Strategic Thinking in Test Selection for Mass SARS-CoV-2 Testing

Sejal Morjaria,[a] Rosa Nouvini,[b] and S. Joseph Sirintrapun[c,*]

INTRODUCTION

Effective mass severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing is critical to mitigating coronavirus disease 2019 (COVID-19) outbreaks and alleviating the economic impact of COVID-19 lockdowns. Although vaccination will stymie severe infection and potentially mitigate spread, the possibility of asymptomatic transmission, logistical issues with vaccinating entire communities in a timely fashion, and the questionable duration of immunity jeopardize infection control. The threat of new variants escaping vaccine-induced immunity and leading to outbreaks also remains. For this reason, a robust testing and vaccination strategy must be implemented alongside each other. Likewise, robust testing to control transmission helps to maintain COVID-19 elimination status once achieved either through postinfection surges or vaccination efforts. It is important to not only test and quarantine individuals who display symptoms of COVID-19 but to also identify individuals who are asymptomatic and presymptomatic. These individuals are significant contributors to community SARS-CoV-2 transmission (1), and their identification can help curb outbreaks. This is especially important for vulnerable communities that contain individuals of lower socioeconomic status, who are often essential workers who rely on public transportation. Such communities contain a higher proportion of ethnic minorities and often have higher rates of COVID-19 (2).

Given the variability of COVID-19 susceptibility and prevalence among communities, a comprehensive SARS-CoV-2 testing strategy that combines economic, logistic, and public health considerations must be adopted. As a starting point, we show a thought experiment with 4 commonly encountered scenarios on how strategic thinking in SARS-CoV-2 testing can tailor healthcare policies based on community factors.

ABSENCE OF STRATEGIC THINKING TO TESTING

At the onset of the pandemic, no national testing strategy existed, leaving states and local jurisdictions to develop their own. The testing landscape that emerged varied widely, with more wealthy states and robust medical sectors devising comprehensive plans, while other states

[a]Infectious Disease, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [b]Medical Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [c]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
*Address correspondence to this author at: Infectious Disease, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA. E-mail sirintrs@mskcc.org.
Received January 11, 2021; accepted June 21, 2021.
DOI: 10.1093/jalm/jfab078

lagged behind. Furthermore, some testing gaps in local communities required a federal strategy to solidify production and supply chain logistics (3), which has been lagging throughout the pandemic. Even in New York, one of the richest states, communities of lower socioeconomic status and minority groups, where rates of COVID-19 positivity and deaths were greatest, had less access to testing (4).

TWO IMPERFECT APPROACHES TO TESTING

Public health experts, such as Mina et al., have advocated for a nationwide rapid testing program using paper-based antigen tests (5). Such point-of-care tests (POCTs) offer accessibility and operational simplicity for mass SARS-CoV-2 testing. However, POCTs are less sensitive and specific than PCR, which can lead to further viral spread due to false-negative (FN) results (6). POCTs advocates show that when factoring viral load kinetic patterns, high testing frequency with rapid turnaround times (TATs), and affordability to dispense on a massive scale, POCTs can overcome lower sensitivity vs PCR testing. Mina et al. further conclude that POCTs are most effectively used in communities where the transmissibility window is highest (5).

In contrast, the Great Barrington Declaration argues for communities to "perform frequent polymerase chain reaction (PCR) testing" (7). Although PCR testing is the most accurate, it lacks the accessibility and operational simplicity of POCTs. It also is susceptible to false-positive (FP) results given its high sensitivity. FPs also pose individual risks and can undermine confidence in clinical and public health efforts. As an example, FP results can delay asymptomatic patients from undergoing potentially curative cancer surgery and chemotherapy. PCR also depends on strained supply chains and technical expertise for processing. Such dependencies lead to slow TATs for results and higher testing expenses. Slow TATs can render PCR results obsolete if contagious individuals continue exposing others while awaiting results. Moreover, mass PCR testing requires costly laboratory equipment, expertise, and testing supplies that are scarce in underresourced communities.

In this article, we do not incorporate a specimen-pooling strategy for simplicity in our quest to illustrate strategic thinking in the COVID-19 domain. Although specimen pooling has advantages in conserving lab reagents and resources, reducing TATs, and lowering costs (8), it is riddled with flaws. Specimen pooling is prone to FN results due to sample dilution, making it applicable only in low COVID-19 prevalence communities. Moreover, this testing strategy is mostly unregulated, requiring laboratory expertise that not often accessible in underresourced communities. Last, guidelines are absent on the optimal number of individual samples pooled before FN results arise (8).

