Modeling Robustness of COVID-19 Containment Policies to Heterogeneity and Uncertainty: the TRACE model

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1. Introduction

Efforts to contain the COVID-19 pandemic have led to episodic and sometimes drastic shut-downs of economies, schools, and social life around the world. Policymakers in the United States and many other countries have had to balance resumption of these activities with controlling the spread of the novel coronavirus, and have adopted heterogeneous blends of policy actions to do so—including testing, contact tracing, quarantine, mask mandates, and (more recently) vaccines. Yet key quantitative questions central to designing or implementing effective containment policy (including specific capacities needed, timing, and synergy or substitutability of options) have remained difficult to answer in the face of both high heterogeneity among individuals and contexts and continued uncertainty about the underlying epidemiological characteristics of SARS-CoV-2 virus itself [1].

In this paper, we report on results from the application of a computational model entitled TRACE (Testing Responses using Agent-based Computational Epidemiology) which is designed specifically to help address these challenges. While many COVID-19 models have offered important insights for policy discussions, TRACE differs in important ways that allow us to offer new insights. First, we have designed TRACE as a “policy laboratory” [2-3], rather than a forecasting model—and we use it to explore a wide range of possible policy solutions and implementation choices combining variations around social distancing, polymerase testing, antigen testing, contact tracing and quarantine, serological testing, mask usage, and vaccine uptake. Second, rather than relying on any one set of epidemiological or behavioral parameter estimates, we embrace the uncertainty surrounding SARS-CoV-2 to consider the robustness of potential intervention designs across a large multi-dimensional assumption space and to assess the fit between context and strategy. Third, using the technique of agent-based computational modeling [4], we are able to include substantial heterogeneity among people and contexts that is important in how the virus spreads and how well containment policies work. This includes non-random mixing and variation in age, infectivity, asymptomatic and pre-symptomatic transmission, geography, and adherence [3-6].

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Below, we describe the design and implementation of TRACE, and then present results from a series of analyses aimed at uncovering and detailing robust containment policies for COVID-19. A *robust* containment policy is one that is effective across a broad range of potential epidemiological or behavioral assumptions in the model. This approach also allows us to assess the relative importance of different policy elements and identify important synergies and tradeoffs in containment design and fit to context. We present both a national-scale version of the model that was used to address policy questions of primary importance early in the pandemic, and a subsequent extended version of the model applied to a major metropolitan area to inform policy decision-making later in the pandemic.

2. Materials and Methods

A. TRACE-US

The U.S. national-level version of the model (TRACE-US) simulates the spread of COVID-19 through a population of individuals designed to be nationally representative of the United States during a six-month time period roughly corresponding to June through December, 2020 (details and data sources in SI). For computational tractability, a population of 50,000 individuals was used for the analysis presented here, with all relevant parameters scaled appropriately.

Initialization

Agents (individuals in the agent-based model) are assigned ages based on US data. Instead of assuming random mixing, we use an empirically-informed network contact structure based on age and setting, to reflect important aspects of COVID-19 and containment policy. At the beginning of each simulation, each agent is assigned a contact list, divided across four settings (home, work, school, other). The size and contents of this list are determined based on the age of the agent according to a weighted sampling procedure from empirical contact density data (details and animation in SI).

Dynamics

The model follows a modified version of the canonical SEIR formulation for mathematical modeling of communicable disease. The model accounts for both true asymptomatic and pre-symptomatic infectious states as well as heterogeneity in infectivity across individuals, all of which are known features of COVID-19 (state transition chart and empirically-informed infectivity distribution in SI). Analysis is conducted by stochastic simulation in discrete time intervals. During every simulated day, agents interact with their contacts in ways that potentially transmit SARS-CoV-2, with those infected progressing through disease states until they are “recovered.”

Epidemiological scenarios and Uncertainty

The COVID-19 pandemic has been characterized by ongoing uncertainty about underlying epidemiological parameters regarding SARS-CoV-2 and its spread. A key focus of our analysis is to assess robustness of containment measures in light of this uncertainty. Thus, we explore a wide range of potential epidemiological assumptions, while co-varying parameters across a large multidimensional space.

Among the parameters co-varied in TRACE-US are: the latent duration of infection, the duration of the infectious period, the proportion of infections that are asymptomatic, the degree to which asymptomatic cases are contagious to others, the proportion of infections that are presymptomatic (contagious to others before symptom onset), the distribution of infectivity across individuals, the background level of immunity in the population, the starting proportion of the population actively infectious, the percent of the population affected concomitantly with an influenza-like-illness (ILI) with overlapping symptoms to COVID-19, and the underlying R_0 . These parameters were all the source of substantial uncertainty early in the pandemic, and are varied over wide ranges (see SI)--including configurations more pessimistic than even the CDC's "worst-case" scenario [7] as well as the most optimistic parameter estimates found in our literature review.

In this way, we test the dependency of outcomes projected for any particular intervention design on the set of specific assumptions used, identify robust policy choices, and uncover inter-relationships between aspects of policy implementation (e.g. who is given priority for testing) and aspects of underlying epidemiology (e.g. how much asymptomatic transmission is occurring).

Modeling interventions

The primary focus of our analysis with TRACE-US was to assess the potential impact of a wide array of specific implementation options for three types of containment policies available at the time—mass social distancing, polymerase chain reaction (PCR) testing with contact tracing and quarantine, and serological (antibody) testing. Across these policy dimensions, we consider a total of 10,380 combinations of specific containment policies.

Three forms of social distancing policy are simulated in our model. The first, school closure, eliminates all contacts that occur in the school setting (for parsimony schools are simulated either to be all open or all closed). The second, workplace closure, eliminates contacts that occur in the workplace—completely (100%), partially (33%), or not at all (0%). The third, shelter-in-place, eliminates all contacts except those in the "home" category when it is enacted. Each of these policies can be activated alone or in combination with each other or with containment policies based on PCR test-and-trace or serological testing.

