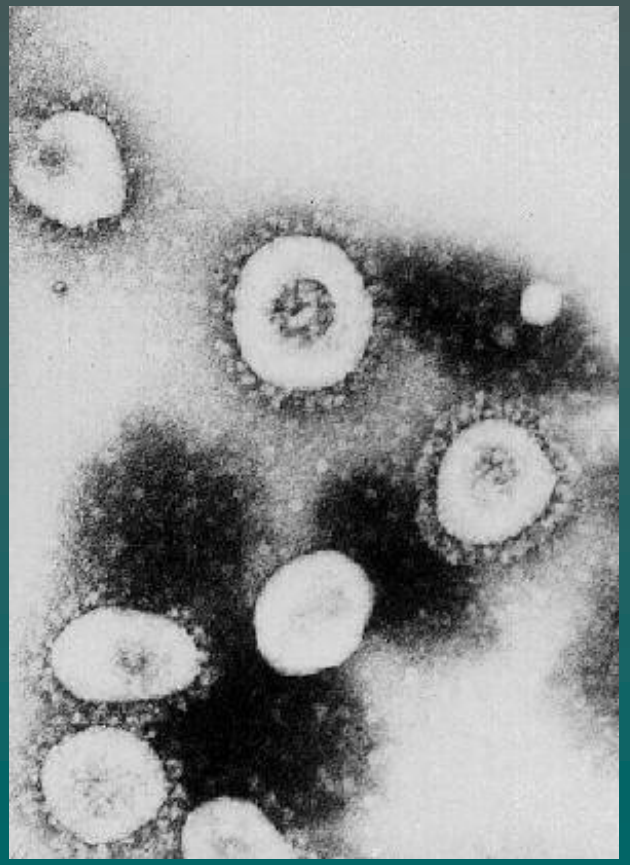
Epidemiology of coronaviruses: SARS, MERS and SARS-COV-2

Objectives

- Gain basic knowledge of the conditions needed for pandemic spread
- Appreciate the similarities and differences between spread of SARS and SARS-COV-2
- Understand the impact of flattening the curve of case incidence on healthcare management
- Understand the impact of R_0, S_i and secondary attack rates on disease progression



Centers for Disease Control

Conditions required for pandemic disease

- Introduction of an antigenically novel virus
  - May arise through mutation or recombination (e.g., influenza virus)
  - May arise through introduction from another species (influenza virus, coronavirus)
- Virus must be readily transmissible between humans
- Virus must be able to cause serious illness or death

What will be the impact of a pandemic?

- Impossible to predict with accuracy….
- Historically, earlier influenza pandemics took 6-9 months to spread around the world.
- Thanks to extensive international air travel, a modern pandemic can spread around the world in less than 3 months.
- A pandemic may not be a one-time event, and may occur in several waves. Total duration is likely to be 12-18 months, and may follow through several cycles.
- Practical experience with SARS-COV-2 has largely confirmed the cyclical sequence of events.

Severe Acute Respiratory Syndrome (SARS)

- First described in Guangdong province, southern China, in late 2002
- Initial outbreak peaked in April 2003, tailing off a few months later
- 8,096 cases worldwide, with 774 deaths
- Virus isolated and identified as a new coronavirus
- Transmission by close contact, handling infected animals
- SARS present in sweat, urine, feces
- Aerosol/droplet transmission between humans

Clinical features of SARS

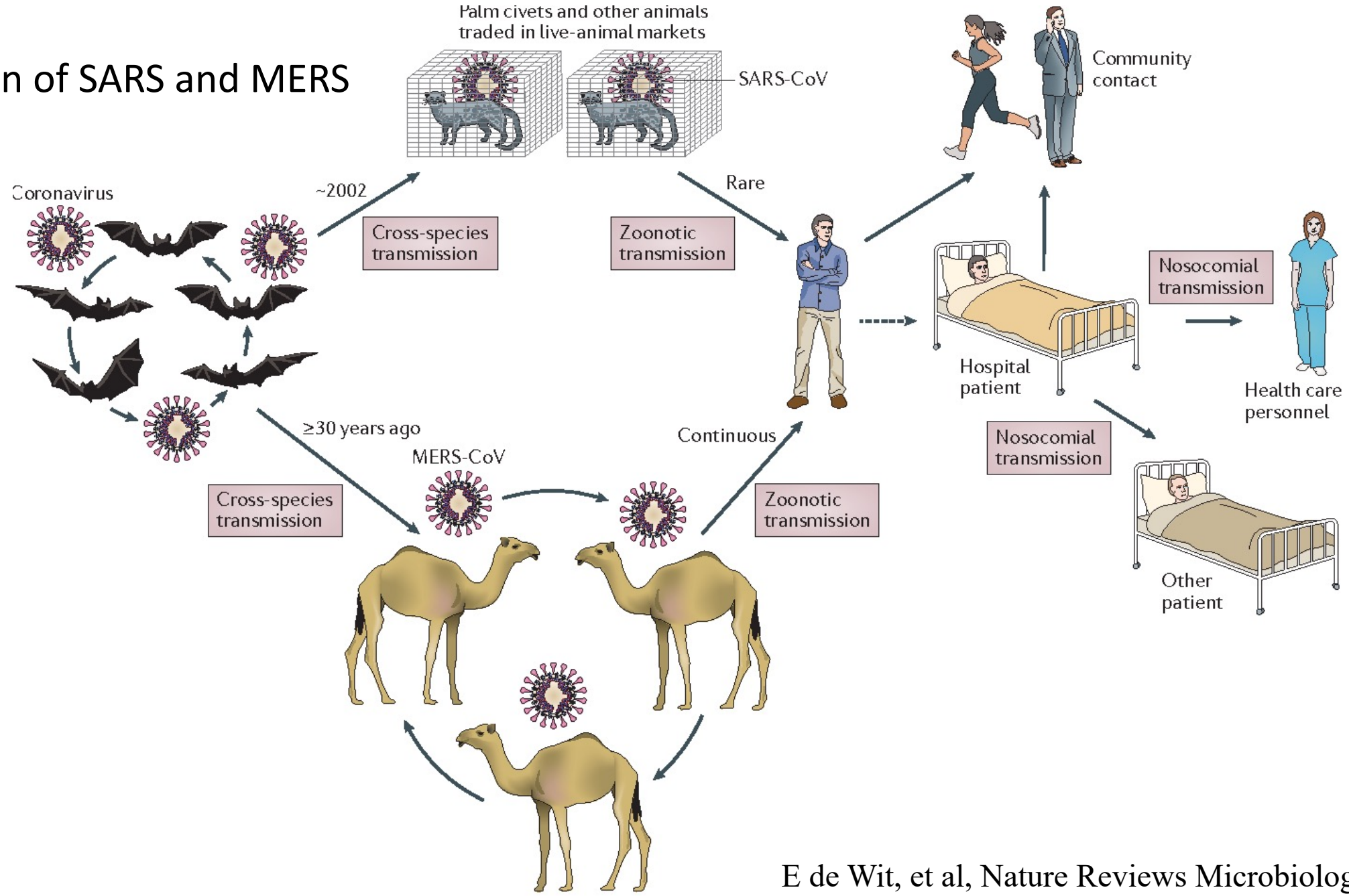
- In young children, SARS is usually a mild respiratory disease
- Fever, runny nose, cough, diarrhea are common
- Unlike other human coronaviruses, SARS can replicate at 37^{o}C and cause systemic disease
- In adults, SARS causes pneumonia, high fever, chills, rigors, myalgia, headache, breathing difficulties - intensive care and ventilation may be needed for dyspnea and hypoxemia
- Mortality about 10% for adults under 60, but >40% for those over 60
- **Diagnosis**
  - Exclusion of other probable causes
  - Detection of viral RNA, ELISA for antibodies
- **Treatment**
  - Isolation
  - Management of symptoms

SARS and Civet Cats?