FRAMEWORK FOR STRATEGIC THINKING IN SARS-COV-2 TEST SELECTION

Our strategic framework for SARS-CoV-2 test selection accounts for 3 factors: (a) whether a community is a "cold spot" (low COVID-19 prevalence) or "hot spot" (high COVID-19 prevalence), (b) whether a community has a limited testing capacity, and (c) whether the specific scenario warrants the aforementioned desirable testing features (accessibility, fast TATs, high test accuracy). By evaluating these factors and making a public health risk assessment, we provide an optimal testing strategy with testing logistics and performance along with policy recommendations.

Important measurements of test performance include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). PPV and NPV are meaningful in a clinical setting, but these values depend on the COVID-19 prevalence. Take a cold-spot community, for example, which can either be one not affected by COVID-19, postsurge, or with a high level of population immunity via vaccination or natural infection. The NPV for such a community is higher given the low amount of circulating virus. In hot-spot communities, on the other hand, PPV is higher given the higher amount of circulating virus (9).

Of import, people of color and low socioeconomic status often reside in hot-spot communities with limited testing capacities (4). There is an urgency to create better testing strategies for them as such populations have more COVID-19 cases and suffer more morbidity and mortality. According to the CDC, when compared to non-Hispanic White persons, Black, Hispanic, and American Indian/Alaska Native persons are 2.8, 2.8, and 2.6 times, respectively, more likely to die from COVID-19 (10). Part of these disproportionate effects arises from existing healthcare and structural disparities that have led to a higher prevalence of severe COVID-19 risk comorbidities such as respiratory illnesses and hypertension (11). Furthermore, structural disparities such as living in multigenerational homes and employment as essential workers make social distancing and quarantine/isolation much more difficult thereby increasing the risk of contracting COVID-19. Despite these known risks, these communities often have less access to testing than their wealthier neighboring communities as was seen in New York City during the surge (4). This argues for increasing the availability of POCTs given their higher accuracy in such higher prevalence settings as well as their lower cost and resource utilization.

THOUGHT EXPERIMENT

Taking all of this into consideration, we introduce thought experiments for 4 frequently encountered community scenarios (Fig. 1).

Scenario 1 applies to the asymptomatic screening of nonvulnerable individuals in a cold-spot community for sporadic interactions. Sporadic interactions include testing all individuals dining at restaurants and shopping at malls, where the penalty for high FPs and FNs is more tolerable for less vulnerable younger, healthier populations prone to doing such activities and less likely to have severe COVID-19 outcomes. POCTs work best because of the desirable features of easy accessibility and fast TATs.

Scenario 2 includes individuals in a cold-spot community with continual exposure to vulnerable patients such as those in nursing homes and many segments of populations of color. In these healthcare settings, testing is critical to mitigating the impact of COVID-19. Here, accurate tests with high PPV and NPV are paramount, which means a testing strategy that must incorporate PCR testing. Given the known pitfalls of PCR testing (poor accessibility and slow TATs), logistics and policy responses to increase testing supplies and facilities for these individuals are necessary. Alternatively, to improve the detection of COVID-19 disease, new testing guidelines can consider the combined integrated use of POCTs and PCR testing for SARS-CoV-2.

Scenario 3 includes individuals with a COVID-19 symptom complex (i.e., loss of smell plus taste) (12) in a cold-spot community with limited testing capacity. In such communities, POCTs provide the only available and viable means of testing (9). Although the NPV is better given the lower prevalence in those communities, a negative test is not a trusted license to interact with vulnerable populations and engage in transmissible behaviors. Because of the nonoverlap between the windows of viral transmissibility and timing of tests in obtaining a positive result, the use of serial POCTs targeted to various SARS-CoV-2 antigens would increase the test's sensitivity and achieve a sufficient trust level for a series of negative results (13). The optimal serial testing regimen, leveraging different

