Modeling the implementation of LAMP on a college campus for rapid, frequent, scalable surveillance of SARS-CoV-2

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Executive Summary:

Abstract: SARS-CoV-2 can spread quickly through a college campus, posing a threat to students, faculty, and staff. We simulate an outbreak of SARS-CoV-2 on a university campus using a compartmental susceptible exposed infectious recovered (SEIR) model. We explore the implementation of rapid, repeated, widespread screening for SARS-CoV-2 using a novel loop-mediated isothermal amplification (LAMP) assay. We examine the influence of the number of tests deployed, the frequency of testing, and the sensitivity of tests on the overall epidemic size. We also track the demand on capacity (e.g., confirmatory PCR testing, staff, isolation rooms) given different testing scenarios. Next, we will refine our parameter values to reflect an outbreak at Montana State University and will integrate pooled testing approaches into the SEIR models.

1. Introduction

We explore the implementation of an inexpensive, rapid, scalable COVID-19 test on the Montana State University campus. Reverse-transcription loop-mediated isothermal amplification (RT-LAMP), is new technology that can detect viruses in saliva with minimal reagents and equipment. Results can take less than 30 minutes and can be sensitive (>90%) and specific (>98%). We simulate the widespread and frequent screening of students at MSU with LAMP to assess the optimal magnitude and frequency of testing required to control an outbreak of SARS-CoV-2 during spring semester. We assume that LAMP testing is a part of a suite of mitigation strategies including mask wearing, social distancing, and hygiene. We also assume that LAMP surveillance is employed concurrently with diagnostic PCR for symptomatic students and that infected students identified during LAMP surveillance are isolated, and that their contacts are traced and quarantined with varying levels of compliance. Future work will integrate pooling scenarios into the LAMP testing framework. Symptomatic screening on MSU campus during fall semester, with associated tracing and isolation, was unable to stop the spread of SARS-CoV-2 on campus. Given that over 50% of students are likely to be asymptomatic (Denny et al. 2020 Duke Surveillance), a substantial proportion of infected students at MSU were not identified with symptomatic testing and probably contributed to the epidemic that led to over 1,193 detected cases of COVID-19 on campus. Here we provide initial model output from simulations of frequent, rapid screening of students with LAMP.

2. Testing Strategies

2.1 Surveillance and Testing on College Campuses

Numerous other college campuses have implemented testing and asymptomatic surveillance plans. We provide a brief overview of the salient details from select colleges and summarize the effectiveness of those plans.

Synthetic College Population

Larremore et al. (2020) show that frequent testing, even with lower sensitivity (in terms of detection) can effectively drive epidemics to extinction. The major takeaway point was that testing frequency, and not test sensitivity, was the primary driver of controlling epidemics.

University of Colorado Boulder

- Initial PCR (Polymerase Chain Reaction) testing for fall move-in/return to campus of approximately 9,000 individuals, giving priority to higher risk areas and populations. This will help identify and quickly isolate positive cases among those returning to campus.
- Ongoing monitoring/testing. Pooled testing is one of multiple strategies the campus is exploring to provide the greatest ability to detect the early presence of COVID-19 in large populations. Weekly testing is required for on campus students.

- CU Boulder faculty, staff and students with a Buff OneCard can bring their immediate family/members of their household to participate in the campus surveillance monitoring program. All participants must be asymptomatic and arrive at the testing site accompanied by their immediate family/member of their household with a Buff OneCard.

  CU Boulder had a total of 1577 positive on campus tests.

Duke University

Duke University (Denny TN (2020)) implemented the "Duke Compact" which among other things included:

- 14 day self quarantine prior to arrival on campus,
- required testing upon arrival to campus,
- (roughly) bi-weekly asymptomatic surveillance testing using pools of 5, and
- daily symptom monitoring via a cell phone app.

From August 2 to October 11, Duke tested nearly 70,000 specimens (using pooled testing) for 10,265 graduate and undergraduate students. A total of 84 (.8%) were positive, which includes 17 cases that were detected as students returned to campus. Furthermore, about half of the students were asymptomatic.

