Evaluating Effectiveness of Public Health Intervention Strategies for Mitigating COVID-19 Pandemic [1,2]

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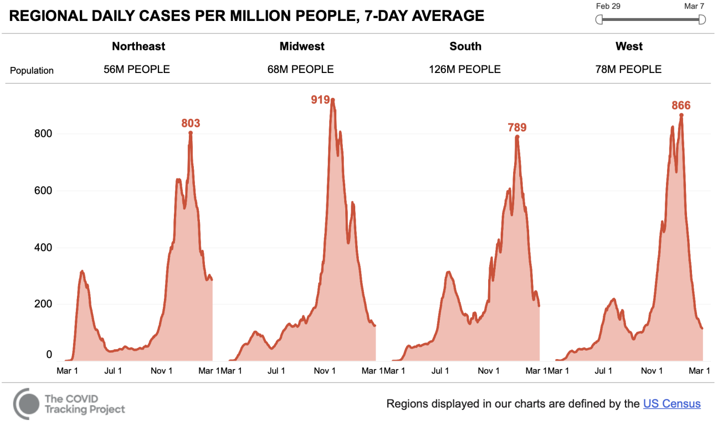
[1]: Xie et al. (2022). Evaluating Effectiveness of Public Health Intervention Strategies for Mitigating COVID-19 Pandemic. *Statistics in Medicine.* In press.

[2]: Wang and Xie et al. (2020). Survival-Convolution Models for Predicting COVID-19 Cases and Assessing Effects of Mitigation Strategies. *Frontiers in Public Health*. 8:325. Github site.

Funding support: GM124104A1-S1.

COVID-19 Pandemic: Global Health Challenge

Figure. Incident COVID-19 Cases per 1M (7-day average) from March, 2020 to March 7, 2021[3]

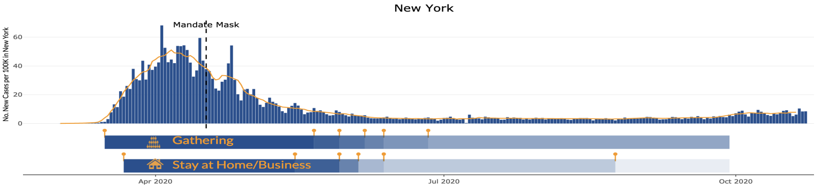


[3] COVID Tracking Project.

States-level Responses

States have implemented series of non-pharmaceutical interventions (NPIs) to mitigate COVID-19

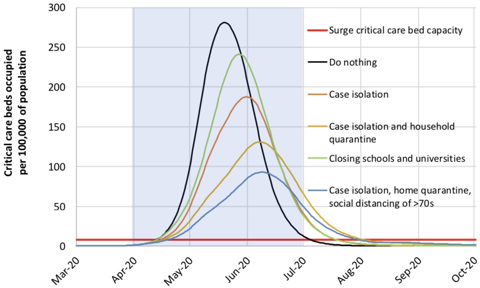
- Lockdown: physical distance closures of schools/businesses/gyms/restaurants/bars/theaters, ban visitors to long term care facility
- Stay-at-home orders
- Mask mandates
- Re-opening business, restaurants, bars



https://msph.shinyapps.io/dscovr_dashboard/

How to Estimate the Effects of NPIs?

- Process-based infectious disease models to simulate counterfactual outcomes under interventions (Ferguson et al. 2020)

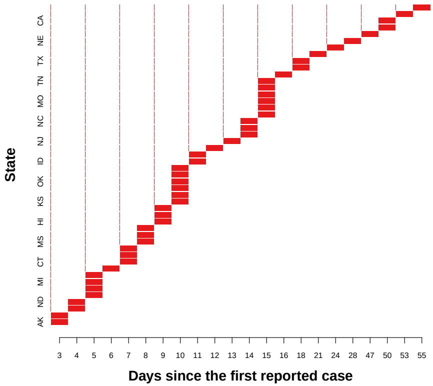


- Usual regression models to study association between NPIs and outcome (e.g., mask wearing and $I(R_t < 1)$; Radar et al. 2021)

How to Estimate the Effects of NPIs?

Quasi-experiments longitudinal pre-post intervention design. Often used to study health policies when randomized trials are not feasible.

