Optimizing COVID-19 control with asymptomatic surveillance testing in a university environment

Cara E. Brook1*, Graham R. Northrup2, Alexander J. Ehrenberg1,3,4,5, the IGI Testing Consortium3, Jennifer A. Doudna3,6,7,8,9, and Mike Boots1,10

1 Department of Integrative Biology, University of California, Berkeley
2 Center for Computational Biology, College of Engineering, University of California, Berkeley
3 Innovative Genomics Institute, University of California, Berkeley
4 Helen Wills Neuroscience Institute, University of California, Berkeley
5 Memory and Aging Center, Weill Institute for Neurosciences, University of California, San Francisco
6 Department of Molecular and Cell Biology, University of California, Berkeley
7 College of Chemistry, University of California, Berkeley
8 J. David Gladstone Institutes, San Francisco, CA
9 Howard Hughes Medical Institute, University of California, Berkeley
10 Department of Biosciences, University of Exeter, Penryn, UK

*corresponding author: Cara E. Brook
address: 5017 Valley Life Sciences Building, University of California, Berkeley
phone: 707-241-5550
email: cbrook@berkeley.edu

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

The high proportion of transmission events derived from asymptomatic or presymptomatic infections make SARS-CoV-2, the causative agent in COVID-19, difficult to control through the traditional non-pharmaceutical interventions (NPIs) of symptom-based isolation and contact tracing. As a consequence, many US universities have developed asymptomatic surveillance testing labs, to augment existing NPIs and control outbreaks on campus. We built a stochastic branching process model of COVID-19 dynamics to advise optimal control strategies in a university environment. Our model combines behavioral interventions in the form of group size limits to deter superspreading, symptom-based isolation, and contact tracing, with asymptomatic surveillance testing. We find that behavioral interventions offer a cost-effective means of epidemic control: group size limits of six or fewer greatly reduce superspreading, and rapid isolation of symptomatic infections can halt rising epidemics, depending on the frequency of asymptomatic transmission in the population. Surveillance testing can overcome uncertainty surrounding asymptomatic infections, with the most effective approaches prioritizing frequent testing with rapid turnaround time to isolation over test sensitivity. Importantly, contact tracing amplifies population-level impacts of all infection isolations, making even delayed interventions effective. Combination of behavior-based NPIs and asymptomatic surveillance also reduces variation in daily case counts to produce more predictable epidemics. Furthermore, targeted, intensive testing of a minority of high transmission risk individuals can effectively control the COVID-19 epidemic for the surrounding population. We offer this blueprint and easy-to-implement modeling tool to other academic or professional communities navigating optimal return-to-work strategies for the 2021 year.
Introduction

Non-pharmaceutical interventions (NPIs) to control the spread of infectious diseases vary in efficacy depending on the natural history of pathogen that is targeted (1). Highly transmissible pathogens and pathogens for which the majority of onward transmission events take place prior to the onset of symptoms are notoriously difficult to control with standard public health approaches, such as isolation of symptomatic individuals and contact tracing (1). SARS-CoV-2, the causative agent in COVID-19, is a now a clear example of one of these difficult-to-control pathogens (2). While the first SARS-CoV was effectively contained via the isolation of symptomatic individuals following emergence in 2002 (3), at the time of writing, SARS-CoV-2 remains an ongoing public health menace that has infected more than 82 million people worldwide (4). Though the two coronaviruses are epidemiologically comparable in their basic reproduction numbers (R\textsubscript{0}) (3), SARS-CoV-2 has evaded control efforts largely because the majority of virus transmission events occur prior to the onset of clinical symptoms in infected persons (2)—in stark contrast to infections with the first SARS-CoV (3). Indeed, in many cases, SARS-CoV-2-infected individuals never experience symptoms at all (5–8) but, nonetheless, remain capable of transmitting the infection to others (9–13). Due to the challenges associated with asymptomatic and presymptomatic transmission (10), surveillance testing of asymptomatic individuals has the potential to play a critical role in COVID-19 epidemic control (14–16).

Surveillance testing is always valuable for research purposes, but its efficacy as a public health intervention will depend on both the epidemiology of the focal infection and the characteristics of the testing regime. Here, we explore the effects of both behavior-based NPIs and asymptomatic surveillance testing on COVID-19 control in a university environment.

As the North American winter advances, the United States leads the globe with over 21 million reported cases of COVID-19 (4), and universities across the nation continue to struggle to control epidemics in their campus communities (17). To combat this challenge, colleges have adopted a variety of largely independent COVID-19 control tactics, ranging from entirely virtual formats to a mix of in-person and remote learning, paired with strict behavioral regulations, and—in some cases—in-house asymptomatic surveillance testing (18). As we approach the 2021 academic semester, asymptomatic surveillance testing is likely to play a key role in university plans for expanding reopening in the new semester (18, 19). In March 2020, shortly after the World Health Organization declared COVID-19 to be a global pandemic (20), the University of California, Berkeley, launched its own pop-up SARS-CoV-2 testing lab in the Innovative Genomics Institute (IGI) (21) with the aim of providing COVID diagnostic services to the UC Berkeley community and underserved populations in the surrounding East Bay region. Though the IGI RT-qPCR-based pipeline was initially developed to service clinical, symptomatic nasopharyngeal and oropharyngeal swab samples (21), the IGI subsequently inaugurated an asymptomatic surveillance testing program for the UC Berkeley community, through which—at the time of this writing—over 18,000 faculty, students, and staff in the UC Berkeley community have since been serviced with over 105,000 tests and counting (22).
Here we developed a stochastic, agent-based branching process model of COVID-19 spread in a university environment to advise UC Berkeley on best-practice approaches for surveillance testing in our community and to offer guidelines for optimal control in university settings more broadly. Previous modeling efforts have used similar approaches to advocate for more frequent testing with more rapid turnaround times at the expense of heightened test sensitivity (14, 15) or to weigh the cost-effectiveness of various testing regimes against symptom-based screening in closed university or professional environments (16). Our model is unique in combining both behavioral interventions with optimal testing design in a real-world setting, offering important insights into efficient mechanisms of epidemic control and an effective tool to optimize control strategies.

**Model design.**

Our model takes the form of a stochastic branching process model, in which a subset population of exposed individuals (0.5%, derived from the mean percentage of positive tests in our UC Berkeley community (22)) is introduced into a hypothetical 20,000 person community that approximates the campus utilization goals for our university in spring 2021. With each timestep, the disease parameters for each infected case are drawn stochastically from distributions representing the natural history of the SARS-CoV-2 virus, paired with realistic estimates of the timeline of corresponding public health interventions (2, 16, 23) (Figure 1). Our flexible model (published here with open-access R-code (24)) allows for the introduction of NPIs for COVID-19 control in four different forms: (1) group size limits, (2) symptom-based isolations, (3) surveillance testing isolations, and (4) contact tracing isolations that follow after cases are identified through screening from symptomatic or surveillance testing. Because we focus our efforts on optimal surveillance testing regimes, we do not explicitly model other NPIs, such as social distancing and mask wearing; however, the effects of these behaviors are captured in our representation of R-effective (hereafter, $R_E$) for both within-campus and out-of-campus transmission. We do not explicitly incorporate vaccination in the current analysis, but our open-access R-code is programmed to facilitate easy extension of our work to include exploration of the varied effects of NPIs on populations with a subset of vaccinated individuals (24), as these scenarios become more pervasive in the 2021 year.
Figure 1. Conceptual schematic of branching process model of SARS-CoV-2 dynamics.