The set of PCR test-and-trace policies we simulate is extensive, and consists of assumptions about the test themselves, assumptions about contact tracing, assumptions about targeting of both test and tracing, and assumptions about quarantine. In the simulations below, we vary the number of PCR tests available per day in a range equivalent to 250,000 - 500,000/day for a population of 300 million (scaled to our agent population size). We vary assumptions about test accuracy from a false-negative rate of 5% to 30%, while holding the false-positive rate constant at 5% [8-9].

Contact tracing that results in timely isolation of potentially exposed individuals is indicated as a potentially effective containment strategy in both prior literature on other epidemics as well as recent experience with COVID-19 [10-12]. Crucially, the extent to which contact tracing strategies can successfully aid in disease suppression is determined by capacity to engage in contact tracing relative to prevalence of the disease at a given time [12], requiring trained

workers [13]. We represent contact tracing within our model as *the number of potentially exposed contacts who the available workforce can identify and reach each simulated day*. This allows us to realistically represent the possibility that disease prevalence will outstrip contact tracing capacity at a given point in time and thus render it less effective because some exposed individuals are not communicated with and as a result spread the disease to others. We vary contact tracing capacity over a wide range (from a daily capacity to trace a number of contacts equivalent to 1/500th of the population up through a capacity equivalent to the entire population).

In our model, PCR testing and contact tracing are used in concert to identify a set of agents who are asked to self-quarantine. An important dimension of difference across policy implementations is the strategy used to target available PCR tests and to decide who to quarantine. We simulate four primary strategies (additional configurations in SI):

- (1) *Prioritize Symptomatic*: Symptomatic agents are given priority for testing (with any remaining tests used to sample the population at random). Any agent with a positive PCR test is asked to self-quarantine, their contacts are traced, and all successfully traced contacts are asked to self-quarantine. This is intended to represent common practice across much of the United States at the time of simulation.
- (2) *Random Testing*: Tests are allocated randomly across the population. Any agent with a positive PCR test is asked to self-quarantine, their contacts are traced, and all successfully traced contacts are asked to self-quarantine. This is intended to represent an approach discussed in some policy proposals, with the goal of catching asymptomatic cases and transmission.
- (3) *Prioritize Senior Citizens*: Symptomatic agents over age 65 are given priority for testing (with any remaining tests used to sample the population at random). Any agent with a positive PCR test is asked to self-quarantine, their contacts are traced, and all successfully traced contacts are asked to self-quarantine. Symptomatic agents who are not tested are also asked to self-quarantine, but do not have contacts traced. This is intended to reflect policy discussions based on the relatively high case rate among the elderly.
- (4) *Prioritize Contacts*: In this strategy, all symptomatic agents are asked to self-quarantine (as is done with other respiratory illnesses such as influenza) and to report contacts. PCR testing is then reserved for successfully traced contacts; only those contacts who test positive are asked to self-quarantine. To our knowledge, this type of policy has not been widely used in COVID-19 containment, but we explore it here as an innovation.

Following standard practice worldwide at the time of simulation, quarantine in our model is assumed to be 14 days in length. During this time, agents who are adherent will have no contact with other agents, including their “home” contacts. The fraction of agents who are non-adherent is a parameter of the model (ranging from 10% to 50%); these agents continue with their full set of normal contacts (which may be shaped by other policies such as workplace or school closure).

Serological testing for antibodies was also modeled to represent policy discussions early in the pandemic around selective exemption from social distancing or quarantine based on presumed immunity among those with antibodies. These simulations are described in the Supplementary Information.

Computational Implementation

TRACE-US was programmed in R version 3.6.3. Using Azure cloud computing, 3.2 million simulation runs were generated, with output data on both population-level and individual level outcomes and dynamics stored in a database. Source code is available on a public repository⁶.

B. TRACE-STL

We extended the model described above to answer questions of highest relevance later in the pandemic (including new antigen test technologies, novel emergent SARS-CoV-2 variants, and vaccine uptake), and to permit close tailoring to specific real-world geographic settings. Here, we report application of this extended model to the St. Louis metropolitan area, comprising approximately 2.5 million people spread across 8 counties and two U.S. states. We worked closely with the St. Louis City Department of Health on appropriate representation of local context and potential policy priorities in order to maximize real-world utility of TRACE-STL as a tool to support decisions made during a critical phase of the pandemic: the first half of 2021.

Changes to the model from the U.S. National version fell into three broad categories (for full details and implementation see SI):

Tailoring to local geography and conditions, and retrospective testing

For TRACE-STL, we improve demographic and geographic accuracy using population, household, school, and workplace information from the U.S. Synthetic Population developed by RTI International for the NIH MIDAS project [14]. We construct an agent population for St. Louis City and seven surrounding counties and assign for each individual based on household and age-stratified sampled work, school, and social context. The resulting population of 2.4 million agents are geographically situated within the St. Louis metro area, permitting us to include the possibility of differing policy regimes in different municipal authorities in the region (e.g. City vs each county government). See SI for implementation details and a visualization of the TRACE-STL synthetic population.

Agents are initialized as in TRACE-US, but we use St. Louis-specific initial infection rates for January 2021 (the start of the simulated period). These are adjusted to account for potential undercounting of true cases due to limited testing and asymptomatic infection (see SI for details). Dynamics of transmission are similar to TRACE-US except for the variations detailed below. To build confidence in our assigned population structure and dynamics, we assess the model's "retrospective" prediction power by seeding the model with starting conditions (including infection rates, recovered rates, and containment policies in place throughout the region) representative of autumn 2020 in St. Louis and comparing simulated endpoints for December with those observed (see SI).

Changes to epidemiological scenarios to reflect late-pandemic shifts

In early 2021, the point of transition between TRACE-US and TRACE-STL, new virus variants of concern began to emerge in the pandemic (e.g. B.1.1.7 and others) characterized by substantially increased infectivity. Policymakers faced uncertainty regarding if and when these variants might become widespread locally and affect the efficacy of control measures. In

⁶ URL to be provided once accepted at journal

TRACE-STL we include additional epidemiological scenarios to represent this possibility (see SI).

