Efficiency of differentiated pooled testing for SARS-CoV-2

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**Title:** Optimizing SARS-CoV-2 Pooled Testing Strategies Through Differentiated Pooling for Distinct Groups

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Running Head: Efficiency of differentiated pooled testing for SARS-CoV-2

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Abbreviations: COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2; UNC: University of North Carolina
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Abstract

Pooled testing has been successfully used to expand SARS-CoV-2 testing, especially in settings requiring high volumes of screening of lower-risk individuals, but efficiency of pooling declines as prevalence rises.

We propose a differentiated pooling strategy that independently optimizes pool sizes for distinct groups with different probabilities of infection to further improve the efficiency of pooled testing. We compare the efficiency (results obtained per test kit used) of the differentiated strategy to a traditional pooling strategy in which all samples are processed using uniform pool sizes under a range of scenarios.

For most scenarios, differentiated pooling is more efficient than traditional pooling. In scenarios examined here, an improvement in efficiency of up to 3.94 results per test kit could be obtained through differentiated versus traditional pooling, with more likely scenarios resulting in 0.12 to 0.61 additional results per kit. Under circumstances similar to those observed in a university setting, implementation of our strategy could result in an improvement in efficiency between 0.03 to 3.21 results per test kit.

Our results can help identify settings, such as universities and workplaces, where differentiated pooling can conserve critical testing resources.
Coronavirus disease-2019 (COVID-19) was the third leading cause of death in the United States in 2020 (1) and remains a leading cause of death globally (2,3). Public health professionals have emphasized that increased testing is a key strategy to minimize transmission of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and decrease subsequent COVID-19 mortality (4–9). In settings such as universities and workplaces, wide-scale testing of asymptomatic individuals is gaining traction as an infection control mechanism, with many administrators implementing mandated testing policies, generally in lieu of proof-of-vaccination (10–12). For example, unvaccinated students enrolled in courses at the University of North Carolina at Chapel Hill (UNC-Chapel Hill) in Fall 2021 were required to test twice weekly and unvaccinated employees were required to test once weekly (13). Testing for individuals who were either symptomatic or were known close contacts of an individual testing SARS-CoV-2 positive was recommended regardless of vaccination status (13). However, as new SARS-CoV-2 variants emerge and sweep the globe, facility and system-level barriers such as supply chain bottlenecks and laboratory throughput capacity continue to impede efficient scale-up of testing efforts across a number of settings (6,14–18).

Pooled testing, also called group testing, is an established and effective testing strategy that can conserve testing resources, save personnel time, minimize turnaround time from testing to receipt of results, and improve testing efficiency (i.e., increase the number of results obtained or individuals screened per test kit used) (10,19–32). Pooled testing is a process by which multiple specimens are combined, or “pooled”, and the pooled samples are screened for the agent of interest (in this case, SARS-CoV-2). Pools that screen positive are then re-tested in sub-pools or as individual samples (33). In a recent article on pooled testing as a means for optimizing the
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efficiency of SARS-CoV-2 testing, the authors demonstrate that for a given number of test kits, testing programs using pooled testing could screen between 2 and 20 times as many specimens when compared to programs using individual-specimen testing (19). However, in high-prevalence settings where a large proportion of individual samples would be SARS-CoV-2-positive, the efficiency gains of pooled testing are reduced or eliminated and improvements in turnaround time obtained through pooling are lost because a large proportion of pools would screen positive, necessitating further sub-pool or individual-specimen testing (34).

We propose a differentiated pooled testing strategy, similar to the Informative Dorfman Screening strategy previously proposed by McMahan et. al. for use in chlamydia and gonorrhea testing (35), to improve efficiency gains of pooled SARS-CoV-2 testing across a range of settings, including high-prevalence settings and lower-prevalence settings where identifiable subgroups of the testing population are at substantially higher risk of infection. In this paper, we explore the improvement in efficiency, expressed as the number of additional test results that can be obtained per test kit used, through implementation of our considered strategy versus a traditional two-stage hierarchal (i.e., “pooling”) testing strategy where samples are processed in uniform pool sizes (27).

METHODS

Overall strategy
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In a traditional two-stage pooling strategy, samples are processed in uniform pool sizes and the calculation of the optimal pool size is based on the prevalence of SARS-CoV-2 in the overall population being tested. In a differentiated pooled testing strategy (i.e., “differentiated pooling”), pool sizes are independently optimized for two or more distinct groups with different test-positive probabilities. Here we will consider two easily distinguishable groups with characteristics shown to be reliable predictors of infection: 1) a higher risk group in which individuals have known or probable exposure to SARS-CoV-2 or self-report symptoms consistent with COVID-19 (i.e., “symptomatic or exposed individuals”) and 2) a lower risk group in which individuals are asymptomatic and have no known or probable exposure to SARS-CoV-2 (i.e., “asymptomatic and unexposed individuals”) (36). Optimal pool sizes are determined separately for the two groups based on a range of SARS-CoV-2 prevalences in each group and pools screening positive are subsequently tested as individual samples.