University of New Hampshire

University of Notre Dame

University of Illinois Urbana Champaign

- The University of Illinois Urbana Champaign (UIUC) developed the shield saliva test that costs about 20 - 30 dollars and results can be returned in about 6 to 12 hours.
- All university faculty, staff and students participating in any on-campus activities are required to participate in the on-campus COVID-19 testing program.
- If you are working on-campus, attending in-person classes or participating in any on-campus activities, you will need to participate in the on-campus testing program.
- All students living on-campus or residing in Champaign, Urbana, or Savoy must test, even if they are taking a fully online schedule.
- All faculty, staff and graduate students should move from a once-per-week test schedule to a twice-per-week test schedule. Continue testing at this frequency until notified otherwise.
- You must continue your twice-per-week test schedule. You can choose Monday-Thursday, Tuesday-Friday, or Wednesday-Saturday/Sunday, schedules. Undergraduate students must still show a Wellness Support Associate their Safer Illinois app or Boarding Pass at building entrances.

UIUC had a total of about 4000 confirmed positive cases from July 6 to November 22.

A note of comparison

When comparing the total number cases at a school like CU Boulder or UIUC with Montana State there is an important consideration. Schools that are screening asymptomatic students at a regular frequency are likely to catch all or most of the cases on campus. At many of these colleges, the proportion of asymptomatic cases are roughly 50%, so it is likely that the total number of cases on campus is about twice as large as the numbers reported through the Gallatin County Health Department.

2.2 Testing Plans at MSU

We propose a set of scenarios to consider and evaluate in the context of epidemiological models.

1. Same as Fall 2020: testing for symptomatic students
2. Campus re-entry screening required for all students or students on campus
3. Minimal asymtomatic surveillance screening
4. Extensive, high frequency asymtomatic surveillance screening (pooled testing)
5. Minimal asymtomatic surveillance screening + re-entry screening
6. Extensive, high frequency asymtomatic surveillance screening (pooled testing) + re-entry screening

3. Modeling

3.1 Comparing Model Output to empirical data from MSU

We collected cumulative case counts (weekly) from the Gallatin County Department of Health [**?**]. These data were assumed to be the aggregated totals of symptomatic students associated with Montana State University, as asymptomatic students are unlikely to seek care. We compared these counts to the output of a susceptible-exposed-infected-recovered (SEIR)compartment model of a potential outbreak on campus. The conditions for the 200 simulations[1] assumed that 75% of students comply with behavioral controls post-testing or contact tracing, 50% of students with symptoms seek a test, a mean of 5 contacts can be traced per positive case - 20% symptomatic, 80% asymptomatic, there is a 1 day delay in action on contact tracing and there is no asymptomatic testing, there are 50 infectious introductions, 15% of Students are immune (recovered or otherwise), R0 is 2.6, RE is 2.6*0.85, or 2.21, PCR has perfect sensitivity and specificity.

This is not a truly "fit" model, instead we have chosen reasonable estimates from parameter space to approximate fit. In the future, this will entail a model-fitting procedure, augmented by data from the campus outbreak. However, our intention is not to predict cases, we only show this to demonstrate that our model, developed in summer 2020, captures the trend of the outbreak at MSU during fall 2020.