- About one third of initial cases of SARS were in food handlers
- SARS detected in eight species of animals, including palm civet cats, badgers, rabbits, raccoon dogs and barking deer, on sale at food markets in Guangdong
- All civet cats tested positive for SARS, but may not be the original source of the virus – bats have tested seropositive for SARS

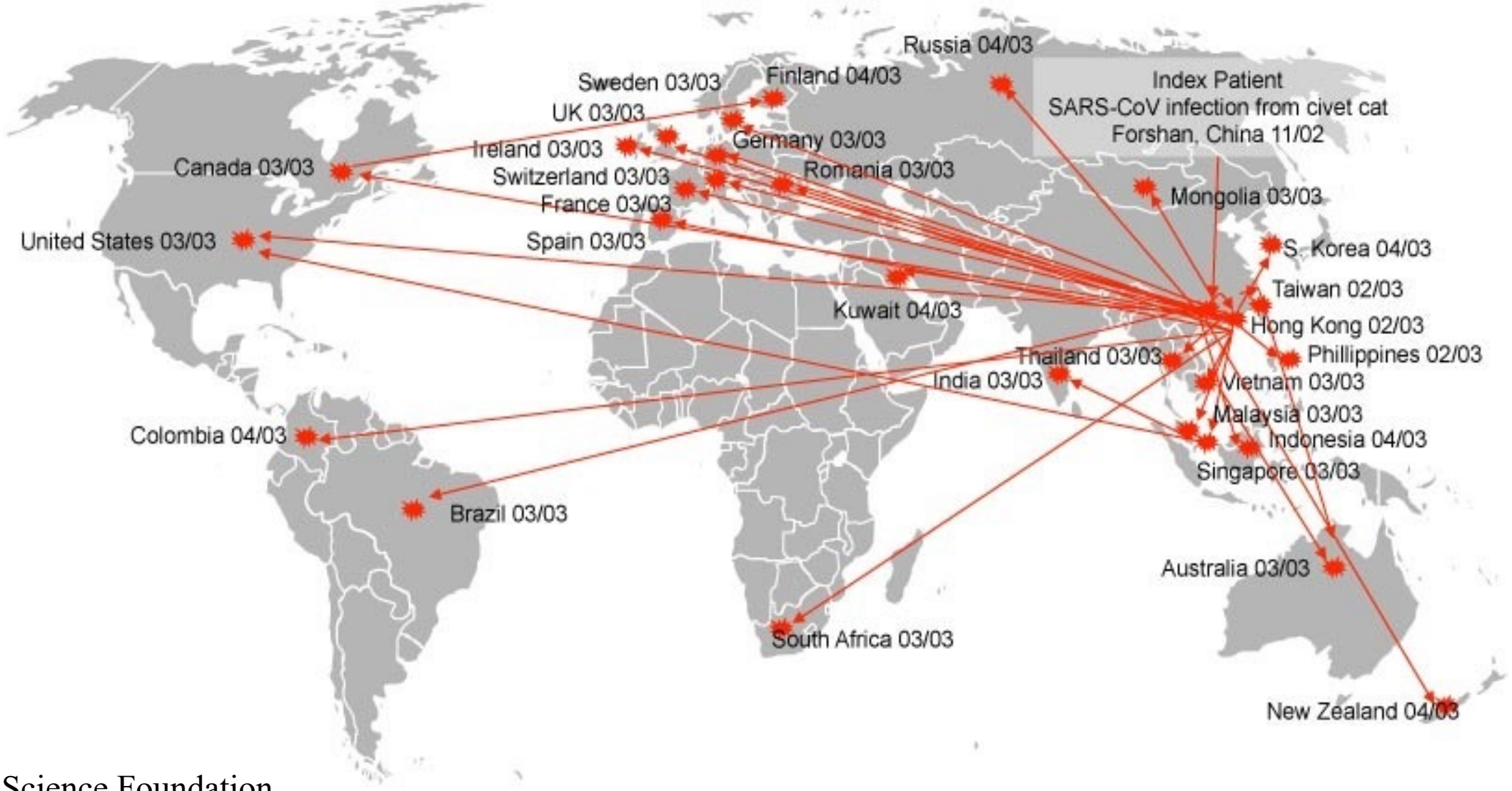
Asian palm civet, widely used for production of kopi luwak