Calculating efficiency

We consider the average number of individual results obtained per test kit used as a measure of efficiency. Computing testing strategy efficiency requires assumptions regarding the diagnostic test performance, specifically the assay sensitivity ($S_e$) and specificity ($S_p$), and local viral dynamics, specifically the prevalence of SARS-CoV-2 ($P(D)$) in the population of interest. Given the loss in diagnostic sensitivity that can result from pooling specimens together (as positive samples are diluted with negative samples) (34,37), a maximum allowable dilution, or the proportion of diagnostic sensitivity one is willing to lose through pooling, should be established. This determines the maximum allowable pool size, or maximum pool size that
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With these input parameters defined, the efficiency of a particular testing strategy can be calculated using the methods and viral dynamics model originally developed by Pilcher et al (19). We have adapted these methods for our specific test strategy approach and outlined the details in Web Appendix 1.

**Estimating efficiency of a differentiated pooled testing strategy ($\psi$)**

In calculating the efficiency, or number of results obtained per test kit used, in our differentiated pooling strategy ($\psi$), we first estimated the optimal pool size for each of our two groups, symptomatic or exposed individuals, and asymptomatic and unexposed individuals separately. To estimate these pool sizes, we used the prevalence of infection among symptomatic or exposed individuals ($P(D|G = 1)$) and the prevalence of infection among asymptomatic and unexposed individuals ($P(D|G = 0)$). We considered two sets of assay performance scenarios: 1) a conservative diagnostic assay $S_e$ of 0.75 and $S_p$ of 0.95 among symptomatic or exposed individuals and $S_e$ of 0.50 and $S_p$ of 0.95 among asymptomatic and unexposed individuals; and 2) a higher $S_e$ of 0.85 and $S_p$ of 0.99 among symptomatic or exposed individuals and $S_e$ of 0.60 and $S_p$ of 0.99 among asymptomatic and unexposed individuals (38–40). We allowed the diagnostic assay sensitivity and specificity to differ between the two groups as existing literature suggests assay performance is diminished in cases of mild infection (41–44). In each scenario, we set the maximum allowable dilution at 0.20 to ensure the reduction in analytic sensitivity of
pooled SARS-CoV-2 testing was less than 20% relative to individual-specimen testing. Using the viral dynamics model proposed by Pilcher et al. and further outlined in Web Appendix 1, this corresponds to a maximum allowable pool size of 25 in all scenarios.

After determining the optimal pool size for each group, we used the adapted viral dynamics model outlined in Web Appendix 1 to calculate the efficiency, or number of results obtained per test kit used, in each group, separately. Finally, we calculated $\psi$ by taking a weighted average of the efficiency in symptomatic or exposed individuals ($\varphi_{G=1}$) and the efficiency in asymptomatic and unexposed individuals ($\varphi_{G=0}$) using the formula:

$$\psi = (\varphi_{G=1} \times P(G = 1)) + (\varphi_{G=0} \times P(G = 0))$$

where $P(G = 1)$ is the proportion of individuals in the population being tested who self-report symptoms or known or probable exposure to SARS-CoV-2 and $P(G = 0)$ is the proportion of individuals in the population being tested who self-report no known symptoms or exposure to SARS-CoV-2.

*Estimating efficiency of a traditional pooled testing strategy ($\varphi$)*

In estimating the efficiency of a traditional pooling strategy in the overall testing population ($\varphi$), we first estimated the optimal pool size using the prevalence of infection in the overall population of individuals being tested, $P(D)$, and the assay sensitivity and specificity in the overall population of individuals being tested. $P(D)$ was calculated using $P(D|G = 1)$, $P(D|G = 0)$, $P(G = 1)$, and $P(G = 0)$:
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\[
P(D) = (P(D|G = 1) \times P(G = 1)) + (P(D|G = 0) \times P(G = 0))
\]

Assay sensitivity and specificity in the population being tested were determined in a similar manner using weighted averages. After determining the optimal pool size and assay sensitivity and specificity in the testing population overall, we then used the adapted viral dynamics model outlined in Web Appendix 1 to estimate \( \varphi \).