Staggered adoption of lockdown (physical distance closures) across states:

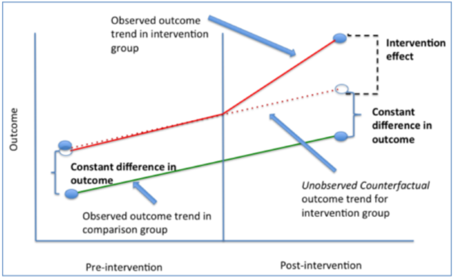


Evaluation of NPI Effect

Causal inference methods for studies with longitudinal (panel) data and staggered adoptions of treatments:

- Difference in difference (DID) regression, or interrupted time series analysis (Wing et al. 2018; DID Estimator)
- Synthetic controls (Abadie et al. 2010): create weights to match pre-treatment period of control units.

DID Regression



Assumptions:

- Parallel trends in groups; regression with time effect and unit effect, test time$\times$group interaction
- Outcomes do not influence treatment allocation
- Stable unit treatment value assumption (SUTVA)

California's Tobacco Control Program (Abadie et al. 2010[4]):

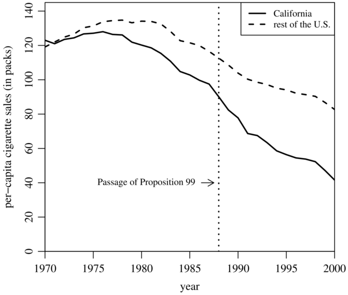


Figure 1. Trends in per-capita cigarette sales: California vs. the rest of the United States.

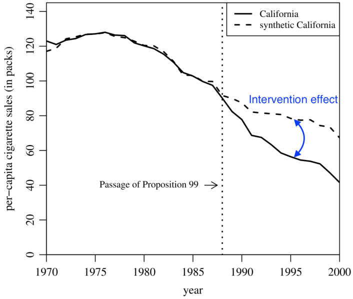


Figure 2. Trends in per-capita cigarette sales: California vs. synthetic California.

- Designed for a single treated unit.
- The weights may not be adequate for the average effect.

[4] Abadie, A., Diamond, A., & Hainmueller, J. (2010). Synthetic control methods for comparative case studies: Estimating the effect of California's tobacco control program. JASA, 105(490), 493-505.

Proposed Method

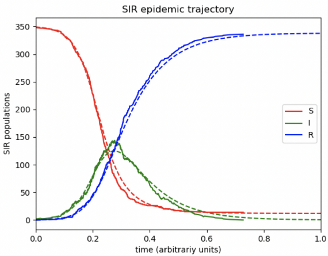
Considerations in the Estimation of NPIs

- Choice of the outcome measure for COVID-19 transmission
  - Observed cases are subject to high variations/noises
  - Underlying mechanism of disease transmission can be summarized by the effective reproduction number R_t
  - More meaningful time scale is to match by disease stage: shift calendar time to time since first reported case
- Goal: use quasi-experiment framework to account for confounding and estimate average treatment effect (ATE) and heterogeneity of treatment effect (HTE)

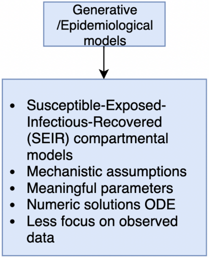
Estimation of R_t

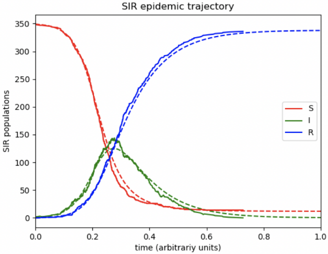
Generative /Epidemiological models

- Susceptible-Exposed-Infectious-Recovered (SEIR) compartmental models
- Mechanistic assumptions
- Meaningful parameters
- Numeric solutions ODE
- Less focus on observed data



Estimation of R_t



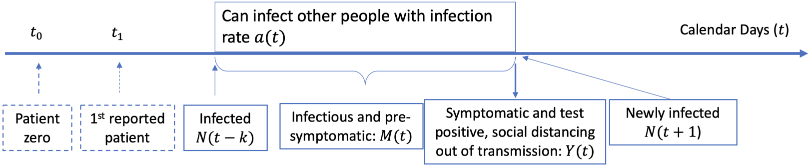


- Modeling population-level transmission using summary statistics (daily incidence cases in 50 states), not at individual-level
- SARS-CoV-2: long incubation period, highly infectious in the pre-symptomatic phase (50% transmission during this phase CDC)
- Time-varying transmission rate as societal behavior changes and NPIs are implemented
- Intervention effect may be time-dependent

Combine mechanistic-based model with statistical model and provide important parameter effective reproduction number R_t.