	Desired Features of Testing Strategy			Testing Regimen	Risk Assessment	Logistics and Policy
"Cold spot" Community						
Scenario 1: Asymptomatic individual screening and daily sporadic interactions between non-vulnerable individuals	Easy Accessibility	Fast TAT	NPV is a priority	POC testing (i.e. PATs)	Though not perfect, NPV is better and possibly acceptable, given the lower community prevalance. Likewise, the penalty of FN is lower, given the scenario is screening and non-vulnerable individuals. Consider that PPV is lower.	Restrictions and isolation for "spreader" individuals testing positive, particularly those interacting with vulnerable subpopulations. Follow-up of positive tests with confirmatory PCR.
Scenario 2: Individuals with continual interactions with vulnerable subpopulations	Easy Accessibility	Fast TAT	PPV and NPV is a priority	PCR	The high penalty for FP and FN results are best addressed by performing PCR testing regimens.	Increase PCR testing supplies and improve logistics for deployment to enhance accessibility and TAT.
"Cold spot" Community with <u>limited testing capacity</u>						
Scenario 3: Individuals developing a new onset of predictive COVID-19 associated symptoms	Easy Accessibility	Fast TAT	PPV and NPV is a priority	Start with POC testing (i.e. PATs). Develop serial POC testing regimens to strengthen trust in the POC results. Consider judicious use of follow-up PCR testing (when available).	NPV more trustworthy, particularly when a developed serial POC testing regimen is negative. PPV is lower, though developing a serial POC testing regimen may enhance the sensitivity.	Weighing the penalty of a FN, consider confirmatory PCR (if available) where the penalty is high. Or without PCR, blanket restrictions for all with symptoms where penalty is high.
"Hot spot" high RO, high COVID-19 prevalence community with <u>limited testing capacity</u>						
Scenario 4: Individuals developing a new onset cough	Easy Accessibility	Fast TAT	PPV and NPV is a priority	Start with POC testing (i.e. PATs). Develop serial POC testing regimens to strengthen trust in the POC results. Consider judicious use of follow-up PCR testing (when available).	PPV more trustworthy, negatives are more suspect.	Weighing the penalty of a FN, consider confirmatory PCR (if available) where the penalty is high. Or without PCR, blanket restrictions for all with symptoms where penalty is high. The latter may not be practical given that such communities in reality, regularly interact with vulnerable subpopulations. Therefore, efforts should be made to increase access to more accurate confirmatory tests like PCR.

What the testing regimen delivers for desirable features of the testing strategy.

What is not associated with the testing regimen and must be worked upon to meet the desirable features of the testing strategy.

NPV = Negative predictive value
PPV = Positive predictive value
POC = Point of care
FN = False negative
FP = False positive
PATs = Paper-based antigen tests
TAT = Turn-around time
RO = Level of contagiousness

Fig. 1. SARS-COV-2 testing strategy for 4 commonly encountered community scenarios.

antigens and specific testing time intervals, remain under investigation.

The most conservative policy is restrictions for all individuals with the COVID-19 symptom complex, regardless of the test result. This policy, however, potentially disengages a significant subset of the community that may have essential duties. It also potentially results in noncompliance to COVID-19 restrictions if the FP rate is too high. The optimal approach is the judicious yet integrated approach in using PCR, when available, to confirm negatives when the penalty of inaccuracy

Table 1. How a mass testing strategy will help to control transmission, monitor rates, and mitigate the impact of COVID-19 in healthcare and social settings.

	To control transmission	To monitor rates	To mitigate the impact of COVID-19 in healthcare and social settings
Solution	Affordable POCTs provide the scaled accessibility and high testing frequencies for any resourced community.	POCTs provide the affordability for scaled accessibility and high testing frequencies for any resourced community.	POCTs provide the scaled accessibility and high testing frequencies that healthcare and social care setting need, covering the subsequent time periods after diagnostic PCR testing.
	POCTs can be leveraged at scale to detect clusters and outbreaks in any specific setting, which in turn controls transmission, while continually monitoring rates and mitigating impacts of COVID-19 in those specific settings		
Reasoning	A significant proportion of transmission occurs through asymptomatic spread, and testing the asymptomatic population requires scaled accessibility and high testing frequencies to catch the initiation of clusters and outbreaks in specific settings.	Monitoring requires scaled accessibility and high testing frequencies.	Healthcare and social care settings may not have the ability for sustained continuous diagnostic PCR testing, and POCTs fill that gap where diagnostic PCR testing is not continually available.
	With vaccinations underway, questions still remain of vaccination durations and breakthrough infections; POCTs can be an integral scalable component to maintaining COVID-19 elimination status once achieved.		

is high, such as those who interact with vulnerable populations. Unfortunately, there is no available research on the optimal integrated use of POCTs with limited PCR to help these communities.

Scenario 4 are individuals in hot-spot communities with limited testing capacity who develop a new cough onset. New cough onset alone is arguably predictive for SARS-CoV-2 positivity in a community with a high COVID-19 prevalence. However, the current state where tests get performed infrequently cannot stop transmission chains. As previously stated, although not as accurate as PCR tests, POCTs tests are very cheap to produce and can be performed by individuals much more frequently, and such POCTs are nonetheless effective at detecting virus when individuals are most infectious (14).