*Estimating change in efficiency (\( \Delta \)) from implementation of differentiated versus traditional pooling*

To demonstrate the improvement in efficiency (\( \Delta \)) associated with differentiated versus traditional pooling in the overall population of individuals being tested, we compared the results obtained per test kit used in a differentiated pooling strategy (\( \psi \)) to the results obtained per test kit used in a traditional pooling strategy (\( \varphi \)) via

\[
\Delta = \psi - \varphi
\]

Here, the difference in estimates, \( \Delta \), is the total improvement in efficiency, or number of additional individual test results that can be obtained per test kit used through implementation of differentiated compared to traditional pooling.

First, we examined \( \Delta \) for scenarios similar to those observed in the Carolina Together Testing Program at UNC-Chapel Hill between August 18\textsuperscript{th}, 2021 and August 31\textsuperscript{st}, 2021 during the first two weeks of classes. During this period, 12,629 individuals were tested, 91% of whom self-reported to be asymptomatic and unexposed, and were tested as a part of the requirement for
unvaccinated students and faculty (13). The percent testing positive was 1.9 among asymptomatic and unexposed individuals and 6.2 among symptomatic or exposed individuals (13). To explore scenarios similar to the observed data, we allowed $P(D|G = 1)$ to range from 0.01 to 0.20 and $P(D|G = 0)$ to range from 0.01 to 0.05 at $P(G = 1)$ of 0.10. These estimates of $\Delta$ are presented visually in a heat map in which we highlight scenarios where differentiated pooling is equivalent to or more efficient than traditional pooling (i.e., $\Delta \geq 0$) and $P(D|G = 0)$ is less than $P(D|G = 1)$ (Figure 1; Web Figure 1). These scenarios are most plausible in settings where there is both screening for asymptomatic and unexposed individuals and symptomatic or exposed individuals (e.g., universities, workplaces).

We then explore $\Delta$ under a range of scenarios for $P(D|G = 0)$, $P(D|G = 1)$, and $P(G = 1)$. Specifically, we estimate $\Delta$ for $P(D|G = 1)$ values ranging from 0.01 to 0.60 and $P(D|G = 0)$ values ranging from 0.01 to 0.20 at $P(G=1)$ values of 0.01, 0.10, 0.50, and 0.75. Under this set of parameters, $P(D)$ values ranged from <0.01% to 40%. Estimates of $\Delta$ in each of these scenarios are presented in an additional series of heat maps (Figures 2-5; Web Figures 2-5). We present estimates of the optimal pool size for select values in tables (Tables 1-2). A comprehensive range of scenarios (i.e., where $P(D|G = 1)$ values range from 0.01 to 0.99, $P(D|G = 0)$ values range from 0.01 to 0.50, and $P(G=1)$ values range from 0.01 to 0.99) that could represent the circumstances of nearly all testing programs are presented in Web Videos 1 (conservative assay performance) and 2s (higher assay performance).

RESULTS
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Under conditions similar to those observed at UNC-Chapel Hill during the first two weeks of classes, assuming a conservative assay sensitivity of 0.75 and specificity of 0.95 among symptomatic or exposed individuals and 0.50 and 0.95 among asymptomatic and unexposed individuals, the efficiency estimates for differentiated pooling ($\psi$) are typically higher than the efficiency estimates for traditional pooling ($\varphi$) (i.e., $\Delta > 0$) when $P(D|G = 1)$ exceeds $P(D|G = 0)$. Specifically, an improvement in efficiency between 0.03 to 2.37 results per test kit could be obtained through implementation of differentiated versus traditional pooling (Figure 1A). Slightly higher estimates of $\Delta$ could be obtained when utilizing a higher performing assay ($\Delta = 0.03$ to 3.21; Figure 1B).

In a population where just 1% of individuals are symptomatic or exposed and $P(D|G = 1)$ exceeds $P(D|G = 0)$, $\psi$ is, under most scenarios, similar to $\varphi$ (i.e., $\Delta \sim 0$) (Figures 2A and 2B). However, an improvement in efficiency of up to 1.70 results per test kit (i.e., $\Delta$ up to 1.70) could be obtained (Figures 2A and 2B). In a population where 10% of individuals are symptomatic or exposed, an improvement in efficiency of up to 3.97 results per test kit could be obtained through implementation of a differentiated versus traditional pooling strategy (Figures 3A and 3B). In a population where 50% of individuals are symptomatic or exposed, an improvement in efficiency of up to 2.95 results per test kit could be obtained through implementation of a differentiated versus traditional pooling strategy (Figures 4A and 4B). In a population where 75% of individuals are symptomatic or exposed, an improvement in efficiency of up to 1.48 results per test kit could be achieved (Figures 5A and 5B). In these scenarios, the improvement in efficiency obtained through differentiated versus traditional pooling was most often between 0.12 to 0.61 results per test kit. There were some circumstances where traditional pooling was more efficient.
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than differentiated pooling with values of $\Delta$ between -1 and 0 (see white portion of Figures; Table 1).