Transmission of SARS and MERS

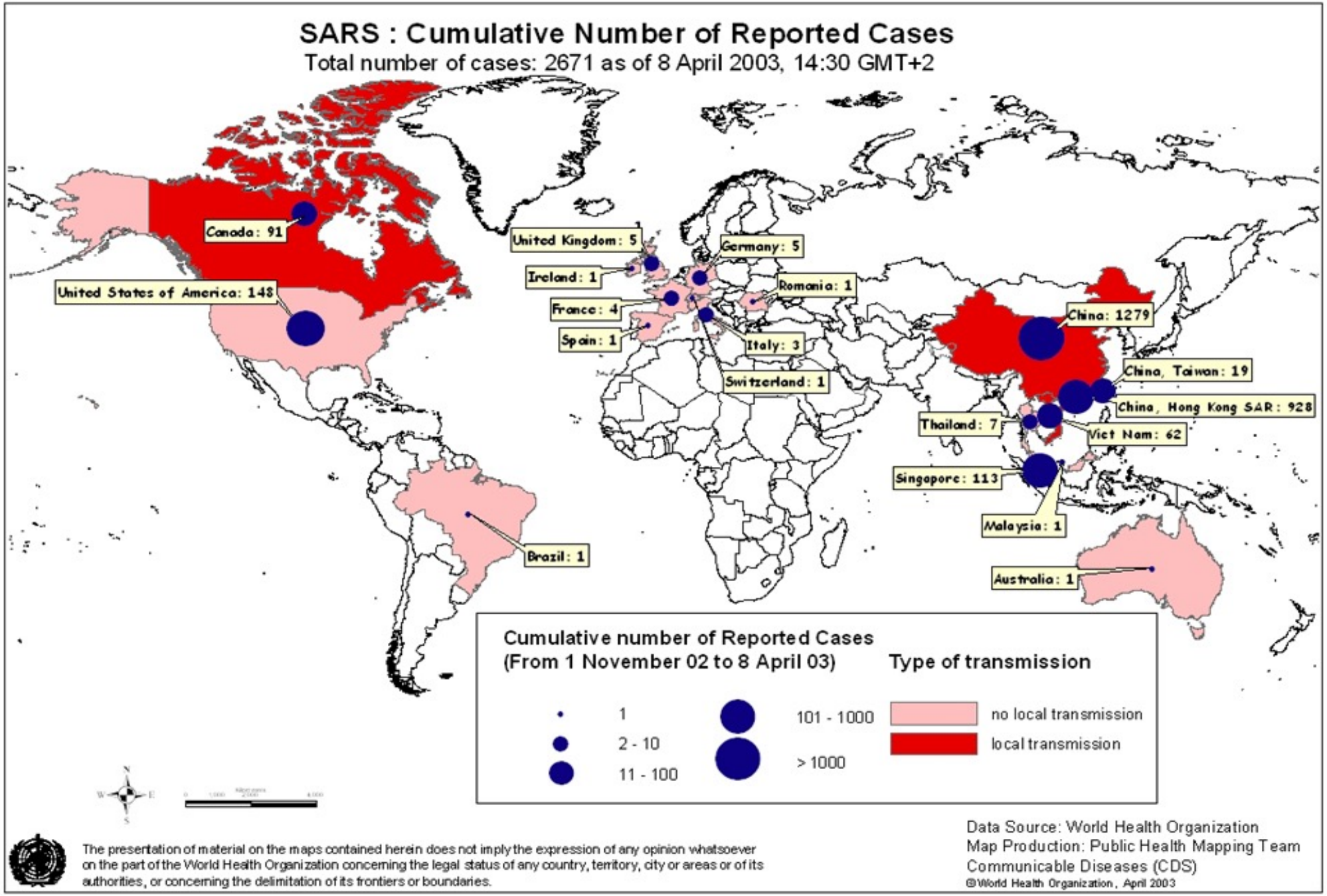


E de Wit, et al, Nature Reviews Microbiology, 2016

Spread of SARS along international travel routes



National Science Foundation


SARS : Cumulative Number of Reported Cases
Total number of cases: 2671 as of 8 April 2003, 14:30 GMT+2
Canada: 91
United States of America: 148
Brazil: 1
United Kingdom: 5
Ireland: 1
France: 4
Spain: 1
Germany: 5
Romania: 1
Italy: 3
Switzerland: 1
China: 1279
China, Taiwan: 19
China, Hong Kong SAR: 928
Thailand: 7
Viet Nam: 62
Singapore: 113
Malaysia: 1
Australia: 1
Cumulative number of Reported Cases
(From 1 November 02 to 8 April 03)
1
2 - 10
11 - 100
101 - 1000
> 1000
Type of transmission
no local transmission
local transmission
N
W
E
S
The presentation of material on the maps contained herein does not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or areas or of its authorities, or concerning the delimitation of its frontiers or boundaries.
Data Source: World Health Organization
Map Production: Public Health Mapping Team
Communicable Diseases (CDS)
©World Health Organization, April 2003

SARS and MERS today

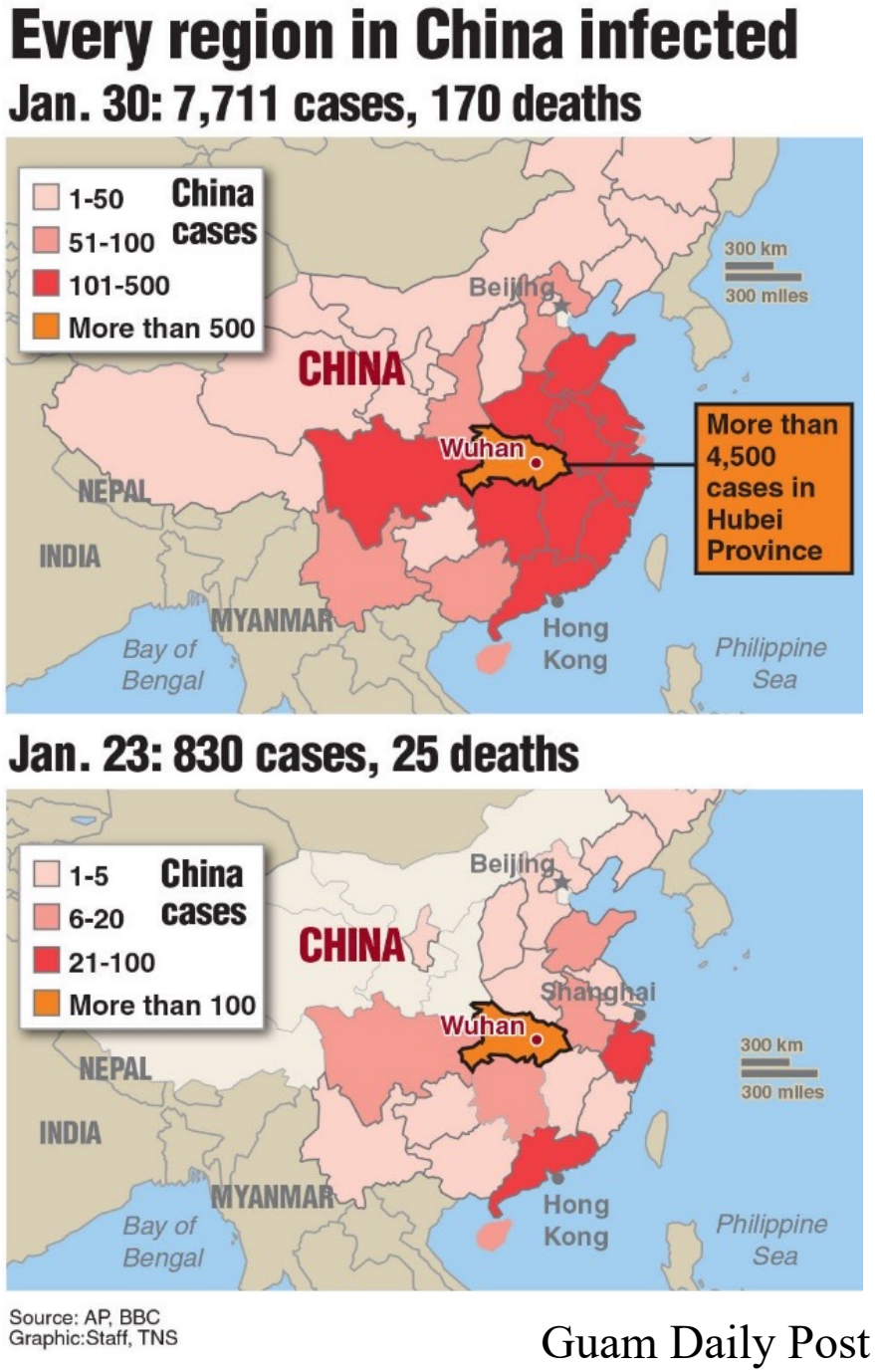
- No known SARS transmission anywhere in the world
- Novel coronavirus infection, September 2012
  - 49 year old male Qatari national with acute respiratory syndrome and renal failure
  - Isolated a novel coronavirus with 99.5% identity to a virus isolated from earlier fatal case in Saudi Arabia
- **MERS – Middle East Respiratory Syndrome**
  - 2,458 cases and 851 deaths reported by WHO up to Sept 2019
  - Majority of cases in Saudi Arabia and neighboring countries; travel-related cases in Europe, US
  - WHO recommends that at risk groups (diabetics, individuals with renal failure or chronic lung disease) should avoid camels, and should not drink raw camel milk or urine

From the M2 Pulmonary module, 11/6/2019

- Coronaviruses have high potential for mutation, recombination and adaptation
- High capacity to change tropism and disease
- Many new animal coronavirus diseases in last 20 years
- Demonstrated movement between species
- Continued risk of animal to human transmission and emergence of pandemic severe disease

Emergence of SARS COV-2

- First case of COVID-19 detected on November 17
- Disease advanced slowly at first, and then accelerated
- Change from Jan 23 to Jan 30 shows dramatic progression



Guam Daily Post

Wuhan: a city of 11 million people

- Airport served 25 million passengers in 2018
- Widespread travel for Lunar New Year
- Airport closed on January 23

