Memo on Testing Strategies for Covid-19

June 12, 2020

Prepared by Kajal Claypool, Munther Dahleh, Sarah Fay, Peko Hosoi, Dalton Jones, Simon Johnson, Ron Rivest, Cecilia Stuopis

It is important to begin this document by recognizing that MIT is in a fortunate position. We are very lucky to have access to the Broad Institute and to the superb staff and facilities at MIT Medical; relative to other entities (e.g. companies and services), our demographics are quite young and technically literate; and we have resources at our disposal that may not be available to other educational entities. These are enormous advantages and we should not forget the relative strength of our position in the current landscape.

Having said that, it will take all of our efforts to navigate this crisis. In this document, we will focus on the current testing landscape, but testing is just one tool in the considerable arsenal of weapons that we can bring to bear on the virus (e.g. masks, ventilation, scheduling, hygiene, education, etc.).

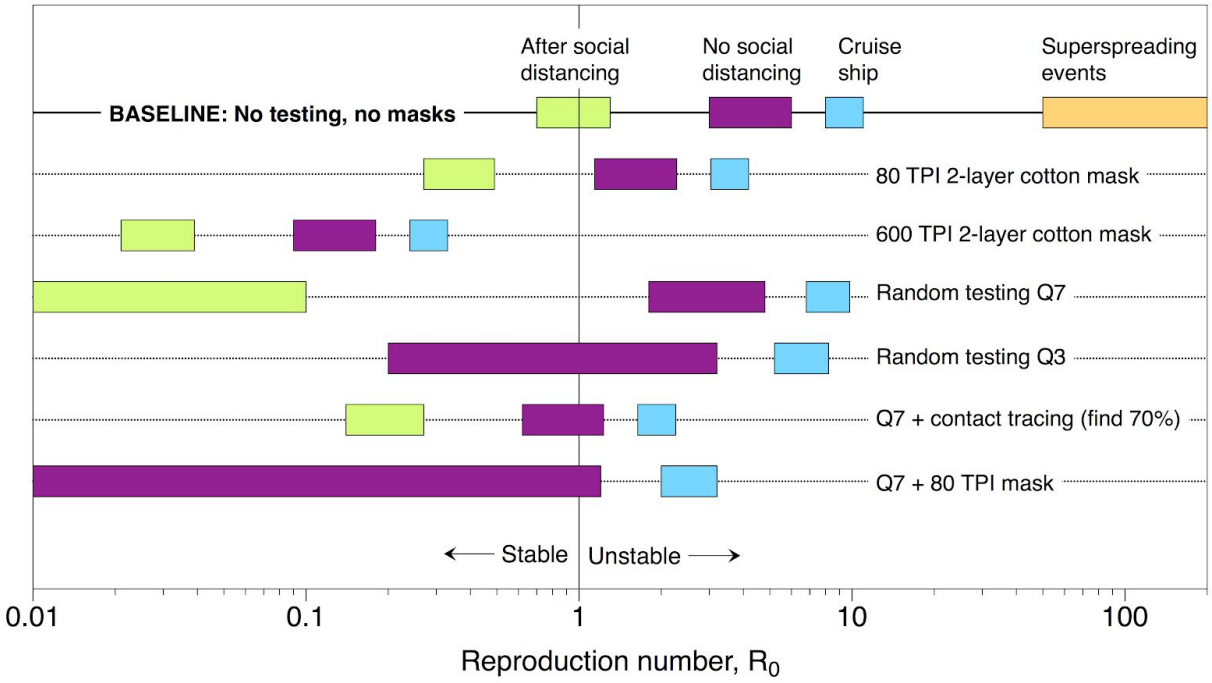

Figure 1: The top row of boxes show approximate measured values of R_0 before (purple) and after (light green) the lockdown, on a cruise ship (the Diamond Princess, blue), and estimates for super spreading events such as the Guangzhou restaurant, the Canandian curling event and the Korean call center (orange). The subsequent rows on the chart show estimates of what the effective R_0 would have been for a given policy, all else being equal. For example, the dark green box in the second row shows the decrease in R_0 if there was no social distancing (dark green = no social distancing) but everyone in the population wore (well-fitted) 80 TPI 2-layer cotton masks; in this case, the masks drop the average R_0

from about 4.5 (first row) to 1.8 (second row). Here Q7 refers to a testing strategy of randomly testing every person in the community weekly; similarly Q3 refers to testing everyone every three days. The mask estimates in this figure assume (near) perfect compliance (i.e. everyone wears a mask).

R_0 Primer: How much can we change / control R_0?

