COVID-19
Impacting mortality for those who don’t even get the infection

The pandemic is causing deaths not directly associated with the virus.
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

Timeline

- Feb 29, 2020
- March 13
- March 18
- April 15
- July 26
- November 11, 2020

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

Dramatic drops in cancer screenings and new cancer dx

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.

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

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).**


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.

CHF admissions have dropped

- 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
Out-of-hospital cardiac arrests

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

Excess deaths

[Graph showing weekly number of deaths from all causes with an indication of excess deaths.]

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

Excess deaths caused by indirect causes quantified

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

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

Baseline

Worldwide the age-adjusted mortality rates declined to about 1/3 of the 1960’s baseline by 2000

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/hus/contents2018.htm?search=Heart_disease, Trend tables
Quantifying the factors decreasing CV mortality during the last few decades

- 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.

<table>
<thead>
<tr>
<th>Evidence-based medical and surgical treatments</th>
<th>Ford et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>11% Secondary preventative therapies after MI</td>
<td>[Chart]</td>
</tr>
<tr>
<td>10% MI/angina treatment (initial tx)</td>
<td></td>
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<tr>
<td>9% CHF treatment</td>
<td></td>
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<tr>
<td>5% Revascularization for chronic angina</td>
<td></td>
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<tr>
<td>12% Other</td>
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<tr>
<td>47% TOTAL</td>
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</table>

<table>
<thead>
<tr>
<th>Risk Factor Reduction</th>
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<tbody>
<tr>
<td>24% Cholesterol reduction</td>
</tr>
<tr>
<td>20% BP reduction</td>
</tr>
<tr>
<td>12% Smoking reduction</td>
</tr>
<tr>
<td>5% Physical Activity Improvement</td>
</tr>
<tr>
<td>-7% BMI</td>
</tr>
<tr>
<td>-10% DM prevalence</td>
</tr>
<tr>
<td>44% TOTAL</td>
</tr>
</tbody>
</table>


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

Decreasing the risk
- Fear of dying from COVID

Increasing the risk
- Pandemic induced stress
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.

- Yang, Y. et al. Determinants of physical activity maintenance during the COVID-19 pandemic: a focus on fitness apps. Translational Behavioral Medicine, August 2020
## Medical and surgical treatment improvements

<table>
<thead>
<tr>
<th>Evidence-based medical and surgical treatments</th>
<th>Change in deaths/100k</th>
<th>Lockdown (&quot;Immediate phase&quot;) reaction lasting 4-6 weeks</th>
<th>Post-lockdown I (&quot;Transition phase&quot;) first 3 months that followed the lockdown</th>
<th>First 5 months deaths/100k</th>
<th>Post-lockdown II (&quot;Active phase&quot;) subsequent months and prior to a significant decrease in COVID cases</th>
<th>Subsequent quarters</th>
</tr>
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<tbody>
<tr>
<td>11% Secondary Preventative therapies after MI</td>
<td>47</td>
<td>~40% reduction in treatment impact (1.6 deaths/mo x 2 = 3.2 deaths)</td>
<td>~10% reduction in treatment impact (0.4 deaths/mo x 3 = 1.2 deaths)</td>
<td>4.4</td>
<td>~2-4% reduction</td>
<td>0.09 - 16 deaths/mo (0.24 – 0.48 deaths per 3 months)</td>
</tr>
<tr>
<td>10% MI/Angina treatment (initial treatment)</td>
<td>42</td>
<td>~40% reduction in treatment impact (1.4 deaths/mo x 2 = 2.8 deaths)</td>
<td>~10% reduction in treatment impact (0.35 deaths/mo x 3 = 1.05 deaths)</td>
<td>3.85</td>
<td>~2-4% reduction</td>
<td>0.035 - 0.07 deaths/mo (0.11 – 0.22 deaths per 3 months)</td>
</tr>
<tr>
<td>9% CHF treatment</td>
<td>38</td>
<td>~40% reduction in treatment impact (1.28 deaths/mo x 2 = 2.56 deaths)</td>
<td>~10% reduction in treatment impact (0.32 deaths/mo x 3 = 0.96 deaths)</td>
<td>3.52</td>
<td>~2-4% reduction</td>
<td>0.032 - 0.065 (0.092 – 0.2 deaths per 3 months)</td>
</tr>
<tr>
<td>5% Revascularization for chronic angina</td>
<td>21</td>
<td>~40% reduction in treatment impact (0.7 deaths/mo x 2 = 1.4 deaths)</td>
<td>~10% reduction in treatment impact (0.18 deaths/mo x 3 = 0.54 deaths)</td>
<td>1.94</td>
<td>~2-4% reduction</td>
<td>0.018 - 0.036 (0.05 – 0.10 deaths per 3 months)</td>
</tr>
<tr>
<td>12% Other</td>
<td>51</td>
<td>No clear pattern</td>
<td>No clear pattern</td>
<td>-</td>
<td>No clear pattern</td>
<td>-</td>
</tr>
<tr>
<td>47% TOTAL</td>
<td>199</td>
<td></td>
<td></td>
<td>12.86/100k 42,180 deaths</td>
<td>~0.5 – 1.0 deaths/100k 1,640 - 3,280 deaths per quarter</td>
<td>-</td>
</tr>
</tbody>
</table>

