Optimal Testing Strategies to Monitor COVID-19 Traced Contacts.

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Optimal Testing Strategies to Monitor COVID-19 Traced Contacts.

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Abstract

The quarantine of identified close contacts has been vital to reducing transmission rates and averting secondary infection risk before symptom onset and by asymptomatic cases. The effectiveness of this contact tracing strategy to mitigate transmission is sensitive to the adherence to quarantines, which may be lower for longer quarantine periods or in vaccinated populations (where perceptions of risk are reduced). This study develops a simulation model to evaluate contact tracing strategies based on the sequential testing of identified contacts after exposure as an alternative to quarantines, in which contacts are isolated only after confirmation by a positive test. The analysis considers different number and types of tests (PCR and lateral flow antigen tests (LFA)) to identify the cost-effective testing policies that minimize the expected infecting days post-exposure considering different levels of testing capacity. This analysis suggests that even a limited number of tests can be effective at reducing secondary infection risk: two LFA tests (with optimal timing) avert infectiousness at a level that is comparable to 14-day quarantine with 90% adherence; adding a third test (PCR or LFA) reaches the efficiency of a 95% quarantine adherence. These results are robust to the exposure dates of the contact, which suggests that simple testing rules can be effective for improving contact tracing in settings where strict quarantine adherence is difficult to implement.

1 Introduction

The COVID-19 pandemic has imposed many challenges on societies around the world. The virulence of the outbreak has required strict nonpharmaceutical interventions, such as massive lockdowns, curfews, contact quarantines, sanitary measures, travel restrictions, and testing surveillance. Although many of these policies have been useful for containing outbreaks (Chinazzi et al. 2020, Tang et al. 2020), they have also imposed a significant social and economic burden on most countries (Jin et al. 2021).

Since the first outbreak of COVID-19 in early 2020, new scientific knowledge has been rapidly developed regarding the characteristics of this virus, such as the viral load evolution of an infected individual (Larremore et al. 2021), infectiousness profile (He et al. 2020), transmission patterns (Meyerowitz et al. 2020) and cardinal symptoms (Zoabi et al. 2021). A significant challenge in containing transmission is to halt infections generated before symptom onset and by asymptomatic cases, thus making symptom monitoring insufficient to contain the spread of the virus (Ferretti et al. 2020, Li et al. 2020), even with close monitoring of close contacts (Peak et al. 2020). Therefore, preventive quarantines of potentially exposed individuals have been a fundamental mitigation measure to reduce transmission in the community. These quarantine policies vary across countries, both in terms of the target population and the quarantine protocol. Most countries require preventive quarantine of traced contact between 10 and 14 days (UK 2021,CDC 2021). Restrictions to incoming international travelers also vary across countries, ranging from no quarantine when a recent negative test result is provided to others requiring strict quarantines ranging from 10 to 14 days. Some countries even use dedicated facilities to quarantine incoming travelers. These traveling restrictions have led many traveling website hubs to provide detailed information on quarantine and testing protocols by country, (Wego: https://blog.wego.com/covid19-travel-restrictions-by-destination-country/; Kayak: https://www.kayak.com/travel-restrictions).

The design of quarantine protocols for traced contacts and higher-risk individuals should account for the associated risk reduction of the policy as well as the costs imposed on the target population. Quarantines have been associated with economic cost and adverse mental health effects (Brooks et al. 2020, Bonaccorsi et al. 2020), and quarantine measures that are too strict may reduce compliance and the incentives to report close contacts, thereby reducing the effectiveness of contact tracing strategies (Webster et al. 2020). Approximately 75% of U.S. subjects who were surveyed indicated that they would adhere with quarantine for 14 days when mandated by a health official; however, compliance can be as low as 60% in specific demographic groups (McClain and Rainie 2020). Of those who declare their lack of willingness to comply, 44% indicate that they do not think that quarantining is necessary.

Improvements in testing technologies have helped to shorten quarantine periods while maintaining a low risk of secondary infections by exposed contacts (Xu et al. 2020). For example, the WHO quarantine recommendations for contacts of individuals with a confirmed or probable case of COVID-19 have been made more flexible and evolved from 14 days from their last exposure (WHO 2020b) to more discretionary measures, such as advising local public health authorities to account for local conditions and needs to determine the length of quarantine. These options include stopping quarantine for contacts that have not presented symptoms after day 10 or after day 7 with a negative diagnostic specimen test (CDC 2021, CDC 2020).

As vaccination campaigns continue to advance, transmission rates are expected to fall, thereby reducing the risk of infection of contacts exposed to a confirmed case. Nevertheless, some risk of transmission is still present due to the lower effectiveness of some vaccines and uncertainty associated with virus variants (WHO 2020a); therefore, contact tracing will continue to be relevant. However, vaccination is likely to reduce the perception of risk of exposed contacts, which could lower compliance with strict quarantine measures (Webster et al. 2020). Hence, the focus of this study is to analyze alternatives to quarantine of traced contacts to reduce the risk of secondary infections.

