7)	1.58 (1.29 to 1.94)[b]
Small for gestational age (<10th centile)[f]	97 (13.7)	181 (12.7)	1.03 (0.81 to 1.31)
Exclusive breastfeeding at discharge	378 (53.5)	953 (66.9)	0.80 (0.74 to 0.87)
Any breastfeeding at discharge	588 (83.3)	1290 (90.6)	0.92 (0.88 to 0.96)
SNMI[g]	44 (6.2)	33 (2.3)	2.66 (1.69 to 4.18)[b]
Severe perinatal morbidity and mortality index[h]	120 (17.0)	113 (7.9)	2.14 (1.66 to 2.75)[b]

Nature preprint online , April 22nd: 2021
Al-Aly et al: High-dimensional characterization of post-acute sequalae of COVID-10

Beyond 30 days post acute COVID-19 patients exhibit higher risk of death and health resource utilization:

- **Respiratory system**
- **Nervous system system**
- **Neurocognitive disorders,**
- **Cardiovascular disorders,**
- **Gastrointestinal disorders**
- **Malaise**
- **Fatigue**
- **Musculoskeletal pain**
- **Anemia**

Increased use of opioids and non-opioids, antidepressants, anxiolytics, antihypertensives and oral hypoglycemics and multiple laboratory abnormalities