Person A is isolated through testing after exposing Person B and Person C. Person B is then isolated through contact tracing, while Person C is not traced but is nonetheless ultimately isolated through symptomatic surveillance. A viral titer trajectory (right) is derived from a within-host viral kinetics model (Supplementary File 1), yielding the mean titer trajectory and 95% confidence interval shown here. The 25th and 75th titer threshold percentile for the onset of symptoms are depicted in pink, such that 32% of individuals modeled in our simulations did not present symptoms.

Schematic is adapted in concept from Hellewell et al. (2020).

\[ R_E = R_0 \times S \]

\( R_E \) is the product of the pathogen basic reproduction number \((R_0)\) and the proportion of the population that is susceptible to disease. \( R_E \) is thus a dynamic value which corresponds to the number of new infections caused by a single infection at a given timepoint within a specified community. We compute an independent \( R_E \) for each infectious person in our population that is the combined result of both heterogeneity in individual infectiousness and heterogeneity in individual contact events that could result in transmission. To determine \( R_E \), we first draw a value of potential cases for each infectious individual in our population from the SARS-CoV-2 negative binomial distribution for \( R_0 \), estimated to have a mean value of 2.5 and a dispersion parameter \((k)\) of 0.10 (26). Though representation of \( R_E \) in log-normal vs. negative binomial form will not change the average number of cases generated per epidemic, the negative binomial distribution replicates the dynamics of superspreading events, which are known to play an important role in SARS-CoV-2 dynamics (27–32). Indeed, there is growing direct empirical evidence that COVID-19 epidemiology exhibits a negative binomial \( R_E \) across multiple systems (31, 33–35); as few as 10% of infectious individuals may be responsible for 80% of onward SARS-CoV-2 transmissions (36).

We next assume that a minority (10%) of possible onward transmissions are lost to the external community (e.g. an infectious UC Berkeley community member infects someone outside the UC Berkeley community), and we remove these from our model, such that we ultimately aim to report within-campus \( R_E \) as the number of onward cases that a single infectious university community member causes within the university community (Supplementary File 1).

To achieve this, we next assume that social distancing, masking, and behavioral modifications in our community will modulate dynamics such that some of the remaining 90% of the original \( R_0 \)-
derived potential infections do not take place. Because we are specifically interested in advising UC Berkeley on group size limits for gatherings, we next draw a number of possible onward transmission events for each infectious individual from a simple Poisson distribution with $\lambda = 3$, signifying the average number of possible encounters (i.e. cross-household dining, shared car rides, indoor meetings, etc.) per person that could result in transmission. We then use published estimates of the generation time of onward transmission events for SARS-CoV-2 infection (2) to draw event times for these encounters, and we distribute each infectious person’s original number of $R_0$-derived potential cases among these events at random. This ensures that multiple transmissions are possible at a single event; the most extreme superspreading events occur when persons with heterogeneously high infectiousness draw a large number of potential cases, which are concentrated within a relatively small number of discrete transmission events. When group size limit NPIs are imposed, case numbers for each event are truncated at the intervention limit.

For each infectious individual, we additionally generate an independent virus trajectory, using a within-host viral kinetics model for SARS-CoV-2 upper respiratory tract infections, which is structured after the classic target cell model (37–40). From each independent virus trajectory, we can then infer a time-varying transmissibility, which is modeled as a Michaelis-Menten-like function of viral load (40). Deviating from the original published model, we fix the within-host viral kinetics model constant, $\theta$, at a value that allows for a ~50% probability of infection occurring per transmissible contact event at an infectious individual’s peak viral load (40). Because all possible onward transmissions have been assigned an event generation time, we next evaluate the viral load of the infectious person at the time of each potential transmission to determine whether or not it actually takes place. By these metrics, our original $R_0$-derived possible cases are halved, such that $R_E$, the number of average onward infections caused by a single infectious person in the UC Berkeley community, is reduced to just over one ($R_E=1.05$), consistent with published estimates of Bay Area $R_E$ and initial asymptomatic test results in our community (22, 41). The majority of transmission events occur when the infectious host has higher viral titers, thus biasing new case generations towards earlier timesteps in an individual’s infection trajectory, as is realistic for COVID-19 (23) (Figure 1).

In addition to modulating the probability of onward transmission events, each infectious individual’s virus trajectory additionally allows us to compute a timing of symptom onset, which corresponds to the timepoint at which an individual’s virus trajectory crosses some threshold value for presentation of symptoms. We draw each threshold randomly from a log-normal distribution with a mean of $10^5$ virus copies per $\mu l$ of RNA; by these metrics, roughly 32% of our modeled population presents as asymptomatic, in keeping with published estimates for SARS-CoV-2 (6, 7). Using each infectious individual’s viral load trajectory, we are next able to compute a period of test sensitivity, corresponding to the time during which viral load is high enough for detection by the virus test in question, based on the modeled limit of detection (LOD). Surveillance testing results in higher “false-negative” test results both very early and very late in infection when viral loads are below the LOD for the adopted assay (42) (Figure 1), though most tests should reliably detect infectious cases with viral titers $>10^6$ cp/$\mu l$ (43–45).
explore dynamics across a range of published values for test LOD: $10^1$, $10^3$, and $10^5$ virus copies per μl of RNA. The IGI’s RT-qPCR-based testing pipeline has a published sensitivity of 1 cp/μl (21), while the majority of SARS-CoV-2 RT-qPCR tests nationally are reliable above a $10^3$ cp/μl threshold (46); less-sensitive antigen-based and LAMP assays report detection limits around $10^5$ cp/μl (47, 48).

In addition to within-community transmissions, all individuals in the modeled population are also subjected to a daily hazard (0.15%) of becoming infected from an external source, based on published estimates of $R_0$ and COVID-19 prevalence in Alameda County (41, 49). We report the mean results of 100 stochastic runs of each proposed intervention.

Results.
Comparing behavioral NPIs for COVID-19 control.

We first ran a series of epidemic simulations using a completely mixed population of 20,000 individuals subject to the infection dynamics outlined above to compare and contrast the impacts of our four NPIs on COVID-19 control. We introduced an initial population of 100 infectious individuals (0.5%) at timestep 0 and compared the effects of a single target intervention on epidemic trajectories after the first 50 days of simulation. Less intensive or intervention-absent scenarios allowed infectious cases to grow at unimpeded exponential rates, rapidly exhausting our susceptible supply and making it necessary to compare results at a consistent (and early) timepoint in our simulated epidemics.

As a consequence of our representation of $R_E$ in negative binomial form, we first considered the COVID-19 control effectiveness of group size limits on in-person gatherings, which doubled as upper thresholds in transmission capacity (Figure 2). Assuming that 90% of the modeled population adhered to assumed group size regulations, we found that limiting outdoor gatherings to groups of six or fewer individuals saved a mean of $\sim$7,900 cases per 50-day simulation (in a 20,000 person population) and corresponded to an $R_E$ reduction of nearly 0.20 (reducing $R_E$ from 1.05 to subclinical 0.86; Figure 2; Supplementary File 2). By contrast, a large group size limit of 50 persons had almost no effect on epidemic dynamics; under published estimates of SARS-CoV-2 negative binomial $R_E$ (26), a group size limit of 50 will restrict transmission from only 0.00039% of infectious individuals (Figure 2). Gains in epidemic control from group size limits resulted from avoidance of superspreading events, an approach that was effective for negative binomial but not log-normal representations of $R_E$ that lack the transmission “tail” characteristic of a superspreader distribution (32) (Figure 2-S1). Importantly, by avoiding superspreading events, group size limits also reduced variance in daily case counts, yielding more predictable epidemics, which are easier to control through testing and contact tracing (2, 23, 25).

