

2020

Client Advisory
Board Meeting

COVID-19

Impacting mortality for those who don't even get the infection

The pandemic is causing deaths not directly associated with the virus

2020

Client Advisory
Board Meeting

TOPICS

COVID Mortality
Indirect Causes

Vaccines

Questions

Direct Cause

A person develops a COVID-19 infection and dies

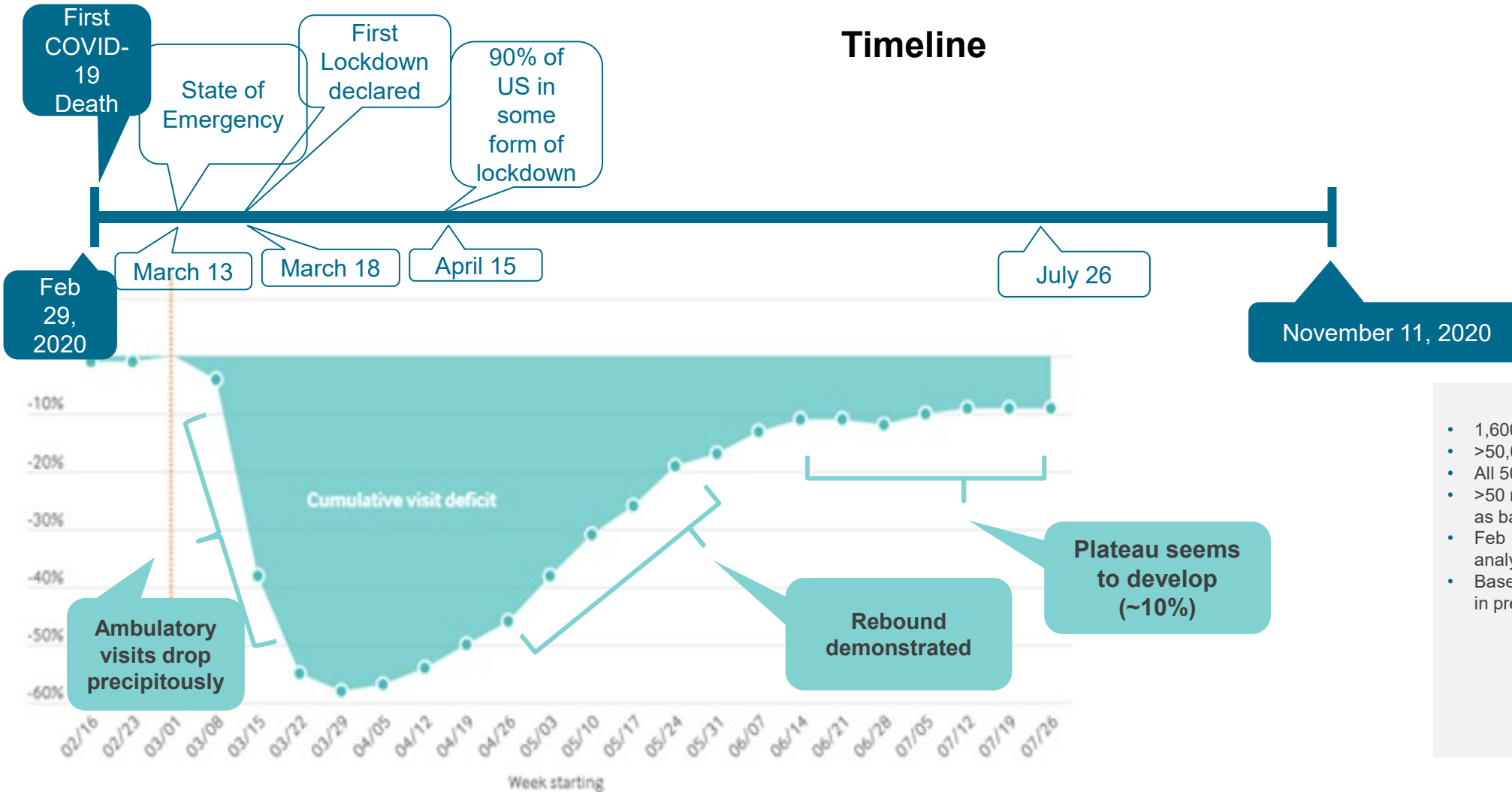
**Indirect Cause
(Lockdown
associated)**

A person dies during the COVID-19 pandemic
not by obtaining the infection but instead by
being impacted by the pandemic in another way

Today we will look at this “indirect cause” category

COVID-19 lockdown

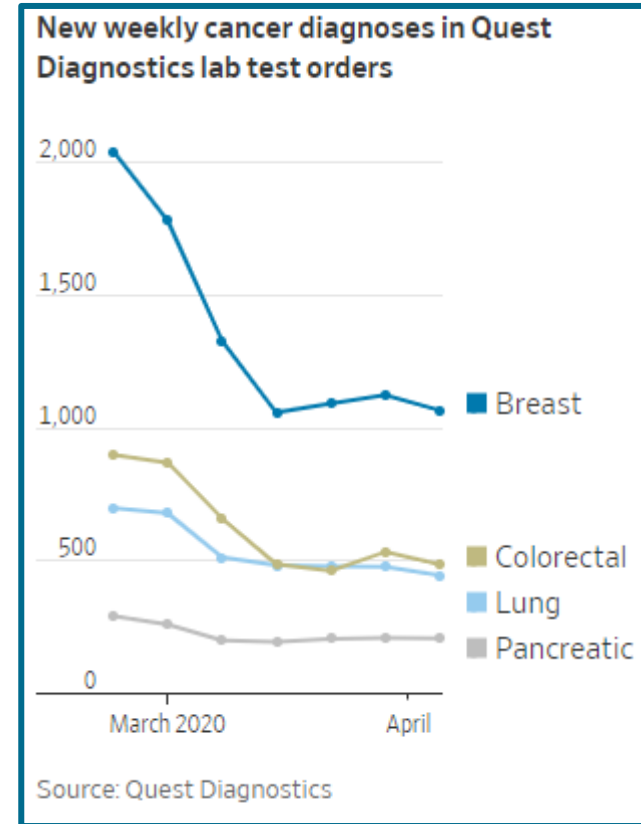
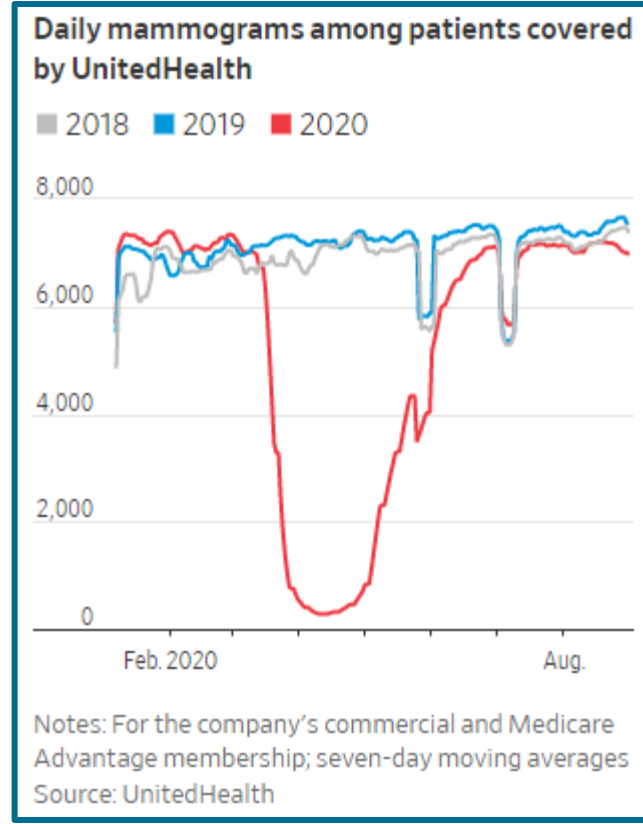
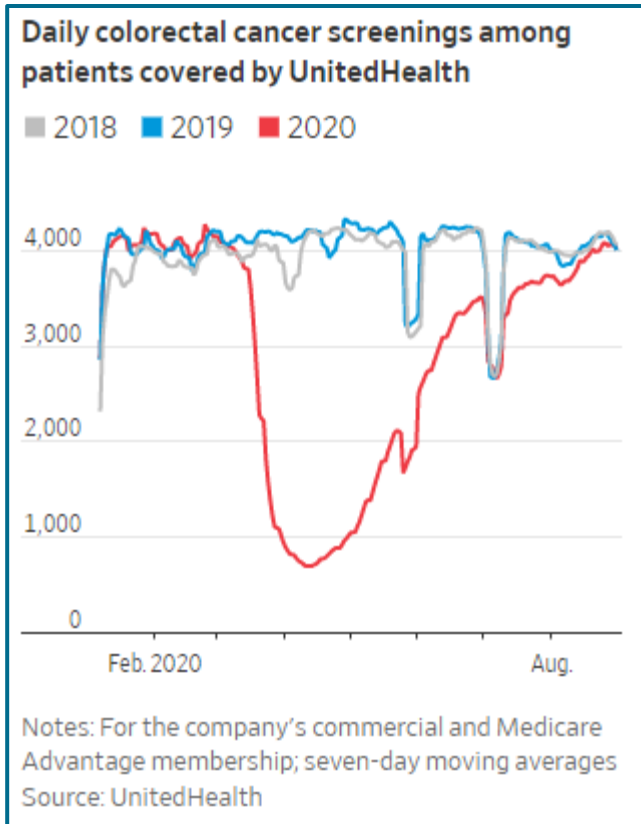
Defining the problem



- Key Methods/Findings**
- 1,600 provider organizations
 - >50,000 providers
 - All 50 states in the USA
 - >50 million outpatient visits per year as baseline
 - Feb 1, 2020 to Aug 1, 2020 analyzed
 - Baseline visits: Same time period in previous years
 - 47% -primary care physicians
 - 53% -25 other specialists

Mehrotra, A et al. The impact of the COVID-19 pandemic on outpatient visits: Changing patterns of care in the newest COVID-19 hotspots August 13th, 2020. The Commonwealth Fund. <https://www.commonwealthfund.org/publications/2020/aug/impact-covid-19-pandemic-outpatient-visits-changing-patterns-care-newest>