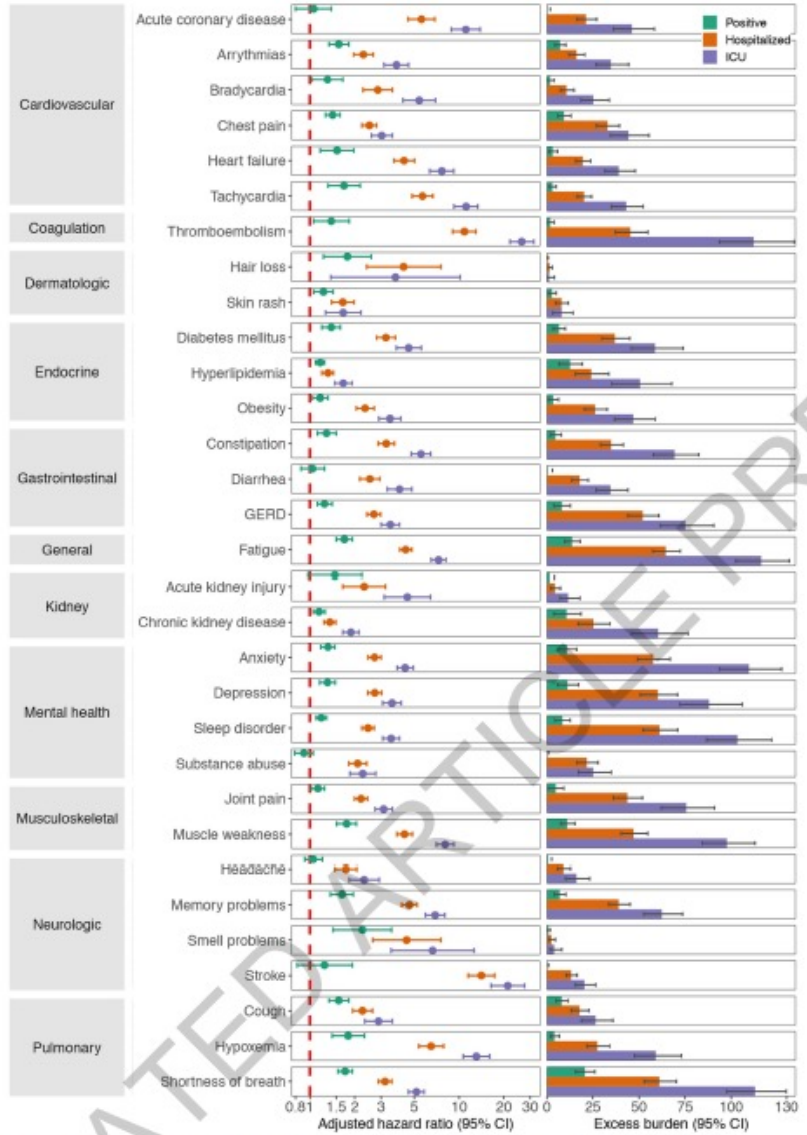
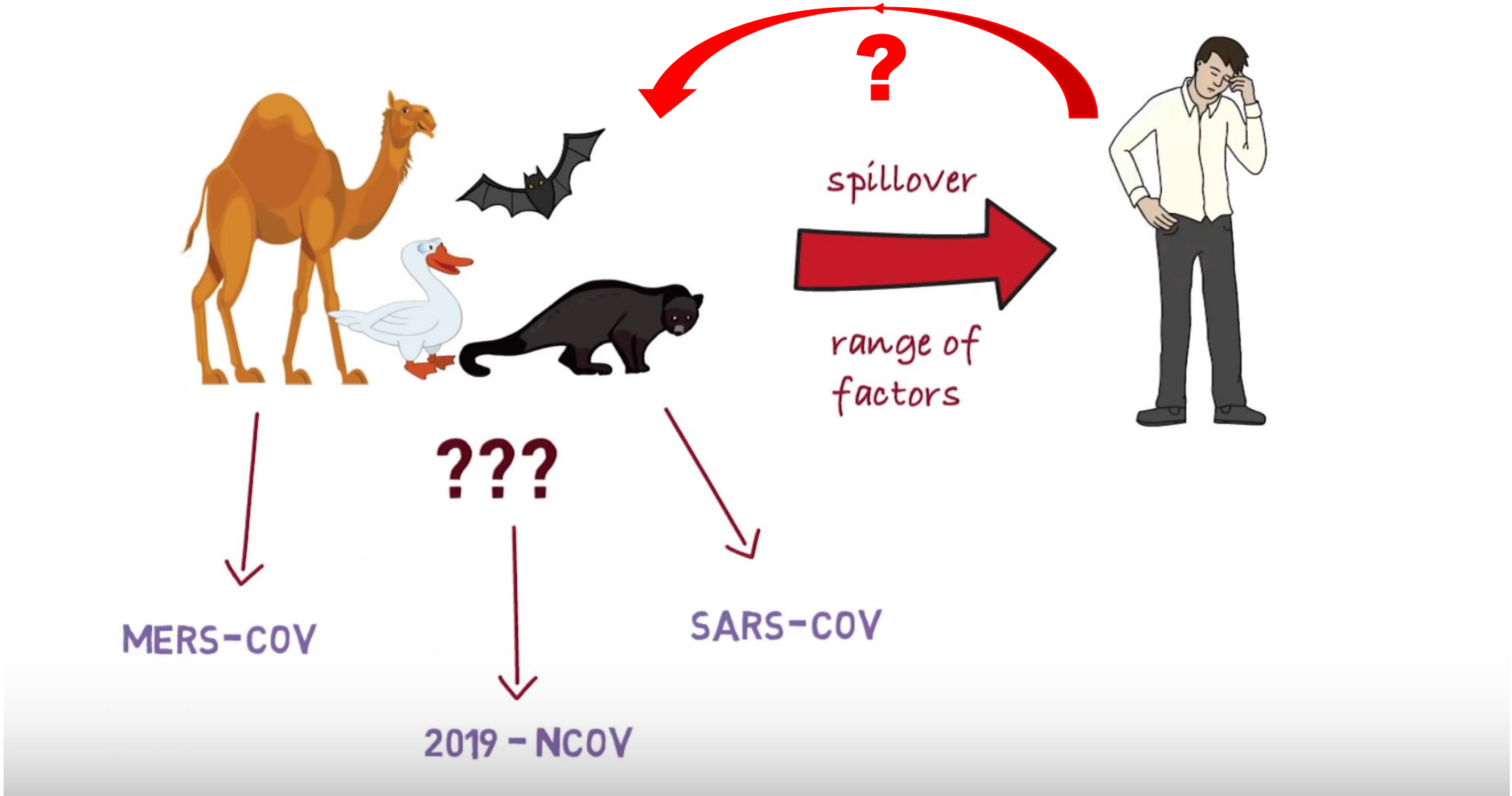