Over the July 4 weekend, surveillance testing resources in our UC Berkeley community were overwhelmed and containment efforts challenged after a single superspreading event on campus (50).
Figure 2. Effects of group size limits on COVID-19 dynamics.

A. Negative binomial $R_E$ distribution with mean = 1.05 and dispersion parameter ($k$) = 0.10. The colored vertical dashes indicate group size limits that ‘chop the tail’ on the $R_E$ distribution; for 90% of the population, coincident cases allocated to the same transmission event were truncated at the corresponding threshold for each intervention.

B. Daily new cases and, C. Cumulative cases, across a 50-day time series under corresponding, color-coded group size limits.

We next investigated the impacts of variation in lag time to self-isolation post-symptom onset for the just under 70% of individuals likely to present with COVID-19 symptoms in our modeled population (Figure 3). At UC Berkeley, all essential students, faculty, and staff must complete a digital ‘Daily Symptom Screener’ before being cleared to work on campus; here, we effectively model the delay post-initial symptom onset to the time at which each individual recognizes symptoms sufficiently to report to the Screener and isolate. For each infected individual in our population, we draw a symptom-based isolation lag from a log-normal distribution centered on a mean of one to five days, assuming the entire population to be compliant with the selected lag.
Figure 3. Impacts of NPIs on COVID-19 control.

A. Mean reduction in $R_E^*$ and B. cumulative cases saved across 50-day simulated epidemics under assumptions of differing non-pharmaceutical interventions (NPIs). NPIs are color-coded by threshold number of persons for group-size limits, lag-time for symptom-based isolations, and mean turnaround time from test positivity to isolation of infectious individuals for testing isolations. For testing isolations, shading hue corresponds to test limit of detection (LOD) with the darkest colors indicating the most sensitive tests with an LOD of $10^3$ virus copies/µL of RNA. Progressively lighter shading corresponds to LOD = $10^3$, $10^5$, and $10^7$ cp/µL.

*Note: $R_E$ reduction (panel A) is calculated as the difference in mean $R_E$ in the absence vs. presence of a given NPI. The upper confidence limit (uci) in $R_E$ reduction is calculated as the difference in uci $R_E$ in the absence vs. presence of NPI. In our model, mean $R_E$ in the absence of NPI equals 1.05 and uci $R_E$ in the absence of NPI equals 8.6.

By these metrics, a rapid, one day lag in symptom-based isolation is the fourth-most effective intervention in our study, with a mean of more than 13,100 cases saved in a 50-day simulation (again, in a 20,000 person population), corresponding to an $R_E$ reduction of 0.67, from 1 to 0.38 (Supplementary File 2). Longer lag times to isolation produced less dramatic results, but even an average five-day lag to isolation post-symptom onset nonetheless yielded more than 4,000 cases saved and reduced $R_E$ by a mean of 0.06. The efficacy of symptom-based isolation decreased at higher virus titer thresholds for symptom onset, corresponding to a higher asymptomatic proportion (~50%) of the population (Figure 3-S1); some empirical findings suggest that these higher titer thresholds for symptom onset may more accurately reflect COVID-19 epidemiology (51). Because both group size limits and daily screening surveys to facilitate symptom-based isolation can be implemented without expending substantial resources, we advocate for these two approaches as particularly cost-effective COVID-19 control strategies for all university and small community environments—especially those lacking an on-site surveillance testing lab.

Comparing surveillance testing NPIs for COVID-19 control.

Our primary motivation in developing this model was to advise UC Berkeley on best-practices for asymptomatic surveillance testing. As such, we focused efforts on determining the most effective use of testing resources by comparing surveillance testing across a range of approaches that varied test frequency, test turnaround time (TAT, the time from which the test was administered to the timing of positive case isolation), and test sensitivity (based on the LOD).

We compared all permutations of surveillance testing NPIs, varying test frequency across semi-weekly, weekly, and every-two-week regimes, investigating TAT across delays of one to five and ten days, and exploring LODs of $10^1$, $10^3$, and $10^5$ virus copies per µL of RNA. These test frequency regimes reflect those under consideration at UC Berkeley today: from August-December 2020, UC Berkeley undergraduates residing in university residence halls were subject to compulsory semi-weekly asymptomatic surveillance testing, while all other campus community members were permitted to take part in voluntary testing with a recommended weekly or every-two-week frequency. TAT values in our model reflect the reality in range of testing turnaround times from in-house university labs like that at UC Berkeley to institutions.
forced to outsource testing to commercial suppliers (52), and LOD values span the range in
sensitivity of available SARS-CoV-2 tests (21, 46–48).
Across testing regimes broadly, we found test frequency, followed by TAT, to be the
most effective NPIs, with LOD exerting substantially less influence on epidemic dynamics,
consistent with findings published elsewhere (14, 15). The top three most effective NPIs in our
study corresponded to semi-weekly testing regimes with one- and two-day TATs across 10^1 and
10^3 cp/µl LODs. These three scenarios yielded mean cases saved ranging from just over 14,000
to just over 13,500 in the first 50 days of simulation and produced an R_E reduction capacity
between 0.97 and 0.80 (Figure 3; Supplementary File 2). Halving test frequency to a weekly
regimen, under assumptions of TAT=1 and LOD=10^1, resulted in a nearly 48% decrease in the
NPI’s R_E reduction capacity. By comparison, a single extra day lag from one to two-day TAT
under semi-weekly testing conditions at LOD=10^1 cp/µl yielded a modest 16% decrease in R_E
reduction capacity. However, longer delays in TAT of up to ten days or more—not unusual in
the early stages of the COVID-19 pandemic (52)—were not significantly different from
scenarios in which no intervention was applied at all. This outcome results from the rapid
generation time of SARS-CoV-2 (2); most infectious individuals will have already completed the
majority of subsequent transmissions by the time a testing isolation with a 10-day TAT is
implemented. Nonetheless, encouragingly, reducing test sensitivity from 10^1 to 10^3 under a semi-
weekly, TAT=1 regime decreased R_E reduction capacity by only 18%, offering support to
advocates for more frequent but less sensitive tests (53) but also highlighting the added benefit
incurred when university testing labs, like that at UC Berkeley, are able to provide both frequent
and sensitive PCR-based testing.

Addition of a contact tracing intervention, in which 90% of infectious contacts were
traced and isolated within a day of the source host isolation, to NPI scenarios already featuring
either symptom-based or surveillance testing isolation enhanced each intervention’s capacity for
epidemic control (Figure 3-S2). Of note, contact tracing boosted performance of some of the
poorest performing testing interventions, such that even those previously ineffective surveillance
regimens with 10-day TAT nonetheless averted cases and significantly reduced R_E when
infectious contacts could be isolated. For a semi-weekly testing regime at LOD=10^1 cp/µl and
TAT=10 days, the addition of contact tracing increased mean cases saved from ~510 to >8,600
and increased R_E reduction capacity from 0.000080 to 0.27 (Supplementary File 3).