Survival-Convolution Model

- $M(t) = \sum_{k=0}^{\infty} N(t-k)S(k)$
- $Y(t) = \sum_{k=0}^{\infty} N(t-k)[S(k) - S(k+1)]$
- $N(t+1) = a(t)[M(t) - Y(t)]$



- $N(t)$: number of new infections on date t.
- $a(t)$: effective transmission rate

$$N(t+1) = a(t) \sum_{k=0}^{\infty} N(t-k)S(k+1). \tag{1}$$

Equation (1) gives a convolution update for the number of new infections given the past infections $N(t), N(t-1), \ldots, N(t_0)$.

- $S(k)$: discrete survival function, proportion of persons remaining infectious after k days of being infected

Time-varying Effective R_t as Outcomes

- Model $a(t)$ as non-negative, piece-wise linear functions with knots at NPI event times and equally spaced in between.
- Model daily confirmed cases accounting for additive errors (optimization under a squared loss).
- Effective reproduction number (R_t): the average number of secondary cases infected by primary cases who are infectious at time t (Cori et al. 2013)

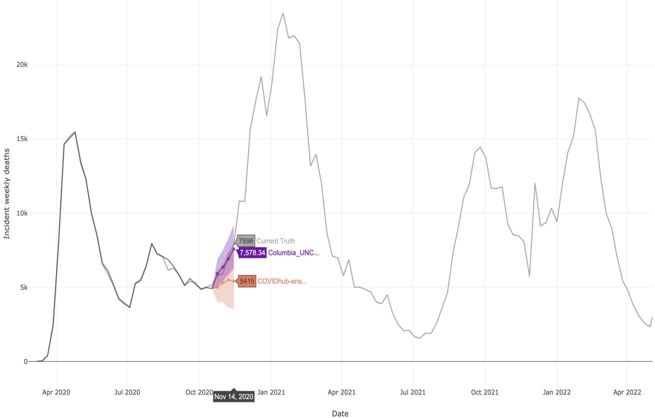
$$R_t = \frac{N(t)}{\sum_{k=1}^{C} N(t-k)w(k)}$$

  $w(k)$ probability mass function of the serial interval distribution.

- R_t captures the temporal changes in the disease spread.

Our Forecasts of COVID-19 Pandemic

We submit our forecasts to COVID Forecast Hub, which is used by the US Centers for Disease Control and Prevention (CDC)[5]

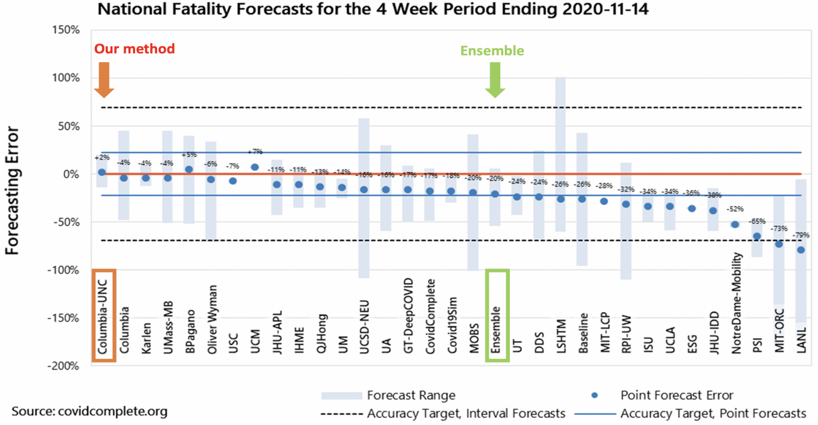


Using data up to 2020-10-17, 4 weeks ahead forecasts of incident weekly deaths till 2020-11-14

[5]: COVID-19 Forecast Hub Consortium (2022). *PNAS 119 (15), e2113561119*

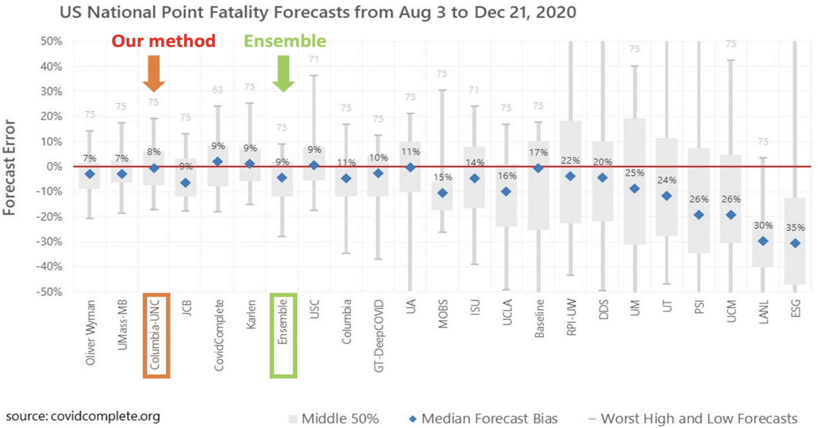
Performance of Our Forecasts

Using data up to 2020-10-17,



Forecast Evaluation from Steve McConnell

Performance of Our Forecasts



Forecast Evaluation from Steve McConnell

Causal Estimand: ATE

$Y_i^{(1)}(t+\Delta;t)$: potential outcome (change of R_t between t and $(t+\Delta)$) when intervention of interest is applied at t and no other interventions in $(t, t+\Delta)$.