Results observed under improved assay sensitivity and specificities (i.e., $S_e = 0.85$ and $S_p = 0.99$ among symptomatic or exposed individuals and $S_e = 0.60$ and $S_p = 0.99$ among asymptomatic and unexposed individuals) were largely similar to those observed under more conservative assay sensitivity and specificities but consistently resulted in higher estimates of $\Delta$ (Figures 2A, 2B, 3A, 3B, 4A, 4B, 5A, 5C, Table 1, Table 2).

DISCUSSION

Differentiated pooling can improve efficiency in settings where subgroups with different test positivity can be reasonably defined. Here, we have illustrated an example where differentiated pooling may be worthwhile in settings where the prevalence of SARS-CoV-2 is predicted by symptoms or known or probable exposure to SARS-CoV-2 versus absence of symptoms and no such probable exposure. Specifically, we see advantages to this approach when testing is required for both symptomatic and unvaccinated individuals, where there are at least two groups of easily distinguishable individuals being tested, and group status is predictive of infection. In a university setting, our results suggest between 0.03 and 3.21 more results could be obtained per test kit used when using differentiated versus traditional pooling. Under a broader range of settings, up to 3.97 more results could be obtained per test kit used.
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The demand for SARS-CoV-2 testing continues to exceed test supply in numerous locations across the globe (7,8,17,18,45–47). In most cases, same-day testing for symptomatic or exposed individuals remains unavailable. High demand for testing has placed unprecedented strains on healthcare systems broadly, which has contributed to test result processing times often exceeding 4-5 days (8,45,47). Given the short duration of viral shedding in individuals with less severe COVID-19 (48,49), results may be far less relevant to public health efforts a week or more after symptom onset (29). These considerations suggest individual-specimen testing strategies are ineffective at meeting current testing needs and necessitate simple, easy-to-implement strategies for improving testing efficiency.

Many proposed SARS-CoV-2 testing strategies, including other pooled testing strategies proposed in the literature, are sub-optimal for various reasons. Traditional pooling and other multi-stage hierarchical testing strategies originally proposed by Dorfman (27) improve testing efficiency when compared to individual-specimen testing strategies. However, these gains are substantially diminished in higher prevalence settings (34). Other pooling strategies, such as the P-BEST strategy (50), slice testing or hypercube strategy (51), and novel context-sensitive approaches (52), can improve testing efficiency beyond what is anticipated through traditional pooling but are logistically difficult to implement in real-world settings. The differentiated pooling strategy considered here can be easily employed in settings where there are separate screening locations for symptomatic or exposed individuals and asymptomatic and unexposed individuals (e.g., universities), or in settings utilizing symptom or exposure-based risk-screening tools. Using this approach, unique testing barcodes that indicate the appropriate specimen testing
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group could be generated at the time of specimen collection, reducing the operational complexity of the strategy.

Other variables, such as vaccination status and type of testing location (e.g., diagnostic center versus screening center for asymptomatic individuals), may also be used to define subgroups in a differentiated pooled testing program, provided the grouping variables are reliable predictors of test positivity. Pool sizes could be further optimized for more than two groups (e.g., those who self-report as exposed or symptomatic and unvaccinated; those who self-report as exposed or symptomatic and vaccinated; those who self-report as asymptomatic, unexposed, and vaccinated; those who self-report as asymptomatic, unexposed, and unvaccinated) provided the test positive probability of each group is distinct and the characteristic used to differentiate each group is a reliable predictor of infection. This approach could further improve the efficiency of a differentiated pooling strategy.

In addition to these advantages, differentiated pooling can reduce result turnaround time, similar to other pooling strategies (19,31,53,54). Given a finite number of assays that can be performed in a period of time, pooling combines samples that would otherwise be processed individually, thereby collapsing samples in the testing queue. Depending on pool size and the number pools that screen positive, even accounting for subsequent individual testing of samples in pools that screen positive, the total number of assays processed can be smaller than in absence of pooled testing (especially in the event of larger pool sizes and a smaller proportion of pools screening positive). This can eliminate bottlenecks in result processing that have been frequently observed in settings utilizing an individual-specimen testing strategy (8,45,47), thereby improving
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population-level result turnaround time. Moreover, this approach allows for individual-specimen testing in groups where the prevalence of infection is relatively high while still allowing for pooling in groups where the prevalence of infection is relatively low and pools are less likely to screen positive.