- 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
## Risk factor reduction

<table>
<thead>
<tr>
<th>Risk factor reduction</th>
<th>Change in deaths/100k</th>
<th>Lockdown (&quot;Immediate phase&quot;) reaction lasting 6-8 weeks)</th>
<th>Post-lockdown I (&quot;Transition phase&quot;) first 3 months that followed the lockdown</th>
<th>First 5 months deaths/100k</th>
<th>Post-lockdown II (&quot;Active phase&quot;) subsequent months and prior to a significant decrease in COVID cases</th>
<th>Subsequent quarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>24% Cholesterol reduction</td>
<td>102</td>
<td>10% reduction in effective dx and tx (0.85 deaths/mo x 2 = 1.7 deaths)</td>
<td>5% reduction in effective dx and tx (0.425 deaths/mo x 3 = 1.275 deaths)</td>
<td>2.975</td>
<td>2% (0.17 mo x 3 = 0.5 deaths)</td>
<td>0.5 q 3 months</td>
</tr>
<tr>
<td>20% BP reduction</td>
<td>85</td>
<td>10% reduction in effective dx, and tx (0.7 deaths/mo x 2 = 1.4)</td>
<td>5% reduction in effective dx and tx 0.35 deaths/mo x 3 = 1.05</td>
<td>2.45</td>
<td>2% (0.14 mo x 3 = 0.42 deaths)</td>
<td>0.42 q 3 months</td>
</tr>
<tr>
<td>12% Smoking reduction</td>
<td>51</td>
<td>No clear pattern</td>
<td>~2% increase in smoking 0.005 deaths/mo x 3 = 0.26</td>
<td>0.26</td>
<td>No clear pattern</td>
<td>-</td>
</tr>
<tr>
<td>5% Physical Activity Improvement</td>
<td>21</td>
<td>~30% reduction in effective PA (0.53 deaths/mo x 2 = 1.06)</td>
<td>~7% reduction in effective PA (0.12 deaths/mo x 3 = 0.36 deaths)</td>
<td>1.42</td>
<td>No clear pattern</td>
<td>-</td>
</tr>
<tr>
<td>7% BMI</td>
<td>30</td>
<td>No clear pattern</td>
<td>No clear pattern</td>
<td>-</td>
<td>No clear pattern</td>
<td>-</td>
</tr>
<tr>
<td>10% DM prevalence</td>
<td>12</td>
<td>No clear pattern</td>
<td>No clear pattern</td>
<td>-</td>
<td>No clear pattern</td>
<td>-</td>
</tr>
<tr>
<td>44% TOTAL</td>
<td>187</td>
<td></td>
<td></td>
<td>6.871/100k 22,500 deaths</td>
<td>~0.02/100k 3,017 deaths per quarter</td>
<td></td>
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- 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
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).