Dramatic drops in cancer screenings and new cancer dx



Mathews, A et al. Wall Street Journal Oct 15, 2020

The CDC's evaluation

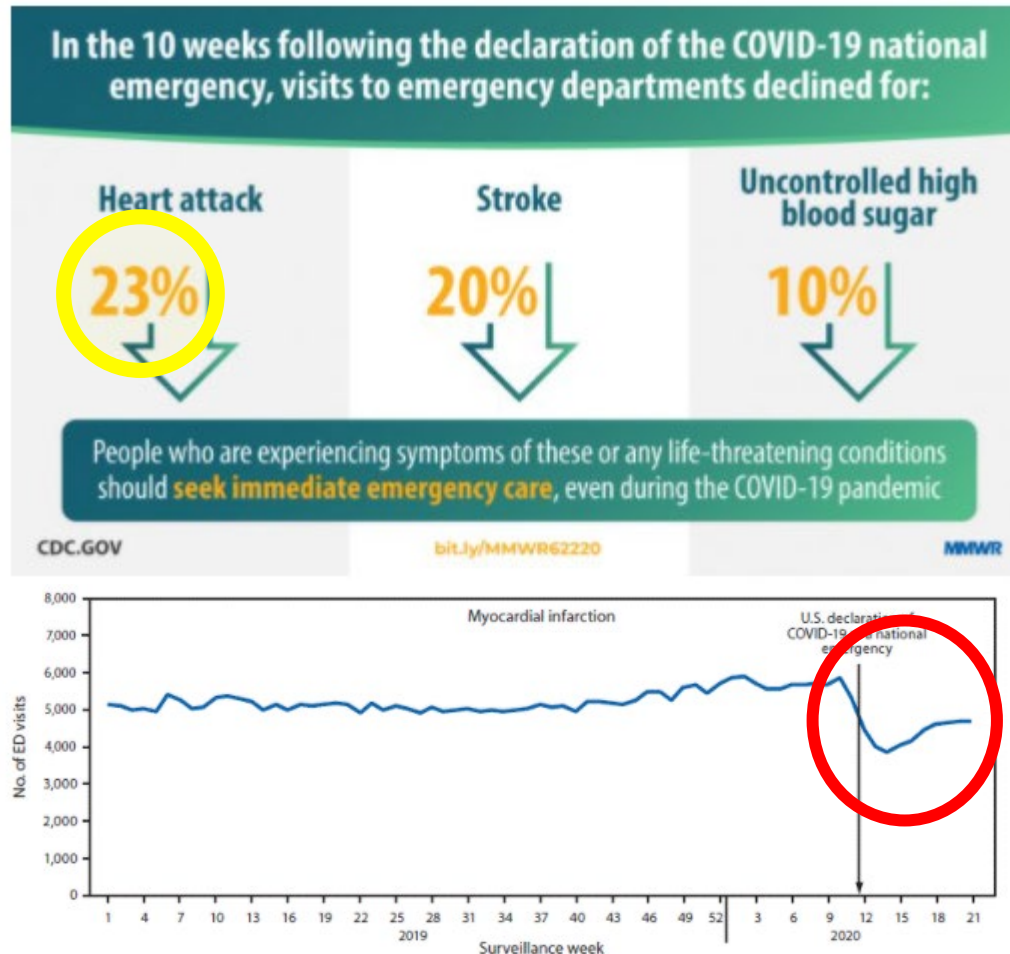


FIGURE 1. Number of emergency department (ED) visits for myocardial infarction, stroke, and hyperglycemic crisis* — National Syndromic Surveillance Program, United States, week 1, 2019–week 21, 2020†

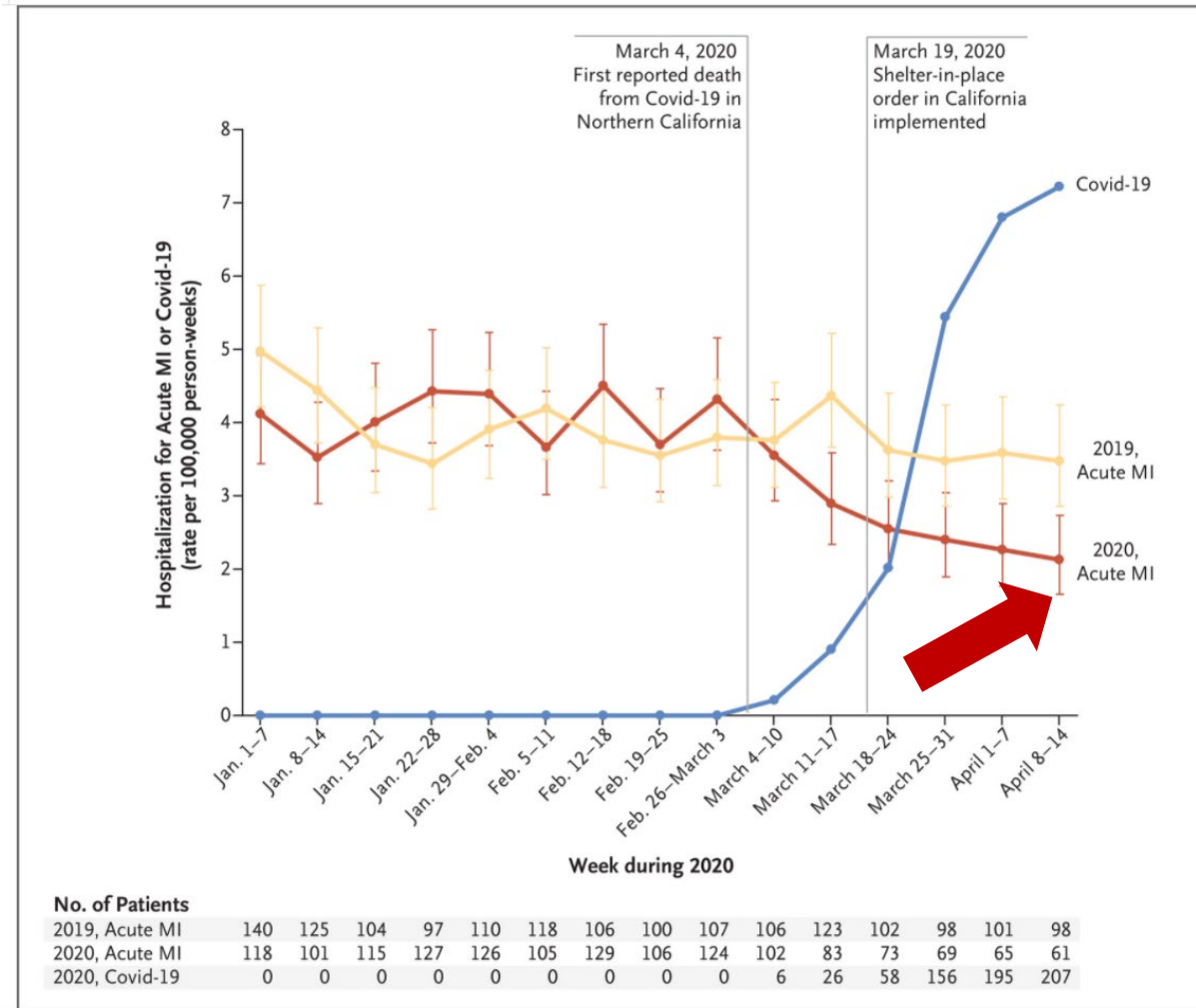
ER Visits:

- Data from the National Syndromic Surveillance Program (NSSP)
- Jan 1, 2019 to May 24, 2020
- This analysis covers 73% of all ED visits nationwide.
- The decrease in visits was most pronounced in the first 4 weeks of the pandemic and then partially rebounded the remainder of the time evaluated.

<https://www.cdc.gov/mmwr/volumes/69/wr/mm6925e2.htm>

Decreased hospitalizations for MIs

- NEJM article
- Data from 4.4 million insured persons in California (43 million person-weeks) – Kaiser Permanente Northern California.
- 1/1 through 4/14/20
- **48% reduction in hospitalizations for acute myocardial infarction** (~equal number of NSTEMI and STEMI).

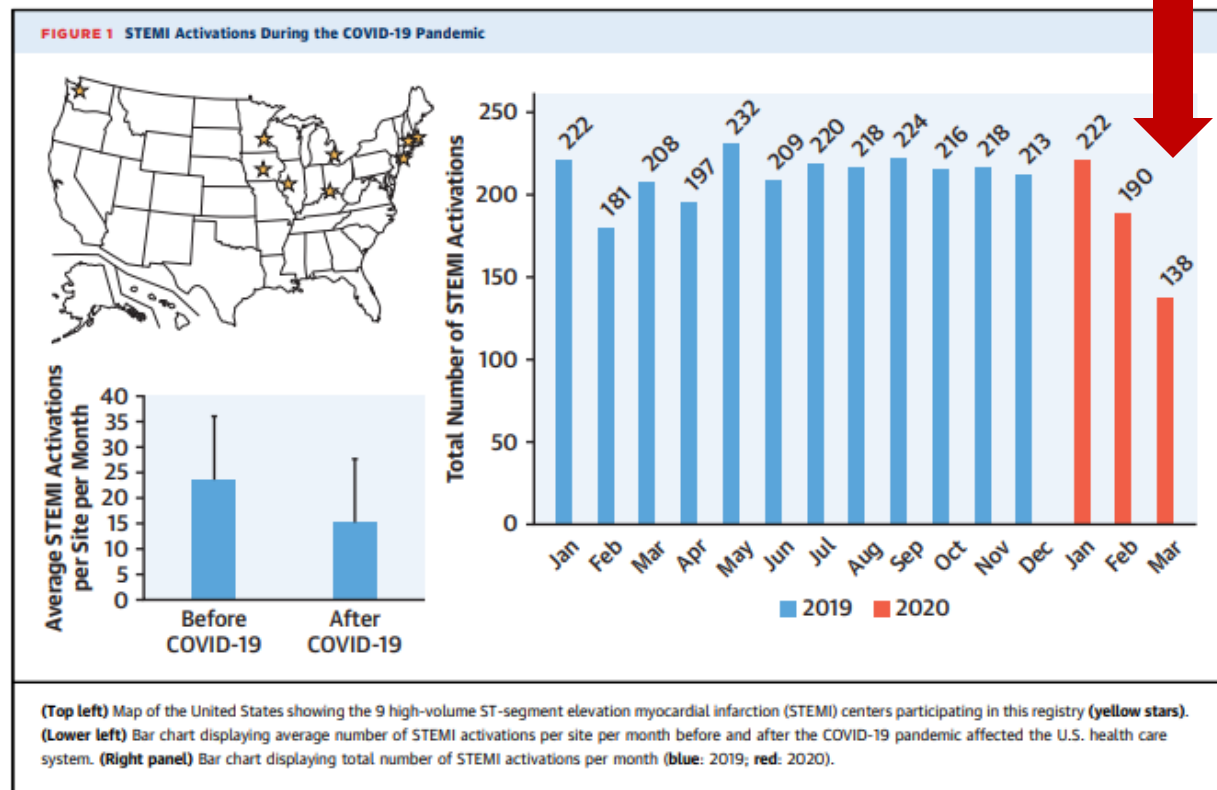


Solomen, M et al. Letter to the NEJM. Aug 113, 2020.

https://www.nejm.org/doi/10.1056/NEJMc2015630?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed

Reduction in cardiac catheterization treatment of ST-segment elevation MI

- PPCI is the standard of care for ST-segment elevation myocardial infarction (STEMI) patients.
- Study done in 9 high-volume cardiac catheterization labs in the US from 1/1/2019 to March 31, 2020.
- **38% reduction** in STEMI procedures during the first month of the lockdown.
- The authors comment on the **40% reduction** reported from Spain.