$Y_i^{(0)}(t+\Delta;t)$: potential outcome when no intervention is applied at time t, and no other interventions in $(t, t+\Delta)$.

Intervention effect Δ days after t:

$$\gamma(\Delta, t) = E[Y_i^{(1)}(t+\Delta;t) - Y_i^{(0)}(t+\Delta;t)].$$

The ATE is defined as:

$$\gamma(\Delta) \equiv \int \gamma(\Delta, t) dF_T(t),$$

where $F_T(\cdot)$ is the distribution of the intervention times T_i.

Assumptions for Estimating ATE from Observed Data

Assumptions:

(a) Suppose no other intervention occurs between t and $t + \Delta$. When $T_i = t$ (i.e., there is an intervention at t), $Y_i^{(1)}(t + \Delta; t) = Y_i(t + \Delta; t)$.

(b) Suppose no other intervention occurs between t and $t + \Delta$ and the intervention of interest has not been imposed before t, $Y_i^{(0)}(t + \Delta; t) = Y_i(t + \Delta; t)$.

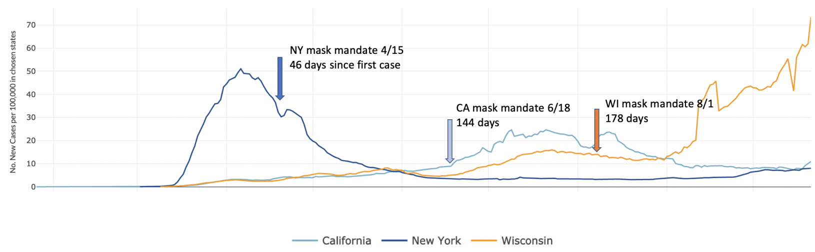
(c) Assume no unobserved confounders: conditional on $T_i \geq t$, $T_i = t$ is independent of $Y_i^{(a)}(t + \Delta; t), a = 0, 1$ given X_i and $H_i(t)$, where $H_i(t)$:observed epidemic history by time t.

(a), (b): SUTVA, implies no delayed effect

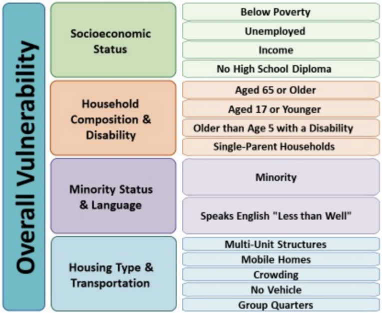
Nested Case-Control Design

Create "case" and "control" states under a nested case-control design to compute propensity scores.

- Align each state's data according to the time since first reported case so states are more similar in stage of the epidemic.
- For each state with an intervention, create "control states" as those without an intervention by t ("at risk") and no interventions in $(t, t + \Delta)$.



Covariates for Propensity Scores



X_i: state-level demographics (e.g., age, race, ethnicity distribution) and social vulnerability index (SVI) variables (available from the CDC).

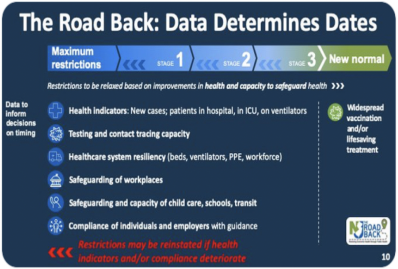
Covariates for Propensity Scores

What data were used for policy decision making?