The rate at which a virus spreads is characterized by the *reproduction number* R_0, i.e. the total number of people that one contagious person infects during the course of their illness. R_0 lumps together a mish-mash of biological and behavioral parameters -- such as average number of contacts per day, lifespan of the virus in droplets, efficiency of ventilation systems, etc. -- into a single number which can be inferred from the measured rate of new cases in the population. This effective R_0 must be kept below 1 in order to keep the spread of the virus under control. To illustrate the impact of different environments, behaviors, and interventions, the figure above shows rough values of R_0 that have appeared in the literature and popular press for Covid-19. (Note that R_0 changes as behavior and policies change so it will evolve in time; these time dependent R_0's are sometimes referred to as R_t).

There are a few messages from this figure that are worth emphasizing. First, we have included it to provide some intuition for the ranges of R_0 we might expect to encounter in the Fall and the impact of various interventions. It is clear from the data that we have a number of measures at our disposal (e.g. social distancing and face masks) that can be quite effective in reducing R_0 and stabilizing the system, and which have proven to lower R_0 in many situations. Second, R_0 in the superspreading events (e.g. large groups of people in poorly ventilated rooms, frat parties, etc.) may be orders of magnitude larger than in other scenarios (note the log scale). As we shall see below, *there is no amount of testing that will save us from those types of events so we are better off keeping people out of environments where high concentrations of viral particles may accumulate.* However, in the more common scenarios on the chart, viral testing combined with isolation is one of the most important levers we have in controlling the spread of the disease.

Testing Basics

One of the challenges with this virus is that a large number of carriers are “hidden” i.e. a significant fraction of the population may be contagious but asymptomatic. Therefore we need strategies that limit the number of people in this group who are interacting with the community; the levers we have to control the number of people in this subset fall into two categories: (1) slow down the rate of people entering the population (via social distancing, improved hygiene, wearing masks, etc.) or (2) speed up the rate at which we remove people from that population via testing + isolation. It is worth emphasizing that a key concept in the second strategy is speed: the faster we can identify infected people and remove them, the better our control of the system.

How much testing do we need?

To prevent the number of infected people from growing, we need to isolate infected people from the community faster than additional people become infected. If we test for the presence of the virus by randomly sampling the population, this criterion can be written as:

$$R_0 \leq 1 + T_F D\, s$$

where T_F is the fraction of the population tested daily, s is the sensitivity of the virus test, and D is the average number of days an infected person is contagious. This relationship is independent of the details of the underlying network, the type of model (SIQR, MCMC, network, etc), and the parameters selected. It simply balances the rates at which people are entering and leaving the asymptomatic contagious population (analogous to a conservation law) and can be used to estimate the amount of testing required to stabilize any population.

MIT by the numbers:

Currently the sensitivity of the PCR test is about 70% and the reported number of days a person is contagious ranges approximately from 10-14 (we'll split the difference and use 12).

No social distancing: In the absence of social distancing measures on campus, R_0 may be at the high end of the spectrum (probably somewhere between the green box and the dark blue cruise ships box in the chart above). If we take R_0 to be approximately 7, we would need to test (7-1)/(0.7*12) = 71% of the population daily. This is unlikely to be a feasible long-term strategy (although the cost and availability of tests are rapidly decreasing so the outlook may be different in the Fall) so current testing efforts will have to be combined with a sensible campus social distancing strategy. However, these numbers also suggest that MIT could handle quite severe fluctuations by temporarily ramping up testing frequencies until the surge subsides.

Reducing R_0: Taking an example from the chart above consider R_0 = 5 (i.e. a typical R_0 without any social distancing or interventions). If we test every member of the community once per week (Q7), our effective R_0 decreases to:

$$R_{0,\text{eff}} = 5 / (1 + 0.7 / 7 \times 12) = 2.27$$

In order to get this below 1, we need to add an additional social distancing measure, e.g. masks. Requiring 80 TPI 2-layer cotton masks scales the original R0 by 0.38, for (nearly) complete compliance our effective R_0 becomes:

$$R_{0,\text{eff}} = 5 \times 0.38 / (1 + 0.7 / 7 \times 12) = 0.86$$

which is safely below 1.

What tests are available?

Note that at this point we haven't made any assumptions about the type of tests. Currently the testing landscape includes PCR virus testing (which we currently do on campus), rapid antigen tests (which are now coming to market), and serology tests (which are already available at low cost to MIT), all of which serve different purposes. The table below summarized the current state-of-the-art in testing.