Asymptomatic and pre-symptomatic transmission of SARS COV-2

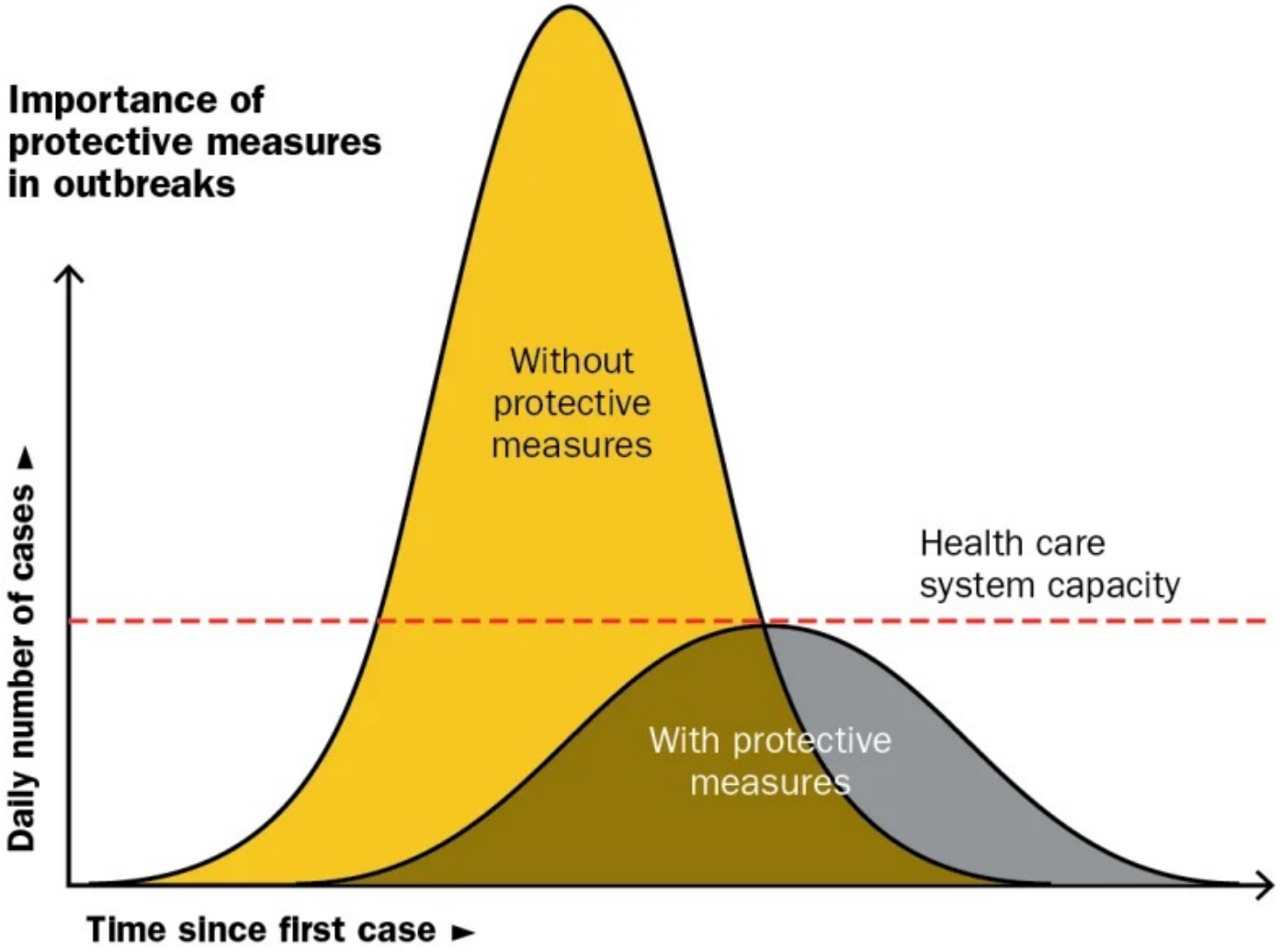
- Opinions differ on whether asymptomatic transmission is a major driver of transmission
- Pre-symptomatic transmission rates may be high (estimated at 48% in Singapore and 62% in Tianjin, China)
- Extensive diagnostic testing in Iceland has suggested that about half of those who tested positive are asymptomatic
- Asymptomatic SARS-COV-2 positive rate of 36% in a community treatment center cohort: asymptomatic individuals carry similar viral loads to symptomatic patients (S Lee al, JAMA Intern Med 180:1447-52, 2020)
- Should isolate infected persons regardless of symptoms

Impact of asymptomatic transmission

- Transmission from asymptomatic individuals estimated to account for more than half of all transmission (MA Johansson et al, JAMA Netw Open 4(1):e2035057, 2021)
- Physical distancing of >1m reduces risk of infection from 12.8% to 2.6%: face masks reduce infection rate from 17.4% to 3.1% (DK Chu et al, Lancet June 1, 2020)
- Findings strongly indicate that measures such as wearing masks, hand hygiene, social distancing, and strategic testing of people who are not ill is critical to slowing the spread of COVID-19

Flattening the curve

- Some success from aggressive early intervention in South Korea, Hong Kong, Singapore, Taiwan
- Washing hands
- Drive-through testing
- Social distancing
- Travel restrictions
- Isolation



