THE PROGRAM IN GLOBAL PUBLIC POLICY AND SOCIAL CHANGE

"The Case of the Missing Cases: Massachusetts COVID19 Case Finding"
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The *Confronting COVID19* briefs, produced by the *Program in Global Public Policy (PGPP)* at Harvard Medical School, aim to inform the public about the country and the Commonwealth's efforts to mitigate the COVID19 crisis. These briefs focus on the debates, challenges, and policy conundrums of the COVID19 crisis. The initial briefs in this series regard the Massachusetts Contact Tracing Collaborative (CTC). Of note PGPP serves as a policy advisor to Partners in Health, a non-profit working for the Commonwealth as a consortium partner to implement its contact tracing program.

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Case finding is the first of four activities that comprise the COVID response strategy—without which the entire enterprise would fail. While Massachusetts has directed substantial effort toward this area, the core issue of missing cases remains.

How do we know we are missing cases?
There are various proposed methods to estimate undiagnosed cases in Massachusetts, including analyzing wastewater and antibody surveys. However, postmortem COVID testing is the most accurate metric currently available to estimate total numbers of active infections. Postmortem estimations, developed by multiple research groups including Jha and Jacobson and the Institute for Health Metrics and Evaluation, back-estimate the total number of infections based on the numbers of deaths from the disease and an estimated case fatality rate. The assumptions that underpin this approach include: deaths reported from the disease are accurate, variations in quality of medical care in a region does not significantly alter the death rate from the disease, the case fatality rate used is correct, and the estimated time from infection to death is not variable and is correct.

How many missing cases are there?
Postmortem models of COVID-19 in Massachusetts use a 1% case fatality rate and estimate a two-week period of time between onset of infection and death. Using this model and cases as of May 4 as an example, there have been an estimated total 580,000 COVID-19 cases in Massachusetts, of which only 69,087, or 12%, cumulatively are confirmed. Assuming it takes two weeks for 80% of all infected people to recover and 1% of infected people to die, we estimate the net number of undiagnosed **active** COVID cases to be roughly 220,000 people, on May 4. Notably, the number of undiagnosed active cases may be as high as 300,000, based on confirmed COVID-19 deaths accounting for only 75% of excess deaths in this time period.

As the overall number of cases in Massachusetts has declined due to social distancing, shut downs and mask wearing, the gross number of missed cases has also declined, but not the percentage. In general, Massachusetts continues only diagnose 10-20% of its total case load.

Why are we missing cases?
Case finding has thus far relied primarily on nucleic acid (PCR) testing of moderately and severely ill people in hospital settings. In mid-May, the Massachusetts Department of Public Health issued guidance to test all symptomatic people and contacts, though many sites still require a referral, an appointment, or meeting a particular threshold on screening questions in order to administer a test. Inadequate testing in non-hospital settings of an infected person's contacts—and among mildly symptomatic people—is a central issue, but not the only obstacle.

Testing sites and laboratories are not optimally coordinated with each other. While there are roughly 230 testing sites distributed across population centers and rural areas, test specimens are not efficiently allocated to laboratories for processing. Approximately one-third of the total number of tests conducted as of April 21 (over 50,000 tests) were processed in academic, public, or non-commercial private labs, versus commercial labs. But a single academic lab, the Broad Institute, could have done the work of all non-commercial labs at that time. Bottlenecks in daily test processing at smaller labs restrict the number of tests conducted at sites that feed into those labs.

There are continued supply chain shortages for PCR (including nasopharyngeal swabs, transport medium, RNA extraction kits, and PCR reagents). The turnaround time between testing and receipt of results, one to five days in outpatient settings, is still too long to usefully inform management and transmission control, leading some providers to forego testing for their patients altogether. Finally, patient interviews by contact tracers are currently the sole means to identify potential exposures, with no role for emerging technologies to aid testing referral or catch missing cases.

How should we find cases now?
The state should establish a network of certified frontline community testing sites, with accurate reporting of daily testing capacity to fully serve the second stage of the epidemic's progression. Sites may be new or pre-existing private clinical care centers, such that all Massachusetts residents have access to a state-certified testing center. They must share standard criteria for testing and publicize their locations, operating hours, and eligibility requirements. This network should be a state priority to address resourcing and supply chain shortfalls and needs to be geographically nimble and flexible in scale as epidemic hotspots move.

PCR testing capacity should be directed towards community diagnosis rather than hospitals. To fill the hole left behind for inpatient populations, the state should commission research into alternative COVID testing modalities. Options include antibody testing, which may be more accurate than PCR later in disease course; and combination modalities of chest computerized tomography (CT) scans, lab markers, and clinical presentation, which together may offer greater diagnostic value than any individual component.

Finally, there is clear untapped capacity in academic labs for test processing that must be harnessed. The Broad, for example, has the potential to accommodate the state's entire testing load, as it routinely processed 250,000 samples per day during the Human Genome Project. Better allocation of test specimens to high-capacity labs would eliminate the current false cap on the number of tests that can be conducted per day in Massachusetts.

How should we find cases in the future?

An eventual reallocation of resources is needed to make the shift from testing to identify missing cases to testing for suppression. These two modes are distinct, and suppression will require much broader coverage. This means moving away from testing in congregate care settings where there is little coming and going of people (i.e. prisons and nursing homes) to a testing scheme that focuses on places of maximal mixing of people: state borders, airports, and tightly-packed workplaces and schools. The state needs to re-envision its role in containing COVID to execute this shift in testing strategy for the next phase of the epidemic.

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Until we are able to find and diagnose the missing cases, COVID cannot be tamed in Massachusetts. Missing cases are a persistent reservoir of disease propagation. Overall, official case counts do not capture the full picture of COVID in Massachusetts. We advise the development and implementation of a state-wide case finding strategy to find the missing cases. This plan should specify state-certified community-based testing network, capitalize on untapped academic laboratory testing capacity, and explore alternatives to PCR tests for diagnosing COVID19. Finally, we recommend the state prepare to rapidly adopt and allocate innovations in diagnosis as they emerge. Harvard University Committee on Regional Studies East Asia