Type	Sensitivity	Specificity	Availability	Cost	Comments
RT-PCR	~70-90`	>99	Multiple labs; Broad	$20-50	Already in operation using anterior nares swabs; possibility for saliva in future
Antigen	80	100	One company with EUA; others pending	$5-10	Respiratory swabs (anterior nares); Several approved; may need equipment purchase; E25Bio awaiting FDA EUA
Serology (IgG)	96.7	>99		Under $10	Sensitivity and specificity numbers refer to tests 10 days after symptoms appear

In both the PCR and antigen tests, the sensitivity is highly correlated with the viral load. On the one hand, this means that these tests may miss people early in the infection cycle. However, this may also work to our advantage as we are unlikely to see a negative test for someone who is highly contagious. In addition, it is worth noting that both the science and the practical deployment capabilities for all of these tests are advancing rapidly which drives down the cost; the cost numbers represent a current snapshot and all three may be lower in the Fall.

MIT by the numbers:

The only test that is currently suited to identifying and isolating infected people is the PCR test (although other testing strategies may become viable by Fall). If we assume that students will be on campus for 11 weeks in the Fall (Labor Day through Thanksgiving), then the cost of a weekly PCR testing strategy for the entire semester would be between $220 - $550 per person on campus (i.e. students, staff, and faculty). The Broad Institute is currently estimating costs at the lower end of that spectrum between $220 - $275 per person for a Q7 testing strategy for the entire semester. (Their cost estimate includes individual kits for self swabbing, transportation of tests, and analysis).

Beyond the Basics: Improvements over random testing

As we alluded to above, there are better strategies than random testing that find infected individuals more efficiently (with fewer tests on average). Two such strategies are *contact tracing,* and *identification of hotspots and superspreaders.*

Contact tracing

Contact tracing aims to find infected individuals efficiently by identifying individuals ("*contacts"*) who might have been infected by each known infected individual (each "*index case"*). Recent studies (e.g., Tian et al., Ferretti et al., or Hellewell et al.) suggest contact tracing can significantly reduce the spread of disease. With *manual contact tracing,* an individual who tests positive for the disease (each *index case*) is promptly interviewed, to quickly identify as many contacts as possible who have been exposed to the virus by the index case, and thus perhaps been infected. *Automated contact tracing* aims to augment manual contact tracing by enabling additional contacts to be quickly identified and notified, using technology (typically, Bluetooth functionality on smartphones or fixed beacons) to detect when individuals are close for a significant duration. Currently manual contact tracing is widely used; automated contact tracing is still in the research phase, and can not yet be counted on to provide significant public health benefits.

To estimate the added benefit of contact tracing, we can use a similar counting argument as we used for random testing above provides a new bound on R_0:

$$R_0 \leq (1 + T_F D\, s)^2 / [1 + T_F D\, s(1 - C_F)]$$

where C_F is the fraction of contacts we find through either manual or automated tracing relative to the actual number contacts.

MIT by the numbers

Reducing R_0: Taking the same number as in the example above (s = 0.7, D = 12 days, T_F = 1/7 and R_0 = 5), we can compute the effective R0 if we employ contact tracing and 70% of the contacts are known:

$$R_{0,eff} = 5 \times (1 + 0.7 / 7 \times 12\, (1 - 0.7) / (1 + 0.7 / 7 \times 12)^2 = 1.4$$

which again can be handled with masks or other social distancing protocols. If on the other hand the original R_0 = 3, then with contact tracing, R_0 effective becomes:

$$R_{0,eff} = 3 \times (1 + 0.7 / 7 \times 12\, (1 - 0.7) / (1 + 0.7 / 7 \times 12)^2 = 0.84$$

which is already below 1 and doesn't require any additional measures.

Hotspots and superspreaders

While an optimal testing strategy would rely on having perfect information of an individual's movement and behavior overtime, these interactions can be approximated through methods like contact tracing, or through inferring their location from building entry. In particular, MIT has the capability to require those on campus to use their ID to enter buildings. The data of who enters where when can then be used to estimate contacts between individuals. With this estimation, it is possible to both identify locations, or ***hotspots***, through which many people pass (and may serve as a vector of disease spread) and to trace back the contacts of those who have tested positive (potentially filling in the gaps of traditional interview-based contact tracing). Data from several studies appears to show that being indoors with poor ventilation can cause higher levels of disease transmission, thus identifying these hotspots will be instrumental in mitigating the spread of Covid-19 on campus and in the community. Once hotspots are identified they can be tested by randomly sampling those who passed through during a certain time window, or by *pool testing* a larger portion of that population. Simulations indicate that testing hotspots outperforms random testing and has the potential to *reduce the infection rate by more than 50 percent*.