Fig. 3 | Risks and burdens of incident pre-specified high resolution post-acute COVID-19 outcomes at 6 months in mutually exclusive cohorts of people with non-hospitalized COVID-19 (green), people hospitalized for COVID-19 (orange), and people admitted to intensive care for COVID-19 (blue) during the acute phase (first 30 days) of the infection. ; all users of the Veteran Health Administration healthcare system served as the referent category. Outcomes were ascertained from day 30 after COVID-19 diagnosis until end of follow-up. Hazard ratios and 95% confidence intervals and excess burdens per 1000 patients and 95% confidence intervals at 6-months are presented.

Coronaviruses are highly mutational that promotes their capacity to 'species jump'

When they do the results can be unexpected

The original host may have no disease, the new host very sick.



METHODS

Archival sewage samples:

- Pre-epidemic period: 40 samples (October 2019 - February 2020)
- Non-epidemic period: 24 samples (September 2018 - June 2019)

* First authoctonous case (21 Feb 2020)

- Sample concentration (WHO, 2003, with modifications)
- Viral nucleic acids extraction with magnetic silica beads
- Real-time RT-PCR (newly designed assay) + Nested RT-PCR and sequencing

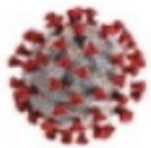
RESULTS

- **First occurrence of SARS-CoV-2 in sewage:**

City	Date of sampling
Milan	December 18, 2019
Turin	December 18, 2019
Bologna	January 29, 2020

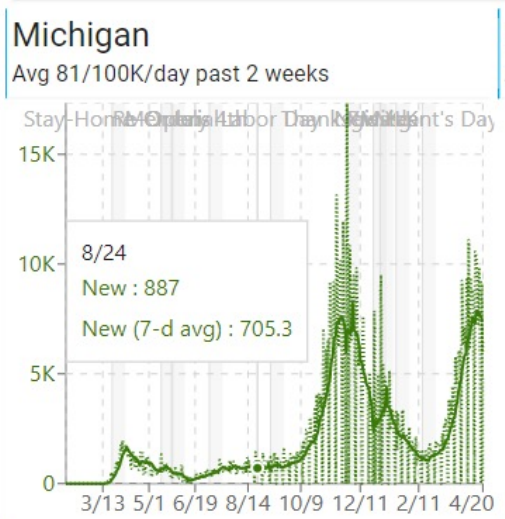
- **Agreement between the two assays:** 65.0% (26/40 paired results)
- **Virus concentration:** from <LOD to 5.6×10^4 g.c./L; most of the samples were below the analytical LOQ