New policy options and associated behavioral elements

In addition to the containment policies explored in TRACE-US, we added three new categories of control measures in TRACE-STL to represent both advances in technology over the course of the pandemic and local priorities in St Louis. These are:

- *Antigen tests.* A variety of new test technologies became more widely available at this time, characterized by more rapid results than PCR but potentially differing false negative and positive rates. We add to the model also a stock of antigen tests and strategies for their allocation (in addition to PCR tests). Positive tests from either PCR or antigen go into the same queue for contact tracing.
- *Vaccine.* Rollout of vaccine was beginning in early 2021, and we added this to the model (representing vaccinated individuals as in state “recovered” i.e. immune for the time period simulated). At baseline, vaccination in TRACE-STL follows a pre-computed rollout trajectory developed in consultation with the regional public health authorities. We also explored variations for sensitivity, including more rapid rollout, age-weighted uptake, and zip-code weighted uptake.
- *Mask usage.* With better evidence available for the impact of mask usage on both transmission and susceptibility, we were able to include this behavior into TRACE-STL. We varied assumptions both about how many agents wear masks regularly, and how effectively they wear them, over wide ranges (see below).

3. Results

A. TRACE-US

We conducted three sets of analyses with the simulations from the model, all aimed at assessing the potential effectiveness of containment policies in the face of uncertainty. These results were presented at the U.S. Congress in an invited briefing in December 2020⁷.

Robust Suppression is Possible while Relaxing Social Distancing

In the first set of analyses, we evaluated all 10,380 policy configurations to identify robust options for suppressing the spread of COVID-19. Iterating through the 16 epidemiological scenarios considered, each policy option was evaluated by comparison across 40 simulations of its associated mean cumulative infection rate against the mean cumulative infection rate for our strongest mass social distancing baseline (“shelter in place”). We then identified the set of policies that satisfied four conditions:⁸

1. Relax shelter-in-place and full business closures (e.g. remote work)
2. Mean cumulative infection rate across simulations less than 1 standard deviation higher than the mean cumulative infection rate under a shelter-in-place policy

⁷ Bipartisan Working Group caucus, December 3rd, 2020.

⁸ These reflect our definition of a robust policy – one that successfully contains the spread of infection not only when averaged across our *a priori* uncertainty, but is also effective even in the worst-case scenario. Varying the specific numerical criteria yields a similar set of robust policies, and the complete set of simulation results are available on the public repository for interested readers.

3. Maximum cumulative infection rate for *any* run of the simulation does not exceed five times the maximum cumulative infection rate under a shelter-in-place policy
4. The policy is not strictly more costly (in terms of resources or restrictions imposed) than any other policy that satisfies conditions 1-3.

The set of policies that satisfied those four conditions were deemed “robust” to a particular epidemiological scenario. Using this approach, we identified a small set of containment policies that were highly robust (Table 1), meaning they were effective across all 16 scenarios, and a larger set of policies which were partially robust (see SI). The highly robust policies all maintain some elements of social distancing blended with efficiently targeted PCR testing and at least moderate contact tracing. In less demanding epidemiological scenarios, policies that fully release social distancing and/or require less testing and tracing capacity also perform well.

Key Elements in Robust Suppression

In a second analysis, we estimated the average treatment effect (ATE) of each policy variable by calculating the average change in cumulative infection rates caused by altering one policy while holding everything else constant (including random seed). This analysis indicated which factors were most important determinants of robust suppression in our simulations (Figure 1). Two key drivers of successful suppression policies in the model are adherence and efficient PCR test targeting. In the most unfavorable epidemiological scenario, increasing quarantine adherence from 50% to 90% decreases the cumulative infection rate by 14 percentage points on average. Testing contacts of symptomatic individuals rather than the symptomatics themselves reduces infection rates by 5 percentage points on average.

The importance of adherence underlines the need for policy interventions to consider ways to facilitate successful quarantine, whether by consistent messaging, legal protections for sick leave, or direct financial or logistical support. The examination of individual policy options finds no policy simulated that can replace any degree mass social distancing if adherence is low (50%) even in the most favorable scenarios. By contrast, higher adherence allows multiple policies to be successful substitutes for mass social distancing, even in the most difficult scenarios (see SI).

We also find that, with limited PCR testing capacity, the common practice early in the pandemic of prioritizing symptomatics for testing is not the most effective approach. Nor do we find that testing the general population at random is especially effective at this level of test capacity. Instead, our model identifies as most successful a strategy that relies on asking symptomatics to self-quarantine without a test (as is done for influenza), and using limited testing to evaluate reported contacts. This result holds even with the introduction of concomitant ILI symptoms in the population.

A final result from this analysis is that the relative impact of individual factors driving successful suppression is magnified for especially pessimistic epidemiological scenarios, whereas in especially optimistic scenarios the differences are attenuated and become indistinguishable (Figure 1).

Tradeoffs, Synergy and Variability

Our third set of analyses are aimed at determining potential tradeoffs, substitutability in multi-dimensional space, or synergy between elements of containment policies. Figure 2 shows potential tradeoffs along four of the dimensions of policy design we examined—testing capacity, test targeting strategy, contact tracing capacity, and adherence to quarantine. Investment in contact tracing capacity, for example, can substitute for testing capacity given sufficient adherence, and efficient targeting of tests improves outcomes for low-test-and-trace capacities at all levels of adherence. The figure also shows important variability across stochastic simulation runs (and thus variability in projected outcomes from policies). Random sampling of the population as a testing strategy, for example, leads to high variability in effectiveness, as does targeting of symptomatics for some levels of capacity.

We also explored the impact of varying the initial percentage of the population in an infected state at time 0 in the simulation. This allows us to address potential timing decisions for the release of mass social distancing so as to maximize the success of test-and-trace policies in containing the epidemic, as well as tradeoffs between the speed of re-opening workplaces and schools versus the testing capacity required for successful containment. Although our model simulates a single, self-contained population, starting the simulation with varying percentages of the population simultaneously in the infected state also provides some insight into the robustness of suppression policies against imported new cases.