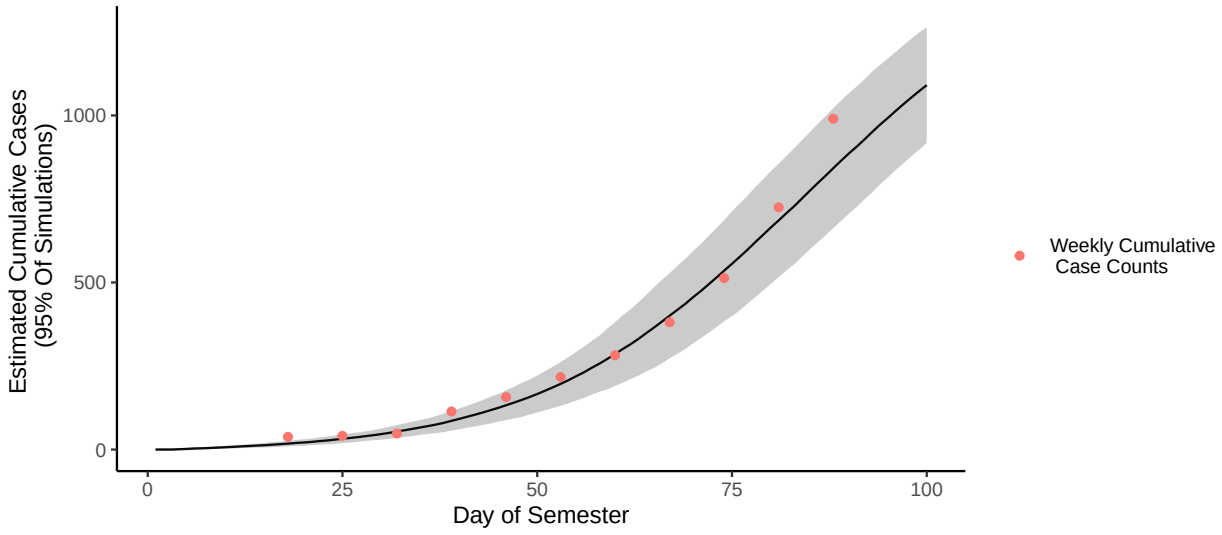


Figure 1:

3.2 Testing frequency, not testing sensitivity, is the major driver of epidemic size

The sensitivity and specificity of LAMP vs. the current standard, qPCR, has been evaluated. While initial estimates of sensitivity and specificity are encouraging (around 92.5% and 98%, respectively), the efficacy of LAMP as a diagnostic vs. surveillance tool is not known. LAMP, as the scales discussed below, may allow for public health officials to identify far more positive cases that would be possible if relying on symptomatic students seeking a diagnostic qPCRtest. However, the lower sensitivity of LAMP than qPCR (meaning that false-negatives are more frequent), could affect the effectiveness of LAMP as a screening tool. We evaluated increasing test frequency versus increasing test sensitivity within the SEIR model.

For the following and all below simulations, we assumed that 100% of students comply with behavioral controls post-testing or contact tracing (to isolate sensitivity), that 100% of students with symptoms seek care (to isolate sensitivity), a mean of 5 contacts can be traced per positive case, 20% symptomatic, 80% asymptomatic, 1 day delay in action on contact tracing, a variable number of LAMP and subsequent dynamic number of PCR confirmation tests per day, 50 infectious introductions, 15% of Students are assumed immune (recovered or otherwise), R0 is 2.6, RE is 2.6*0.85, or 2.21, PCR has perfect sensitivity and specificity, LAMP is has a variable sensitivity, and specificity, though only sensitivity is considered here.

The number of LAMP tests per day (the faceting value across the top of figure 3) was more important than the sensitivity of the LAMP test in driving the total size of an epidemic. Increasing the number of tests available, and increasing the frequency of testing, is more important than increasing the sensitivity of LAMP alone.