Fast TATs with rapid results from POCTs are critical to interrupting SARS-CoV-2 transmission, particularly in hot-spot communities with outbreak settings or clusters with high transmission levels. Positive results from POCTs combined with new cough onset further substantiate SARS-CoV-2 positivity, justifying quarantine. If positive individuals, particularly those with new-onset cough, stay home and quarantine measures get enforced, the widespread effect breaks transmission chains across the country, similar to vaccine deployment. Therefore, for individuals with a new onset of cough, negative results from POCTs are more suspect than in a cold-spot community. Because of the ramifications of testing inaccuracy with POCTs, creating a better policy to prioritize mass PCR testing for such communities should be attempted.

Overall, our testing strategy will increase the accessibility and therefore the frequency of testing. This in turn will allow for transmission control, infection rate monitoring, and mitigation of the impact of COVID-19 in healthcare and social care settings (Table 1).

CONCLUSION

Mass SARS-CoV-2 testing and other proven strategies (e.g., social distancing, mask-wearing) help mitigate COVID-19 and its community impacts. We address the most significant gap in the COVID-19 public policy conversation: a one-size-fits-all mass testing edict. By leveraging testing resources strategically, our framework applies risk assessments for frequently encountered community scenarios.

Our thought experiments show logical reasoning, based on community variables, in selecting, prioritizing, and allocating testing resources to communities affected by the COVID-19 pandemic. We intend for our thought experiments to stimulate consensus among expert groups, presumably consisting of physicians, health policymakers, epidemiologists, economists, and politicians. Such groups are more apt to build testing strategies with logistics and policy for more complicated community scenarios, such as back-to-school/college and return-to-work situations, that optimize individual health, public health, and economic interests.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

S.J. Sirintrapun, administrative support, provision of study material or patients.

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

REFERENCES

1. Centers for Disease Control. Guidance for expanded screening testing to reduce silent spread of sars-cov-2. https://www.cdc.gov/coronavirus/2019-ncov/php/testing/expanded-screening-testing.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fphp%2Fopen-america%2Fexpanded-screening-testing.html (Accessed February 2021).
2. Karmakar M, Lantz PM, Tipirneni R. Association of social and demographic factors with COVID-19 incidence and death rates in the US. JAMA Netw Open 2021;4:e2036462.
3. Eilperin J, McGinley L, Mufson S, Dawsey J. In the absence of a national testing strategy, states go their own way. The Washington Post, April 8, 2020. https://www.washingtonpost.com/health/2020/04/07/testing-coronavirus-trump/ (Accessed February 2021).
4. Lieberman-Cribbin W, Tuminello S, Flores RM, Taioli E. Disparities in COVID-19 testing and positivity in New York City. Am J Prev Med 2020;59:326–32.
5. Mina MJ, Parker R, Larremore DB. Rethinking covid-19 test sensitivity: a strategy for containment [Editorial]. N Engl J Med 2020;383:e120.
6. Brooks ZC, Das S. COVID-19 testing. Am J Clin Pathol 2020;154:575–84.
7. Bhattacharya J, Gupta S, Kulldorff M. Great Barrington Declaration. October 2–4, 2020. https://gbdeclaration.org/ (Accessed December 2020).
8. Centers for Disease Control. Interim guidance for use of pooling procedures in SARS-CoV-2 diagnostic, screening, and surveillance testing. https://www.cdc.gov/coronavirus/2019-ncov/lab/pooling-procedures.html (Accessed February 2021).
9. Vandenberg O, Martiny D, Rochas O, van Belkum A, Kozlakidis Z. Considerations for diagnostic covid-19 tests. Nat Rev Microbiol 2021;19:171–83.
10. Centers for Disease Control. Covid-19 hospitalization and death by race/ethnicity. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html (Accessed January 2021).
11. Alcendor DJ. Racial disparities-associated covid-19 mortality among minority populations in the US. J Clin Med 2020;9:2442.
12. Centers for Disease Control. Symptoms of coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html (Accessed February 2021).
13. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020;26:672–5.
14. Powell A. Cheap, frequent covid tests could be 'akin to vaccine,' professor says. The Harvard Gazette, August 11, 2020. https://news.harvard.edu/gazette/story/2020/08/cheap-daily-covid-tests-could-be-akin-to-vaccine/ (Accessed February 2021)