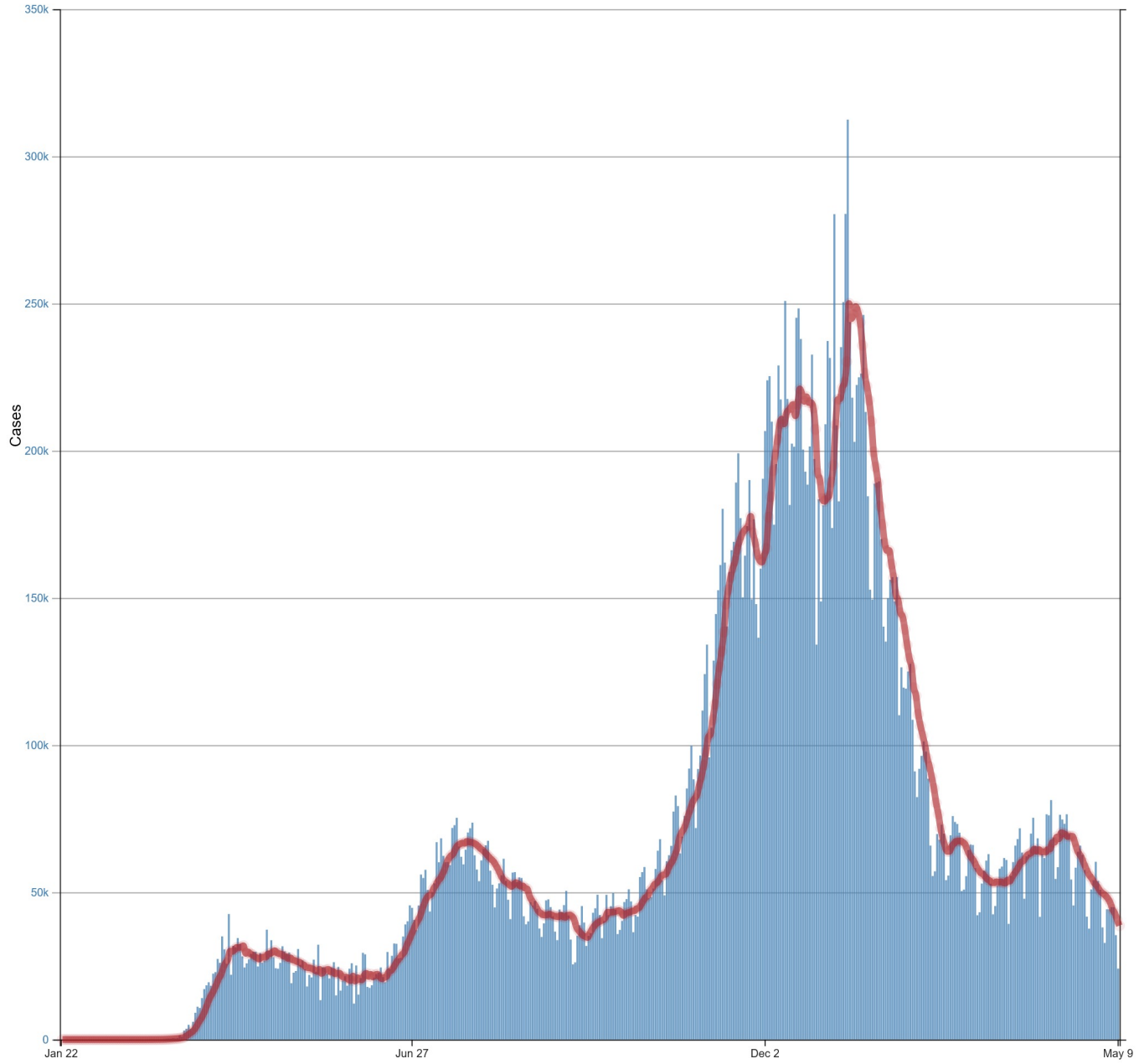
Emily Barone/Lon Tweeten for TIME

Flattening the curve

- There are some very dangerous consequences of an inability to flatten the curve
- Assuming social controls flatten the curve, when and how do you ease off? As discussed earlier, there’s a high probability of a rebound, resulting in several cycles of infection

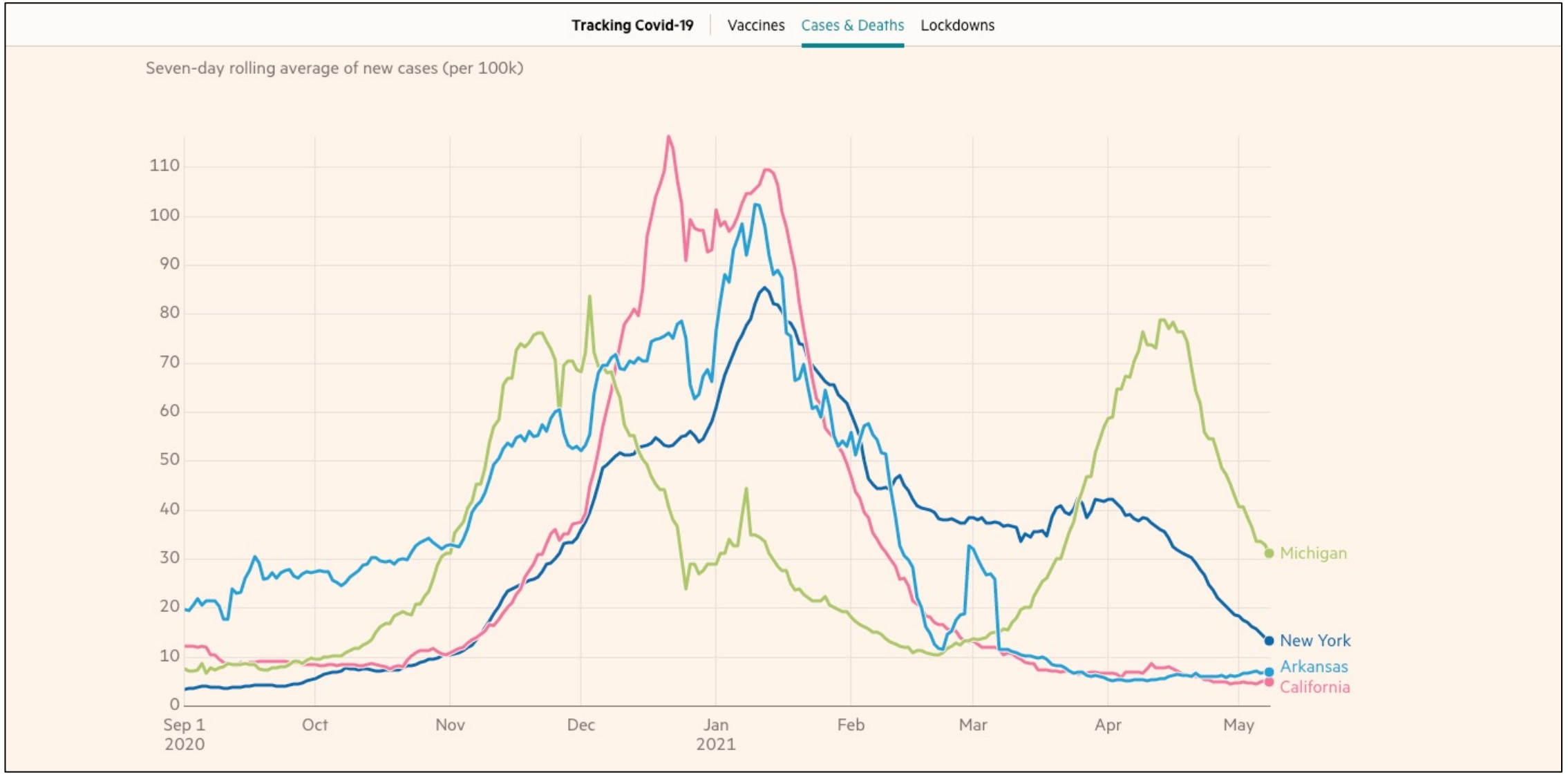
Daily cases reported to CDC from Jan 22, 2020 to May 9, 2021

- Blue bars show daily cases
- Red line is sum of cases over 7 days, divided by 7
- Data clearly show several periodic waves of infection



2nd wave COVID-19 infection state by state, Nov 2020 – March 2021

(Note 3rd wave in Michigan, April-May 2021)



The Basic Reproduction Number (R_0)

- R_0 measures transmission potential of a disease
- Average number of secondary infections produced by an infected case where everyone in the population is susceptible
- One problem with estimating R_0 is that not all cases are reported and so they are not included
- R_0 is governed by several factors
  - Rate of contacts
  - Probability of infection being transmitted by contact
  - Duration of infectiousness
- For an epidemic/pandemic to progress, R_0 must be >1
- To limit spread, we must drop R_0 to <1, i.e., each case of infection results in transmission to <1 new individual on average

The Serial Interval (S_i)

- Time of onset of infectiousness in the primary case to the time of onset of infectiousness in a secondary case
- S_i for Covid-19 variously estimated at 4-6 days, whereas S_i for influenza is about 3 days
- If the Covid-19 S_i is as low as 4 days, there is increased potential for pre-symptomatic transmission

Covid-19 secondary attack rates

- Secondary attack rate is defined as the probability that an infection occurs among susceptible people with a specific group, e.g., close contacts or household members
- Secondary attack rate for SARS COV-2 has been estimated at under 1% among close contacts of US patients, but over 10% for household members.
- Japanese study pointed to SAR of >20% for 50-59 years age group
- Other studies on close gatherings (e.g., meetings, restaurant meals) in China have found secondary attack rates as high as 35%
- Bottom line – this is likely to be highly variable, depending on emergence of new more transmissible SARS-Cov-2 variants, and risk associated with different social settings