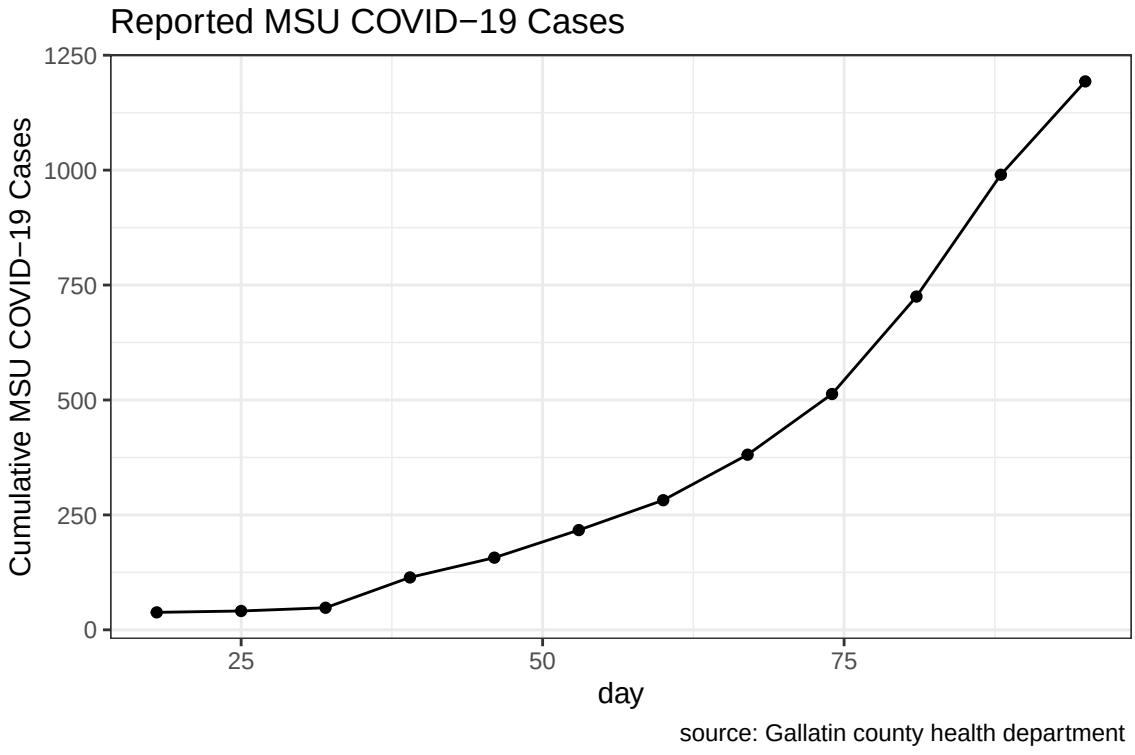


Figure 2: Figure created directly from R code

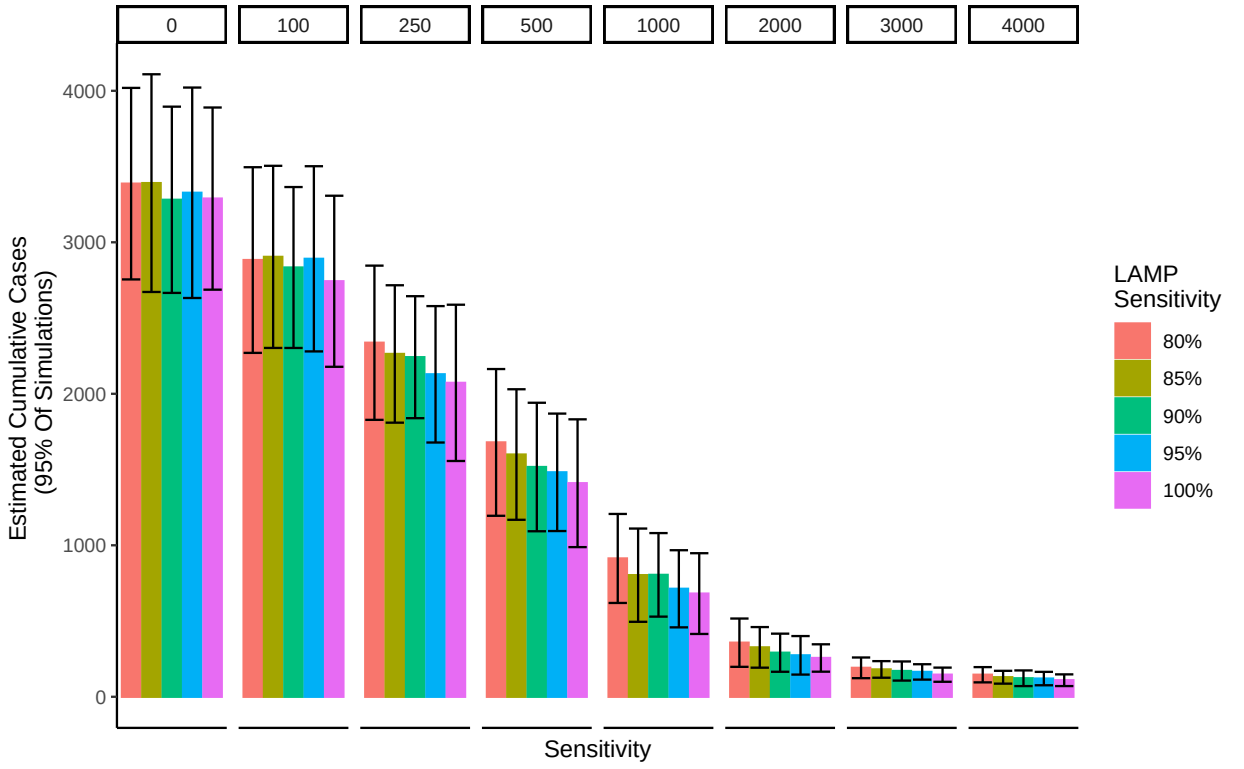


Figure 3:

3.3 High testing frequency reduces epidemic size and consequently reduces PCR demand

The number of qPCR tests available for MSU students is inadequate to meet the current demand. Currently, all LAMP-positive individuals need to be verified via qPCR before public health action is taken (isolation, contact tracing). If LAMP identifies more cases, more qPCR tests will be required.