Note:

- Similar findings reported in a July 2020 study. March 2020 showed a **43% reduction in hospitalizations** for primary acute CV reasons.
- In-hospital mortality rates did not differ significantly from baseline trends.

• Garcia, S et al. Letter. Journal of the American College of Cardiology. Vol 75 No 22, June 2020 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151384/pdf/main.pdf>

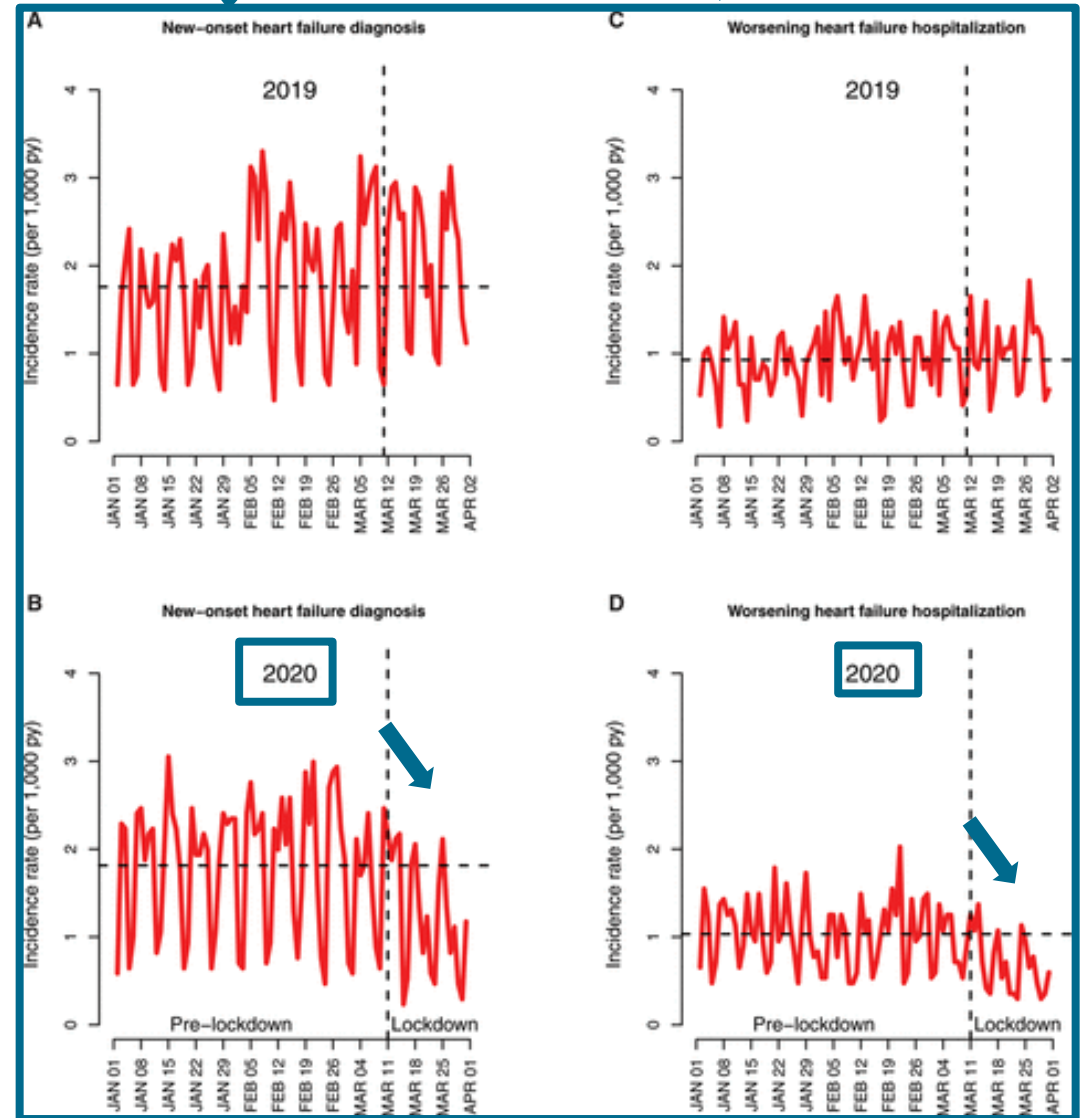
• Bhatt, A et al. J Am Coll Cardiol July 2020 Fewer hospitalizations for acute cardiovascular condition during the COVID-19 pandemic. <https://pubmed.ncbi.nlm.nih.gov/32470516/>

CHF admissions have dropped

New onset
CHF

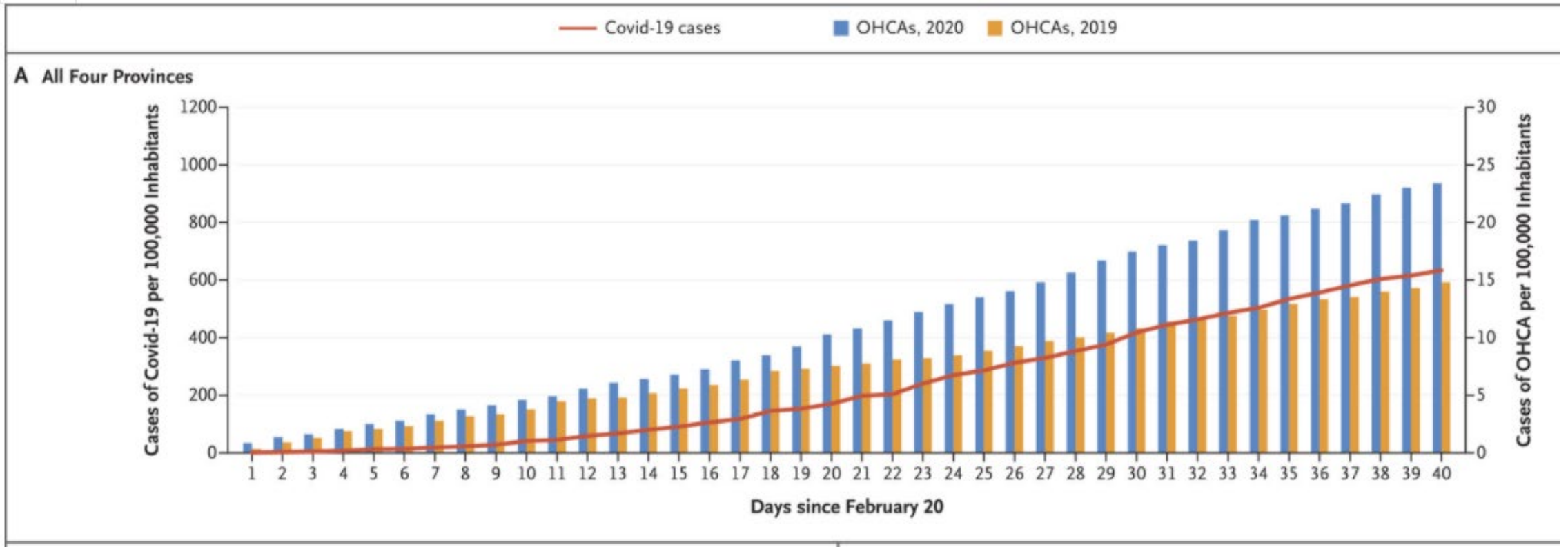
Worsening
CHF

- Evaluation of CHF admissions.
- Rates of new-onset CHF admissions dropped from 2.25 to 1.26 (per 1000 person-years)
 - **44% reduction**
- Rates of worsening CHF admissions dropped from 0.99 to 0.63
 - **36% reduction**



Andersson C. Circulation: Heart Failure. Incidence of New-Onset and Worsening Heart Failure Before and After the COVID-19 Epidemic Lockdown in Denmark, Volume: 13, Issue: 6, DOI: (10.1161/CIRCHEARTFAILURE.120.007274)

Out-of-hospital cardiac arrests



July 2020 NEJM article

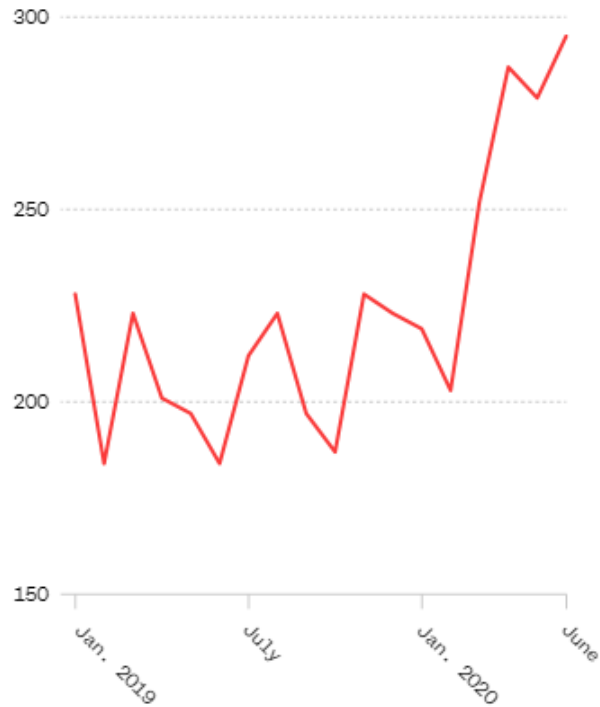
- A 58% increase in out of hospital cardiac arrests were seen
- (362 vs 229)
- **An increase of ~10 cases per 100,000**

Baldi, E et al. Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy. July 30, 20 NEJM.