As noted, SARS-CoV-2 viral titer among symptomatic and infected individuals may be higher than that among asymptomatic and infected individuals. Therefore, test sensitivity may differ and the dilution effects of pooling may be more extreme among the asymptomatic and unexposed group. The approach and efficiency calculations described here allow for differential sensitivity and specificity by groups. Ultimately, the relatively low assumed performance of the utilized assay among asymptomatic and unexposed individuals resulted in few scenarios where \( \Delta \) was negative (i.e., traditional pooling was more efficient compared to differentiated pooling). While the differentiated pooling strategy was not beneficial in these instances, we readily identified such scenarios further highlighting the applicability of our approach to the establishment of evidence-informed, tailored testing strategies.

In summation, differentiated pooling improves efficiency in testing settings where strong predictors of infection define easily distinguishable groups of people. Here we demonstrated the improvements obtained through implementation of a differentiated versus traditional pooling strategy in settings such as universities and workplaces and where the prevalence of SARS-CoV-2 in symptomatic or exposed individuals is high, the prevalence of SARS-CoV-2 in asymptomatic and unexposed individuals is low, and the proportion of individuals in the testing population who self-report as symptomatic or exposed is at least 10%. Drawing on existing
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testing program setup and symptom and exposure screening tools, differentiated pooling imposes a minimal increase in operational complexity, offering a simple-to-implement opportunity to conserve critical testing resources. Broadly, this approach holds the potential to increase SARS-CoV-2 testing capacity and should be considered a viable option in testing program planning and implementation across the United States and globally.

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Table 1. Optimal pool sizes among symptomatic or exposed individuals, asymptomatic and unexposed individuals, and the testing population overall with corresponding estimates of additional results obtained per test kit used through implementation of a differentiated versus traditional pooling strategy assuming conservative assay performance parameters

| P(G = 1) | P(D|G = 1) | Optimal pool size among symptomatic or exposed | P(D|G = 0) | Optimal pool size among asymptomatic and unexposed | P(D) | Optimal pool size in overall testing population | | |
|----------|------------|-----------------------------------------------|------------|--------------------------------------------------|------|-----------------------------------------------|----------|------|
| 0.10     | 0.05       | 7                                             | 2.65       | 0.01                                             | 19   | 6.06                                         | 5.72     | 0.01 |
| 0.10     | 0.10       | 6                                             | 1.98       | 0.03                                             | 12   | 4.04                                         | 3.83     | 0.04 |
| 0.10     | 0.20       | 1                                             | 1          | 0.05                                             | 10   | 3.31                                         | 3.08     | 0.06 |
| 0.10     | 0.30       | 1                                             | 1          | 0.07                                             | 9    | 2.90                                         | 2.71     | 0.09 |
| 0.10     | 0.40       | 1                                             | 1          | 0.09                                             | 8    | 2.64                                         | 2.47     | 0.12 |
| 0.10     | 0.50       | 1                                             | 1          | 0.11                                             | 8    | 2.45                                         | 2.30     | 0.11 |
| 0.10     | 0.60       | 1                                             | 1          | 0.13                                             | 25   | 2.33                                         | 2.22     | 0.18 |
| 0.50     | 0.05       | 7                                             | 2.65       | 0.01                                             | 19   | 6.06                                         | 4.36     | 0.03 |
| 0.50     | 0.10       | 6                                             | 1.98       | 0.03                                             | 12   | 4.04                                         | 3.01     | 0.06 |
| 0.50     | 0.20       | 1                                             | 1          | 0.05                                             | 10   | 3.31                                         | 2.16     | 0.12 |
| 0.50     | 0.30       | 1                                             | 1          | 0.07                                             | 9    | 2.90                                         | 1.95     | 0.18 |
| 0.50     | 0.40       | 1                                             | 1          | 0.09                                             | 8    | 2.64                                         | 1.82     | 0.24 |
| 0.50     | 0.50       | 1                                             | 1          | 0.11                                             | 8    | 2.45                                         | 1.72     | 0.30 |
| 0.50     | 0.60       | 1                                             | 1          | 0.13                                             | 25   | 2.33                                         | 1.66     | 0.36 |
| 0.75     | 0.05       | 7                                             | 2.65       | 0.04                                             | 19   | 6.06                                         | 3.51     | 0.04 |
| 0.75     | 0.10       | 6                                             | 1.98       | 0.03                                             | 12   | 4.04                                         | 2.49     | 0.08 |
| 0.75     | 0.20       | 1                                             | 1          | 0.05                                             | 10   | 3.31                                         | 1.58     | 0.16 |
| 0.75     | 0.30       | 1                                             | 1          | 0.07                                             | 9    | 2.90                                         | 1.48     | 0.24 |
| 0.75     | 0.40       | 1                                             | 1          | 0.09                                             | 8    | 2.64                                         | 1.41     | 0.32 |
| 0.75     | 0.50       | 1                                             | 1          | 0.11                                             | 8    | 2.45                                         | 1.36     | 0.40 |
| 0.75     | 0.60       | 1                                             | 1          | 0.13                                             | 25   | 2.33                                         | 1.33     | 0.48 |