The full set of simulations conducted with TRACE-US can be accessed via an interactive dashboard⁹.

B. TRACE-STL

We conducted over 50,000 simulations with the extended TRACE-STL model, representing 1,152 combinations of policy elements co-varied with multiple epidemiological scenarios. Our analysis of these simulations resulted in three focal policy-oriented findings (detailed below). These results were presented to the Joint Board of Health and Hospitals of St. Louis City in February 2021, and were featured in a public outreach effort by the health department via their website¹⁰. The modeling effort provided support for existing policy prevention strategies in place in St. Louis City, while highlighting the continued importance of adherence to social distancing measures. In a politically diverse region anxious to return to a state of pre-pandemic normalcy, these results enhanced public health decision-makers credibility in maintaining social distancing restrictions. The work also served as a “proof of concept” for application to other city and state settings.

Impact of potential novel variants of SARS-CoV-2

Baseline scenarios intended to represent the status quo—levels of infection, immunity, vaccination as well as policies in effect in St. Louis at the start of the simulation, and without any new variants becoming widespread—projected successful control of the epidemic, with rapid downward curve of prevalence over 6 months as vaccinations ramped up and with cumulative infections increasing only moderately (Figure 3a&b). This finding was not sensitive to opening of businesses, or low adherence to mask use (see SI), but did assume control measures in place in February were continued.

⁹ <https://www.brookings.edu/TRACE>

¹⁰ See <https://www.brookings.edu/TRACE-STL> and <https://www.stlouis-mo.gov/covid-19/data/trace.cfm>

By contrast, the same set of initial assumptions led to explosive growth in cases under the scenario in which a more virulent variant became the dominant one circulating in St Louis. In this case, status quo controls were insufficient to prevent a large additional wave of cases peaking after about 60 days and increasing cumulative infection levels by an order of magnitude [Figure 3c&d]. These results helped quantify for policy makers the potential risk associated with new variants. Given the ongoing uncertainty regarding if and when variants might become widespread, we next searched the multidimensional policy space within the simulation to identify robust options for rapid and effective response to high-infectivity scenarios.

Robust policy options to contain spread in high-infectivity scenarios

As with TRACE-US, we were able to identify a number of robust policy choices. Our metric for successful policies was that they reliably reduced cumulative infections by more than half relative to the baseline scenario, even with the highly infective variant in place, across 10 independent stochastic simulations. Options that met this criteria included: substantially increasing investment in contact tracing capacity (while keeping it within feasible ranges used earlier in the US model) [Fig 4a], increasing PCR testing capacity while also investing in more contact tracing [Fig 4b], and restrictions on business activity regionwide [Fig 4c]. Of particular interest given the heterogeneous landscape of municipal authority across the St. Louis metro area, we found that unilateral business restrictions in the city alone would *not* be an effective containment measure [Fig 4d].

Importance of widespread and proper mask usage in the face of variants

Our analysis of the simulation results highlighted the high importance adherence to mask usage could have as an effective control measure in the high-infectivity scenarios. Table 2 shows an analysis which co-varies two aspects of mask usage: the fraction of agents regularly wearing masks outside the home (columns) and the “effectiveness” of masks as worn (rows). The latter variable is intended to reflect real-world conditions in which the fit, materials, or placement of masks causes effectiveness of masks in blocking virus spread to fall short of the laboratory-measured ideal by some degree. As the table shows, moving from low adherence and effectiveness to high led to a four-fold decrease in cumulative prevalence over the simulated time period, and even moderate improvements in mask usage made a significant difference in control. This finding inspired a public outreach campaign¹¹ by the public health department, and was underlined by the subsequent CDC emphasis on masks in March 2021.

The full set of simulations conducted with TRACE-STL can be accessed via an interactive dashboard¹².

4. Conclusions and Future Work

Computational models have played an important role in informing both the public and policymakers throughout the COVID-19 pandemic. The TRACE model and analysis presented here offer a distinct approach that differs from and complements many other uses of models. Building on our previous experience in other areas of population health and previous pandemics

¹¹ <https://www.stlouis-mo.gov/covid-19/data/trace.cfm>

¹² <https://brookings-csdp.shinyapps.io/trace-stl-dash/>

[3-5], TRACE was designed as a “policy laboratory” and a practical decision-support tool for policymakers rather than a forecasting model. Our design was informed by stakeholders and by the exigencies of decision-making under extreme uncertainty that has characterized the pandemic throughout. Rather than representing the most probable single course of the pandemic based on somewhat uncertain assumptions and a fixed policy course, our analysis helped policy-makers both to explore a wide range of potential formulations of pandemic control, and to evaluate robustness to a full range of potential epidemiological scenarios. Unlike many other models, TRACE is also built around the technique of agent-based modeling (ABM) [2,4], allowing it to address behavioral, biological, and geographic heterogeneities that have been characteristic of the COVID-19 pandemic [6]. For TRACE-STL, the ABM also approach allowed us to leverage substantial investments made by the federal government in pandemic preparedness via the creation of demographically and geospatially accurate synthetic populations designed for exactly this type of model [14]. The practical application of TRACE at both the federal and state/local level, described here, also serves a “proof of concept” for use of this modeling approach and for the interactive dashboard and other policy engagement tools built to support both versions of TRACE [15-16]. As the world continues to grapple with this pandemic, and consider future ones, we hope the approach taken by TRACE will offer a framework for future work to support difficult policy decisions.

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Figures and Tables

Target for PCR Tests	PCR False Negative Rate	PCR Tests Per Day	Daily Trace Capacity	Quarantine Adherence	Schools Closed	Remote Work
Symptomatics	5%	350,000	Unlimited	90%	Yes	33%
Symptomatics	5%	500,000	Unlimited	90%	No	33%
Contacts	30%	250,000	Unlimited	90%	Yes	No
Random	30%	500,000	Unlimited	90%	Yes	No
Symptomatics	5%	500,000	1 per 50 individuals	90%	Yes	No
Symptomatics	30%	500,000	1 per 50 individuals	90%	Yes	33%
Contacts	30%	350,000	1 per 50 individuals	90%	Yes	No

Table 1. The complete set of “highly robust” policies that successfully contain the epidemic while relaxing shelter-in-place and work-from-home orders, even under the most pessimistic epidemiological assumptions. Note that every policy in this set requires 90% adherence to self-isolation requests.