Out-of-hospital cardiac arrests

Dead on arrival calls in Houston

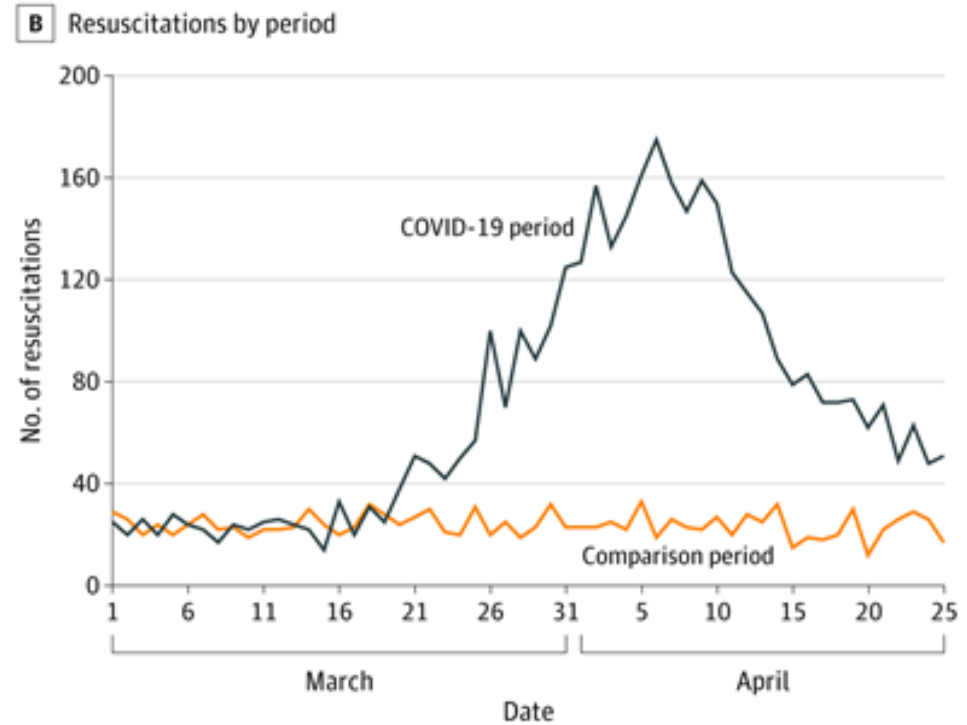
Houston has seen a spike in the number of people dying of cardiac arrest before paramedics can reach them.



Source: Houston Fire Department
Graphic: Robin Muccari / NBC News

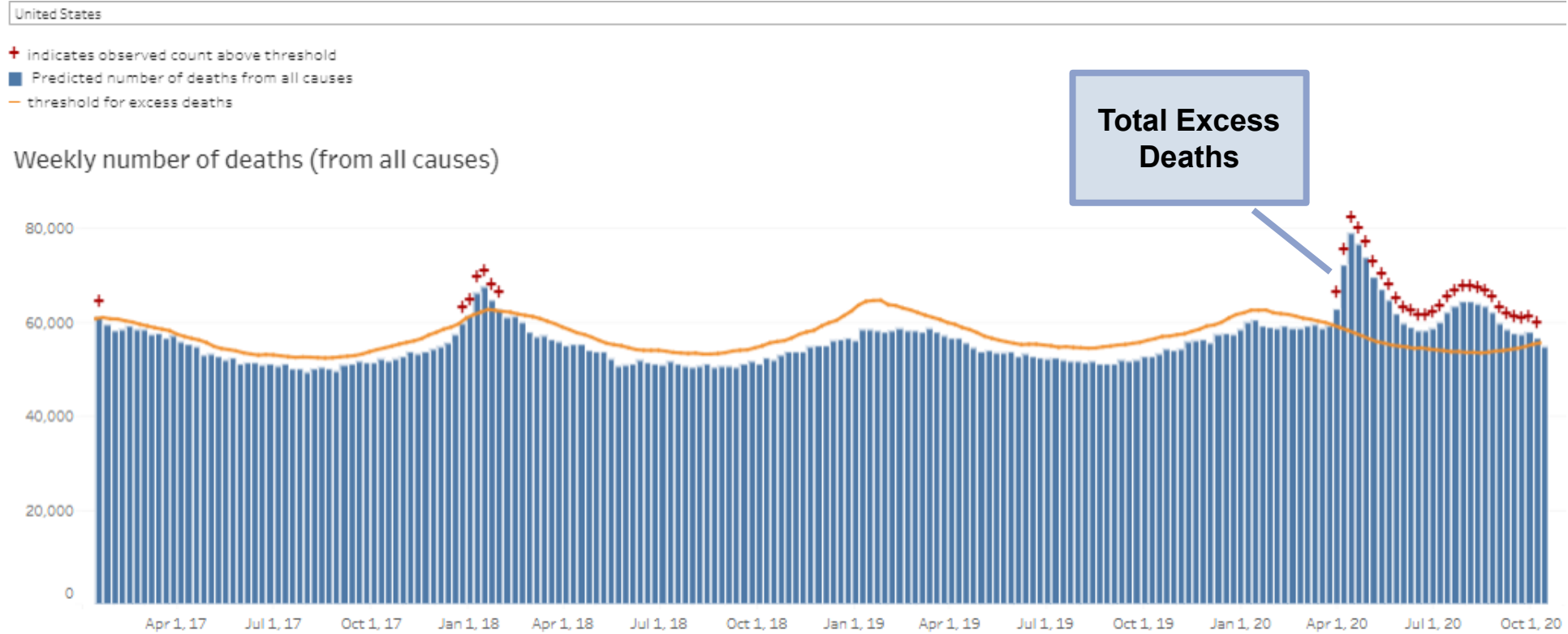
<https://www.propublica.org/article/a-spike-in-people-dying-at-home-suggests-coronavirus-deaths-in-houston-may-be-higher-than-reported>

Figure. New York City Out-of-Hospital Nontraumatic Cardiac Arrest Resuscitations, March 1 through April 25, 2020



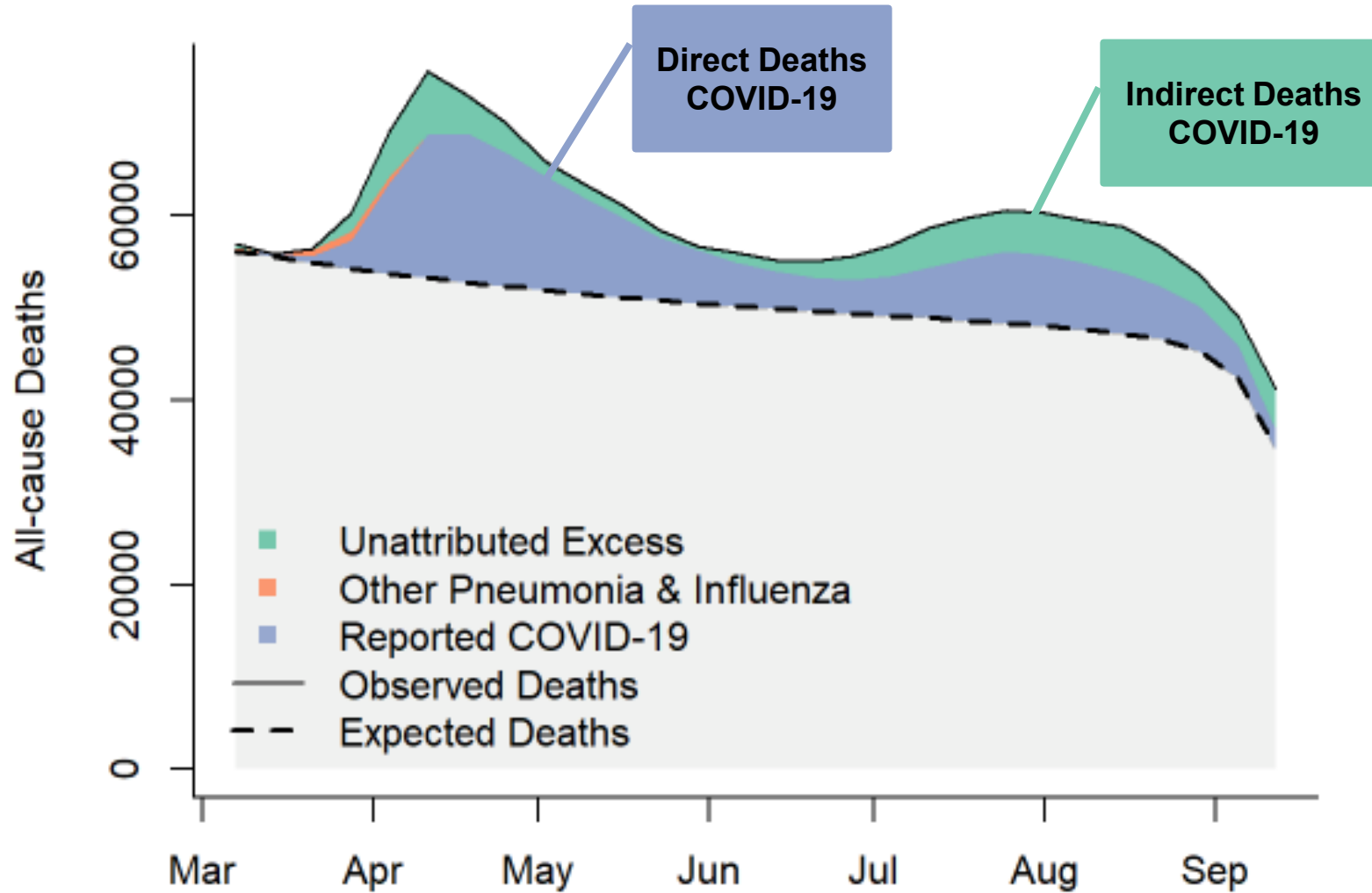
<https://jamanetwork.com/journals/jamacardiology/fullarticle/2767649>

Excess deaths



CDC DATA: https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm#dashboard

Excess deaths



Weinberger, D et al. 9/25/2020. Estimating the early death toll of COVID-19 in the United States. https://weinbergerlab.github.io/excess_pi_covid/.