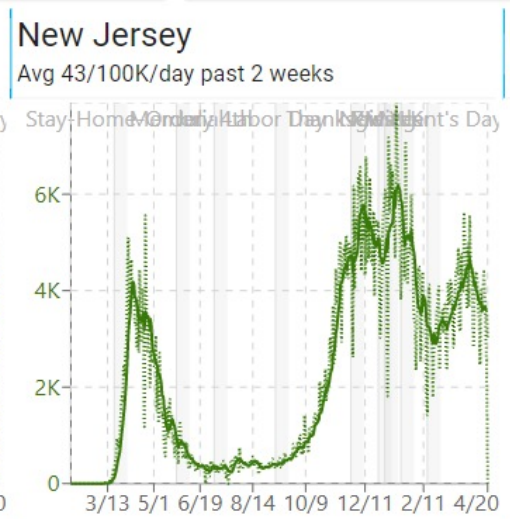
CONCLUSIONS

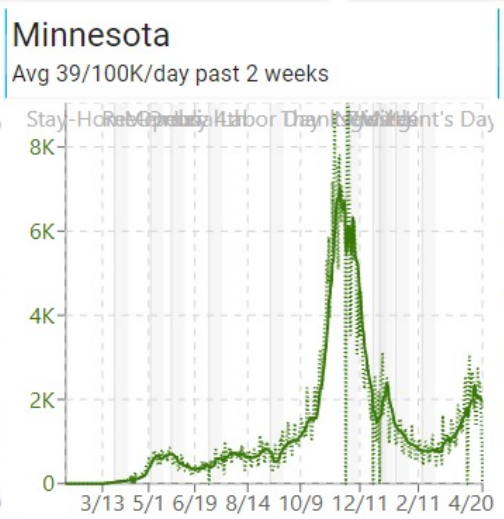


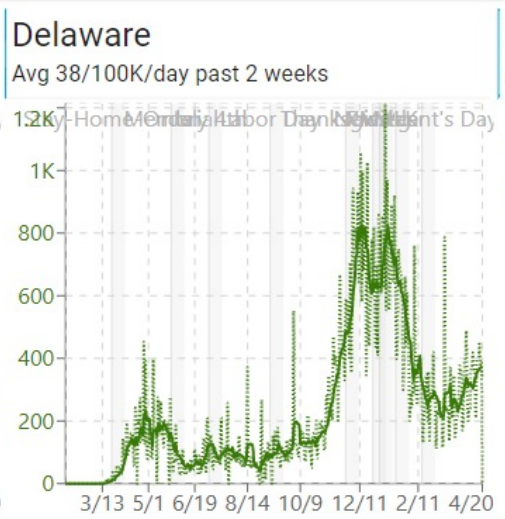
- **SARS-CoV-2 has been circulating in northern Italy since December 2019**
- **WBE could contribute to the early detection of a possible second wave of infection**