Explainer: Why COVID-19's Reproduction Rate Is Crucial to NJ's Restart

LILO H. STAINTON, HEALTH CARE WRITER | JUNE 12, 2020 | CORONAVIRUS IN NJ, EXPLAINER

Gov. Murphy says the state's Rt is among the lowest in the nation



$H_i(t)$: previous week's R_t, new cases, new deaths, testing positivity rate, hopitalizations

Estimation Methods

Observe that under SUTVA and NUC assumptions (a), (b), (c)

$$
\begin{aligned}
\gamma(\Delta, t) &= E\left[\frac{I(T_i = t)}{P(T_i = t | T_i \geq t, H_i(t), X_i)}\left\{Y_i^{(1)}(t+\Delta; t)\right\}\right] \\
&- E\left[\frac{I(T_i > t+\Delta)}{P(T_i > t+\Delta | T_i \geq t, H_i(t), X_i)}\left\{Y_i^{(0)}(t+\Delta; t)\right\}\right] \\
&= E\left[\frac{I(T_i = t)}{P(T_i = t | T_i \geq t, H_i(t), X_i)}\left\{Y_i(t+\Delta; t)\right\}\right] \\
&- E\left[\frac{I(T_i > t+\Delta)}{P(T_i > t+\Delta | T_i \geq t, H_i(t), X_i)}\left\{Y_i(t+\Delta; t)\right\}\right],
\end{aligned}
$$

and the ATE is

$$\gamma(\Delta) \equiv \int \gamma(\Delta, t) dF_T(t).$$

Estimation Methods

Propensity score model:

$$\text{logit}\left\{P(T_i = t | T_i \geq t, H_i(t), X_i)\right\} = (H_i(t), X_i)^T \beta$$

to obtain $\widehat{p}_i(t) = \frac{\exp\{(H_i(t), X_i)^T \widehat{\beta}\}}{1+\exp\{(H_i(t), X_i)^T \widehat{\beta}\}}$. Let $\widehat{q}_{ij} = \widehat{p}_i(t_j)$.

The ATE is estimated as:

$$\widehat{\gamma}(\Delta) = \frac{\sum_{i=1}^n \sum_{j\in S(i)} d_{ij}\delta_{ij}/\widehat{q}_{ij}}{\sum_{i=1}^n \sum_{j\in S(i)} \delta_{ij}/\widehat{q}_{ij}} - \frac{\sum_{i=1}^n \sum_{j\in S(i)} d_{ij}(1-\delta_{ij})/(1-\widehat{q}_{ij})}{\sum_{i=1}^n \sum_{j\in S(i)} (1-\delta_{ij})/(1-\widehat{q}_{ij})},$$

d_{ij}: change in reproduction number, δ_{ij}: intervention status at time j for state i, $S(i)$ set of eligible control states for state i.

Inference

Theorem 1. Suppose that the propensity score model holds. Under assumptions (a)-(c) and assuming that $(H_i(t), X)$ is linearly independent with positive probability for some t in $\mathcal{T}$ and that $H(t)$ has a bounded total variation in $\mathcal{T}$, $\sqrt{n}(\widehat{\gamma}(\Delta) - \gamma(\Delta))$ converges to a mean-zero normal distribution.

Variance can be estimated explicitly by a sandwich estimator.

HTE by Regression Model

With hypothesized moderators Z_i, postulate model for the conditional average treatment effects (CATE)

$$E[Y_i^{(1)}(t+\Delta;t) - Y_i^{(0)}(t+\Delta;t)|Z_i] = \theta^T Z_i.$$

The estimator for θ can be obtained by solving

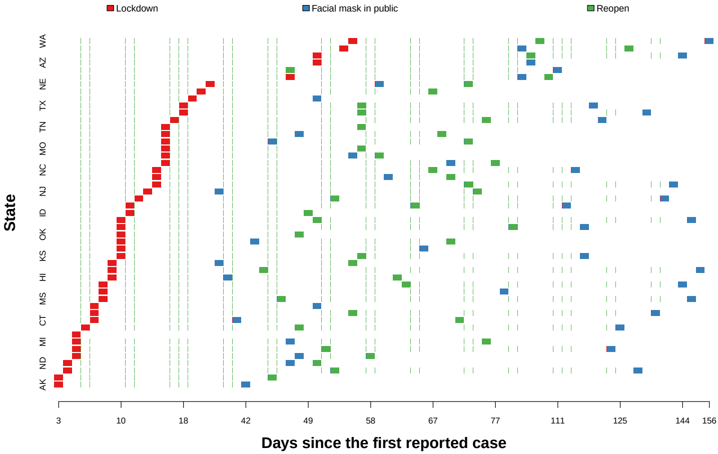
$$\sum_{i=1}^{n} Z_i \left[\sum_{j \in S(i)} \left\{ d_{ij} \left\{ \frac{\delta_{ij}}{\widehat{q}_{ij}} - \frac{1-\delta_{ij}}{1-\widehat{q}_{ij}} \right\} - \theta^T Z_i \right\} \right] = 0.$$

Inference: asymptotic distribution for $\widehat{\theta}$ and variance can be derived.