Abbreviations: P(G = 1)= probability of being symptomatic or exposed; P(D|G = 1)= prevalence of infection among symptomatic or exposed; \( \psi_{G=1} \)= results obtained per test kit used in pooled testing strategy among symptomatic or exposed; P(D|G = 0)= prevalence of infection among asymptomatic and unexposed; \( \psi_{G=0} \)= results obtained per test kit used in pooled testing strategy among asymptomatic and unexposed; \( \gamma \)= results obtained per test kit used in differentiated pooling strategy; P(D)= prevalence of infection in testing population overall; \( \psi \)= results obtained per test kit used in traditional pooling strategy in testing population overall; \( \Delta \)= change in efficiency, or additional results obtained per test kit used, through implementation of differentiated pooling strategy versus traditional pooling strategy in testing population overall.

a assay performance parameters were as follows: sensitivity of 0.75 and specificity of 0.95 among symptomatic or exposed individuals and 0.50 and 0.95 among asymptomatic and unexposed individuals.
### Efficiency of Differentiated Pooled Testing for SARS-CoV-2

Table 2. Optimal Pool Sizes among Symptomatic or Exposed Individuals, Asymptomatic and Unexposed Individuals, and the Testing Population Overall with Corresponding Estimates of Additional Results Obtained per Test Kit Used Through Implementation of a Differentiated versus Traditional Pooling Strategy Assuming Less Conservative Assay Performance Parameters\(^a\)

| \(P(G = 1)\) | \(P(D|G = 1)\) | Optimal Pool Size among Symptomatic or Exposed | \(\varphi_{G = 1}\) | \(P(D|G = 0)\) | Optimal Pool Size among Asymptomatic and Unexposed | \(\varphi_{G = 0}\) | \(\psi\) | \(P(D)\) | Optimal Pool Size in Overall Testing Population | \(\varphi\) | \(\Delta\) |
|----------------|----------------|-----------------------------------------------|-----------------|----------------|-----------------------------------------------|-----------------|-----|-------------|-----------------------------------------------|-----|-----|
| 0.10           | 0.05           | 6                                             | 2.67            | 0.01           | 16                                            | 6.91            | 6.48 | 0.01        | 13                                           | 5.49 | 1.00 |
| 0.10           | 0.10           | 5                                             | 1.93            | 0.03           | 10                                            | 4.13            | 3.91 | 0.04        | 8                                            | 3.52 | 0.38 |
| 0.10           | 0.20           | 4                                             | 1.40            | 0.05           | 8                                             | 3.25            | 3.02 | 0.06        | 7                                            | 2.68 | 0.38 |
| 0.10           | 0.30           | 1                                             | 1               | 0.07           | 7                                             | 2.79            | 2.61 | 0.09        | 6                                            | 2.27 | 0.34 |
| 0.10           | 0.40           | 1                                             | 1               | 0.09           | 6                                             | 2.48            | 2.33 | 0.12        | 5                                            | 2.01 | 0.32 |
| 0.10           | 0.50           | 1                                             | 1               | 0.11           | 6                                             | 2.27            | 2.15 | 0.15        | 5                                            | 1.83 | 0.31 |
| 0.10           | 0.60           | 1                                             | 1               | 0.13           | 6                                             | 2.11            | 2.0  | 0.18        | 1                                            | 1    | 1.00 |
| 0.50           | 0.05           | 6                                             | 2.67            | 0.01           | 16                                            | 6.91            | 4.79 | 0.03        | 8                                            | 3.51 | 1.28 |
| 0.50           | 0.10           | 5                                             | 1.93            | 0.03           | 10                                            | 4.13            | 3.03 | 0.06        | 6                                            | 2.46 | 0.57 |
| 0.50           | 0.20           | 4                                             | 1.40            | 0.05           | 8                                             | 3.25            | 2.33 | 0.12        | 5                                            | 1.8  | 0.53 |
| 0.50           | 0.30           | 1                                             | 1               | 0.07           | 7                                             | 2.79            | 1.89 | 0.18        | 4                                            | 1.51 | 0.39 |
| 0.50           | 0.40           | 1                                             | 1               | 0.09           | 6                                             | 2.48            | 1.74 | 0.24        | 1                                            | 1    | 0.74 |
| 0.50           | 0.50           | 1                                             | 1               | 0.11           | 6                                             | 2.27            | 1.64 | 0.30        | 1                                            | 1    | 0.64 |
| 0.50           | 0.60           | 1                                             | 1               | 0.13           | 6                                             | 2.11            | 1.56 | 0.36        | 1                                            | 1    | 0.56 |
| 0.75           | 0.05           | 6                                             | 2.67            | 0.01           | 16                                            | 6.91            | 3.73 | 0.04        | 7                                            | 3.01 | 0.73 |
| 0.75           | 0.10           | 5                                             | 1.93            | 0.03           | 10                                            | 4.13            | 2.48 | 0.08        | 5                                            | 2.14 | 0.33 |
| 0.75           | 0.20           | 4                                             | 1.4             | 0.05           | 8                                             | 3.25            | 1.87 | 0.16        | 4                                            | 1.56 | 0.30 |
| 0.75           | 0.30           | 1                                             | 1               | 0.07           | 7                                             | 2.79            | 1.45 | 0.24        | 1                                            | 1    | 0.45 |
| 0.75           | 0.40           | 1                                             | 1               | 0.09           | 6                                             | 2.48            | 1.37 | 0.32        | 1                                            | 1    | 0.37 |
| 0.75           | 0.50           | 1                                             | 1               | 0.11           | 6                                             | 2.27            | 1.32 | 0.40        | 1                                            | 1    | 0.32 |
| 0.75           | 0.60           | 1                                             | 1               | 0.13           | 6                                             | 2.11            | 1.28 | 0.48        | 1                                            | 1    | 0.28 |