Using the same parameters as above, we recorded the total number of symptomatic cases and random, LAMP-detected cases per day. We considered varied scenarios of LAMP implementation (number of tests per day is the faceting variable in figure 4) and LAMP sensitivity 80%-100%. We then multiplied the total number of symptomatic qPCR positive tests per day by 10, approximating how many tests would need to be run to find that many positive cases based on a 10% test positivity rate. Test positivity is a dynamic response to both the prevalence of infection and the sampling of the infected population. As such, the simple modifier presented here is too simplistic and is overestimating current test positivity (that is exceeding 20%).

In general, LAMP identifies cases which would otherwise go undetected if testing is based only on symptomatic qPCR. As such, even minor increases in LAMP testing are capable of reducing the epidemic size and thus overall qPCR demand. This trend continues until scenarios of 2000-4000 LAMP tests per day flatten the curve so that COVID-19 is extirpated and there is no qPCR demand. The additional effort to confirm LAMP tests with qPCR is compensated by the overall ability for LAMP to identify asymptomatic cases and reduce the size of the epidemic.

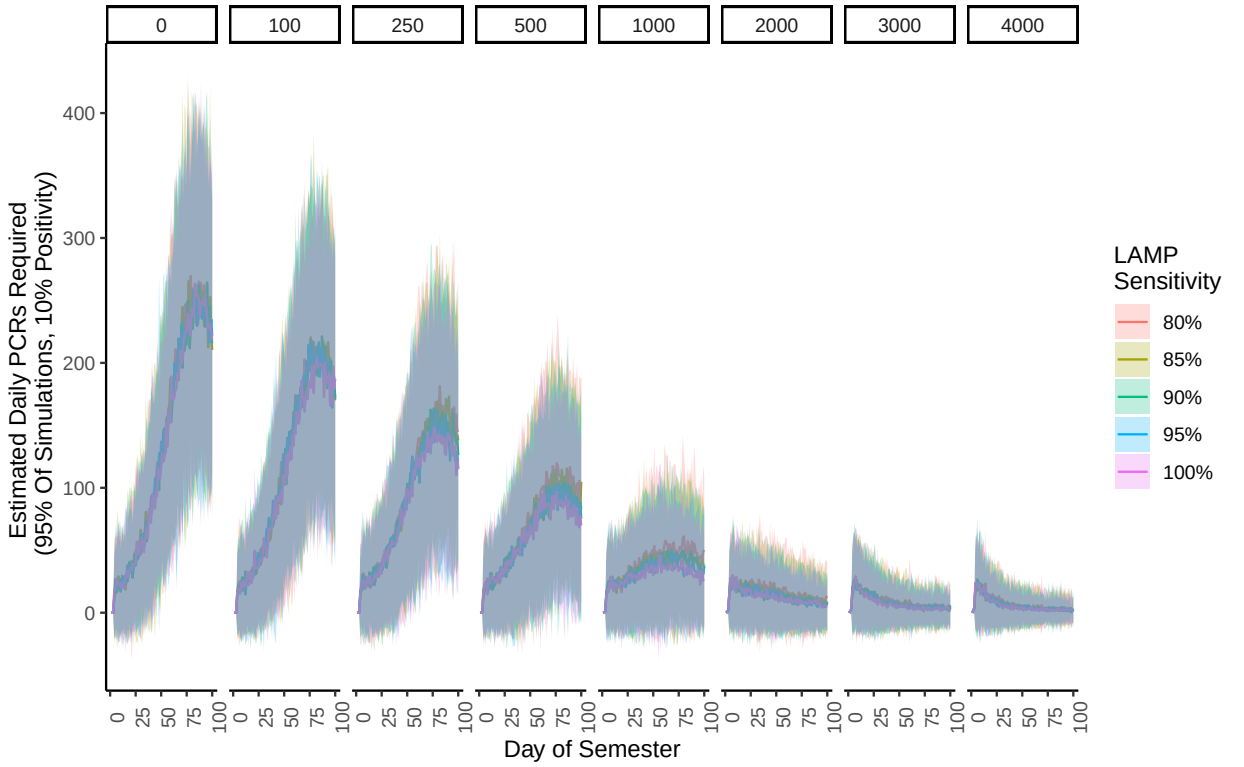


Figure 4:

3.4 The total number of missed cases is driven by prevalence and testing frequency

One concern with lower sensitivity testing, such as LAMP, is how many students will be provided with inaccurate test results. Negative LAMP results will not be confirmed via qPCR. The ability to create false negative results is relevant certainly legally or optically for the university, and may have some epidemiological implications. Foremost, low-sensitivity tests will produce false negatives, causing positive students to not isolate and potentially engage in riskier behaviors than otherwise. Secondly, as the epidemic grows in size, there are more positive students to be randomly ruled as false negatives. Therefore, the number of missed cases, or true-positive cases which are ruled as negatives, will consequently be shaped by the size of the epidemic and the sensitivity of LAMP.