Analysis and Results

Interventions of Interest

Timeline of NPIs: lockdown; mask mandate; reopening business[6].
(Implemented March 13, 2020–August 5, 2020)



[6] COVID-19 US state policy database (CUSP)

Data: JHU Center for System Science and Engineering (CSSE)
https://github.com/CSSEGISandData/COVID-19

Fig. Observed (red curve) and fitted (black curve) daily COVID-19 cases from February, 2020 to March, 2021

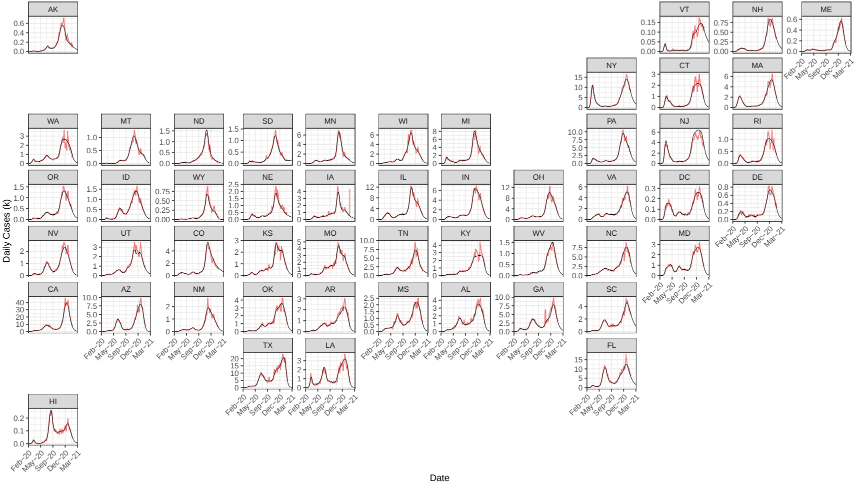


Fig. Estimated R_t in All States

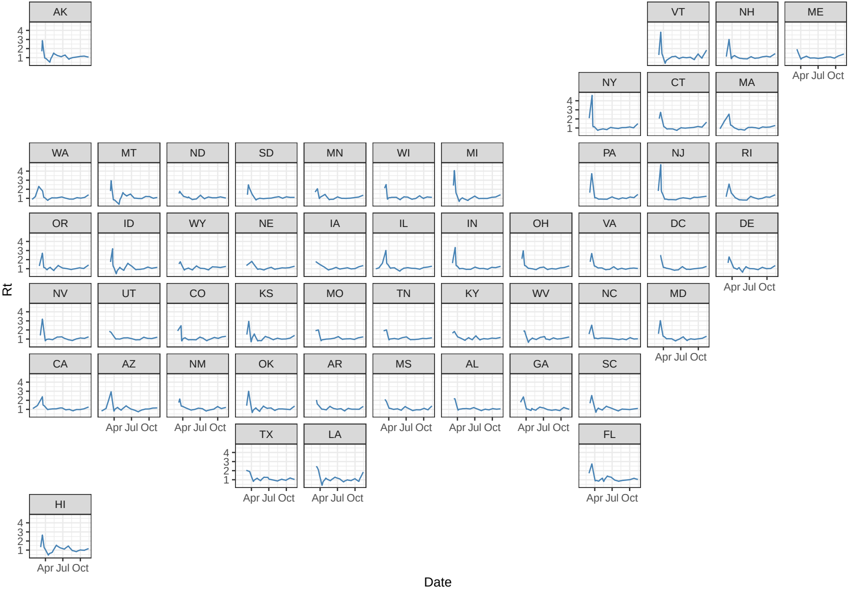
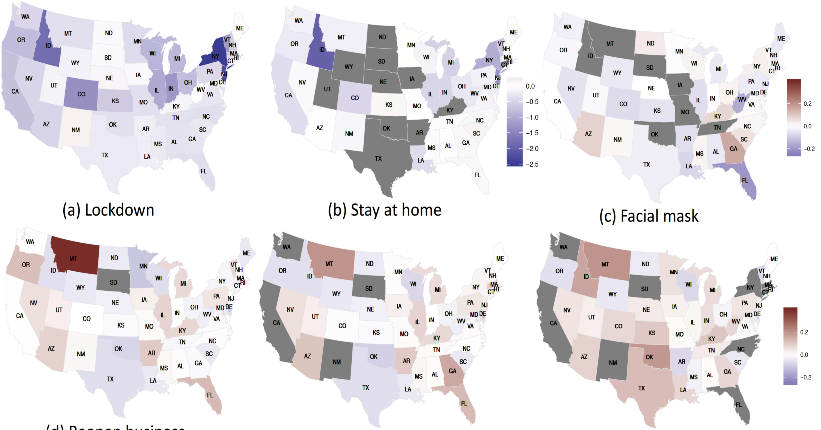