Optimizing combined NPIs for COVID-19 control.
Our modeled simulations indicate that it is possible to achieve largely equivalent gains in
COVID-19 control from NPIs in the form of group size limits, symptom-based isolations, and
surveillance testing isolations—though gains from symptom-based behavioral isolations are
jeopardized under assumptions of a higher proportion of asymptomatic individuals (Figure 3-S1).
Nonetheless, the most effective interventions are realized when behavioral control mechanisms
are combined with surveillance testing (Figure 4). Assuming a one day TAT and 10^1 cp/µl LOD,
we found that adding (a) contact tracing with 90% adherence and a one-day lag, plus (b)


symptom-based isolation with a one-day lag, plus (c) a group size limit of twelve persons to an every-two-week surveillance testing regimen could elevate the $R_E$ reduction capacity from 0.22 to 0.83 and almost double the ~6,600 cases saved from the testing intervention alone (Supplementary File 4). Combining interventions enables less rigorous testing regimes to rival the effectiveness of semi-weekly surveillance testing without expending additional resources. In addition, combining interventions results in less variation in the cumulative case count, as many layers of opportunity for infection isolation help limit the likelihood of a superspreading event spiraling out of control (Figure 4-S1).

Figure 4. Combining behavioral and surveillance testing NPIs for COVID-19 control.
A. Mean reduction in $R_E$, B. cumulative cases saved, and C. daily case counts for the first 50 days of the epidemic, across regimes of differing testing frequency and a combination of surveillance testing, contact tracing, symptomatic isolation, and group size limit interventions. All scenarios depicted here assumed test TAT, symptomatic isolation lags, and contact tracing lags drawn from a log-normal distribution with mean=1. LOD was fixed at $10^4$ and group size limits at 12. Dynamics shown here are from biweekly testing simulations in which testing was limited to two test days per week.

Following on this theme, we also experimented with varying the distribution of days allocated to surveillance testing, without changing the frequency with which each individual was tested. Specifically, we explored semi-weekly, weekly, and every-two-week testing regimens in which tests were administered across two, five, and seven available testing days per week. More broadly distributed test days corresponded to fewer tests per day at a population level but, as with more intervention layers, resulted in less variation in the cumulative total cases because testing isolations more closely tracked daily exposures (Figure 4-S1).
Modeling COVID-19 dynamics in the campus community.

In our final analysis, we sought to advise the IGI on surveillance testing strategies explicitly by simulating epidemics in a more realistic, heterogeneous population modeled after the UC Berkeley campus community (Figure 5). To this end, we subdivided our 20,000 person university population into a 5,000 person “high transmission risk” cohort and a 15,000 person “low transmission risk” cohort, assuming “high transmission risk” status to correspond to individuals (such as undergraduates), living in high density housing with a majority of contacts (90%) concentrated within the UCB community and “low transmission risk status” to correspond to individuals (such as faculty members or postdoctoral scholars) with only limited contacts (40%) in the UCB community. We imposed a 12-person group size limit (with 90% adherence) on the population as a whole, as recommended by the City of Berkeley Public Health Department in the early months of the pandemic (54), and assumed a one-day average lag in symptom-based isolation for all cohorts. To add additional realism, we enrolled only 50% of each transmission risk group in our modeled surveillance testing program (to mimic adherence—though surveillance testing is compulsory for undergraduates residing in residence halls at UC Berkeley (22)). We assumed that 95% efficacy in contact tracing (with a mean tracing delay of one day) for those enrolled in our surveillance program but only 50% efficacy for those not enrolled; UC Berkeley has encouraged all community members to enroll in the ‘CA Notify’ digital contract tracing app developed by Apple and Google (55). For all testing interventions, we assumed LOD=10^1 cp/µl and TAT=2 days, the average for the IGI surveillance testing lab (21).

Figure 5. Targeted testing of high transmission risk cohorts in a heterogeneous population.

A. Schematic of transmission risk group cohorts in the heterogeneous model. The population is divided into 5,000 “high transmission risk” and 15,000 “low transmission risk” individuals, for which, 90% and 40% of the proportion of transmission events take place within the UC Berkeley community, respectively. Of those transmission events within the Berkeley community, the majority (80%) are restricted within the same transmission risk group as the infector, while 20% are sourced to the opposing risk group. Half of each cohort is assumed to be enrolled in
asymptomatic surveillance testing and subjected to the differing test frequency regimes depicted in panels B. through D. Panel B. shows the progression of cumulative cases across 730 days of simulation for each testing regime, while panel C. and D. give, respectively, the reduction in R_E and the total cases saved achieved by each test regime vs. a no intervention baseline.

We found that targeted, semi-weekly testing of 50% of individuals in the high transmission risk cohort, paired with every-three-week testing of enrolled individuals in the low transmission risk cohort yielded mean R_E reduction and cumulative cases saved on par with that achieved from weekly testing (and better than that achieved from every-two-week testing) of all enrolled individuals in the population at large (Figure 5). Targeting the highest transmission-risk populations with testing surveillance allows practitioners to save valuable testing resources while simultaneously controlling the epidemic for the entire community. Importantly, while mean R_E reduction and cumulative cases were largely comparable between the targeted, semi-weekly testing regiment and the untargeted, weekly regimen, the observed variance in intervention efficacy (Figure 5C) was substantially greater for the targeted scenario, in which the low transmission risk cohort was only tested once every three weeks. This results from a higher probability that a rare superspreading event could occur in the infrequently monitored low transmission risk cohort, thus reaffirming our previous observation that more frequent surveillance testing regimens result in more predictable—and easier to control—epidemics.

Notably, irrespective of intervention, the diminished transmissibility of the “low transmission risk” population in this heterogeneous model structure greatly reduced epidemic spread in subsequent simulations as compared with those presented previously in the perfectly mixed environment; as a result, we here compared interventions after 500 days of simulation, rather than 50. The heightened realism of our heterogenous population generated slow-moving epidemics more closely resembling those we are currently witnessing in our university environment.

Discussion.
We built a stochastic branching process model of SARS-CoV-2 spread in a university environment to advise UC Berkeley on best-practice strategies for effective asymptomatic surveillance in our pop-up IGI testing lab—and to offer a model for other institutions attempting to control the COVID-19 epidemic in their communities. While previous work has explored the isolated effects of specific NPIs—including group association limits (32), asymptomatic testing (14–16), and contact tracing (2, 23, 25)—on COVID-19 control, ours is the only model to date which investigates these interventions simultaneously and does so in a realistic and easily applicable setting. We offer an easy-to-implement modeling tool that can be applied in other educational and workplace settings to provide NPI recommendations tailored to the COVID-19 epidemiology of a specific environment.

Results from our analysis of behavior-based NPIs support previous work (2, 14–16, 23, 25, 32) in showing that stringent group size limitations to minimize superspreading events and
rapid symptom-based isolations offer an effective means of epidemic control in the absence of surveillance testing resources. However, because of the unique natural history of the SARS-CoV-2 virus, for which the majority of transmission events result from asymptomatic or presymptomatic infections (2, 25), symptom-based NPIs cannot reduce epidemic spread completely, and small community environments will always remain vulnerable to asymptomatic case importation. Moreover, symptom-based NPIs pose less effective means of epidemic control under scenarios assuming a higher proportion of asymptomatic individuals; empirical evidence suggests that SARS-CoV-2 infection may result in asymptomatic infection in up to nearly 70% of the population in select environments (51). For this reason, our results emphasize the importance of asymptomatic surveillance testing to prevent ongoing epidemics in universities and other small community environments. As more data becomes available on both the proportion of asymptomatic infections and their contributions to SARS-CoV-2 transmission, the relative importance of group size interventions, symptom-based isolation, and asymptomatic surveillance testing in different epidemiological contexts will be possible to determine from our modeling framework.