Figure 1. Each gray dot plots the treatment effect of a policy variable on cumulative infection rates (red dots are the average treatment effect across all runs), altering the policy listed on the left while holding all other variables constant. The base categories are as follows: Trace Capacity = 1 per 500 individuals, PCR Target = Random, Quarantine Adherence = 50%, PCR Tests Per Day = 250k, PCR False Negative Rate = 30%. In the most favorable epidemiological scenario, no policy variable has a significant effect on outcomes, because even the weakest policy intervention we tested successfully suppresses the epidemic.

Figure 2 Each dot represents the outcome of a single simulation run, with color corresponding to proportion of total population infected. Each of the 81 cells contains runs at the same point in parameter space, differing only by random seed and positioned by random jitter within the cell. The cells are arranged along four parameter space dimensions: horizontal facets (top labels) represent different PCR testing regimes, vertical facets (right labels) represent different quarantine adherence rates, horizontal plot axes (bottom labels) represent amount of PCR tests, and vertical plot axes (left labels) represent contact tracing capacity.

Figure 3 Instantaneous virus prevalence and cumulative infections for two infectivity levels with then-current control measures. Low infectivity (a & b) corresponds to an approximate R_0 of 2.4, and high infectivity (c & d) represents an approximate R_0 of 3.7.

Figure 4 Comparison of cumulative infection rates against baseline for various policy interventions: a) Expanded contact tracing capacity. b) Expanded contact tracing capacity with more PCR tests. c) Regional closure of workplaces. d) Closure of workplaces within city boundary.

Mask Effectiveness	Mask Adherence	
	Low	High
Low	43.4	37.4
Moderate	34.4	23.1
High	23.5	11.8

Table 2. Cumulative percentage of St Louis City population infected after 6 simulated months under various masking scenarios. Parameterizations in SI.

Supplementary Appendix

for “Modeling Robustness of COVID-19 Containment Policies to Heterogeneity and Uncertainty: the TRACE Model”

Section A: Detailed Model Description

In this appendix section, we describe agent-based model design and parameterization in detail, and we present additional results beyond those described in the main text. Throughout, we differentiate between two iterations of the model:

- 1) TRACE-US is nationally representative with respect to population and disease conditions, and reflects a six-month time period analogous to June through December, 2020.
- 2) TRACE-STL is localized for application to the city of St. Louis and the surrounding metropolitan region, and represents a six-month time period analogous to January through June, 2021.

Initialization

TRACE-US

Agents in the model are each initialized with a disease state (S = susceptible, E = exposed, P = presymptomatic, I = symptomatic, A = asymptomatic, R = recovered). We allow for heterogeneous infectivity (i.e. ability to transmit disease during contact) for agents in an infectious state.

Fig S1. Potential disease state transition pathways

The number of agents initialized, the proportion starting in each state, and infectivity distribution are detailed in Table 1. Agents are assigned an age category (a 5-year age bin), with proportions of agents in each age category derived from ACS 2018 data.

Each agent is also initialized with a set of contacts with whom they may interact during the course of a simulation run; contact initialization is disaggregated by setting and weighted by age category as follows:

For each of four settings (s = home, work, school, and other) we initialize each agent's contacts using a contact matrix μ^s , where each entry $\mu_{\alpha,\beta}^s$ represents for an agent with age category α the expected number of contacts with age category β . Each agent is given a total number of setting contacts equal to the appropriate row sum of this matrix: for an agent with age category α , the total number of contacts in setting s is $\sum_{\beta} \mu_{\alpha,\beta}^s$. Each agent's specific contacts for setting s are then sampled from the full list of agents, each weighted by the appropriate entry in μ^s . That is,

for agent i we select their setting s contacts by conducting $\sum_{\alpha} \mu_{a(i),\beta}^s$ draws without replacement from the pool of other agents, where each agent j is drawn with weight $\mu_{a(i),\beta(j)}^s$. Contact matrices are taken from Prem et al. (2017). We ran this contact generation process ten times, creating unique populations that we used for each combination of disease and policy conditions described below.

Figure S-1. In this animation, a small subset of the agent population is shown as the epidemic spreads through social contacts. Each dot is one agent; the size of the dot corresponds to the age of the agent (small dots are children, medium dots middle-aged adults, large dots over 65). The colors of the dots change through time to reflect disease state as in the previous two figures. Lines represent social contact between agents. Light colored lines represent contacts at home, dashed lined represent contacts at work, and dark lines represent contacts at school and other settings.

Table 1

Parameter	Value	Sensitivity Analysis Variation	Details
Population	50,000	50,000	Size selected to balance runtime and observational power; roughly intended to be nationally representative
Initial infected (%)	0.114	0.606%	Baseline value calculated as: (confirmed cases-recovered cases)/total US population Source: <i>COVID Tracking Project</i> , 2020 Higher variation based on estimated 16% of cases detected (Russell et al., 2020)

			Of those who are initially infected, 50% are placed in state I and 50% in states E, P, or A based on model Presymptomatic and Asymptomatic Rate parameters.
Initial recovered (%)	0.005%	15%	Baseline value calculated as: (confirmed cases-recovered cases)/total US population Source: <i>COVID Tracking Project</i> , 2020
Infectivity distribution	Gamma (1, 0.25)	Homogeneous	Distribution means are selected to produce model R_0 values given agent contact patterns under baseline conditions (discussed further below) Distribution source: Ferguson et al., 2020

TRACE-STL

A population of agents is generated using the U.S. Synthetic Population 2010 (Version 1) developed by RTI International (Wheaton et al., 2010). We use the populations of St. Louis city, St. Louis County, and the other counties that adjoin one or both of these, for a total of eight: the above, plus Franklin, Jefferson, and St. Charles counties in MO, and Madison, Monroe, and St. Clair counties in IL. We use the population, household, school, and workplace files from the population.