In addition to testing hotspots, identifying *superspreaders* can increase the efficiency of the testing strategy. Superspreaders are individuals who come into contact with a large proportion of the population or who emit an unusually high viral load (e.g. through sneezing, shouting, or simply having a high viral baseline). These individuals have the potential to significantly increase the rate of disease spread and detecting and isolating them -- which may be done through a combination of building tracking and contact tracing -- is likely to be advantageous in mitigating the spread of Covid-19.

Pooled testing

Pooled testing or group testing combines biological specimens from multiple subjects into a "common" pool for RT-PCR-based diagnostic confirmation. In its simplest form if the pool tests negative, all individuals within the pool are declared to be negative. If the pool tests positive, re-testing is required to deconvolve the positive individuals from the negative individuals (Bilder and Tebbs 2012; Hogan, Sahoo, and Pinsky 2020, IDSS COVID-19 Collaboration).

Prevalence rate (%)	Optimal pool size	Reduction in expected # of tests (%)
1	11	80
3	6	67
7	4	50

Table taken from (Abdalhamid et al. 2020)

Pooled testing works well when the prevalence of the pathogen in the community is low. The table above shows the results reported in (Abdalhamid et al. 2020) that examine the inter-relationships between the overall prevalence of the pathogen in the community, the pool size, and the expected increase in testing efficiency.

Pooling will be most effective when the chance of positive detection of SARS-CoV-2 is low, that is when the overall prevalence of COVID-19 within the MIT community remains low, less than 10%. It can also be a useful surveillance tool for identifying asymptomatic individuals, increasing testing throughput, pairing with pods (as described below) and increasing overall testing efficiency while conserving resources (although there is likely to be some minimal loss of sensitivity). While pooled testing is appealing, it is our understanding that pooled testing has not yet been operationalized, but it is our understanding that the Broad Institute is looking into the possibility of offering such a service.

Families / pods / cohorts [1]

Recently there has been considerable interest around the idea of "pods" i.e. groups of students within which social distancing is relaxed much like it is relaxed between family members in a household. It is important to state up front that if we *decrease* social distancing protocols within the pods, we have to make up for that luxury elsewhere e.g. we can compensate by *increasing* social distancing measures between members of different pods (though this raises issues regarding non-compliance) and/or increasing our rate of testing. As before, we can derive a stability criterion,

$$R_o \leq 1 + s\, n\, T_F D$$

where R_o is now the reproduction number between pods and n is the number of people in the pod. In this relationship we have taken advantage of the built-in mechanism for increasing the effective testing rate by assuming fast dynamics within the pods such that all members of the pod are in the same state i.e. one positive test in a pod results in the entire pod being isolated.

Up to this point, the stability criterion reflects the conservation-like arguments above and is independent of the details of the underlying social network. However, in order to estimate numbers for the MIT campus, we now need to take these details into account and make some assumptions about the dependence of R_o on the number of people within each pod. Two MIT groups (Ozdaglar and the IDSS Covid-19 Collaboration) have been working on this problem; the stability criterion from both groups takes the form:

$$p_o\, f(n)\, D \leq 1 + s\, n\, T_F\, D$$

In selecting the dependence on n, Ozdaglar *et al* take f(n) = hn where h is a constant (i.e. each of the n students within the pod has h interactions outside the pod), and the IDSS group chose

[1] The authors would like to thank Asu Ozdaglar and Francesca Parise for their valuable input in the "Families / pods / cohorts" section.

$f(n) = n^2$ (i.e.there is a small probability that any of the n students in one pod will interact with any of the n students in the other pod so the number of potential interactions scales like n^2).

MIT by the numbers

Maximum pod size: Taking again T_F = 1/7, D = 12 days and s = 70%, we can rearrange the stability criteria above to find the maximum allowable pod sizes for p_o = 0.02 and 0.05 for both models with h = 6 (moderate interactions / non-compliance between pods) and h = 12 (high interactions / non-compliance between pods):

Maximum number of people per pod

	f(n) = 6n	f(n) = 12n	$f(n) = n^2$
p_o = 0.02	4	0	5
p_o = 0.05	0	0	2

These numbers suggest that small pods may be feasible; however the stability boundary is sensitive to small changes in p_o so pod design should be carefully considered and approached with caution.