Abbreviations: \(P(G = 1)\)=probability of being symptomatic or exposed; \(P(D|G = 1)\)=prevalence of infection among symptomatic or exposed; \(\varphi_{G = 1}\)=results obtained per test kit used in pooled testing strategy among symptomatic or exposed; \(P(D|G = 0)\)=prevalence of infection among asymptomatic and unexposed; \(\varphi_{G = 0}\)=results obtained per test kit used in pooled testing strategy among asymptomatic and unexposed; \(\psi\)=results obtained per test kit used in differentiated pooling strategy; \(P(D)\)=prevalence of infection in testing population overall; \(\varphi\)=results obtained per test kit used in traditional pooling strategy in testing population overall; \(\Delta\)=change in efficiency, or additional results obtained per test kit used, through implementation of differentiated pooling strategy versus traditional pooling strategy in testing population overall

\(^a\)Assay performance parameters were as follows: sensitivity of 0.85 and specificity of 0.95 among symptomatic or exposed individuals and 0.60 and 0.95 among asymptomatic and unexposed individuals.
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Figure 1. Additional results obtained per test kit used through implementation of a differentiated pooled testing strategy as compared to a traditional two-stage hierarchical pooling strategy (Δ) for scenarios similar to those observed at the University of North Carolina at Chapel Hill.

Improvement in efficiency, or additional results obtained per test kit used (Δ) through implementation of a differentiated versus traditional pooling strategy in settings with a probability of infection given symptomatic or exposed (P(D|G = 1)) ranging from 10-20%, a probability of infection given asymptomatic and unexposed (P(D|G = 0)) ranging from 1-2%, and a probability of being symptomatic or exposed in the population being tested (P(G = 1)) of 10%. In panel A, assay sensitivity and specificity were set to 0.75 and 0.95 among symptomatic or exposed individuals and 0.50 and 0.95 among asymptomatic and unexposed individuals. In panel B, assay sensitivity and specificity were set to 0.85 and 0.99 among symptomatic or exposed individuals and 0.60 and 0.99 among asymptomatic and unexposed individuals. White areas represent scenarios in which P(D|G = 0) is greater than P(D|G = 1) or traditional pooling is more efficient than differentiated pooling (i.e., Δ < 0).

Figure 2. Additional results obtained per test kit used through implementation of a differentiated pooled testing strategy as compared to a traditional two-stage hierarchical pooling strategy (Δ) in a population where 1% of individuals testing are symptomatic/exposed.