We apply some additional filtration and cleaning to the synthetic populations to conform to our model architecture and to incorporate simplifying assumptions:

1. We ignore “Group Home” synthetic persons, focusing only on households and individuals.
2. We remove persons whose workplaces are outside the eight county region. (In the synthetic population workplaces are assigned stochastically based on economic and commuting data).
3. Similarly, we remove persons assigned to schools outside the region.

Agents are initialized with disease states and infectivity values as described in the TRACE-US model. However, initial infection rates in the population are taken from 10-day reported “new case” totals and recovered rates from historical greater than 10-day reported “new case” totals for each of the 8 counties included in model, adjusted to model population (*The New York Times*. (2021). *Coronavirus (Covid-19) Data in the United States*, 2020/2021). Rates are proportionally distributed across zip codes for St. Louis City and St. Louis County using county COVID-19 data. We adjust initial infection rates across runs using an “undercount factor” parameter, selecting values of 2 and 5 (Reese et al., 2020; Russell et al., 2020).

Figure S-2. This image depicts the St. Louis region synthetic population with model states from a run in progress; red agents are in one of the infected states, green agents recovered, and blue agents susceptible.

From the synthetic population data, each agent has a household geographic location (longitude and latitude). We then use the R package *sf* to denote agents who reside in St. Louis City. Using the above, we have an agent population $G = \{g_j\}$ for $1 \leq j \leq 2431826$, a list of households $H = \{h_i\}$ for $1 \leq i \leq M_H$, a list of schools $S = \{s_i\}$ for $1 \leq i \leq M_S$, and a list of workplaces $W = \{w_i\}$ for $1 \leq i \leq M_W$. We use notation $G(h_i)$ to refer to the set of agents in the household h_i , $H(g_j)$ to refer to the household of agent j , and similar terms for school and workplace settings.

Each agent is assigned a list of contacts, which is constructed from separate lists for each of four settings, that is we assign to each agent g_j a list $L_{j,s}$ for $s = \text{home, work, school, and other}$. Since we have restricted our population to members of specific synthetic households, we assume that all agents have contact with their other household members; that is, $L_{j,H} = G(H(g_j)) \setminus \{g_j\}$. For each of the other settings ($s = \text{work, school, and other}$) we initialize each agent's contacts using a contact matrix μ^s , where each entry $\mu_{a,\beta}^s$ represents for an agent with age category α the expected number of contacts with age category β .

Each agent is given a total number of setting contacts equal to the appropriate row sum of this matrix: for an agent with age category a , the total number of contacts in setting s is $\sum_{\alpha} \mu_{a,\beta}^s$. Each agent's specific contacts for setting s are then sampled from a subset of the full list of agents,

each weighted by the appropriate entry in μ^s . That is, for agent i we select their setting s contacts by conducting $\sum_{\alpha} \mu_{\alpha(i),\beta}^s$ draws without replacement from the pool of other agents, where each agent j is drawn with weight $\mu_{\alpha(i),\beta(j)}^s$.

The sampling pools for agent j are as follows: for school contacts, we sample the pool of other agents who attend the same school, $G(S(g_j)) \setminus \{g_j\}$; similarly for work contacts, the pool is $G(W(g_j)) \setminus \{g_j\}$. If an agent is not assigned to a school or workplace, they have no contacts from that setting.

The other sampling pool is constructed as follows: we use the geocoded locations of households to create a set $O(h_k)$ which is comprised of all agents in a 3.5 mile radius of household h_k , not including the members of h_k (Ver Ploeg et al., 2015). Each agent's other contact list $L_{j,O}$ is sampled from $O(H(g_j))$ using the appropriate age weights.

Contact matrices are taken from Prem et al. (2017). We ran this contact generation process ten times, creating unique populations that we used for each combination of disease and policy conditions described below.

Baseline model dynamics

TRACE-US

Each simulated day t , agents are randomly ordered and each agent i performs the following actions:

1. Interact with all agents j on their current active contact list (C_{it})
2. If agent i is in state S , interaction with an agent j in states A , P , I will result in agent i transitioning from state S with probability

$$\Pr(\text{transition}_{ijt}) = T_j * A_j A'$$

where T_j is the transmission value for agent j , A_j indicates whether j is asymptomatic, and A' is an asymptomatic transmission rate multiplier. When such state transition occurs, it is to state A with probability A^* , P with probability P^* , or E with probability $1-A^*-P^*$.

3. If agent i is in state E or P , it will transition to state I if time since infection is greater than the disease latent period ($E_t > L$)
4. If agent i is in state A or state I , it will transition to state R if time since infection is greater than the disease latent period and the disease duration (based on their time since infection and the latest duration and infectious duration parameter ($E_t > L + D$))

Parameter values related to baseline model dynamics are described in Table 2.

Table 2

Parameter	Value	Sensitivity Analysis Variation	Details
R_0^{13}	2.2	2.5, 3.4	Sources: <i>CurveFit</i> , 2020/2021; Ferguson et al., 2020; Gollier, 2020; Hellewell et al., 2020; Keeling et al., 2020;

¹³ This is used to determine the mean of the infectivity distribution (described above) through calibration as follows:

			Legrand et al., 2004; Murray, 2020; Prem et al., 2017; Verity et al., 2020; Walker et al., 2020
Asymptomatic transmission rate	0	0.5, 1	Source: Ferguson et al., 2020
Asymptomatic rate	18%	35%	Primary value source: Mizumoto et al., 2020 Sensitivity value source: Kimball, 2020
Presymptomatic rate	20%	40%	Sources: Du et al., 2020; Hoehl et al., 2020; Kimball, 2020; Wei, 2020
Latent Duration (days)	6		Sources: Ghinai et al., 2020; Prem et al., 2017
Infectious Duration (days)	5	6, 10	Sources: Ferguson et al., 2020; Liu et al., 2020
Influenza-like Illness (ILI) prevalence	0.4%		Absent additional information, agents with ILI erroneously consider themselves infected with COVID-19 Source: Siddarth & Weyl, 2020

TRACE-STL

Baseline model dynamics are similar to those in TRACE-US, but model runs used R_0 values of 2.4 and 3.7 to reflect uncertainties about the properties and prevalence of emerging variants (WHO: SARS-CoV-2 Variant – United Kingdom of Great Britain and Northern Ireland, 2020).