As with behavioral interventions, our exploration of optimal surveillance testing regimes supports findings that have been published previously but with a few key extensions and critical novel insights. As has been recently highlighted (14, 15), we find that the most cases are saved under asymptomatic testing regimes that prioritize heightened test frequency and rapid turnaround time over test sensitivity. Importantly, we extend previous work to highlight how more rigorous testing regimes—and those combined with one or more behavioral interventions—greatly reduce variance in daily case counts, leading to more predictable epidemics. We find that the reduction in daily case variation is even more pronounced when test regimes of equivalent frequency are distributed more broadly in time (i.e. tests are offered across more days of the week), thus minimizing the likelihood of compounding transmission chains that may follow upon a superspreading event. Additionally, we demonstrate how a focused stringent testing regime for a subset of “high transmission risk” individuals can effectively control a COVID-19 epidemic for the broader community. Taken together, our model shows the utility of a multi-faceted approach to COVID-19 control and offers a flexible tool to aid in prioritization of interventions in different university or workplace settings.

Finally, our paper presents the only COVID-19 surveillance model published to date that combines asymptomatic testing with contact tracing, thus highlighting the compounding gains effected by these two interventions: contact tracing amplifies the control impacts of both symptom-based and surveillance testing-based isolations, such that even intervention scenarios assuming long delays in isolation after symptom onset or slow turnaround-times for test results can nonetheless greatly reduce the transmission capacity of COVID-19. These findings further emphasize the critical role that asymptomatic surveillance testing is likely to play in ongoing efforts to control COVID-19 epidemics into the 2021 year. Even limited surveillance testing may offer substantial gains in case reduction for university and workplace settings that already have
efficient symptomatic isolation and contact tracing programs in place. Our model allows us to prioritize when and where these gains are most likely to be achieved.

Because we do not explicitly model SARS-CoV-2 transmission in a mechanistic, compartmental framework (56, 57), our analysis may overlook some more subtle insights into long-term disease dynamics. More complex analyses of interacting epidemics across larger spatial scales or investigations of vaccination delivery and the duration of immunity will necessitate implementation of a complete compartmental transmission model. However, our use of a stochastic branching process framework makes our model simple to implement and easily transferrable to other semi-contained small community environments, including a wide range of academic settings and workplaces (24). We make this tool available to others interested in exploring the impacts of targeted public health interventions—in particular, surveillance testing regimes—on COVID-19 control in more specific settings in the upcoming 2021 year. We at the University of California, Berkeley are committed to maintaining the safest campus environment possible for our community, using all intervention tools at our disposal. We advise those in similar positions at other institutions to employ the behavioral interventions outlined here, in concert with effective surveillance testing regimes, to reduce community epidemics of COVID-19 in the upcoming spring season.

Acknowledgments and Funding Sources

CEB was funded by the Miller Institute for Basic Research at the University of California, Berkeley, the Branco Weiss Society in Science Fellowship from ETH Zurich, a DARPA PREEMPT Cooperative Grant (no. D18AC00031), and a COVID-19 Rapid Response Research grant from the Innovative Genomics Institute at the University of California, Berkeley. MB was supported by NIH grant no. R01-GM122061-03 and NSF EEID grant no. 2011109.
References

1. Fraser C, Riley S, Anderson RM, Ferguson NM (2004) Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci U S A 101(16):6146–6151.

2. Ferretti L, et al. (2020) Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. Science 368(6491):eabb6936.

3. Petersen E, et al. (2020) Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. Lancet Infect Dis 20(9):e238–e244.

4. WHO (2020) Coronavirus disease (COVID-2019) situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports [Accessed June 30, 2020].

5. Oran DP, Topol EJ (2020) Prevalence of asymptomatic SARS-CoV-2 infection: A narrative review. Ann Intern Med Med 173(5):362–367.

6. Mizumoto K, Kagaya K, Zarebski A, Chowell G (2020) Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance 25(10):1–5.

7. Nishiura H, et al. (2020) Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis 94:154–155.

8. Treibel TA, et al. (2020) COVID-19: PCR screening of asymptomatic health-care workers at London hospital. Lancet 395(10237):1608–1610.

9. Emery JC, et al. (2020) The contribution of asymptomatic SARS-CoV-2 infections to transmission on the Diamond Princess cruise ship. Elife 9:1–68.

10. Gandhi M, Yokoe DS, Havlir D V. (2020) Asymptomatic transmission, the achilles’ heel of current strategies to control COVID-19. N Engl J Med 382(22):2158–2160.

11. Boyles S (2020) Covid-19: Asymptomatic transmission fueled nursing home death toll. Physicians’ Wkly.

12. Kam KQ, et al. (2020) A well infant with Coronavirus Disease 2019 (COVID-19) with high viral load. Clin Infect Dis:ciaa201.

13. Bai T, et al. (2020) Presumed asymptomatic carrier transmission of COVID-19. J Am Med Assoc 382(13):1199–1207.

14. Larremore DB, et al. (2020) Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. bioRxiv:1–21.

15. Bergstrom T, Bergstrom CT, Li H (2020) Frequency and accuracy of proactive testing for COVID-19. medRxiv:2020.09.05.20188839.

16. Paltiel AD, Zheng A, Walensky RP (2020) Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States. JAMA Netw open 3(7):e2016818. 

17. Hubler S, Hartocollis A (2020) How Colleges Became the New Covid Hot Spots. New York Times.

18. Richtel M (2020) Looking to Reopen, Colleges Become Labs for Coronavirus Tests and Tracking Apps. New York Times.
19. Nietzel MT (2020) As Covid-19 Lingers On, Universities Are Adjusting Their Spring Semester Plans, Often Eliminating Spring Break. *Forbes*.

20. Ghebreyesus TA (2020) WHO director-general’s opening remarks at the media briefing on COVID-19. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

21. Amen AM, et al. (2020) Blueprint for a pop-up SARS-CoV-2 testing lab. *Nat Biotechnol* (March). doi:10.1038/s41587-020-0583-3.

22. UC Berkeley COVID-19 Dashboard Available at: https://coronavirus.berkeley.edu/dashboard/?utm_source=Response+and+Recovery&utm_campaign=5247da06c4-Response_Recovery_2020_10_09&utm_medium=email&utm_term=0_940930e328-5247da06c4-389116456 [Accessed October 1, 2020].

23. Peak CM, et al. (2020) Individual quarantine versus active monitoring of contacts for the mitigation of COVID-19: a modelling study. *Lancet Infect Dis* 3099(20):2020.03.05.20031088.

24. Brook CE, Northrup GR, Boots M (2020) Code for “Optimizing COVID-19 control with asymptomatic surveillance testing in a university environment.” doi:10.5281/zenodo.4131223.

25. Hellewell J, et al. (2020) Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. *Lancet Glob Heal* 8(4):e488–e496.

26. Endo A, Abbott S, Kucharski AJ, Funk S (2020) Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. *Wellcome Open Res* 5:67.

27. Jumar S, Jha S, Rai SK (2020) Significance of super spreader events in COVID-19. *Indian J Public Health* 64(6):139–141.

28. Althouse BM, et al. (2020) Stochasticity and heterogeneity in the transmission dynamics of SARS-CoV-2. *arXiv* (425):1–10.

29. Hébert-Dufresne L, Althouse BM, Scarpino S V., Allard A (2020) Beyond R0: Heterogeneity in secondary infections and probabilistic epidemic forecasting. *medRxiv* 0(1):1–8.

30. Liu Y, Eggo RM, Kucharski AJ (2020) Secondary attack rate and superspreading events for SARS-CoV-2. *Lancet* 395(10227):e47.

31. Adam DC, et al. (2559) Clustering and superspreading potential of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Hong Kong. *J Vis Lang Comput* 11(3):55.