Case Fatality Rates

- A study in the Journal of the American Medical Association from China's CDC reported that the case fatality rate (CFR) in approximately 45000 patients with confirmed Covid-19 in mainland China was 2.3%.
- The CFR varies by age and underlying health status, and ranges from 0 in patients 9 years of age and under to 14.8% in those 80 and older.
- The CFR is high in people with underlying cardiovascular disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%) and hypertension (6%).
- The CRR may also be influenced by the extent of testing and identification of mildly infected or asymptomatic individuals – the higher the number tested, the lower the overall CFR.
- Covid-19 less lethal than the two other coronaviruses that have caused recent outbreaks (SARS had a CFR of 9.6% and MERS of 34.4%), but COVID-19 is more lethal than influenza (between 0.05-0.1% depending on the year).
- Overall CFR in US is about 1.77% (as of May 13, 2021)

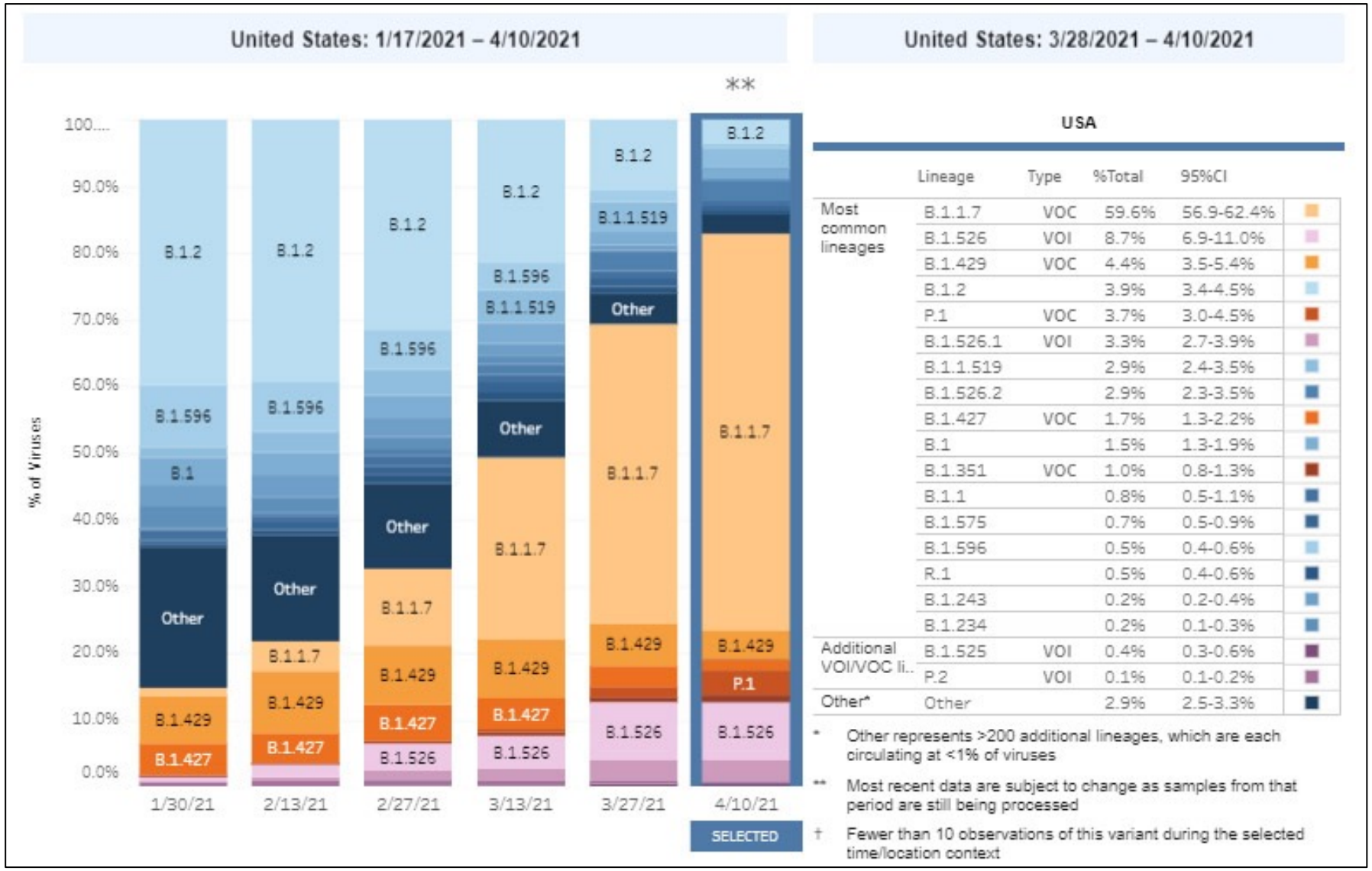
Epidemiologic considerations of the impact of a high frequency of asymptomatic/mild COVID-19 cases

- This would likely raise the estimated R_0 value and secondary attack rates, and also raise the threshold for herd immunity
- On the plus side, a much higher frequency of infection would suggest that populations can reach a threshold for herd immunity earlier than thought
- The downside is that asymptomatic COVID-19^+ individuals may still transmit infection to others
- A high frequency of asymptomatic cases would raise an argument that lockdown policies are ineffective, while also causing an economic meltdown
- Antibody testing will provide more reliable data, and will aid in decisions on when to relieve stay-at-home orders and ease restrictions on social distancing

Emerging SARS-COV-2 variants

- B.1.1.7 lineage (UK, September 2020) – N510Y mutation in the receptor binding domain of the spike protein
- Also has several other mutations, including 69/70 deletion in spike protein, P681H near the S1/S2 furin cleavage site
- Increased transmissibility, increased risk of death
- Pfizer vaccine efficacy estimated at 89.5% after two doses (NEJM, May 5, 2021)
- B.1.351 lineage (South Africa, October 2020) – multiple mutations, including K417N, E484K, N501Y, but no evidence of any impact on disease severity
- Pfizer vaccine efficacy estimated at 75% after two doses (NEJM, May 5, 2021)
- P.1 lineage (Brazil, January 2021) – 17 amino acid changes, 10 in the spike protein, including K417T, E484K, N501Y
- Higher viral load in infected individuals, more transmissible, more lethal
- May evade immunity from prior infection or vaccination

SARS-COV-2 variants circulating in the US, January-April, 2021



Pfizer vaccine-elicited neutralization against new SARS-CoV-2 variants

Several recent SARS-CoV-2 variants are cause for concern in the US, including California B.1.429, New York B.1.526 and the UK B.1.1.7 lineage with a new E484K substitution in the Spike protein