Other types of testing: serology and waste-water tracking

For fast-moving viruses (or other diseases), best practice for predicting and detecting outbreaks does not rely solely on virus tests (or the equivalent). The reason is simple -- it is hard to find positive cases even when a major outbreak is developing because the disease moves through people's bodies relatively quickly. As a complement to viral testing, well-functioning public health systems use serology (antibody testing) to determine who has already been exposed to the disease. Because serology provides a historical record of whether an individual has been infected, it does not rely on timing the test to the moment that the individual is sick (something that is very unlikely when one is only sampling a small fraction of the population).

Although serology is effective as a tool for population health monitoring, we will not likely rely on it for individual diagnostics in the Fall. However, as a relatively inexpensive alternative, serology could potentially be used to concentrate our limited PCR testing resources on e.g. individuals who are connected to emerging hotspots and away from people who have already had the disease. To estimate the potential savings associated with serology testing, consider a scenario in which everyone receives a PCR test every T_{PCR} days (i.e. $T_F = 1/T_{PCR}$) and in addition the entire population receives a serology test every T_s days. If someone tests positive on a

serology test k times, we take them out of the PCR testing pool and save the relatively expensive PCR tests for the susceptible population. If r is the ratio of the cost of a serology test to the cost of a PCR test and b is the fraction of the population that has already had the virus at some time in the past, then the cost of PCR + serology testing is *lower* than PCR alone if

$$T_s > T_{PCR}\, kr/b$$

MIT by the numbers

Consider a PCR weekly testing strategy so $T_{PCR} = 7$. The cost of serology testing is roughly an order of magnitude cheaper than PCR so we'll take r = 0.1; if we choose k = 3 (i.e. someone has to test positive 3 times on the serology test before they are removed from the PCR testing population) and if 10% of the population has had the virus at some time in the past, then we can perform serology tests at a rate of:

$$7 \times 3 \times 0.1 / 0.1 = 21 \text{ days}$$

at no extra cost (i.e. the cost savings on PCR balance the cost of the serology test).

Final Thoughts

Finally we would like to end by going back to the 30,000 foot view. Looking forward, it is very unlikely that our campus will be a COVID-free zone in the fall -- or at any time in the foreseeable future. Unless we wish to shut down ***all*** campus operations, including everything that happens in any lab, we must confront this reality. Investing in our resilience now will serve to safeguard the health and wellness of our community, and position MIT as a role model for universities and for the entire education sector.

REFERENCES

Abdalhamid, Baha, Christopher R. Bilder, Emily L. McCutchen, Steven H. Hinrichs, Scott A. Koepsell, and Peter C. Iwen. 2020. "Assessment of Specimen Pooling to Conserve SARS CoV-2 Testing Resources." *American Journal of Clinical Pathology* 153 (6): 715–18.

Bilder, Christopher R., and Joshua M. Tebbs. 2012. "Pooled-Testing Procedures for Screening High Volume Clinical Specimens in Heterogeneous Populations." *Statistics in Medicine* 31 (27): 3261–68.

Dodd, R. Y., E. P. Notari 4th, and S. L. Stramer. 2002. "Current Prevalence and Incidence of Infectious Disease Markers and Estimated Window-Period Risk in the American Red Cross Blood Donor Population." *Transfusion* 42 (8): 975–79.

Dorfman, Robert. 1943. "The Detection of Defective Members of Large Populations." *Annals of Mathematical Statistics* 14 (4): 436–40.

Hogan, Catherine A., Malaya K. Sahoo, and Benjamin A. Pinsky. 2020. "Sample Pooling as a

Strategy to Detect Community Transmission of SARS-CoV-2." *JAMA: The Journal of the American Medical Association*, April. https://doi.org/10.1001/jama.2020.5445.

Hou, Peijie, Joshua M. Tebbs, Dewei Wang, Christopher S. McMahan, and Christopher R. Bilder. 2018. "Array Testing for Multiplex Assays." *Biostatistics* , October. https://doi.org/10.1093/biostatistics/kxy058.

Hourfar, Michael Kai, Anna Themann, Markus Eickmann, Pilaipan Puthavathana, Thomas Laue, Erhard Seifried, and Michael Schmidt. 2007. "Blood Screening for Influenza." *Emerging Infectious Diseases* 13 (7): 1081–83.

Lohse, Stefan, Thorsten Pfuhl, Barbara Berkó-Göttel, Jürgen Rissland, Tobias Geißler, Barbara Gärtner, Sören L. Becker, Sophie Schneitler, and Sigrun Smola. 2020. "Pooling of Samples for Testing for SARS-CoV-2 in Asymptomatic People." *The Lancet Infectious Diseases*, April. https://doi.org/10.1016/S1473-3099(20)30362-5.