Improvement in efficiency, or additional results obtained per test kit used (Δ) through implementation of a differentiated versus traditional pooling strategy in settings with a probability of infection given symptomatic or exposed (P(D|G = 1)) ranging from 0-60%, a
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probability of infection given asymptomatic and unexposed (P(D|G = 0)) ranging from 0-20%, and a probability of being symptomatic or exposed in the population being tested (P(G = 1)) of 1%. In panel A, assay sensitivity and specificity were set to 0.75 and 0.95 among symptomatic or exposed individuals and 0.50 and 0.95 among asymptomatic and unexposed individuals. In panel B, assay sensitivity and specificity were set to 0.85 and 0.99 among symptomatic or exposed individuals and 0.60 and 0.99 among asymptomatic and unexposed individuals. White areas represent scenarios in which P(D|G = 0) is greater than P(D|G = 1) or traditional pooling is more efficient than differentiated pooling (i.e., ∆< 0).

Figure 3. Additional results obtained per test kit used through implementation of a differentiated pooled testing strategy as compared to a traditional two-stage hierarchical pooling strategy (Δ) in a population where 10% of individuals testing are symptomatic/exposed.

Improvement in efficiency, or additional results obtained per test kit used (Δ) through implementation of a differentiated versus traditional pooling strategy in settings with a probability of infection given symptomatic or exposed (P(D|G = 1)) ranging from 0-60%, a probability of infection given asymptomatic and unexposed (P(D|G = 0)) ranging from 0-20%, and a probability of being symptomatic or exposed in the population being tested (P(G = 1)) of 10%. In panel A, assay sensitivity and specificity were set to 0.75 and 0.95 among symptomatic or exposed individuals and 0.50 and 0.95 among asymptomatic and unexposed individuals. In panel B, assay sensitivity and specificity were set to 0.85 and 0.99 among symptomatic or exposed individuals and 0.60 and 0.99 among asymptomatic and unexposed individuals. White
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areas represent scenarios in which \( P(D|G = 0) \) is greater than \( P(D|G = 1) \) or traditional pooling is more efficient than differentiated pooling (i.e., \( \Delta < 0 \)).

Figure 4. Additional results obtained per test kit used through implementation of a differentiated pooled testing strategy as compared to a traditional two-stage hierarchical pooling strategy (\( \Delta \)) in a population where 50% of individuals testing are symptomatic/exposed.

Improvement in efficiency, or additional results obtained per test kit used (\( \Delta \)) through implementation of a differentiated versus traditional pooling strategy in settings with a probability of infection given symptomatic or exposed (\( P(D|G = 1) \)) ranging from 0-60%, a probability of infection given asymptomatic and unexposed (\( P(D|G = 0) \)) ranging from 0-20%, and a probability of being symptomatic or exposed in the population being tested (\( P(G = 1) \)) of 50%. In panel A, assay sensitivity and specificity were set to 0.75 and 0.95 among symptomatic or exposed individuals and 0.50 and 0.95 among asymptomatic and unexposed individuals. In panel B, assay sensitivity and specificity were set to 0.85 and 0.99 among symptomatic or exposed individuals and 0.60 and 0.99 among asymptomatic and unexposed individuals. White areas represent scenarios in which \( P(D|G = 0) \) is greater than \( P(D|G = 1) \) or traditional pooling is more efficient than differentiated pooling (i.e., \( \Delta < 0 \)).

Figure 5. Additional results obtained per test kit used through implementation of a differentiated pooled testing strategy as compared to a traditional two-stage hierarchical pooling strategy (\( \Delta \)) in a population where 75% of individuals testing are symptomatic/exposed.
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Improvement in efficiency, or additional results obtained per test kit used (Δ) through implementation of a differentiated versus traditional pooling strategy in settings with a probability of infection given symptomatic or exposed (P(D|G = 1)) ranging from 0-60%, a probability of infection given asymptomatic and unexposed (P(D|G = 0)) ranging from 0-20%, and a probability of being symptomatic or exposed in the population being tested (P(G)) of 75%.

In panel A, assay sensitivity and specificity were set to 0.75 and 0.95 among symptomatic or exposed individuals and 0.50 and 0.95 among asymptomatic and unexposed individuals. In panel B, assay sensitivity and specificity were set to 0.85 and 0.99 among symptomatic or exposed individuals and 0.60 and 0.99 among asymptomatic and unexposed individuals. White areas represent scenarios in which P(D|G = 0) is greater than P(D|G = 1) or traditional pooling is more efficient than differentiated pooling (i.e., Δ< 0).
Probability of Infection Given No Symptoms/Exposure

A)

Probability of Infection Given Symptoms/Exposure

B)

Efficiency Gain

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