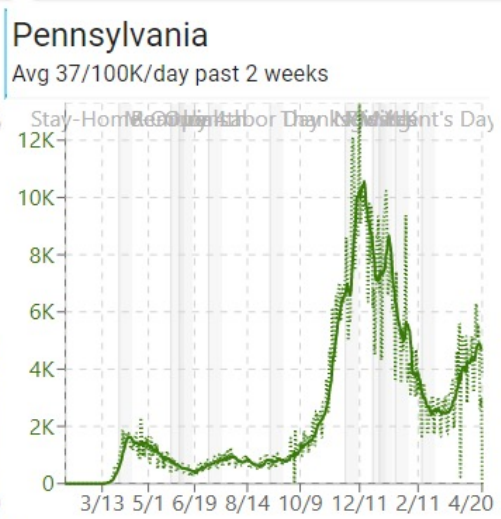
This is what the variants are doing

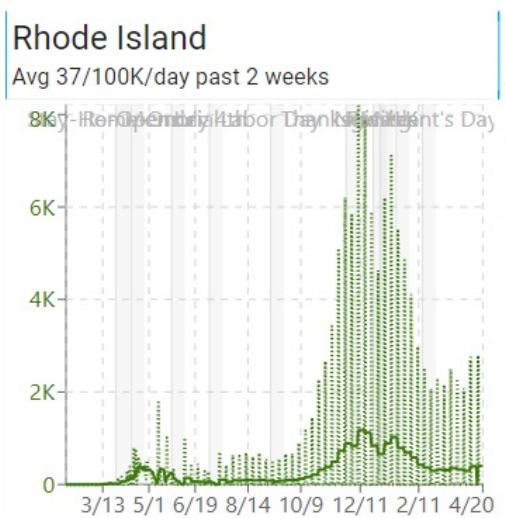


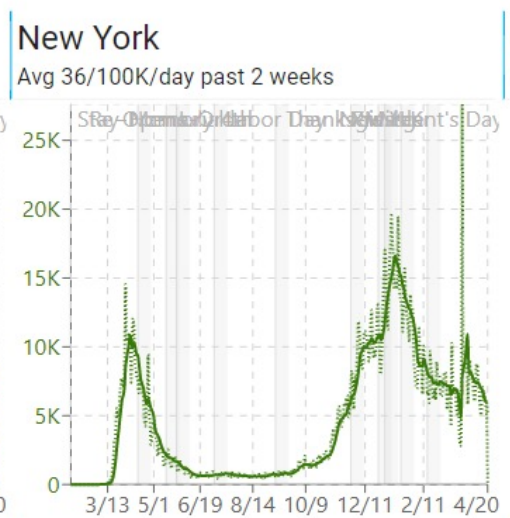


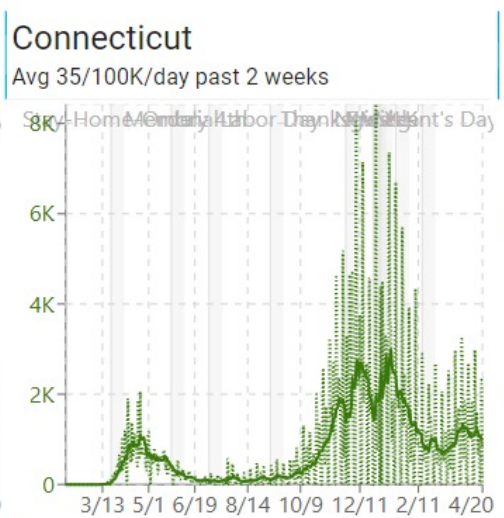


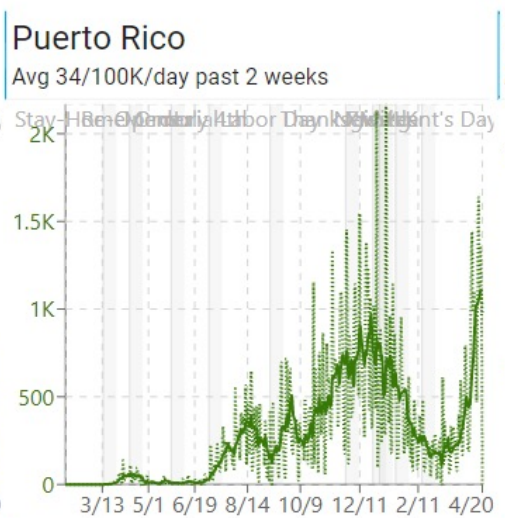