Modeling COVID-19 containment policies and practices

TRACE-US

We represent social distancing measures in our model as:

- 1) Quarantine: agents who believe that they are infected (either because they are actually infected and symptomatic or because they have a similar, influenza-like illness), receive a positive COVID-19 test result (described below), or are identified as being in contact with someone who has been infected (described below) are asked to self-isolate for a period of time determined by the quarantine duration parameter; they comply with this request probabilistically based on the quarantine adherence parameter. When doing so, they do not have contact with other agents. If non-adherent, they interact with other agents as normal, but are considered quarantined for the purpose of testing and contact tracing (described below).
- 2) School closure: agents affected by school closure do not have contact in school settings.
- 3) Remote work: agents affected by school closure do not have contact in work settings.
- 4) Shelter-in-place: agents affected by school closure do not have contact in “other” settings.

-
1. A single, random agent is infected on day one (with probability of asymptomatic infection, etc. using the parameters from the full model)
 2. The model runs as normal, except that new infections can only spread from the initial agent
 3. After fourteen ticks (after the initial infectious period will have ended), we count the number of agents who are in any state other than S.

Repeating this procedure several thousand times gives us an average number of infections, which we compare to R_0 . We select an infectivity mean that produces a very close match.

Thus, an agent who is not quarantined but is affected by active school closure, remote work, and shelter-in-place policies would only have contact in their home setting (i.e. with other members of their household).

In our model, COVID-19 testing and tracing takes place as follows:

1. A sample of non-quarantined agents – up to the number of available daily tests and prioritized based on targeting strategy (described below) – are tested.
 - a. Test returns positive result with some probability of false negative results for infected agents, and false positive results for non-infected agents.
2. Agents who test positive are asked to quarantine.
3. Agents who test positive report the members of their daily contact list. A full list of contacts to trace is created from all such contact lists, and agents on this list up to the available daily tracing capacity are asked to self-isolate. Any remaining contacts remain untraced, but may be traced on subsequent days.

We explore these PCR testing strategies:

- *symptomatic-then-random*: first allocate tests to a random sample of symptomatic agents, then allocate excess capacity randomly.
- *seniors-then-random*: first allocate tests to a random sample of symptomatic agents with age > 65. Ask all other symptomatic agents to self-isolate, but do not trace contacts. Allocate excess capacity randomly.
- *symptomatic-contacts*: ask symptomatic agents to self-isolate; allocate PCR tests to a random sample of their successfully-traced contacts.

In our model, when it is active, serologic (i.e. antibody) testing takes place in parallel to PCR testing. The goal of these tests is to identify agents who have already recovered, in order to clear them from social distancing and free up PCR testing capacity. “Workforce” agents (i.e. those aged 20 to 64 years who are not currently quarantined or previously tested for antibodies) are prioritized for testing. As with PCR testing, false negative and positive results can probabilistically occur.

For each of the parameter values that collectively define disease conditions described above, we explore the full set of parameters that determine policies and practices in Table 3.

Table 3.

Parameter	Values	Details
Quarantine Duration	14 days	
Adherence to quarantine requests	0.5, 0.75, 0.9	Sources: Ahmed et al., 2020; Edwards et al., 2016
Social Distancing: Schools Closed	0, 1	
Social Distancing: Remote Work	0, 0.33, 1	Proportion of agents in workforce engaged in remote work Source: Bartik et al., 2020

Social Distancing: Shelter-in-place	0, 1	
PCR Test False Positive Rate	0.05	Source: Surkova et al., 2020
PCR Test False Negative Rate	0.05, 0.3	Source: West et al., 2020
Number of PCR Tests Per Day	250,000 350,000, 500,000	Values are given in terms of U.S. population and rescaled to the agent population
Daily Tracing Capacity	100, 1000, Unlimited	Source: Li et al., 2020; Watson et al., 2020
Serologic False Positive Rate	0.01, 0.1, 0.3	Sources: Bastos et al., 2020; Mallapaty, 2020
Serologic False Negative Rate	0.01	Sources: Bastos et al., 2020; Mallapaty, 2020
Number Serologic Tests per Day	0, 500,000	Values are given in terms of U.S. population and rescaled to the agent population

TRACE-STL

In addition to the disease containment policies explored using the TRACE-US model, we have additional policies that we characterize and test using the TRACE-STL model

Some proportion of agents are assigned to be mask-wearers; these agents have reduced probability of both infection from other agents, and transmission if they themselves are infected. This reduction is applied by multiplying the transmission rate by a given model parameter at the point of random draw for infection.

Agents can be vaccinated: when this occurs, they are effectively shifted to the ‘Recovered’ state. In TRACE-STL vaccination follows a precomputed curve which specifies a proportion of agents to be vaccinated each day. In the main model runs, this follows a quadratic function that begins at 1% at model initialization and increases to 20% at end of run, and vaccines are administered uniformly at random across the agent population.

Additional vaccination mechanics were explored for sensitivity, including a doubled vaccination rate (increasing to 40%), age-weighted agent choice (by a linear weighting function), and zip code weighted agent choice (by early vaccination registration data).

Mask usage, social distancing, and vaccination policies can be applied heterogeneously across geographies. Since agents are coded by county and zip code, these can be used to determine policy recipients.

Antigen testing implements a parallel but mechanically similar testing functions to PCR testing. Antigen testing differs from PCR testing in this model only by different false negative and positive rates and different optional testing targets. All agents that test positive from either testing mechanism go into the same queue for contact tracing.

Antigen Test Targets:

- *random*: allocate tests at random.

- *repeat*: allocate tests at random, then administer two tests per agent selected, treating at least one positive result as a positive test. This effectively reduces false positive and lowers false negative rates.