Excess deaths caused by indirect causes quantified

Table. Excess Deaths From March 1, 2020, to August 1, 2020, US and Selected States

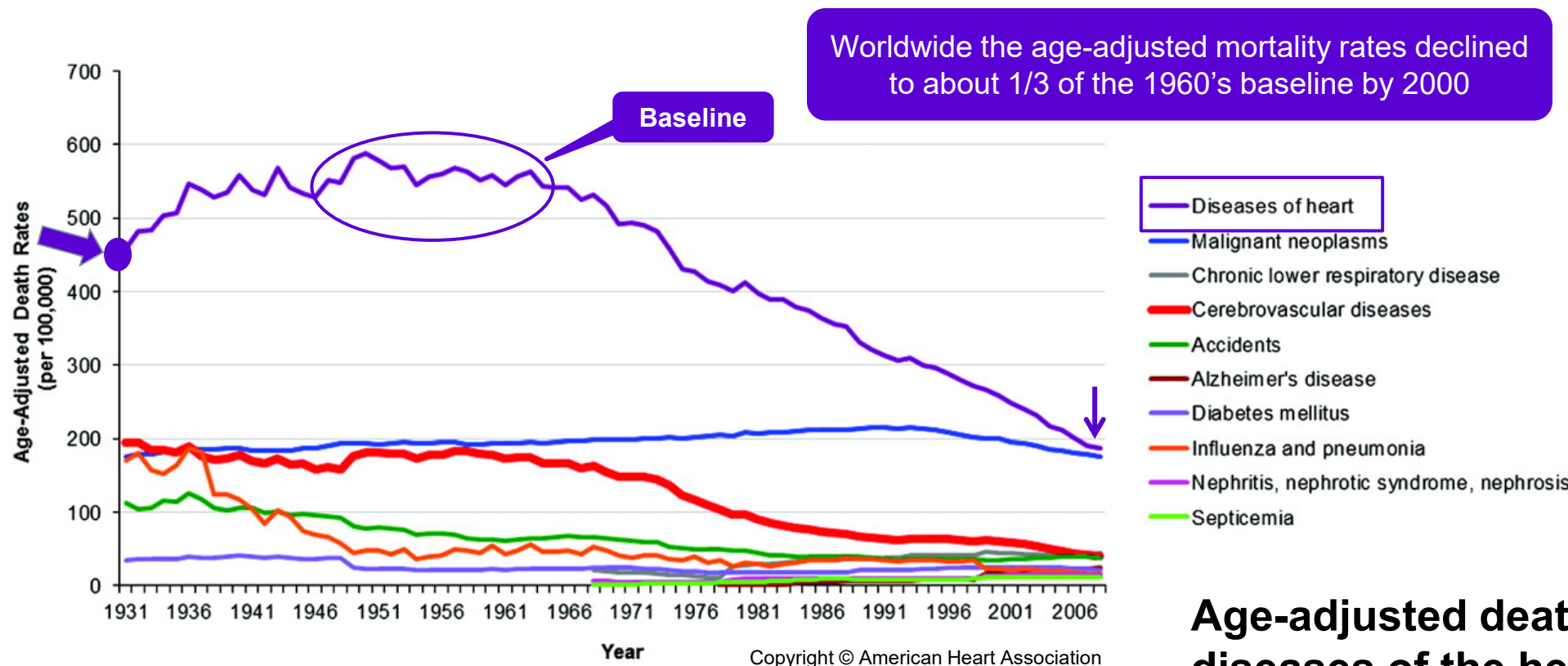
Jurisdiction	Expected deaths (95% CI) ^a	Observed deaths (ratio of observed/expected)	Excess deaths	Mortality rate per 100 000 population	COVID-19 deaths ^b	Excess deaths attributed to COVID-19, % ^b
			No. (95% CI)			
United States ^c	1 111 031 (1 110 364-1 111 697)	1 336 561 (1.20)	225 530 (224 864 to 226 197)	72	150 541	67

Of the 225 530 excess deaths, 150 541 (67%) were attributed to COVID-19.

- Analyses revealed an increase in deaths attributed to causes other than COVID-19, with 2 reaching statistical significance.
- US mortality rates for heart disease
- Mortality rates for Alzheimer disease/ dementia

Woolf, S et al. Excess deaths from COVID-19 and other causes. March-July 2020. Research letter. JAMA Oct 20, 2020

Temporal trends in age-adjusted death rates for the top 10 causes of death in the US from 1931 to 2008



Towfighi A , and Saver J L Stroke 2011;42:2351-2355

Age-adjusted death rate diseases of the heart

- 1950: 588.8 per 100,000
- 2017: 165 per 100,000

<https://www.cdc.gov/nchs/data/hus/2018/005.pdf> from this site:
https://www.cdc.gov/nchs/contents2018.htm?search=Heart_disease, Trend tables

Quantifying the factors decreasing CV mortality during the last few decades

Mensah et al

- Mensah et al describe the findings of Ford et al who used a validated statistical model (IMPACT Coronary heart disease model) to evaluate the decline in CHD mortality rate from 1980-2000.
- Evaluated the impact of smoking, high BP, elevated T.C., obesity, DM, physical activity, established medical and surgical interventions for CHD.

Evidence-based medical and surgical treatments	
11%	Secondary preventative therapies after MI
10%	MI/angina treatment (initial tx)
9%	CHF treatment
5%	Revascularization for chronic angina
12%	Other
47%	TOTAL
Risk Factor Reduction	
24%	Cholesterol reduction
20%	BP reduction
12%	Smoking reduction
5%	Physical Activity Improvement
-7%	BMI
-10%	DM prevalence
44%	TOTAL

Mensah, G et al. Decline in Cardiovascular Mortality: Possible Causes and Implications. Circ Res. 2017.

Ford et al

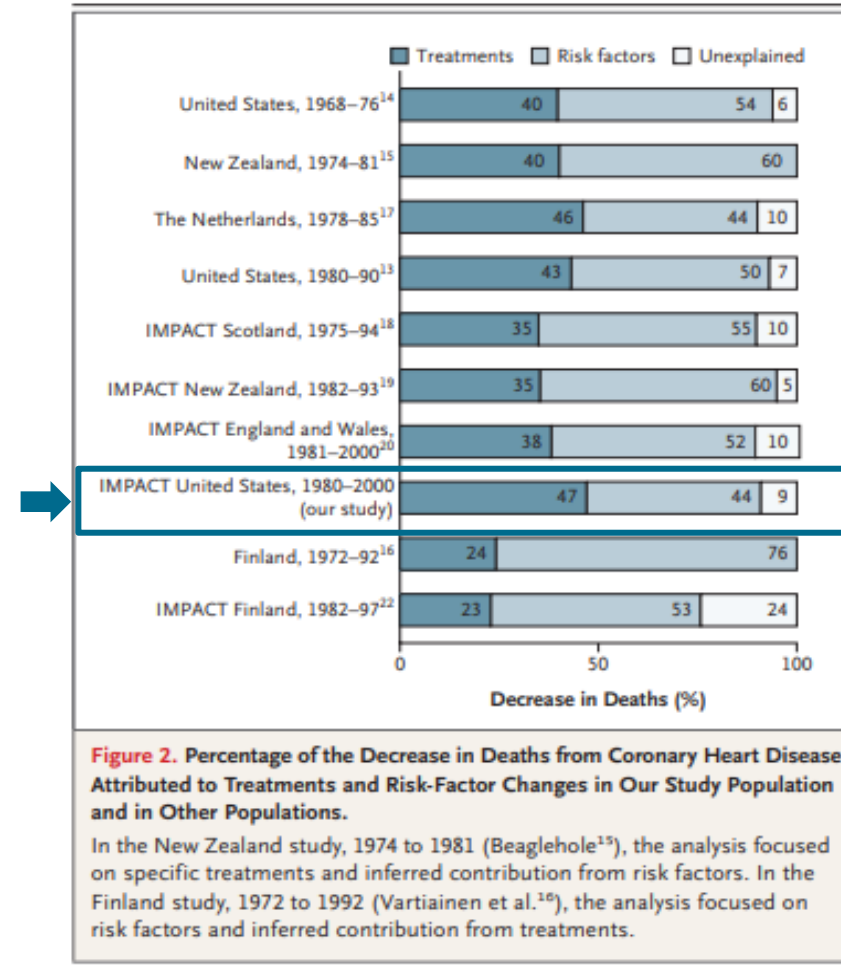


Chart taken from Ford E. et al. NEJM 2007. Explaining the decrease in U.S. deaths from coronary disease. 1980-2000