32. Kain MP, Childs ML, Becker AD, Mordecai EA (2020) Chopping the tail: how preventing superspreading can help to maintain COVID-19 control. *medRxiv Prepr Serv Heal Sci*. doi:10.1101/2020.06.30.20143115.

33. Laxminarayan R, et al. (2020) Epidemiology and transmission dynamics of COVID-19 in two Indian states. *Science* 28(2):eabd7672.

34. Lau MSY, et al. (2020) Characterizing superspreading events and age-specific infectiousness of SARS-CoV-2 transmission in Georgia, USA. *Proc Natl Acad Sci U S A* 117(36):22430–22435.
35. Goyal A, Reeves DB, Fabian Cardozo-Ojeda E, Schiffer JT, Mayer BT (2020) Wrong person, place and time: viral load and contact network structure predict SARS-CoV-2 transmission and super-spreading events. medRxiv:2020.08.07.20169920.

36. Nielsen BF, Sneppen K (2020) COVID-19 superspreading suggests mitigation by social network modulation. medRxiv:2020.09.15.20195008.

37. Perelson AS (2002) Modelling viral and immune system dynamics. Nat Rev Immunol 2(1):28–36.

38. Ho DD, et al. (1995) Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 373:123–126.

39. Nowak MA, May RM (2000) Virus Dynamics: Mathematical Principles of Immunology and Virology (Oxford University Press, Oxford, UK).

40. Ke R, Zitzmann C, Ribeiro RM, Perelson AS (2020) Kinetics of SARS-CoV-2 infection in the human upper and lower respiratory tracts and their relationship with infectiousness. medRxiv:2020.09.25.20201772.

41. Schwab J, Balzer LB, Geng E, Peng J, Petersen ML Local Epidemic Modeling for Management and Action. Available at: https://localepi.github.io/LEMMA/.

42. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J (2020) Variation in false-negative rate of reverse transcriptase polymerase chain reaction–based SARS-CoV-2 tests by time since exposure. Ann Intern Med. doi:10.7326/m20-1495.

43. Wölfel R, et al. (2020) Virological assessment of hospitalized patients with COVID-19. Nature 581(7809):465–469.

44. Quicke K, et al. (2020) Longitudinal surveillance for SARS-CoV-2 RNA among asymptomatic staff in five Colorado skilled nursing facilities: Epidemiologic, virologic and sequence analysis. medRxiv. doi:10.1101/2020.06.08.20125989v1.

45. La Scola B, et al. (2020) Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. Eur J Clin Microbiol Infect Dis 39(6):1059–1061.

46. Vogels CBF, et al. (2020) Analytical sensitivity and efficiency comparisons of SARS-CoV-2 RT–qPCR primer–probe sets. Nat Microbiol (4). doi:10.1038/s41564-020-0761-6.

47. Meyerson NR, et al. (2020) A community-deployable SARS-CoV-2 screening test using raw saliva with 45 minutes sample-to-results turnaround. medRxiv:2020.07.16.20150250.

48. Dao Thi VL, et al. (2020) A colorimetric RT-LAMP assay and LAMP-sequencing for detecting SARS-CoV-2 RNA in clinical samples. Sci Transl Med 12(556). doi:10.1126/SCITRANSLMED.ABC7075.

49. Chitwood MH, et al. (2020) Bayesian nowcasting with adjustment for delayed and incomplete reporting to estimate COVID-19 infections in the United States. medRxiv 20(7):1–6.

50. Public Affairs UB (2020) Social gatherings produce increase in student COVID-19 cases. Berkeley News.

51. Poletti P, et al. (2020) Probability of symptoms and critical disease after SARS-CoV-2 infection. arXiv. Available at: http://arxiv.org/abs/2006.08471.
52. Wu KJ (2020) 'It’s Like Groundhog Day': Coronavirus Testing Labs Again Lack Key Supplies. *New York Times*.

53. Meyer R, Madrigal AC (2020) The Plan That Could Give Us Our Lives Back. *Atl.*

54. Officer C of BPH (2020) *Order of the Health Officer of the City of Berkeley Imposing Measure Necessary to Control the Spread of COVID-19*.

55. Health USD (2020) CA Notify. Available at: https://canotify.ca.gov/ [Accessed December 21, 2020].

56. Anderson RM, May RM, Boily MC, Garnett GP, Rowley JT (1991) The spread of HIV-1 in Africa: sexual conflict patterns and the predicted demographic impact of AIDS. *Nature* 352:581–589.

57. Kermack WO, McKendrick AG (1927) A contribution to the mathematical theory of epidemics. *Proc R Soc London, Ser A* 115:700–721.
Supplementary Figures

Figure 2-S1. Figure replicates Fig. 2 (main text) at a log-normal distribution for $R_E$, instead of negative binomial. A. Log-normal $R_E$ distribution with a mean of 1.05 and a standard deviation of 1.233. The colored vertical dashes indicate the group size limits that ‘chop the tail’ on the $R_E$ distribution. B. Daily new cases and, C. cumulative cases, across a 50-day time series under corresponding, color-coded group size limits.

Figure 3-S1. Figure replicates symptom-isolation panels from Fig. 3 (main text) in top row, showing A. mean reduction in $R_E$ and B. cumulative cases saved across 50-day simulated epidemics under differing lag times to isolation, assuming a threshold titer for symptom onset by which ~32% of the population presents as asymptomatic. A comparison at a titer threshold for which ~51% of the population presents as asymptomatic demonstrates how a higher proportion of asymptomatic individuals in the population erodes the effectiveness of the symptom-based isolation intervention; asymptomatic status has no impact on the effectiveness of group size limits or asymptomatic surveillance testing interventions.
Figure 3-S2. Figure replicates symptom-isolation panels from Fig. 3 (main text) in top row, showing A. mean reduction in $R_E$ and B. cumulative cases saved across 50-day simulated epidemics for NPIs of both symptom-based and testing-based isolation, across a range of different lag times or turnaround times to isolation (for, respectively symptom- or testing-based isolations). All testing-based interventions depicted are shown at a LOD=$10^1$ cp/µl. In the bottom row, A. mean reduction in $R_E$ and B. cumulative cases saved are depicted for a comparative intervention which adds an additional single-day lag in contact tracing to the respective symptom-based or testing-based isolation. Under these combined interventions, even previously ineffective testing interventions with 10-day TAT show gains beyond no intervention at all.

Figure 4-S1. Figure extends results from Fig. 4 (main text), showing the standard deviation in cumulative cases from 50-day simulated epidemics, across regimes of differing testing frequency and a combination of surveillance testing, contact tracing, symptomatic isolation, and group size limit interventions. All scenarios depicted here assume test TAT, symptomatic isolation lags, and contact tracing lags drawn from a log-normal distribution with mean=1. LOD is fixed at $10^1$ and group size limits at 12. Dynamics compare tests of differing frequency (semi-weekly, weekly, every two weeks) distributed across variable numbers of days in a given week (2,5,7). Additional layers of intervention and more testing days per week reduce the standard deviation in cumulative cases.
Supplementary File 1.

Text A. Model Description.

Our publicly-available Github repository (1) provides opensource code to reproduce all simulations and analyses presented in our paper. We summarize the practical implementation details of our modeling design for ease-of-access here.

Our model takes the form of a stochastic branching process model, in which a subset population of exposed individuals (0.5%, derived from the mean percentage of positive tests in our UC Berkeley community (2)) is introduced into a hypothetical 20,000 person community that approximates the campus utilization goals for our university in spring 2021. The model code builds up to a single function `replicate.epidemic()` which runs a specified number of stochastic simulations from a defined parameter set, using the function `simulate.epidemic()`. Within the `simulate.epidemic()` function, we first construct a population of 20,000 persons in the sub-function, `initiate.pop()`. Within this initiation function, each person in our population is individually numbered, assigned a viral titer trajectory that will be followed if that individual becomes infected (Text B), and assigned a suite of disease metrics drawn stochastically from a specified set of parameter distributions, as outlined in Text C.