Fig. Difference in R_t 7-days post-intervention and 1 day before



(a) Lockdown (b) Stay at home (c) Facial mask

(d) Reopen business (e) Reopen restaurants (f) Reopen bars

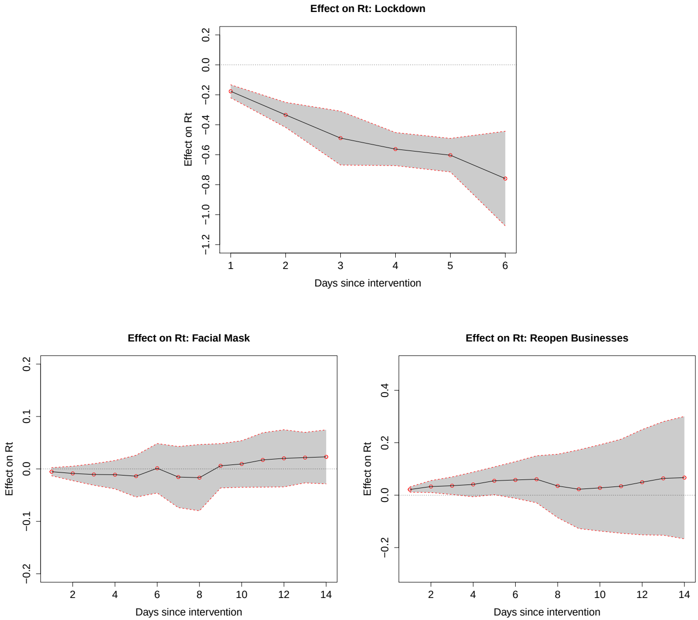
Results on Propensity Scores

22 candidate predictors (pre-intervention new cases, new deaths, R_t, demographics, SVI) for propensity scores. Screened top 10 using marginal correlation.

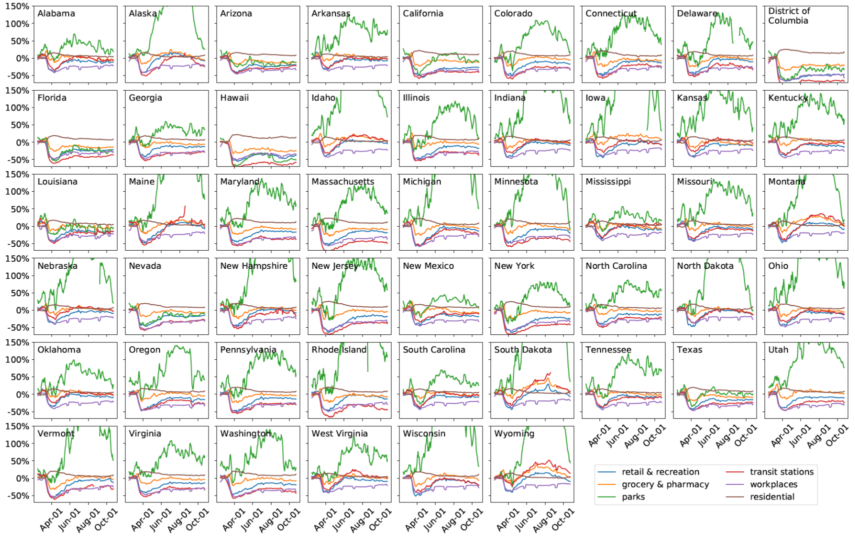
Table. Propensity Score Model for Initiating Interventions

Intervention	Significant Predictors
Lockdown	R_t, new cases, new deaths, Latino population size, Institutionalized population size
Mask mandate	R_t, new cases, new deaths,
Reopen business	R_t, new deaths, mobile home
	Sensitivity analysis
Stay-at-home order	new cases, new deaths, no high school diploma
Reopen restaurants	R_t
Reopen bars	new cases

Figure: Average intervention effects (ATEs) with 95% confidence intervals.