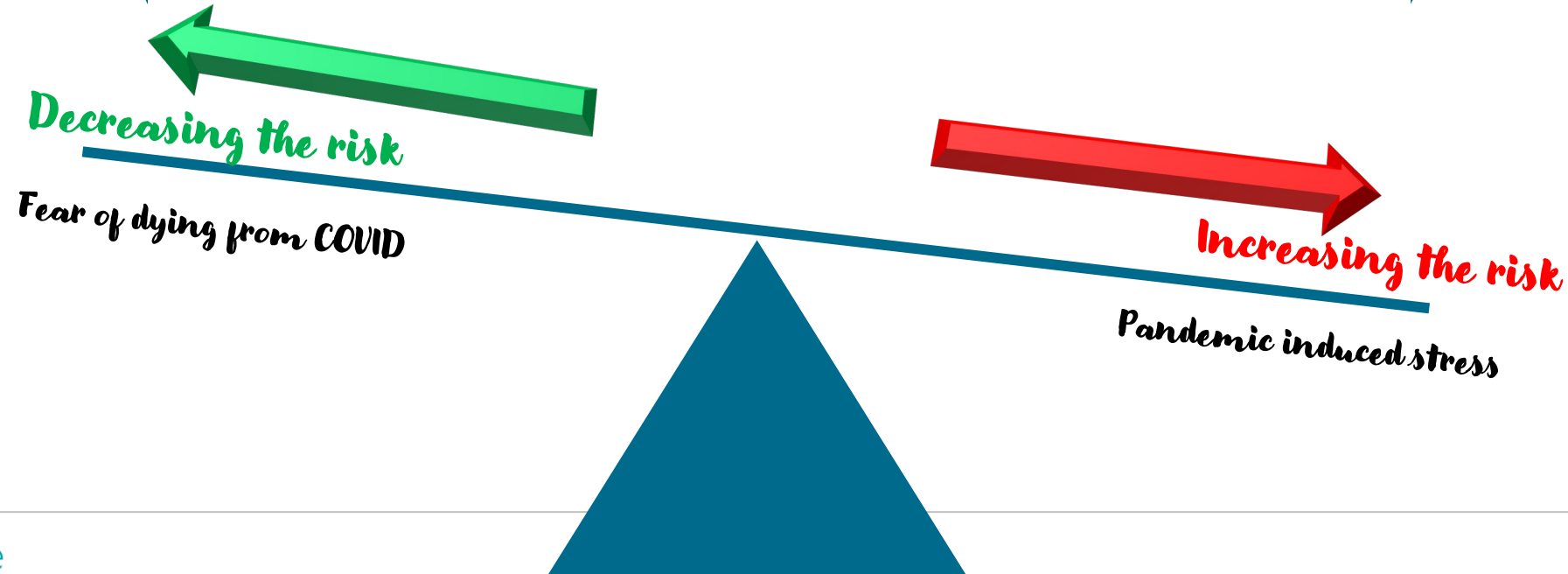
Risk factors during COVID-19

Smoking
Food Intake
BMI Control

Physical Activity
Compliance with medication

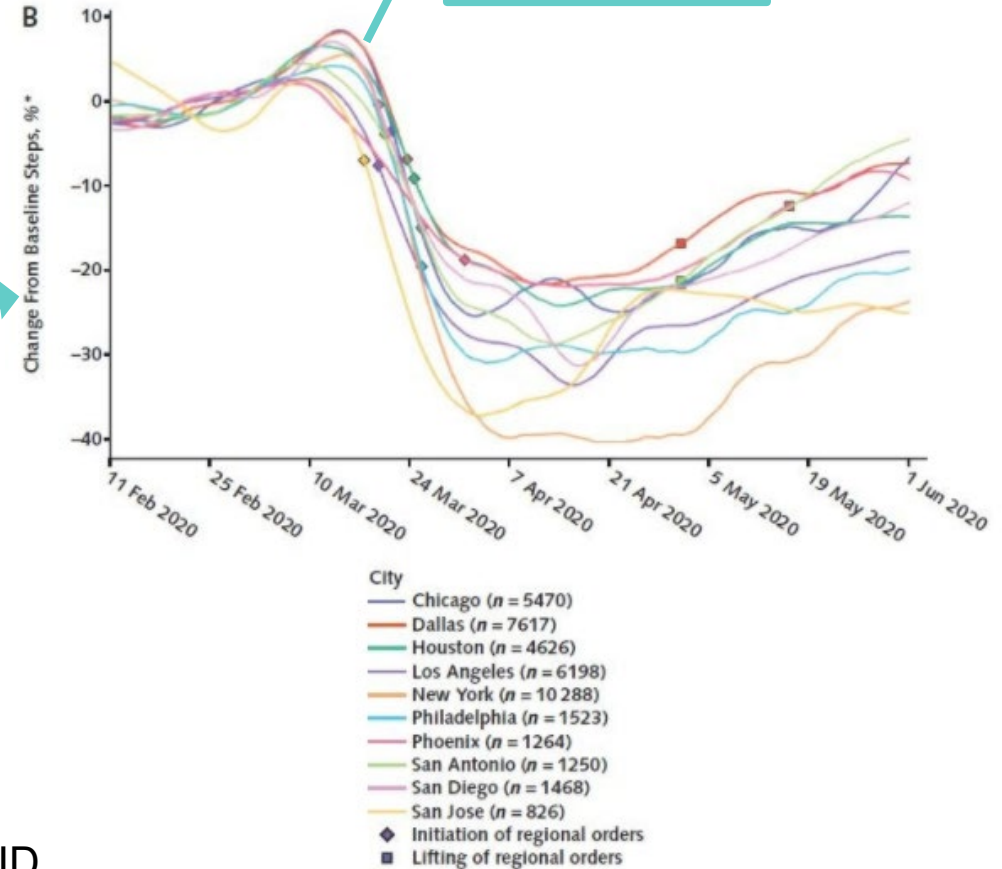
Obtaining Preventative Care
Seeking prompt care for urgent or emergent conditions

Everyone is faced with two opposing forces



Physical activity (PA) during COVID-19

- A June 2020 study published in the Annals of Internal Medicine which monitored step counts globally by use of a smartphone app impacting 455,404 unique users showed:
 - 27.3% decrease in steps within 30 days of the lockdown worldwide.
- US data demonstrated in the chart
- There was a wide variation in impact.
 - 48.7%: Italy
 - 6.9%: Sweden



In a smaller (n=431) self reporting type study focusing on fitness apps in the US:

- 18.2% decrease in physical activity METS.

In a smaller UK study of the initial lockdown in the UK:

- 37% reduction in weekly minutes of exercise was observed.
- 63% of people decreased their level of activity from pre-COVID to the first full week of lockdown.

- Tison, G et al. Worldwide effect of COVID-19 on physical activity: a descriptive study June 2020 Annals of Internal Medicine
- Yang, Y. et al. Determinants of physical activity maintenance during the COVID-19 pandemic: a focus on fitness apps. Translational Behavioral Medicine . August 2020
- McCarthy, H. Physical activity behavior before, during and after COVID-19 restrictions: IE longitudinal smartphone tracking study of 5395 UK adult Journal of medical Internet research August 2020

- There has been an improvement of 424/100,000 since 1950.
 - 589 to 165 which is 424 improved or a 72% improvement in mortality.
- 647,457 people died in 2017 secondary to heart disease in the US
- US population in 2019: 328.2 million

Medical and surgical treatment improvements

Evidence-based medical and surgical treatments		Change in deaths/100k	Lockdown ("Immediate phase") reaction lasting 4-6 weeks)	Post-lockdown I ("Transition phase") first 3 months that followed the lockdown)	First 5 months deaths/100k	Post-lockdown II ("Active phase") subsequent months and prior to a significant decrease in COVID cases)	Subsequent quarters
11%	Secondary Preventative therapies after MI	47	~40% reduction in treatment impact (1.6 deaths/mo x 2 = 3.2 deaths)	~10% reduction in treatment impact (0.4 deaths/mo x 3 = 1.2 deaths)	4.4	~2-4% reduction	.08 - .16 deaths/mo (0.24 - 0.48 deaths per 3 months)
10%	MI/Angina treatment (initial treatment)	42	~40% reduction in treatment impact (1.4 deaths/mo x 2 = 2.8 deaths)	~10% reduction in treatment impact (0.35 deaths/mo x 3 = 1.05 deaths)	3.85	~2-4% reduction	.035 - .07 deaths/mo (0.11 - 0.22 deaths per 3 months)
9%	CHF treatment	38	~40% reduction in treatment impact (1.28 deaths/mo x 2 = 2.56 deaths)	~10% reduction in treatment impact (0.32 deaths/mo x 3 = 0.96 deaths)	3.52	~2-4% reduction	.032 - .065 (0.092 - 0.2 deaths per 3 months)
5%	Revascularization for chronic angina	21	~40% reduction in treatment impact (0.7 deaths/mo x 2 = 1.4 deaths)	~10% reduction in treatment impact (0.18 deaths/mo x 3 = 0.54 deaths)	1.94	~2-4% reduction	.018 - .036 (0.05 - 0.10 deaths per 3 months)
12%	Other	51	No clear pattern	No clear pattern	-	No clear pattern	-
47%	TOTAL	199			12.86/100k 42,180 deaths		~0.5 - 1.0 deaths/100k 1,640 - 3,280 deaths per quarter

Risk factor reduction

Risk factor reduction		Change in deaths/100k	Lockdown ("Immediate phase") reaction lasting 6-8 weeks)	Post-lockdown I ("Transition phase") first 3 months that followed the lockdown)	First 5 months deaths/100k	Post-lockdown II ("Active phase") subsequent months and prior to a significant decrease in COVID cases)	Subsequent quarters
24%	Cholesterol reduction	102	10% reduction in effective dx and tx (0.85 deaths/mo x 2 = 1.7 deaths)	5% reduction in effective dx and tx (0.425 deaths/mo x 3 = 1.275 deaths)	2.975	2% (0.17 mo x 3 = 0.5 deaths)	0.5 q 3 months
20%	BP reduction	85	10% reduction in effective dx. and tx (0.7 deaths/mo x 2 = 1.4)	5% reduction in effective dx and tx 0.35 deaths/mo x 3 = 1.05	2.45	2% (0.14 mo x 3 = 0.42 deaths)	0.42 q 3 months
12%	Smoking reduction	51	No clear pattern	~2% increase in smoking 0.085 deaths/mo x 3 = 0.26	0.26	No clear pattern	-
5%	Physical Activity Improvement	21	~30% reduction in effective PA (0.53 deaths/mo x 2 = 1.06)	~7% reduction in effective PA (0.12 deaths/mo x 3 = 0.36 deaths)	1.42	No clear pattern	-
-7%	BMI	-30	No clear pattern	No clear pattern	-	No clear pattern	-
-10%	DM prevalence	-42	No clear pattern	No clear pattern	-	No clear pattern	-
44%	TOTAL	187			6.871/100k 22,500 deaths		~0.92/100k 3,017 deaths per quarter

- There has been an improvement of 424/100,000 since 1950.
- 589 to 165 which is 424 improved or a 72% improvement in mortality.
- 647,457 people died in 2017 secondary to heart disease in US
- US population in 2019: 328.2 million

Risk factor reduction

Based upon this IMPACT model and the assumptions as illustrated:

- Deaths seen thus far (first 5 months):
 - Cardiovascular type deaths accounted for 64,680 of the 74,989 excess indirect deaths.
- Future CV deaths (Based upon these estimates):
 - Each subsequent quarter might have an additional 4,657- 6,297 deaths per quarter.
 - Annualized this would be ~ 19,000 to 25,000 excessive CV deaths
 - This is a 3-4% increase in the total CV deaths typically seen in the USA.

Cancer & COVID-19: COVID-19 related issues impacting mortality

HealthCare services availability:

- Impacted services:
 - Cancer screening decreased
 - Cancer-like symptoms ignored with a delay in cancer diagnosis
 - Cancer treatment delayed/disrupted
 - Post treatment surveillance impacted
- Contributing factors:
 - Healthcare providers, government, and media guidance on avoiding exposure to COVID-19 by limiting access to non-essential services
 - Public fear of obtaining the novel virus
 - Oncology and primary care doctor availability/access decreased secondary to an increased pace of physicians retiring during the pandemic.
 - Economic downturn with decreased third-party healthcare insurance availability or increased amount of perceived personal cost.

Scientific advances:

- Delay in cancer diagnosis and treatment advances secondary to physician/scientist's diversion to COVID-19 related research activities.

Increased cancer risk:

- Modifiable risk factors associated with increased cancer risk increased (e.g. smoking, alcohol abuse, weight gain, limited physical activity).

20 survey of America's physicians COVID-19 Impact Edition. Survey completed Aug 2020. The Physician's Foundation. www.physiciansfoundation.org

Delay in cancer discovery and initiation of treatment

Cancer diagnosis and treatment delays can significantly impact survival.