We considered scenarios of 100-4000 LAMP tests per day with LAMP sensitivity ranging from 80%-95% [figure 5]. When testing frequency was low, the sensitivity of the LAMP test slightly affected the number of missed cases. As the testing frequency increased, the number of false positives rose, greatest for low sensitivity tests. Beyond 1000 LAMP tests per day, the epidemic size was reduced by broad-surveillance, and so the number of missed cases consequently fell. Across all scenarios, increasing the sensitivity was a strong method for reducing the consequences of LAMP testing. However, we again are faced with testing frequency, not just sensitivity, as a driver of LAMP outcomes.

3.5 next steps

For next steps we will: 1) refine the parameter space using data from case counts on university campuses; 2) incorporate parameters that reflect later-stage epidemics with some herd immunity; 3) consider scenarios of delayed LAMP implementation; 4) include variations in the method of LAMP testing (e.g., daily vs. bi-weekly

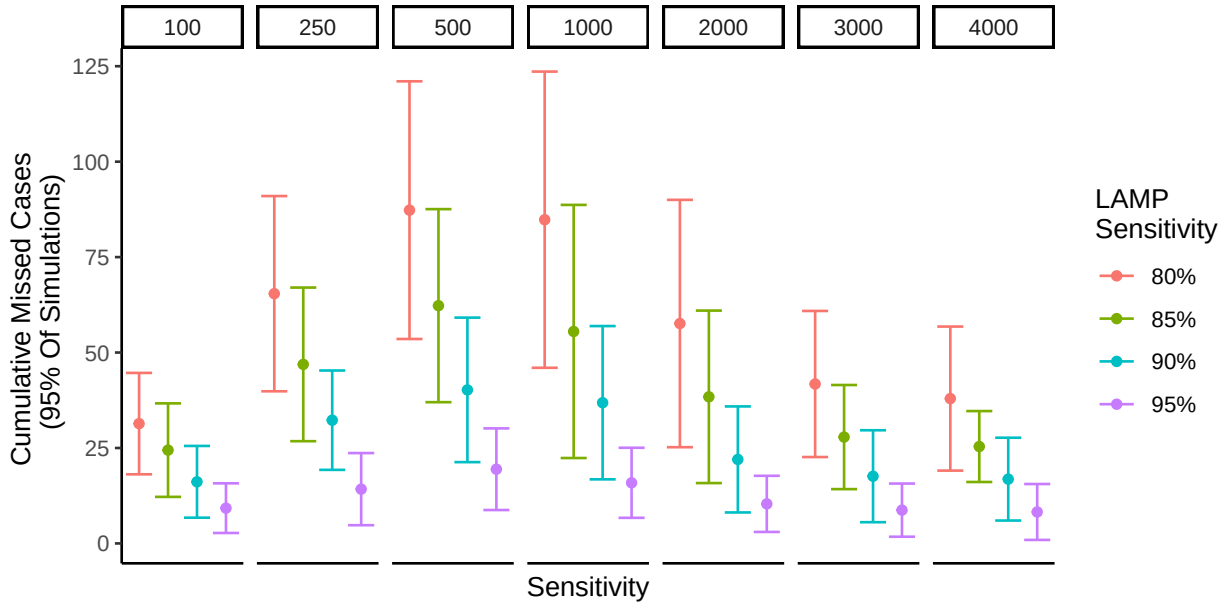


Figure 5:

testing, LAMP as a diagnostic, etc.); integrate pooling approaches into the model that are optimized for the stage of epidemic.