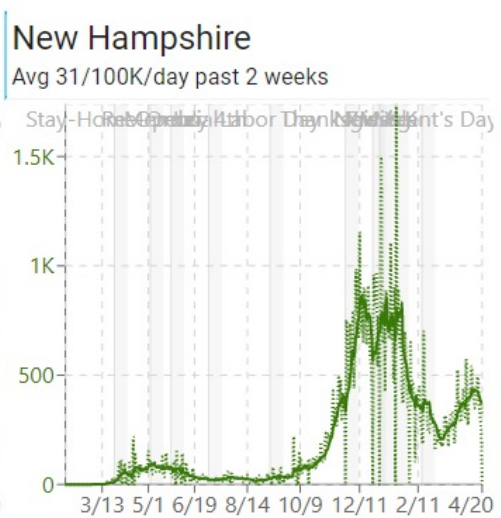


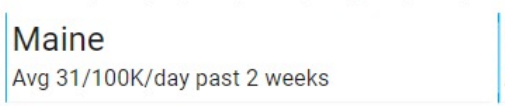


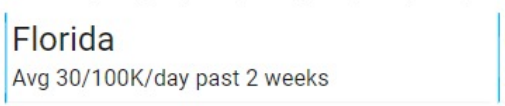


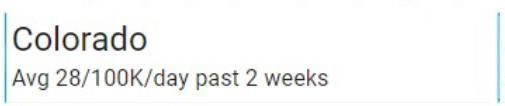






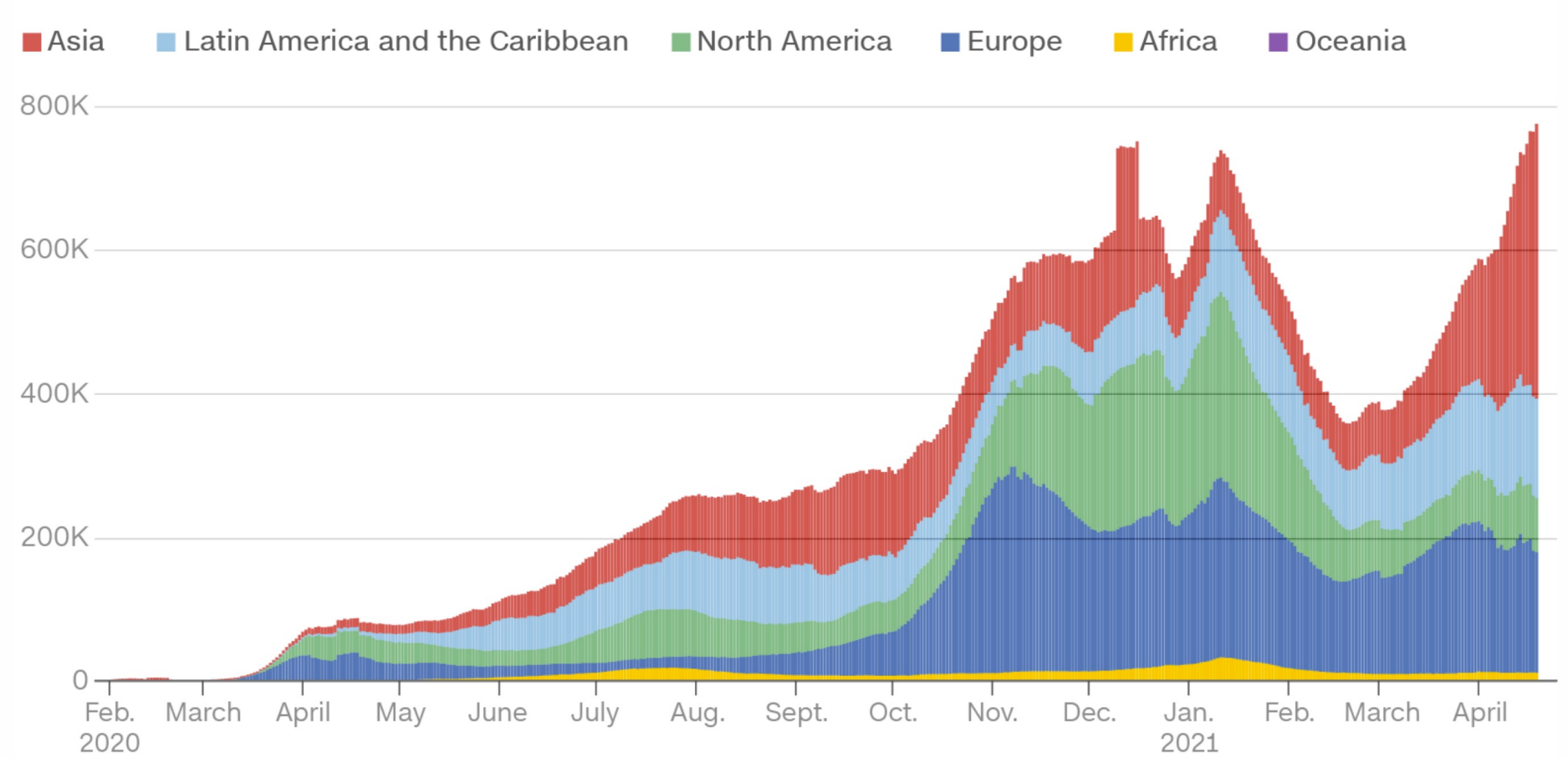