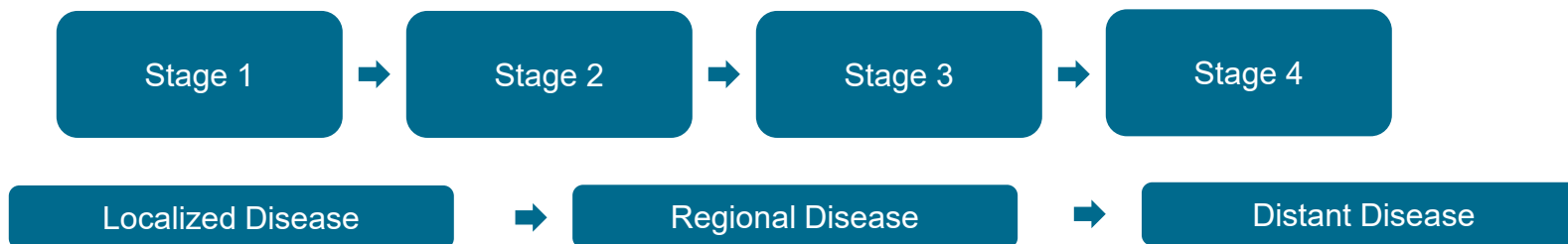
Cancers of different organs have different “doubling times” and even cancers initiating in the same organ can have significantly different rates of growth

- Breast cancer as an example:
 - Triple negative breast cancers (~10-15% of all breast cancers) typically grows at a much faster rate than hormone positive, HER2 negative breast cancers.
 - 5-year survival drops precipitously from 91% for localized disease to 65% for regional spread and 11% for distant spread.

The prognosis of cancer cases is typically impacted by the stage of the cancer.

- Localized cancers tend to do better than regionally advanced cancers which do better than metastatic cancers.

Delays in diagnosis and treatment can result in a cancer progressing from a lower stage to a more advanced stage, thus impacting survival.



<https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/types-of-breast-cancer/triple-negative.html>
<https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/types-of-breast-cancer/triple-negative.html>

Excess cancer-related deaths during the COVID-19 pandemic

Source	Percentage increase in deaths	Observations/Assumptions
Sharpless	1% in breast and colon cancer deaths/10 years	<ul style="list-style-type: none"> All activities return to normal 6 months after lockdown Decreased screening as well as delayed dx. and tx. Evaluation of screening cancers only
Maringue	7.9%-9.6% Breast 15-16% Colorectal 5-6% Lung 5-6% Esophageal 5-year mortality data.	<ul style="list-style-type: none"> 90% decrease in endoscopies in April Services restarted by June but at reduced capacities Services impacted for the foreseeable future. Increase in telemedicine. 45-66% reduction in admissions for chemotherapy and 70-89% reduction in urgent referrals for cancer diagnosis Analysis included only newly diagnosed cancers but included death from cancer or COVID-19 Used a previously published model based on different proportion of the population affected by the emergency (PAE) and relative impact of the emergency (RIE) “at this continued level”
Lai	5-6% increase in deaths among those with cancer in the United States/1 year.	<ul style="list-style-type: none"> Based upon a procedural model evaluating upstage mortality Advanced cancer at the time of discovery increased from 26% (0-3 months) to 29% (7-12 months) and then 33% (>12 months)
Ricciardeiello	12% increase in colorectal mortality if colon cancer dx. is delayed beyond 12 months.	

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Vaccines

Questions

COVID-19 vaccines

- More than 150 COVID-19 vaccine candidates are under development
- Quick distribution of the genetic code for the virus
- Many companies had a head start by previously working on SARS/MERS vaccines
- ~50 vaccine candidates are in clinical trials
- Typically it takes years....the fastest vaccine to market was for mumps (4 years)
- China and Russia have approved vaccines without waiting for phase 3 trials.
- 4 vaccine candidates are in phase 3 clinical trials in the US 30,000 – 60,000 volunteers in each trial. Double-blinded.
- Safety and efficacy are being evaluated. Earlier results from phase I/II studies were favorable.

Vaccine technology platforms			
Non-replicating viral vector	RNA-based	Inactivated Virus (Hepatitis A; Flu; Polio; Rabies)	Protein Subunit
DNA-based	Replicating viral vector	Virus-like particles (Hib; Hepatitis B; HPV; Whooping cough; Pneumococcal; Shingles)	Live attenuated virus (MMR; rotavirus; smallpox; yellow fever)

- WHO: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines>
- NY Times. Vaccine Tracker <https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html>

COVID-19 vaccines in Operation Warp Speed development



mRNA

mRNA



■ **mRNA:** rapid manufacturing facilitating efficient move to clinic, highly immunogenic



Adenovirus vector

Adenovirus vector



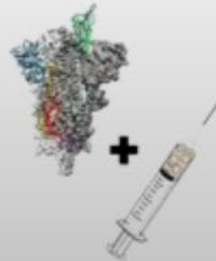
■ **Adenovirus:** rapid manufacturing facilitating efficient move to clinic, vaccine using this platform is approved in Europe



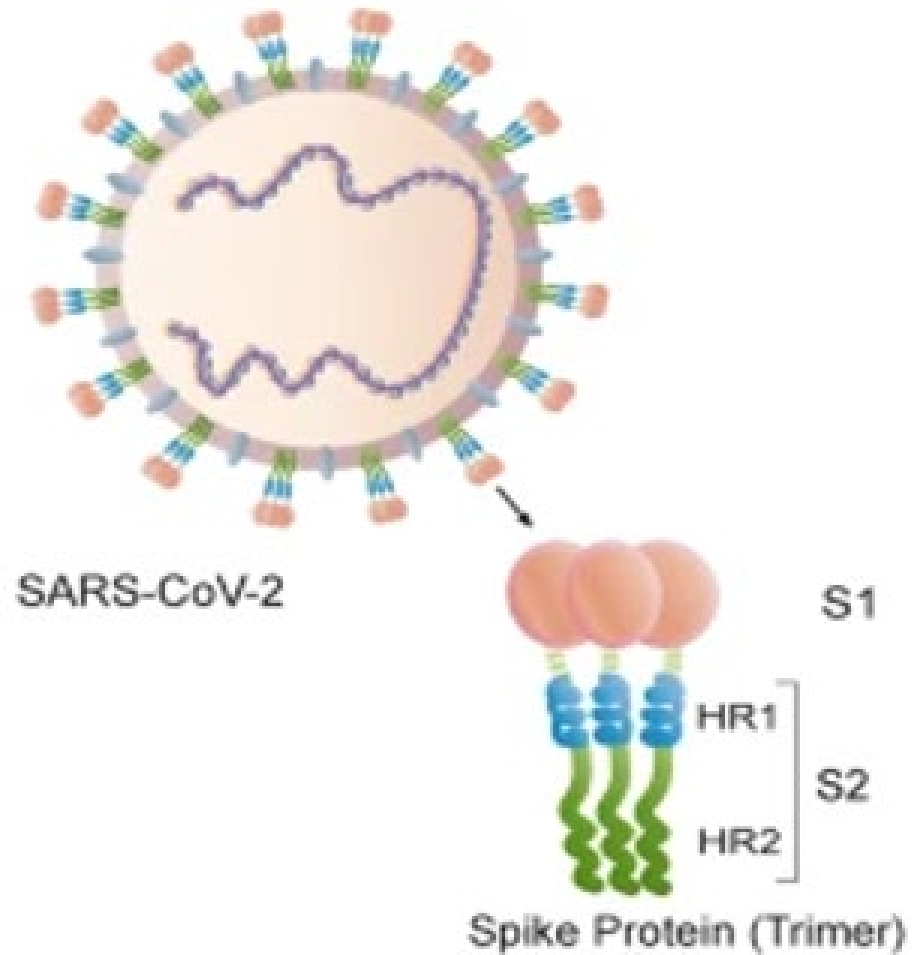
Recombinant protein + adjuvant



Recombinant protein + adjuvant

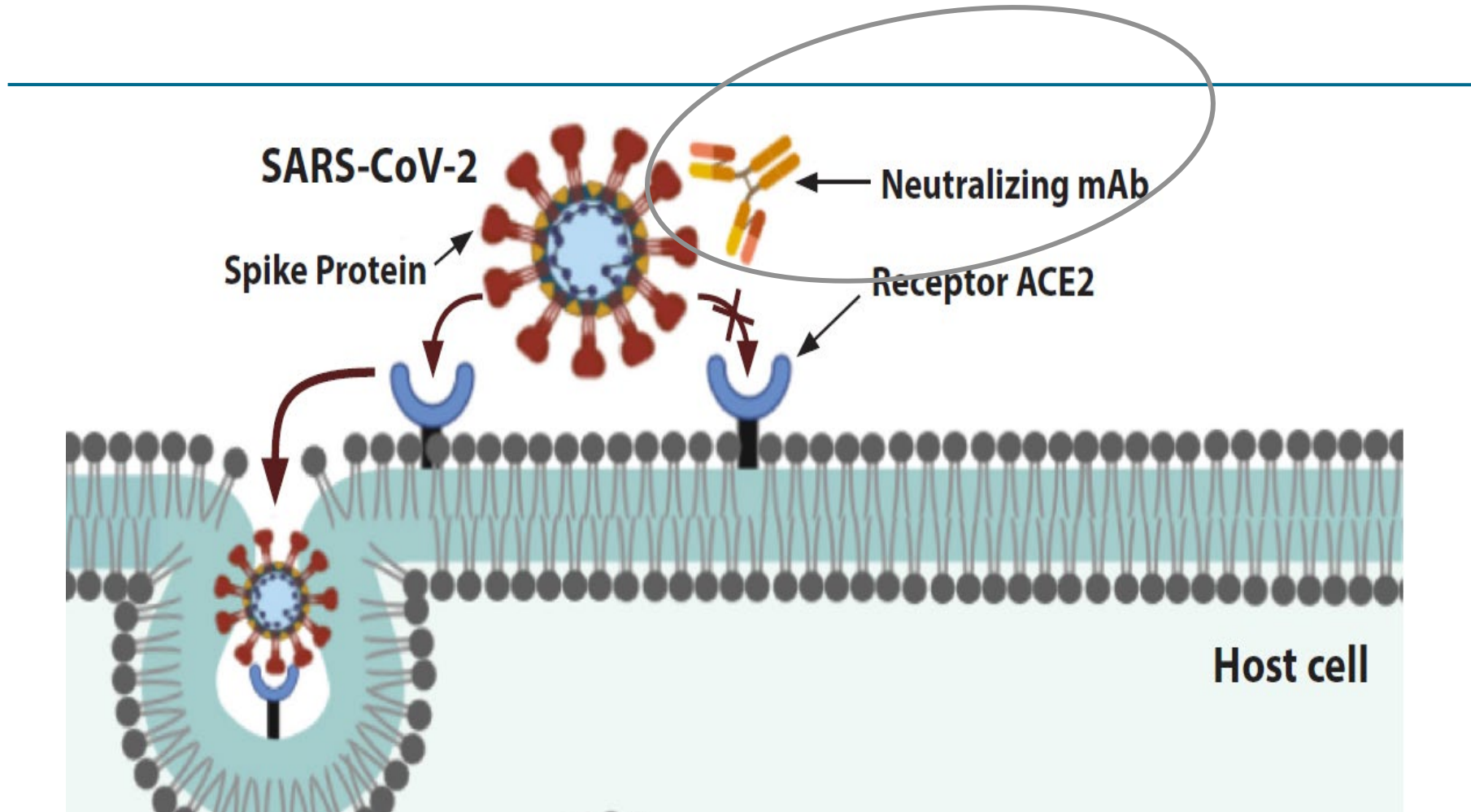


■ **Adjuvanted recombinant protein:** not as fast to manufacture but scalable, several approved vaccines use this approach