Appendix

Model Description

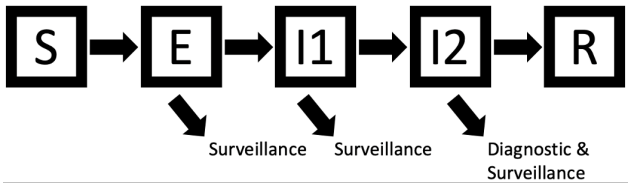
We developed two models: (Model A) a campus-level model with behavioral, testing, and transmission controls and (Model B) a theoretical and simplistic approach to viral load as a moderator of low-sensitivity efficacy. These models are meant to achieve a core set of goals addressing the implementation of loop-mediated isothermal amplification (LAMP), a generally high specificity but lower sensitivity, rapid test for SARS-CoV-2.

Parameter	Priority	Current Value	Source	Comments/Links
Number of PCR tests per day	High	200	S. Walk (August)	Likely Outdated
Number of contacts traced for on-campus students	High	7	M. Ferrari	
Number of contacts traced for on-campus students	High	7	M. Ferrari	
Delays in reporting test results	High	1 day	Campus Updates	
Delays in contact tracing	High	1 day	Campus Updates	
LAMP sensitivity	High	0.92*	C. Chang	Will change
LAMP specificity	High	0.98*	C. Chang	May change
Total number of contact tracing events per day	High	infinite	fixed by contacts per student	Need to incorporate max
Multiplier for dilution effect in pooling	High	1*	C. Chang	Will change
Number of Students	Low	16,750	MSU Office of Planning and Analysis	MSU Quick Facts
On-campus Proportion	Low	0.25	MSU Office of Planning and Analysis	MSU Quick Facts
Days from Infection to infectious	Low	5	Informal Lit Review	
Days infectious until symptoms	Low	2	Informal Lit Review	
Days from symptoms to recovered	Low	7	Informal Lit Review	
Number on Initial Infections	Low	100	Unofficial Fit	
Proportion Immune	Low	0.15	M. Ferrari	
PCR sensitivity	Low	1	C. Chang	More of a control
PCR specificity	Low	1	C. Chang	More of a control
Number of isolation rooms	Low	90	MSU August Comm.	Not important
Number of quarantine rooms	Low	140	MSU August Comm.	Not important
Reffective	Mid	2.5-3	Unofficial Fit	
Proportion of Students seeking care	Mid	0.5	Guess	
Proportion of students complying	Mid	0.75	Guess	
Positivity Rate	Mid	205	Campus Updates	Could have as a check
Daily Cases	Mid		Campus/Community Updates	Could have as a check
Likely LAMP Capacity	Mid	400/day	C. Chang	Might grow over time
Number of samples per pool	Mid	4-10	A. Hoegh	Not yet Implemented

Table 1: Parameter value descriptions and sources.

Alternative tests (e.g., PCR) are more sensitive, but are costly in time and in materials.

Model A:

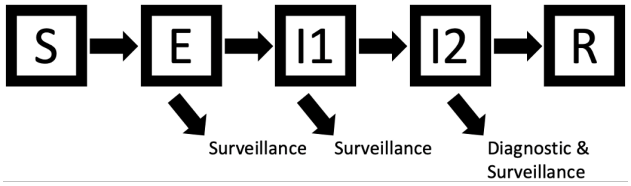


This is a simple SEIR model. SEIR refers to four disease compartments, foo susceptible, exposed (infected but not infectious), infectious, and recovered. The progression from S to E is stochastic and determined by a rate S_{t-1} $(1 - e^{-\beta \frac{I_{t-1}}{N_{t-1}}})$. The rate of progression from E to I is stochastic and determined by the rate $1 - e^{\frac{1}{5}}$, related to an assumed incubation period of about 5 days. I, in our model, is broken into pre-symptomatic (I1) and post-symptomatic (I2) infections. Individuals in I1 are infectious, but not yet symptomatic. Individuals in I2 are infectious and a proportion of I2 infections are symptomatic (e.g., if 20% are I2s are symptomatic, 80% would be asymptomatic). This boxcar approach to modeling approximates a more realistic infectious period than a traditional exponential process. Transition from I1 to I2 is determined by a pre-symptomatic period of 2 days, $1 - e^{\frac{1}{2}}$. Transitions from I2 to R are determined by a post-symptomatic period of 7 days, $1 - e^{\frac{1}{7}}$. There are two basic population components in the model, on-campus and off-campus students. The abundance of each is based on enrollment data from the MSU registrar (estimated). The two populations have homogeneous mixing (this can be altered in future iterations). Each population has a mean number of contacts (assumed to be 7).