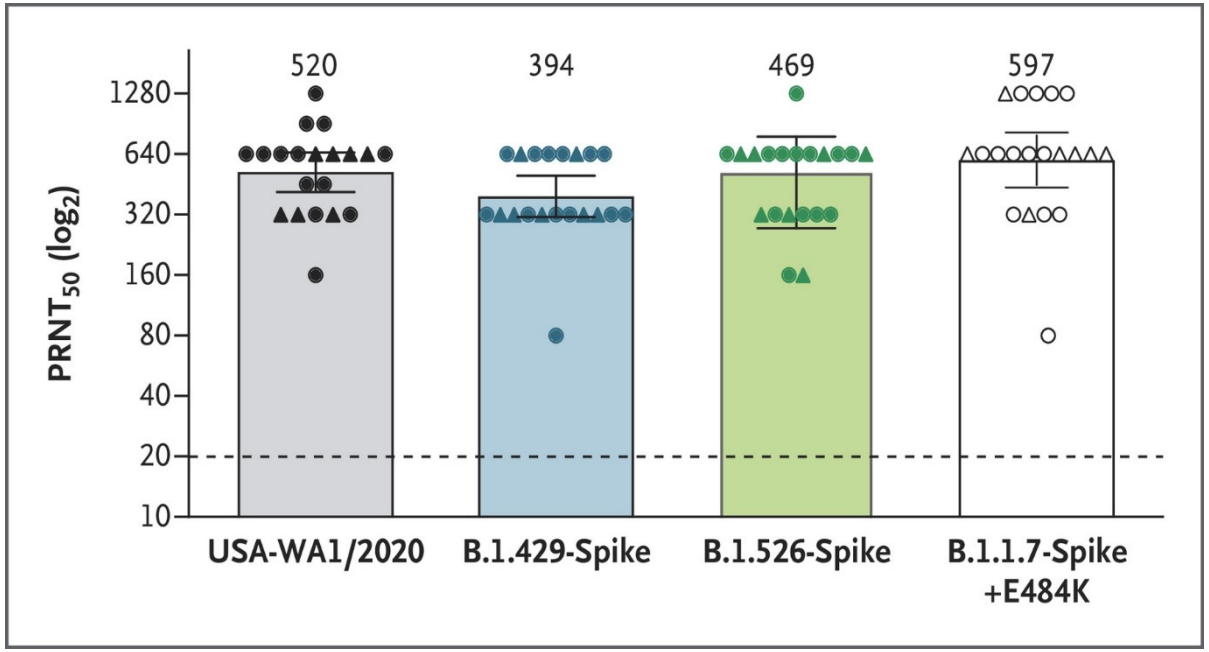
Tested serum neutralization of SARS-CoV-2 USA-WA1/2020 isolated in January 2020 and recent variants after administration of two doses of the Pfizer vaccine (BNT162b2)

50% plaque reduction neutralization testing (PRNT) showed that variants remain susceptible to neutralization, i.e., vaccination remains effective

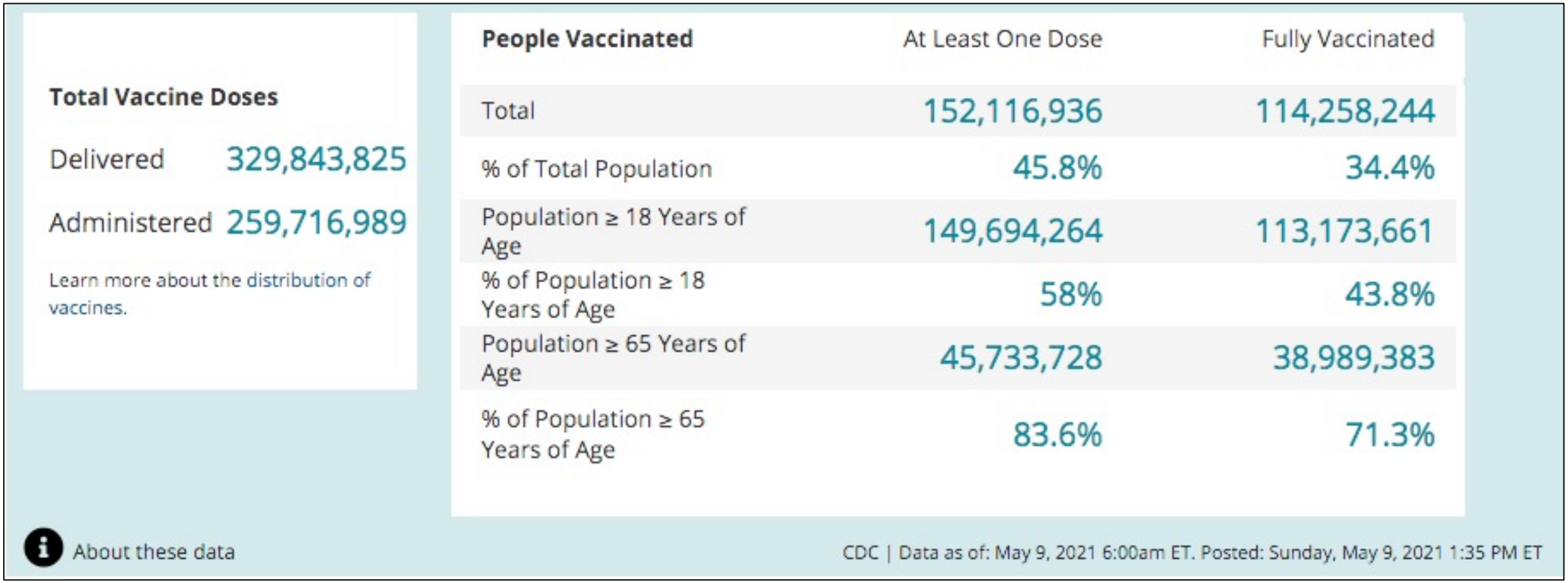
Y Liu et al, NEJM May 12, 2021

Watch this space: serum from Pfizer vaccinees about 67% less potent against B.1.617 variant, which is predominant in India, and has been detected in the US

M Hoffmann et al, bioRxiv, May 5, 2021



COVID-19 vaccinations in the US, as of May 9, 2021



Total Vaccine Doses

Delivered	329,843,825
Administered	259,716,989

Learn more about the distribution of vaccines.

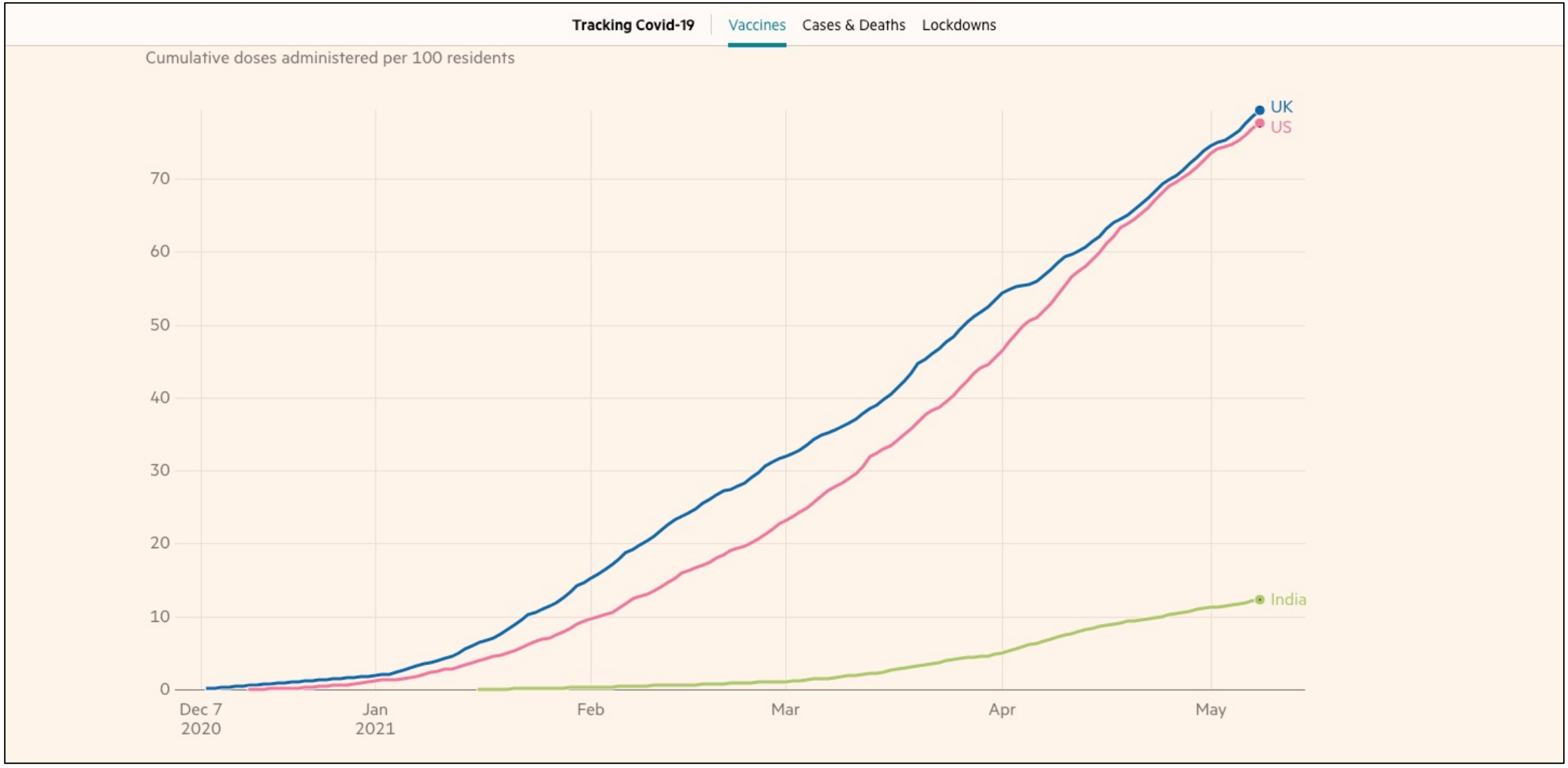
People Vaccinated	At Least One Dose	Fully Vaccinated
Total	152,116,936	114,258,244
% of Total Population	45.8%	34.4%
Population ≥ 18 Years of Age	149,694,264	113,173,661
% of Population ≥ 18 Years of Age	58%	43.8%
Population ≥ 65 Years of Age	45,733,728	38,989,383
% of Population ≥ 65 Years of Age	83.6%	71.3%