Sharp rise in global cases is causing concern

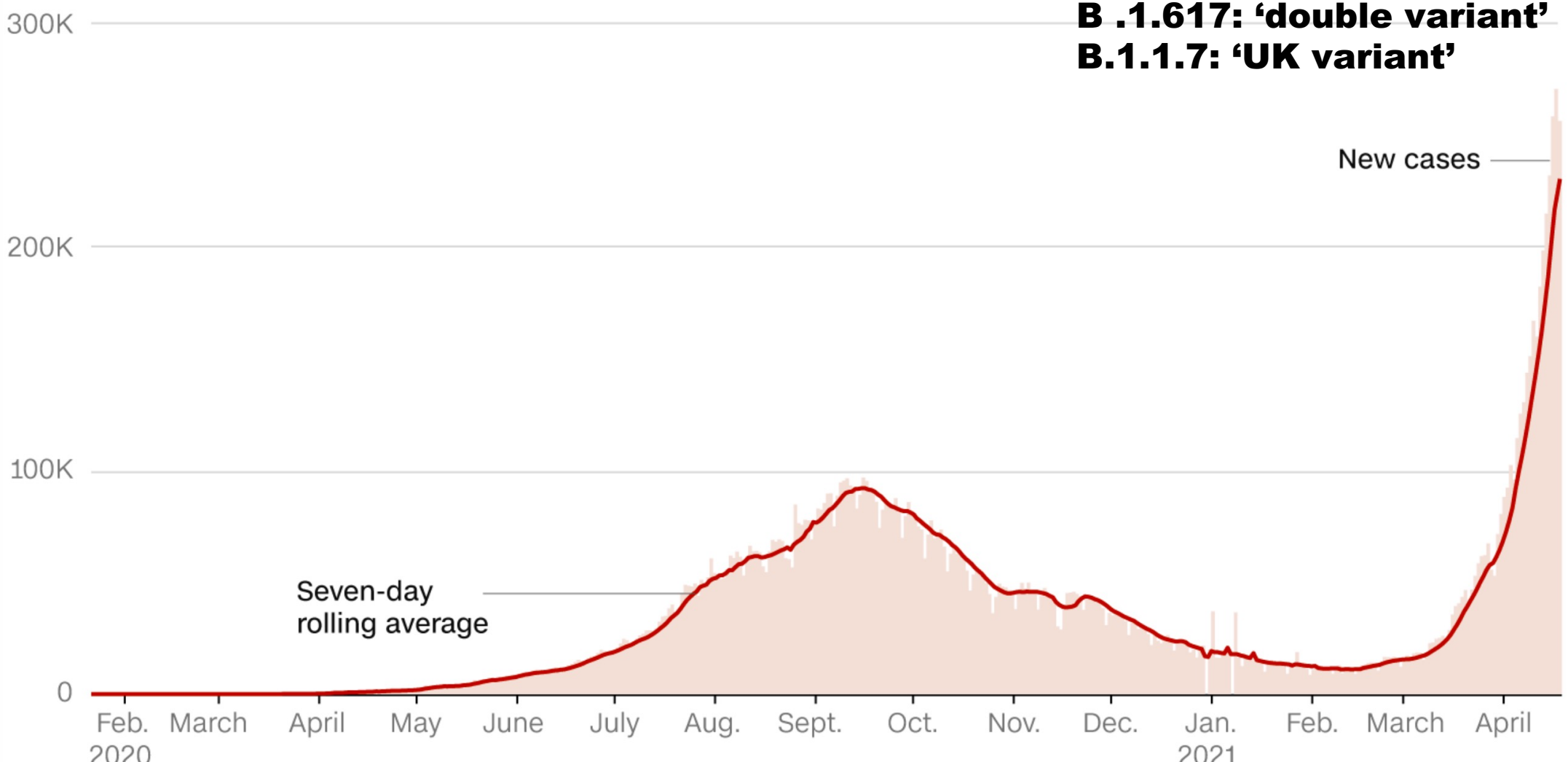
More than 5.2 million new Covid-19 cases were recorded around the world last week, bringing the total to more than 142 million cases since the start of the pandemic.