Individuals can be removed from the population in three ways: (1) when symptomatic cases are tested, they are immediately isolated, (2) when individuals are tested by random surveillance and return a positive test, they are removed after some delay, and (3) when a contact of an infectious person tests positive, they are immediately isolated. The ability to identify infectious cases is determined by the proportion of cases that are symptomatic, the sensitivity of the test, and the probability that a student seeks care after developing symptoms. Surveillance is applied to a random sample of the population, including S, E, I1, I2, and R compartments, and is agnostic to the disease state. The probability that a person is isolated from the population is determined by the number of tests, the prevalence of disease in the population, the sensitivity of the test, and the probability that the student will comply with isolation. Finally, contacts are randomly drawn from a Poisson distribution with a mean of 7. This random generation of contacts is then multiplied by the number of positive cases discovered through diagnostic and surveillance testing. The total number of contacts is then randomly removed from the population, proportional to the number of individuals in each compartment, and the probability that the individual will comply with quarantine. In the current model iteration, all contacts are affected by the sensitivity of the test because we assume that all contacts are tested.

Our models can be adjusted to examine the effects of testing delays. Symptomatic cases are removed at the time of testing (assuming they are told to isolate while waiting for results). Contacts are tested when a close contact returns a positive test and are removed after a delay. Surveillance-tested individuals are tested randomly and are removed after a positive test. So, with a 2-day delay in testing: a symptomatic person tested on day 0 would be removed on day 0. The close contacts of a symptomatic person would be contacted/tested on day 2 and removed on day 4 if positive. Asymptomatic individuals tested on day 0 would be removed after a positive test on day 2, etc. The model operates on a daily timestep and a number of variables are collected and exported across the entire number of simulations and length of simulations.

Model B:



In model B, instead of E, I1, and I2 compartments, there are 14 I compartments, one for each day in the 14 day infectious period, functioning as a large boxcar chain. Individuals move through one bin per day until recovery on day 15. Viral loads are known to vary across the infectious period, rising to a peak around the onset of symptoms and decreasing beyond that. As a result, low-sensitivity tests like LAMP may be most effective in the early stages of the infectious period. We created distributions including uniform, normal, and beta distributions to affect the probability of a positive result as a function of the stage in the infectious period. This model is under development and will be useful for the investigation of test sensitivity in pooled samples and for comparing the efficacy of PCR vs LAMP.

In general, we intend to inform the following goals:

Model A:

1. Explore the effectiveness of LAMP surveillance testing with varying test sensitivity (partially completed)
2. Determine the effectiveness of LAMP given different testing scenarios (e.g., the number and frequency of tests, number of tests per individual) (partially completed)
3. Determine the stage of an epidemic (population) and the infectious period (individual) in which LAMP is most effective 4. Compare LAMP versus PCR, and LAMP used synergistically with PCR, as strategies to manage the epidemic on campus.

Model B:

1. Explore how the distribution of viral load over time in an infected individual affects the value of LAMP and PCR (partially completed) as a tool to manage transmission dynamics on campus (uncompleted)
2. Determine when pooling can improve the efficacy of surveillance (in relation to prevalence, dilution of pools, and the sensitivity of LAMP).

We have completed the first iterations of Models A and B. Are next steps are to:

Model A:

1. Add stochastic introduction of infections from the community (variable)
2. Parametrize contact tracing, isolation efficacy, and characteristics of LAMP and PCR
3. Parametrize epidemiological assumptions of incubation period, proportion asymptomatic, and student behavior and demographics (on/off campus)

Model B:

1. Refine boxcar approach to allow for stochasticity in movement between categories and reduce parameters
2. Make an individual's infectiousness tied to viral load

3. Build a function to describe pooling and integrate with the testing and removal process

References

Denny TN, Bonsignori M, Andrews L. 2020. "Implementation of a Pooled Surveillance Testing Program for Asymptomatic Sars-Cov-2 Infections on a College Campus — Duke University, Durham, North Carolina, August 2–October 11, 2020." *MMWR Morb Mortal Wkly Rep* 69: 1–5.

Larremore, Daniel B, Bryan Wilder, Evan Lester, Soraya Shehata, James M Burke, James A Hay, Milind Tambe, Michael J Mina, and Roy Parker. 2020. "Test Sensitivity Is Secondary to Frequency and Turnaround Time for Covid-19 Screening." *Science Advances*, eabd5393.