About these data

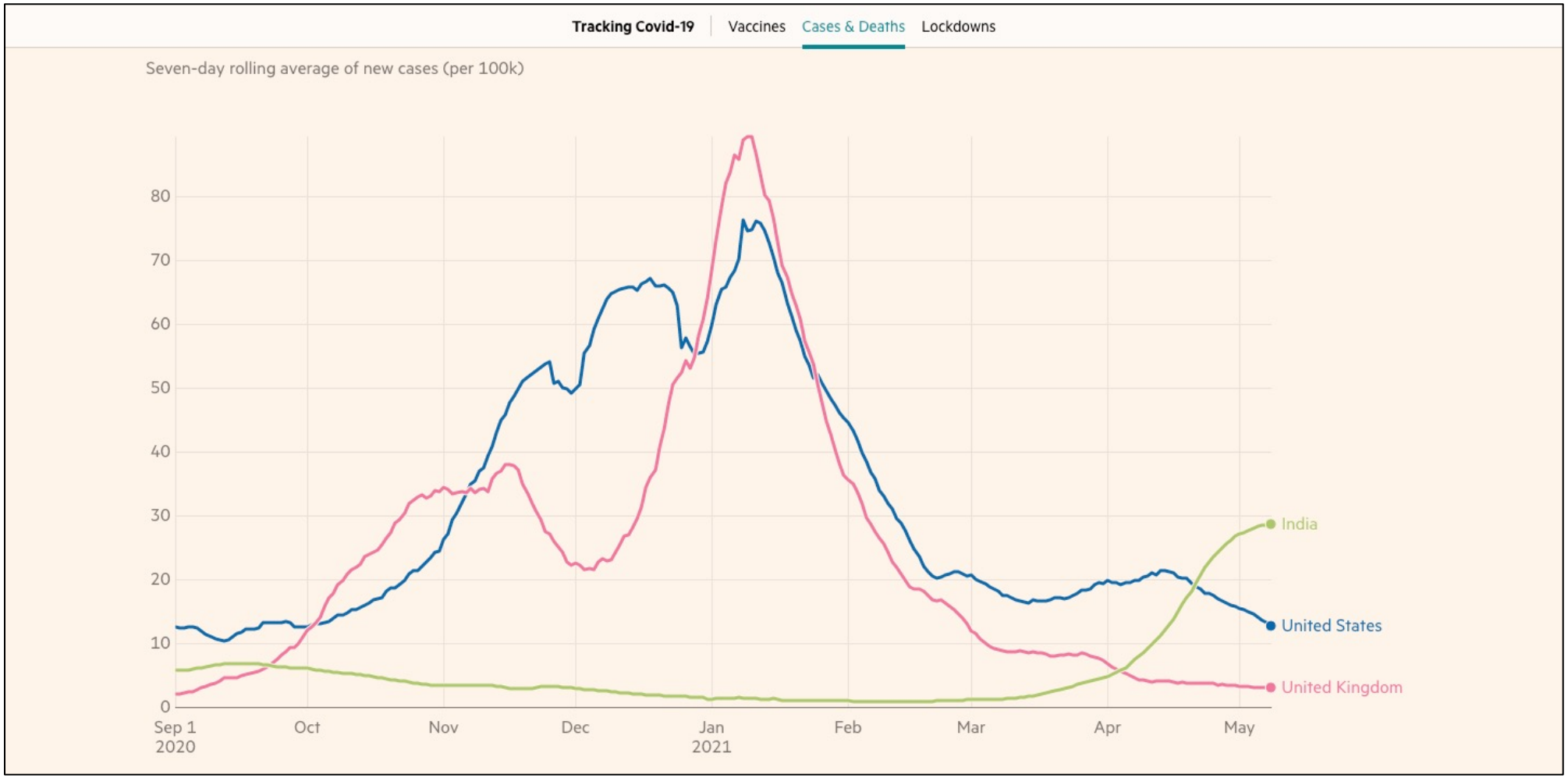
CDC | Data as of: May 9, 2021 6:00am ET. Posted: Sunday, May 9, 2021 1:35 PM ET

- Arkansas has administered 1.9 million doses, at 62,960 per 100K of population (currently ranked 48th of 50 states)
- 36.5% have received at least one dose, and 27.5% are fully vaccinated (VT, MA lead with 59% receiving at least one dose)
- 69.97% of distributed vaccines in Arkansas have been administered (ranked 47th – NM leads at 89.41%)

Cumulative vaccine doses given in the US, UK and India



Confirmed cases of COVID-19 in the US, UK, India, May 2021



Sharp increase in COVID-19 infection in India is a reflection of premature relaxation of social distancing, higher transmissibility of B.1.617 variant, and very poor vaccination rates

Key points

- Like SARS in 2002, SARS COV-2 (Covid-19) originated from zoonotic transmission in China
- Covid-19 has a lower mortality rate than SARS, but a much higher rate of mild/asymptomatic infection, so many cases may go undetected
- Covid-19 has a markedly higher R_0 than influenza (bad), but it also has a longer S_i than influenza (possibly good)
- Pre-symptomatic and asymptomatic transmission is probably a major contributor to spread
- Secondary attack rates are variable and context-dependent
- Case fatality rates are also variable, with some groups markedly more vulnerable than others
- The development of effective vaccines is a tremendous achievement, but impact will be limited by poor distribution in areas of greatest need, and vaccine hesitancy where it is available

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