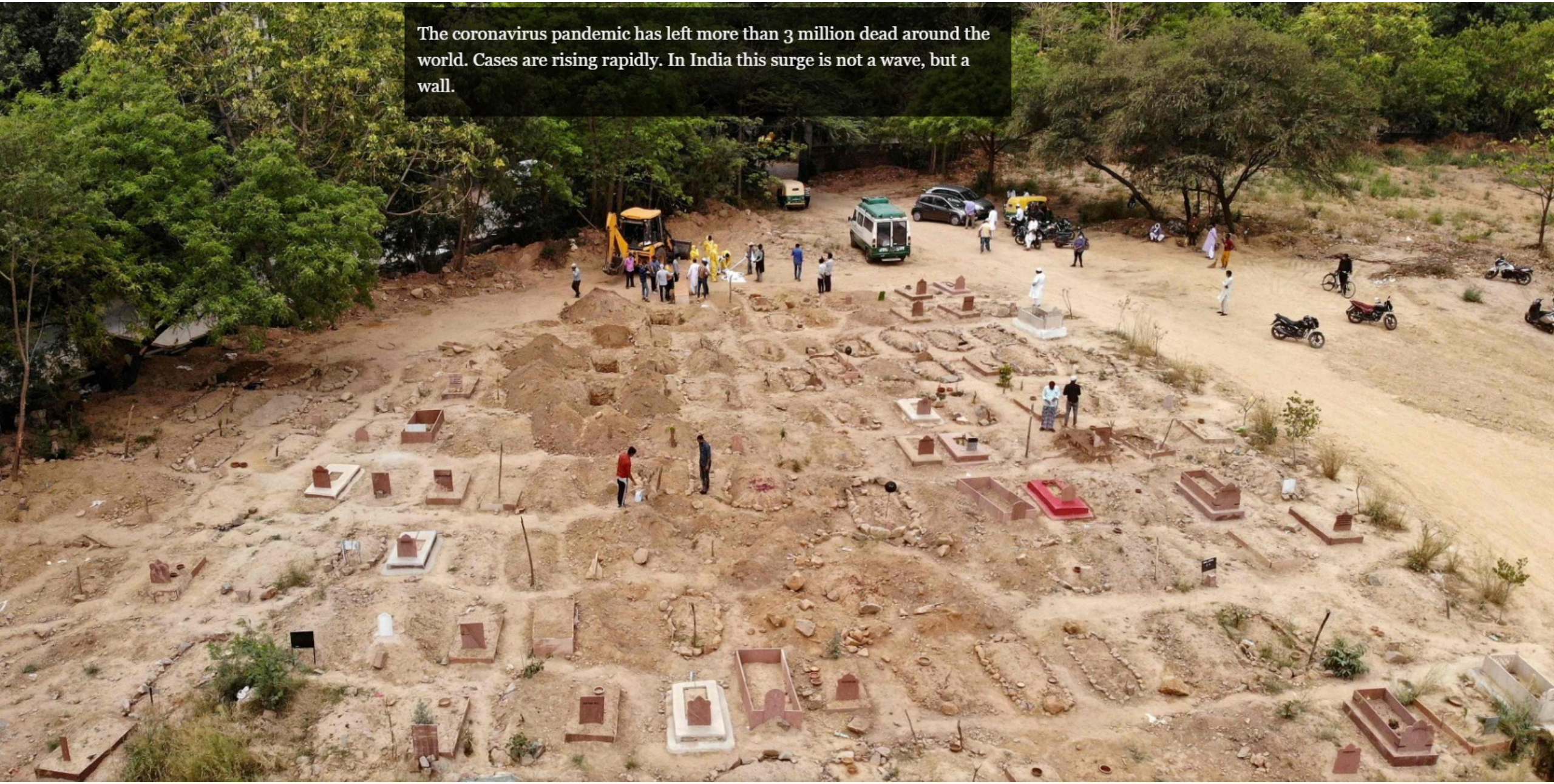


India’s second wave

India has reported an average of over 230,000 new Covid-19 cases each day in the past week, bringing total cases to over 15 million as a second wave sweeps the country.

B .1.617: ‘double variant’
B.1.1.7: ‘UK variant’





The coronavirus pandemic has left more than 3 million dead around the world. Cases are rising rapidly. In India this surge is not a wave, but a wall.

Oxygen is in such short supply that tankers are hauling it in from other states. Patients still face a scramble to find available hospital beds.

SUMMARY

- **This is a bad, bad virus, but is vaccine preventable.**
- **We have vaccines that are both safe & effective**
- **Most vaccine appear so far effective against all variants**
- **Serious vaccine side effects are extremely rare**
- **Protection following vaccination is solid and appears to persist**
- **Vaccines may confer some immunity to infection thus limiting spread at least by lowering virus loads**
- **Immunity following infection is not solid, but is better with vaccine**
- **Distribution in Western countries is progressing well**

- ***Problems remain***
  - **Many parts of the world have insufficient vaccine and delivery systems and continue to be devastated.**
  - **Until this is addressed the virus can mutate and spread**
  - **Vaccine access & hesitancy are real threats to global herd immunity.**
  - **Political and inequality issues need to be addressed.**