Text B. Within-host viral dynamics

Titer Trajectories.

For computational efficiency, we pre-generated 20,000 50-day individual titer trajectories and saved them as an .Rdata file, "titer.dat.20K.Rdata". To generate these trajectories, we used a within-host viral kinetics model structured after the classic target cell model (3–5). Code for this model is available in the ‘model-sandbox’ folder of our Github release, under file `viral-load.R`, which iterates the following simple model and parameter values derived from Ke et al. (2020), describing the dynamics of SARS-CoV-2 proliferation in the upper respiratory tract (6):

\[
\frac{dT_C}{dt} = -\beta T_C V \\
\frac{dE}{dt} = \beta T_C V - kE \\
\frac{dI}{dt} = kE - \delta I \\
\frac{dV}{dt} = pI - cV
\]

where \(T_C\) corresponds to the target cell population, \(\beta\) is the transmission rate of free virus to target cell invasion, \(k\) corresponds to the inverse of the duration of the virus eclipse phase, and \(\delta\) corresponds to the inverse of the incubation period of an infected cell. \(p\) then gives the burst size of a virus-infected cell and \(c\) equals the inverse of the lifespan of free virus subject to natural
virus mortality and immune predation. Parameter values used to generate each titer trajectory (with a standard deviation of 1x the value of each parameter introduced to add stochasticity in each iteration) are derived from Ke et al. (2020) (6), after fitting this model to individual patient data tracking viral loads through time in the upper respiratory tract of SARS-CoV-2-infected individuals:

starting conditions: $T_c = 4 \times 10^6; E = 0; I = 1; V = 0$

parameter values: $\beta = 1.9 \times 10^{-6}; k = 4; c = 10; \delta = 1.9; p = 51.4$

Note that Ke et al. (2020) (6) also explore the within-host dynamics of SARS-CoV-2 infection in the lower respiratory tract; however, since we model human-to-human transmissibility as inferred by viral load in nasopharyngeal swab samples (which better reflect the viral load in the upper respiratory tract), we ignore the lower respiratory dynamics here.

Infectivity by Viral Load.

After Ke et al. (2020) (6), we next estimated the probability of infection given contact at a specific viral load, using a Michaelis-Menton-like function. Following Ke et al. (2020), we described the probability this probability as:

$$P(\text{transmission}) = 1 - \exp\left(-1 \times \left(\theta \left(\frac{V}{V + K_m}\right)\right)\right)$$

where $K_m$ corresponds to the saturation constant by which proportional gains in infectiousness with viral load diminish at increasingly high viral titers and $\theta$ is a constant, such that the maximum transmission capacity at any moment equals $1 - e^{-\theta}$. Ke et al. (2020) modeled a constant hazard of contact events for infectious individuals and therefore fixed $\theta$ at a value of 0.05, corresponding to a ~5% probability of a given contact resulting in transmission. Because we draw possible transmissions events from a negative binomial SARS-CoV-2 $R_0$ distribution, (mean= 2.5 and $k=0.10$ (7)) but ultimately know that $R_E$ for our university environment should have a value of just above one (8), we instead fixed $\theta$ at a value of 0.72, corresponding to a ~51% probability of a given contact resulting in transmission, thus effectively halving $R_0$ to generate $R_E$. The exact probability varied as a function of the timing of each contact event across the trajectory of within-host viral load, with transmissions favored earlier in an infection trajectory when viral load peaks (9).

Text C. Individual disease metrics

Figures in our paper are derived from 100x replications of each set of parameter values, which we manipulate to explore a range of non-pharmaceutical interventions (NPIs) to combat COVID-19 dynamics in our system. Our flexible model allows for the introduction of NPIs for COVID-19 control in four different forms: (1) group size limits, (2) symptom-based isolations, (3) surveillance testing isolations, and (4) contact tracing isolations that follow after cases are identified through screening from symptomatic or surveillance testing. These interventions...
modify the suite of disease metrics drawn upon model initiation for each numbered individual in
the dataset. We summarize the disease metrics drawn at initiation for all members of the
population here:

- **Time of next test**: allocated based on the selected asymptomatic surveillance testing regime. We assume the week starts with day 1 on Saturday and day 7 on Friday. If n.test.days = 2, then tests are distributed on Monday (day 3) and Friday (day 7) of each week. As timesteps advance and individuals reach their respective test days, the next test day is updated based on the testing regime (if semi-weekly, the next test day is advanced 3 days; if weekly, the next test day is advanced 7 days; if every-two-weeks, the next test day is advanced 14 days).

- **Beginning/end time of test sensitivity**: based on test limit of detection (LOD) as specified at model outset, this corresponds to the timestep post exposure at which an individual viral titer crosses the threshold for being detectable by the chosen test, both as titers increase at the beginning of a disease trajectory and decrease at the end.

- **Adherence with testing regime**: Y/N, allocated randomly across individuals based on the proportion of the population modeled as complying with the surveillance testing intervention (90% of individuals in all scenarios modeled in our paper).

- **Adherence with group limit**: Y/N, allocated randomly across individuals based on the proportion of the population modeled as complying with the group size limits imposed at outset (90% of individuals in all scenarios modeled in our paper; see ‘number of potential onward cases generated for’ for how group size interacts with cases).

- **Adherence with contact tracing regimen**: Y/N, allocated randomly across individuals based on the proportion of the population modeled as complying with the contact tracing intervention imposed at outset (90% of individuals in all scenarios modeled in our paper).

- **Time of symptom onset**: determined by randomly drawing a titer limit for symptom onset for each individual from a lognormal distribution with a mean of 1e+05 cp/µl RNA and a standard deviation of 1e+04 cp/µl (10–12). The timing of symptom onset then corresponds to the time post-exposure at which each individual’s titer trajectory crosses the corresponding titer limit. According to this approach, under default parameter values, symptom onset occurred between 2 to 4 days post-exposure in our model, and ~32% of the population never presented with symptoms at all (Fig. 1, main text).

- **Time of symptom-based isolation**: based on delay lag post-symptom onset, drawn from a lognormal distribution with a mean of the specified number of days of symptom isolation lag (1-5 or infinity) and a standard deviation of 0.5 days.

- **Time of tracing-based isolation**: based on contact tracing lag for those adhering to the contact tracing regimen in place. Parameter must be updated with each timestep until individual becomes infected; value then becomes fixed at time of infector isolation, plus corresponding lag drawn from a lognormal distribution with a mean of one day and a standard deviation of 0.5 days.
• **Time of testing-based isolation:** based on turnaround time (TAT) to isolation post testing, drawn from a lognormal distribution with a mean of the specified number of delay days (1-5, 10, or infinity) and a standard deviation of 0.5 days. Parameter is updated when ‘time of next test’ is updated for each individual in our model.