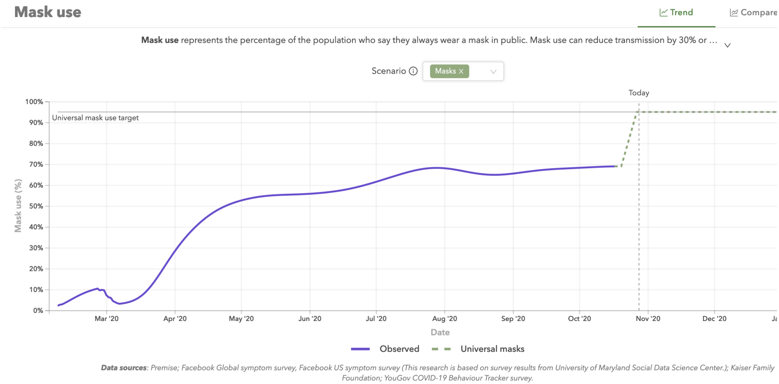
Closures and Mobility[7]



[7]Google mobility report.

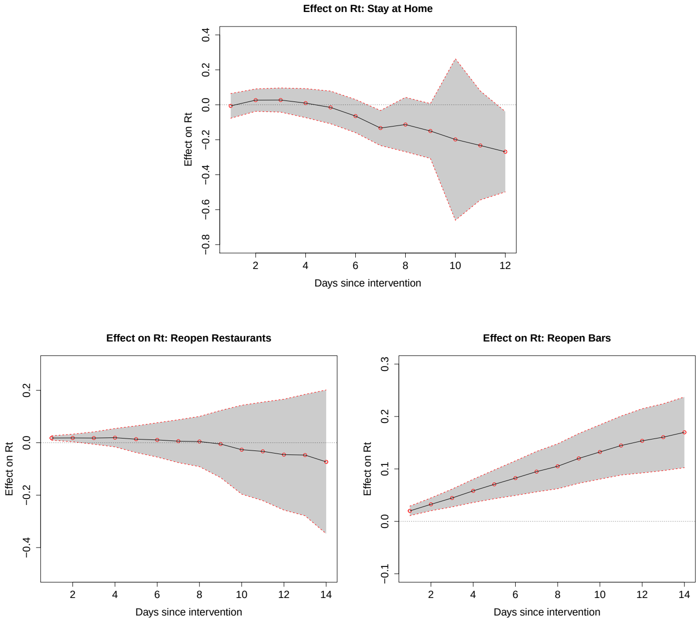
Mask Use

Figure. Self-reported Mask Use (Data Source: IHME, University of Washington)



Mask mandate may not fully correspond to mask use behavior in public (Rader et al., 2021).

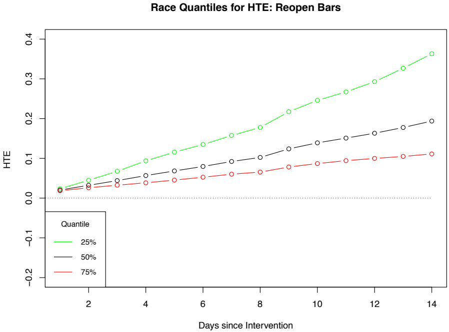
Figure: Sensitivity analysis of ATEs with 95% confidence intervals.



Estimated HTE

Candidate moderators: age, race, gender, and the poverty level

Lockdown effect is universal (no moderator). Race with some suggestive evidence of moderating reopening bars (marginally significant):



Discussion

Summary

Propose a method to evaluate ATE and HTE of mitigation strategies for COVID-19.

- Difference in R_t as measure of intervention effect
- Construct propensity scores under a nested case-control design and use a weighted DID estimator

Limitations and extensions:

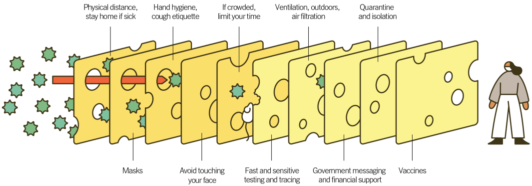
- Lack of data on behavioral change and policy enforcement
- Examine other interventions (i.e., vaccine) and use county-level data to study HTE and precision public health intervention (e.g., speed/equity of vaccine administration)

Summary

- More granular assessments of interventions and evaluate the joint effect or interactions of interventions with county-level data.
- Did not account for delayed effect of prior interventions. May consider dynamic treatment regimens to optimize sequence of interventions.

Multiple Layers Improve Success

The Swiss Cheese Respiratory Pandemic Defense recognizes that no single intervention is perfect at preventing the spread of the coronavirus. Each intervention (layer) has holes.



Source: Adapted from Ian M. Mackay (virologydownunder.com) and James T. Reason. Illustration by Rose Wong

Collaborators

- Ms. Wenbo Wang, University of North Carolina at Chapel Hill
- Dr. Qinxia Wang, Novartis
- Dr. Yuanjia Wang, Columbia University
- Dr. Donglin Zeng, University of North Carolina at Chapel Hill

THANK YOU !