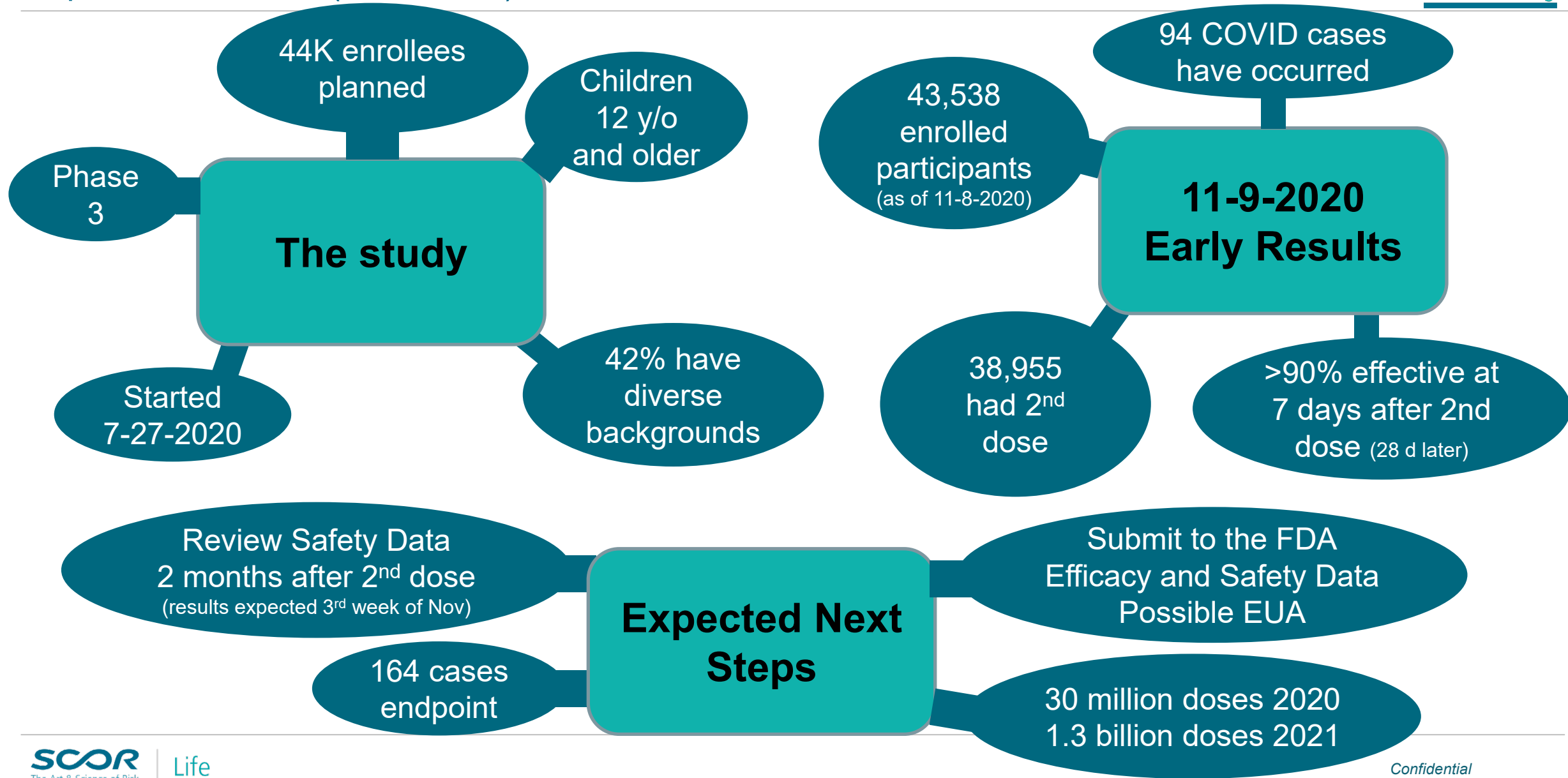
<https://www.nature.com/articles/s41401-020-0485-4>

The immune system's antibody response

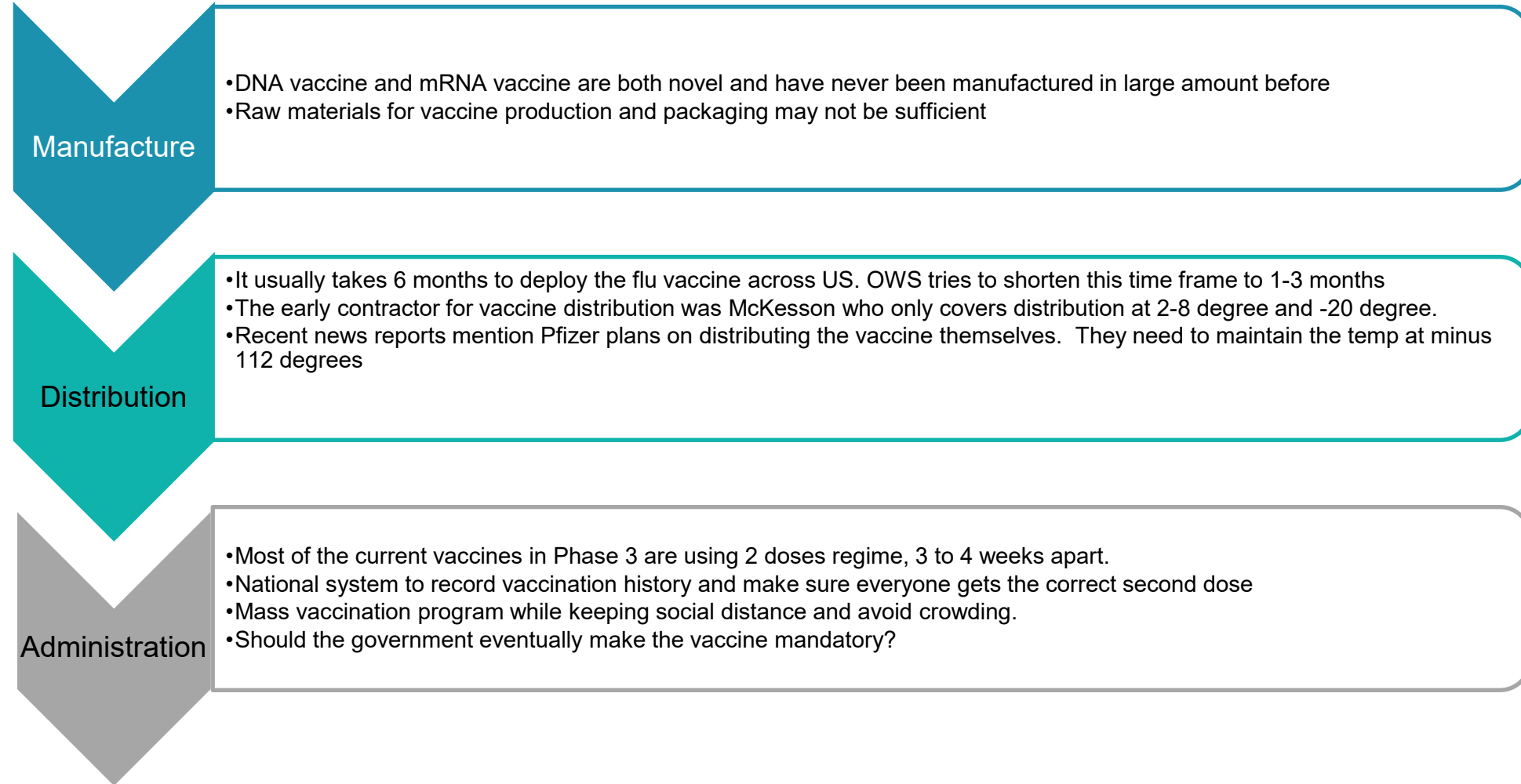


Pfizer/BioNTech announcement on Monday

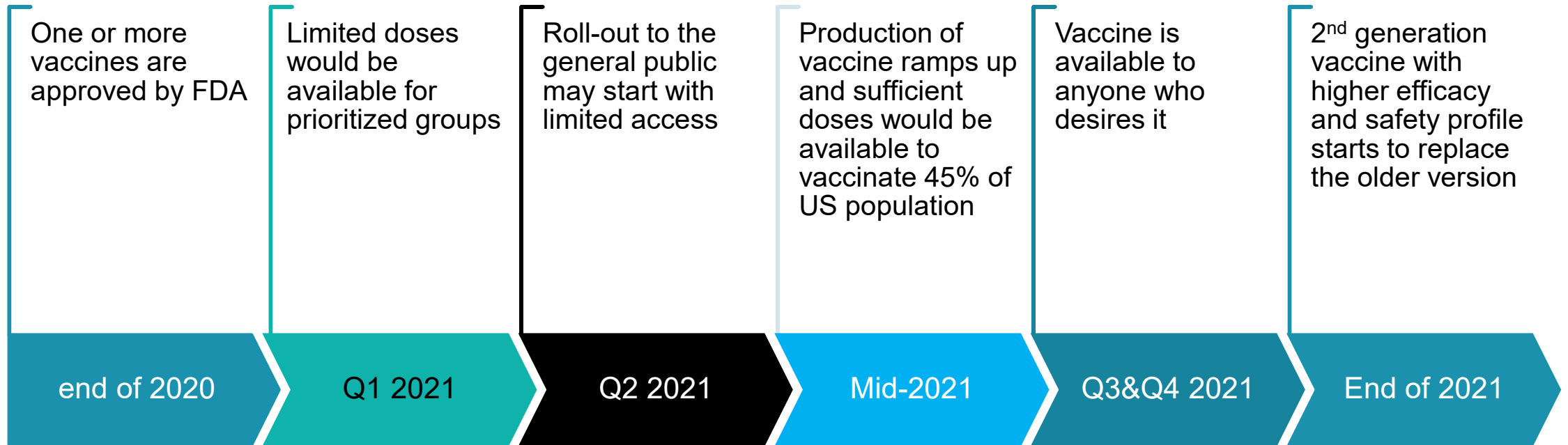
Important Numbers (BNT162b2)



Vaccine challenges



Timeline



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