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 then 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.

### Excess cancer-related deaths during the COVID-19 pandemic

<table>
<thead>
<tr>
<th>Source</th>
<th>Percentage increase in deaths</th>
<th>Observations/Assumptions</th>
</tr>
</thead>
</table>
| Sharpless       | 1% in breast and colon cancer deaths/10 years                                                   | • 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. | • 90% decrease in endoscopies in April  
• Services restarted by June but at reduced capacities  
• Services impacted for the foreseeable future.  
Increase in telemedicine. |
| Lai             | 5-6% increase in deaths among those with cancer in the United States/1 year.                   | • 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” |
| Ricciardeiello  | 12% increase in colorectal mortality if colon cancer dx. is delayed beyond 12 months.          | • 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) |
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.

<table>
<thead>
<tr>
<th>Vaccine technology platforms</th>
<th>Non-replicating viral vector</th>
<th>RNA-based</th>
<th>Inactivated Virus (Hepatitis A; Flu; Polio; Rabies)</th>
<th>Protein Subunit</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA-based</td>
<td>Replicating viral vector</td>
<td>Virus-like particles (Hib; Hepatitis B; HPV; Whooping cough; Pneumococcal; Shingles)</td>
<td>Live attenuated virus (MMR; rotavirus; smallpox; yellow fever)</td>
<td></td>
</tr>
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COVID-19 vaccines in Operation Warp Speed development

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

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

- **Recombinant protein + adjuvant**: not as fast to manufacture but scalable, several approved vaccines use this approach
SARS-CoV-2

https://www.nature.com/articles/s41401-020-0485-4
The immune system’s antibody response
Pfizer/BioNTech announcement on Monday

Important Numbers (BNT162b2)

- **Phase 3**: 94 COVID cases have occurred
  - >90% effective at 7 days after 2nd dose (28 d later)
  - 43,538 enrolled participants (as of 11-8-2020)
  - 42% have diverse backgrounds
  - 38,955 had 2nd dose
  - >90% effective at 7 days after 2nd dose (28 d later)

- **The study**: 44K enrollees planned
  - Children 12 y/o and older
  - 164 cases endpoint
  - Started 7-27-2020

- **Expected Next Steps**: 11-9-2020
  - Early Results
  - Review Safety Data
    - 2 months after 2nd dose (results expected 3rd week of Nov)
  - Submit to the FDA
    - Efficacy and Safety Data
    - Possible EUA

- **Planned**: 30 million doses 2020
  - 1.3 billion doses 2021

**Enrollees**: 44K

**Participants**: 43,538

**Doses**: 30 million (2020)

**Cases**: 164

**Expected EUA**: Children 12 y/o and older
Vaccine challenges

**Manufacture**
- DNA vaccine and mRNA vaccine are both novel and have never been manufactured in large amount before
- Raw materials for vaccine production and packaging may not be sufficient

**Distribution**
- It usually takes 6 months to deploy the flu vaccine across US. OWS tries to shorten this time frame to 1-3 months
- The early contractor for vaccine distribution was McKesson who only covers distribution at 2-8 degree and -20 degree.
- Recent news reports mention Pfizer plans on distributing the vaccine themselves. They need to maintain the temp at minus 112 degrees

**Administration**
- Most of the current vaccines in Phase 3 are using 2 doses regime, 3 to 4 weeks apart.
- National system to record vaccination history and make sure everyone gets the correct second dose
- Mass vaccination program while keeping social distance and avoid crowding.
- Should the government eventually make the vaccine mandatory?
Timeline

- One or more vaccines are approved by FDA (end of 2020)
- Limited doses would be available for prioritized groups (Q1 2021)
- Roll-out to the general public may start with limited access (Q2 2021)
- Production of vaccine ramps up and sufficient doses would be available to vaccinate 45% of US population (Mid-2021)
- Vaccine is available to anyone who desires it (Q3 & Q4 2021)
- 2nd generation vaccine with higher efficacy and safety profile starts to replace the older version (End of 2021)