• **Disease status:** ‘susceptible’ = 0, ‘exposed’ = 3, ‘infectious’ = 1, ‘recovered’ = 5. At onset, all individuals are modeled as susceptible, excepting the 0.5% which are introduced as infectious (1) to seed the epidemic. *Note that our model encodes a “prop-vaccinated” parameter for the proportion of the target population that is vaccinated prior to the start of epidemic simulations. Though we do not explore vaccination scenarios in this analysis, other practitioners interested in exploring the efficacy of each NPI on populations with a subset of immunized individuals could alter this value (currently fixed at 0) to reflect this. The proportion of the population that is specified as vaccinated will then be assigned disease status = 5 (recovered) at the onset of each simulation.*

• **Number of potential onward cases generated:** Several figures in the main text of our manuscript present the $R_0$ reduction capacity of a specified intervention, which we calculate as the difference between the average of the number of potential onward cases generated and the number of actual onward cases generated for each individual after an intervention is adopted. To compute the number of potential onward cases generated for each individual, we first draw a number of possible cases from a negative binomial distribution with a mean of 2.5 and a dispersion parameter (k) of 0.10, as estimated for SARS-CoV-2 (7). Next, we draw a number of possible onward transmission events for each infectious individual from a simple Poisson distribution with $\lambda = 3$, signifying the average number of possible encounters (i.e. cross-household dining, shared car rides, indoor meetings, etc.) per person that could result in transmission. We then distribute each infectious person’s original number of $R_0$-derived potential cases among these events at random, ensuring that multiple transmissions are possible at a single event; the most extreme superspreading events thus occur when persons with heterogeneously high infectiousness draw a large number of potential cases, which are concentrated within a relatively small number of discrete transmission events. For example, if an infectious individual draws an $R_0$ value of 16 and an event number value of 4, then those 16 potential infections are randomly distributed among 4 events.

Next, we use published estimates of the generation time of onward transmission events for SARS-CoV-2 infection to draw event times for each event, based on a weibull distribution with a shape parameter = 2.826 and a scale parameter = 5.665, as specified in Ferretti et al. (2020) (9). Following the above example, 4 discrete generation times would be assigned to cases across the 4 pre-allocated events.

Since each individual is already pre-assigned a within-host viral titer trajectory in our modeling framework, we next examine the viral load specified at the generation time of each transmission event and determine if each case assigned to that event actually occurs. Each case is considered individually, and the probability of transmission is computed stochastically based on the value of the individual’s viral titer at the time of the event (higher titer infections...
are more likely to generate onward transmission events) (Text B). In the above example, all
16 possible transmissions would be individually assessed, though several would have the
same titer, corresponding to the infectious person’s titer at the time point of each contact event
(4 possible). Since our maximum probability of a case occurring at max viral load is ~51%
(Text B), our original R₀-derived cases are here halved, resulting in an average of 1.05 onward
transmission events per infectious individual in the absence of the NPIs examined here (but
reflecting social distancing and mask wearing), which, as specified in the main text, is in line
with current estimates from Alameda County, CA (8).
For the purposes of our example, let’s assume that 10 of those possible 16 cases occur,
allocated across 4 different events, with 7 cases at one event and one case each at 3 other
events.
- **Number of actual onward cases generated:** From the number of possible cases generated,
we next apply the relevant intervention and iterate forward in time to determine the actual
number of cases generated by each infectious individual across the time course of our
modeled epidemics. For symptom and surveillance testing-based isolations, as well as contact
tracing, no cases are generated if an infectious individual is isolated prior to the generation
time of any possible onward cases. For NPIs in the form of group size limits, case reduction in
our model is performed prior to the initiation of the epidemic time series, and case numbers
for each transmission event are truncated at the intervention limit.
Again following the example listed above, if we imagine that the imposed group size limit
is 6, then the 7 cases assigned to a single event will be truncated to 6, meaning that 9 out of
the 10 potential cases is allowed to occur after the intervention. Our model is conservative in
assessing the impact of a group-size intervention by allowing some portion of those
superspreading cases to occur, rather than assuming that a group size limit-abiding infectious
individual does not attend larger-than-allowable events altogether. Because only 90% of the
population adheres to group size intervention in any given simulation, some proportion of
large superspreading events will still take place at random, even after NPIs are imposed.
Following onset of infection, the timings of symptom-, tracing-, and asymptomatic testing-based
isolations are then compared and the earliest time is selected as the actual mechanism (if any) of
isolation for that individual. The number of actual onward cases generated is then updated if
isolation occurs prior to some new case generations. Additionally, all individuals identified as
infectious are additionally assigned the following metrics:
- **Isolation time of infector**
- **Source of infection** (external Alameda County vs. UC Berkeley community member)
- **ID number of infector**, if from UC Berkeley
The cycle then repeats in the next timestep when all “actual infections” for each infectious
individual are then assigned to new susceptible individuals. The epidemic continues with
updated parameters for all newly exposed individuals until either the end of the time series is reached or no more susceptible individuals remain in the population.

References for Supplementary File 1.

1. Brook CE, Northrup GR, Boots M (2020) Code for “Optimizing COVID-19 control with asymptomatic surveillance testing in a university environment.” doi:10.5281/zenodo.4131223.

2. UC Berkeley COVID-19 Dashboard Available at: https://coronavirus.berkeley.edu/dashboard/?utm_source=Response+and+Recovery&utm_campaign=5247da06c4-Response_Recovery_2020_10_09&utm_medium=email&utm_term=0_940930e328-5247da06c4-389116456 [Accessed October 1, 2020].

3. Perelson AS (2002) Modelling viral and immune system dynamics. Nat Rev Immunol 2(1):28–36.

4. Ho DD, et al. (1995) Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 373:123–126.

5. Nowak MA, May RM (2000) Virus Dynamics: Mathematical Principles of Immunology and Virology (Oxford University Press, Oxford, UK).

6. Ke R, Zitzmann C, Ribeiro RM, Perelson AS (2020) Kinetics of SARS-CoV-2 infection in the human upper and lower respiratory tracts and their relationship with infectiousness. medRxiv:2020.09.25.20201772.

7. Endo A, Abbott S, Kucharski AJ, Funk S (2020) Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. Wellcome Open Res 5:67.

8. Schwab J, Balzer LB, Geng E, Peng J, Petersen ML Local Epidemic Modeling for Management and Action. Available at: https://localepi.github.io/LEMMA/.

9. Ferretti L, et al. (2020) Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. Science 368(6491):eabb6936.

10. Wölfel R, et al. (2020) Virological assessment of hospitalized patients with COVID-2019. Nature 581(7809):465–469.

11. Quicke K, et al. (2020) Longitudinal surveillance for SARS-CoV-2 RNA among asymptomatic staff in five Colorado skilled nursing facilities: Epidemiologic, virologic and sequence analysis. medRxiv. doi:10.1101/2020.06.08.20125989v1.

12. La Scola B, et al. (2020) Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. Eur J Clin Microbiol Infect Dis 39(6):1059–1061.
Legends for Supplementary Files 2-4.

Supplementary File 2. Averaged total cases saved and mean $R_E$ reduction across group size limit, symptomatic isolation, and surveillance testing NPIs. Summarized model output from 100x simulations across all NPIs presented in Fig. 2 and Fig. 3, main text. Confidence intervals represent 1.96*standard deviation in case reduction or $R_E$ reduction.

Supplementary File 3. Averaged total cases saved and mean $R_E$ reduction across symptomatic isolation, and surveillance testing NPIs, under regimes with and without contact tracing. Summarized model output from 100x simulations across all NPIs presented in SI-Appendix, Fig. S3.

Supplementary File 4. Averaged total cases saved and mean $R_E$ reduction across combined intervention approaches. Summarized model output from 100x simulations across all NPIs presented in Fig. 4, main text.

All other model output available as saved .Rdata files in our publicly-available Github repository:

Brook CE, Northrup GR, Boots M (2020) Code for “Optimizing COVID-19 control with asymptomatic surveillance testing in a university environment.” doi:10.5281/zenodo.4131223