In addition to the parameters that define disease characteristics described above, we also explore all combinations of the following parameters that determine active policies and practices. Unless otherwise stated, parameter values were determined through consultation with St. Louis City Department of Health personnel.

Table 4.

Parameter	Values	Details
Adherence to quarantine requests	0.75	Sources: Ahmed et al., 2020; Edwards et al., 2016
Business closure	In St. Louis City but not surrounding counties; in St. Louis City and surrounding counties; in neither	Where active, removes workplace contacts (similar to “remote work” policies in the TRACE-US model)
Remote learning	See Table 5.	Where active, removes school contacts for a proportion of agents (similar to the “school closure” policy in the TRACE-US model)
Mask use	“No mandate” (0.5 mask usage outside of St. Louis City, 0.6 inside) “Mask mandate” (0.7 mask usage outside of St. Louis City, 0.85 inside)	Sources: Haischer et al., 2020; Hutchins et al., 2020
Mask effectiveness	High (60% reduction in outgoing transmission from masked agent, 40% reduction of incoming transmission to masked agent) Low (30% reduction in outgoing transmission from masked agent, 20% reduction of incoming transmission to masked agent)	Source: CDC, 2020
PCR test volume	1,750/day; 2,500/day	
Antigen test volume	300/day; 3,000/day; 30,000/day	
Antigen test false-negative rate	0.11, 0.2	Sources: Larremore et al., 2020; Mina et al., 2020
Antigen test false-positive rate	0.05	Source: CDC, 2020b
PCR target	Contacts-of-symptomatics, symptomatics	
Antigen target	Random, repeat	
Trace volume	6,000/day; 60,000/day	

Table 5.

County	Remote learning estimate (Elementary)	Remote learning estimate (Middle/High School)
St. Louis City	40%	65%
St. Louis County	35%	60%
Franklin County	30%	55%
Jefferson County	30%	55%
Madison County (IL)	30%	55%
Monroe County (IL)	30%	55%
St. Charles County	30%	55%
St. Clair County (IL)	30%	55%

Section B: Additional Results

In this appendix section, we present some results from our analyses beyond those that appear in the main paper that may be of interest to some readers.

Retrospective Model Testing: TRACE-STL

Prior to application on potential policies and practices, we assessed our model's ability to retrodict recent, real-world trends in disease prevalence in the St. Louis region. We parameterized the model with starting conditions representative of September 2020 in St Louis and comparing simulated disease trends through December 2020 with real world observations. We use an R_0 value of 2.4 and assume an undercounted infection rate (i.e. we initialize our model with twice the number of infected individuals as observed on September 1, 2020).

Figure S-3 shows the model output from the final 30 days of ten model runs compared to real world observations during that same time period. Our model produces results that are similar in trajectory but slightly higher than those observed in the real world, consistent with our assumption that real-world data do not reflect all actual cases that occurred. This gives us confidence in our characterization of the St. Louis context.

Figure S-3 Comparing model output and real-world cumulative infection observations for the month of November, 2020.

Secondary Findings: TRACE-US

Building on and adding to the results that we highlight in our main text, we present and depict and greater detail some patterns that emerged from our analyses that are worth considering.

- 1) Low quarantine request adherence can undermine any policy. Figure S-4 depicts a policy that successfully suppresses the epidemic when adherence is high, but does poorly when adherence drops. A central aim of policy should thus be to encourage adherence through consistent, widespread messaging, and to make self-isolation financially and logistically feasible for any American if it becomes necessary.
- 2) When testing capacity is low, strategic deployment can have a large impact on disease containment. A limited number of available daily tests (similar to what was experienced during the early months of the pandemic) is likely insufficient to suppress the epidemic if tests are primarily targeted towards symptomatic individuals. Our simulations project that unless we can double the number of daily PCR tests available, a more effective strategy is to assume that symptomatic individuals are infected and ask them to self-isolate for two weeks, reserving tests for potential asymptomatic carriers and priority populations (seniors, healthcare workers, law enforcement, etc.). As shown in Figure S-5, prioritizing tests to contacts of symptomatic cases

and asking symptomatic individuals to self-isolate significantly outperforms testing those with symptoms.

- 3) Highly inaccurate serologic tests can undermine successful policies by releasing susceptible individuals from social distancing too early. Early in the pandemic, one promising strategy that was discussed involved combining PCR testing with serologic (antibody) tests. By identifying individuals who have unknowingly been exposed to the virus and freeing them from social distancing or quarantine orders, we can potentially free up the more limited PCR test capacity and minimize societal disruption by allowing those with potential immunity to get back to economic activities. However, it has become clear that many existing serologic tests suffer from high false positive rates. As shown in Figure S-6, relying on these tests as part of a national strategy could backfire by clearing people as immune who are in fact susceptible or infected.

Figure S-4 Infection curves sampled from the model, varying quarantine adherence rate (dark lines are mean infection curves across all runs). Red lines are from runs with low adherence to quarantine requests (50%), blue lines from runs with medium adherence (75%), and green lines from runs with high adherence (90%). In all runs, we simulate school closures, 250,000 daily PCR tests offered to symptomatic agents, and contact tracing with medium capacity (as described in Table 3).

Figure S-5 Infection curves sampled from the model, varying testing strategy (dark lines are mean infection curves across all runs). Red lines are from runs where tests are administered first to agents who present symptoms. Blue lines are from runs where tests are administered first to the *contacts* of symptomatic agents. In all runs, we simulate school closures, partial remote work, 75% quarantine adherence, 250,000 daily PCR tests, and contact tracing with low capacity (as described in Table 3).

Figure S-6 Infection curves sampled from the model, varying use of serologic testing strategy. Red lines are from runs where 1,000 tests are administered each day within the population of 50,000 agents. Blue lines are from runs where tests are not administered. In all runs, we simulate school closures, partial remote work, 75% quarantine adherence, the equivalent of 500,000 daily PCR tests in the full US population, and contact tracing with medium capacity (as described in Table 3).

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