Access to low-cost PCR and lateral flow antigen (LFA) tests has become widespread (Mercer and Salit 2021), and this massive availability of detection tests enables the close monitoring of traced contacts without the need to confine exposed individuals (unless a positive test result), which lowers the quarantine costs without increasing the secondary transmission risks. Thus, we analyze the optimal timing of different types of tests to reduce the risk of exposure of active (not quarantined) unconfirmed contacts to susceptible individuals, thereby helping to reduce both infection risk and the costs of quarantine through a cost-efficient use of testing resources. This finding is particularly important for minimizing disruptions in essential activities, such as highly specialized workers, teachers, students and healthcare workers, where quarantines may require major re-organization of the operations. Similar strategies could be used to ease quarantine requirements on foreign travel.

Our study contributes to the literature on the analysis of quarantine strategies of traced contact in different settings. Several modeling studies suggest that quarantine periods can be shortened to 7 days with a negative PCR test at the end of this period because it has a residual risk equivalent to a quarantine period of 14 days with no testing (van der Toorn et al. 2021, Wells et al. 2020). The recent modeling study by Quilty et al. 2021 also suggests that daily LFA testing of traced contacts over 5 days *without quarantine* if all tests are negative can actually reduce the risk of secondary infections relative to a mitigation strategy of 14 quarantine days with moderate levels of adherence. Following that idea, we evaluate alternative sequential testing schemes when different numbers and types of tests are available to monitor traced contacts that are not under quarantine, with isolation only triggered when the case is confirmed through a positive test.

This study was motivated through the design of testing and quarantine policies for schools in Chile, where in-person teaching has been prohibited during most of the pandemic. In planning a safe return to in-person schooling, Chilean health authorities have developed protocols on how to handle confirmed cases and require quarantines of the complete classroom of an infected student with flexibility on the quarantine strategies for teachers, who received priority in the immunization campaign and whose quarantine may induce severe disruptions in the school operation. An alternative to quarantine is to allow teachers to

continue face-to-face teaching but closely monitor them through an optimal design of PCR and LFA tests to reduce the risk of secondary infections. A similar strategy could be used to ease the quarantine requirements of the classroom of infected students, where the risk of transmission has been shown to be relatively low for younger students (Viner et al. 2021) along with the adoption of masks and other mitigation measures (Chernozhukov et al. 2021, Lessler et al. 2021).

Our modeling approach is similar to that of Larremore et al. 2021 and Wells et al. 2020 and used simulation methods to generate scenarios of viral loads of infected contacts that may or may not present symptoms. These simulated viral load paths relate the infectiousness of the contact with test sensitivity during post-exposure time, enabling us to model the reduction of secondary infections under alternative sequential testing schemes. Our modeling analysis confirms the findings of Larremore et al. 2021 that despite the lower sensitivity of LFA tests relative to PCR, they are more efficient in averting infections when PCR tests take more than one day to confirm the results. We also corroborate the result of Wells et al. 2020 that daily LFA testing during 5 days postexposure, with isolation required after a positive test result, essentially averts all the risk of secondary infections and is equivalent to a 14-day quarantine policy for high adherence scenarios. We show that these results are robust to the days of exposure of the traced contact with the index case and to alternative models of viral load evolution. When testing resources are scarce, our modeling analysis suggests that using three LFA tests with an appropriate timing during the postexposure period can also achieve a very low risk of secondary infections, which is superior to that of a 14-day quarantine policy with 90% adherence. Our analysis shows that the timing of these sequential tests is important because suboptimal testing schedules may substantially increase the risk of secondary infections.

Another important difference of our work compared to that of Larremore et al. 2021 and Wells et al. 2020 is that we analyze settings with uncertainty on the exact day of exposure of the contact. This difference is important for study settings with structured contact networks that meet recurrently, such as workplaces, schools, healthcare facilities and households. We show that modeling this uncertainty is relevant for the design of an optimal testing schedule and should also account for different types of index cases: we cover scenarios where the index case is identified at symptom onset or by surveillance testing, among others.

Our modeling analysis suggests that an optimal design of testing strategies of traced contacts after exposure can be effective for gradually easing quarantine requirements for essential activities where the costs of quarantines are high or have low adherence rates. Nevertheless, the implications of the proposed quarantine/testing strategies need to be evaluated with caution because they might impact the behavior of confirmed cases and their contacts in multiple dimensions. On the positive side, easing quarantine requirements may lead to higher adherence of these policies by the traced contacts and a higher proportion of contacts reported by an index case. On the negative side, relaxing quarantine policies may reduce the adoption of other mitigation measures in the community and work environments (such as the use of personal protective equipment and physical distancing). Further research is needed to empirically evaluate the overall impact of the proposed contact monitoring schemes on community transmission.

2 Overview of the Modeling Approach

To relate test sensitivity with infectiousness, we model the evolution of viral load of infected individuals by replicating the methodology used in Larremore et al. 2021. Given a set of days of exposure, we generated a sample of random paths describing potential scenarios of viral load evolution over time. Individuals become infectious when their viral load exceeds 10^6 cp/ml. Each viral load path is simulated using five control points generated as random variables: (1) the day of infection; (2) the time (since the infection date) at which the minimum level of detection (LOD) with PCR test is reached; (3) the peak level of viral load and the time it is reached; (4) the time of symptom onset for symptomatic cases; and (5) the time at which the infectious period ends. This simulation procedure is illustrated in Figure 1, where the horizontal axis is a timeline, with $t = 0$ representing the time at which the index case is confirmed and the

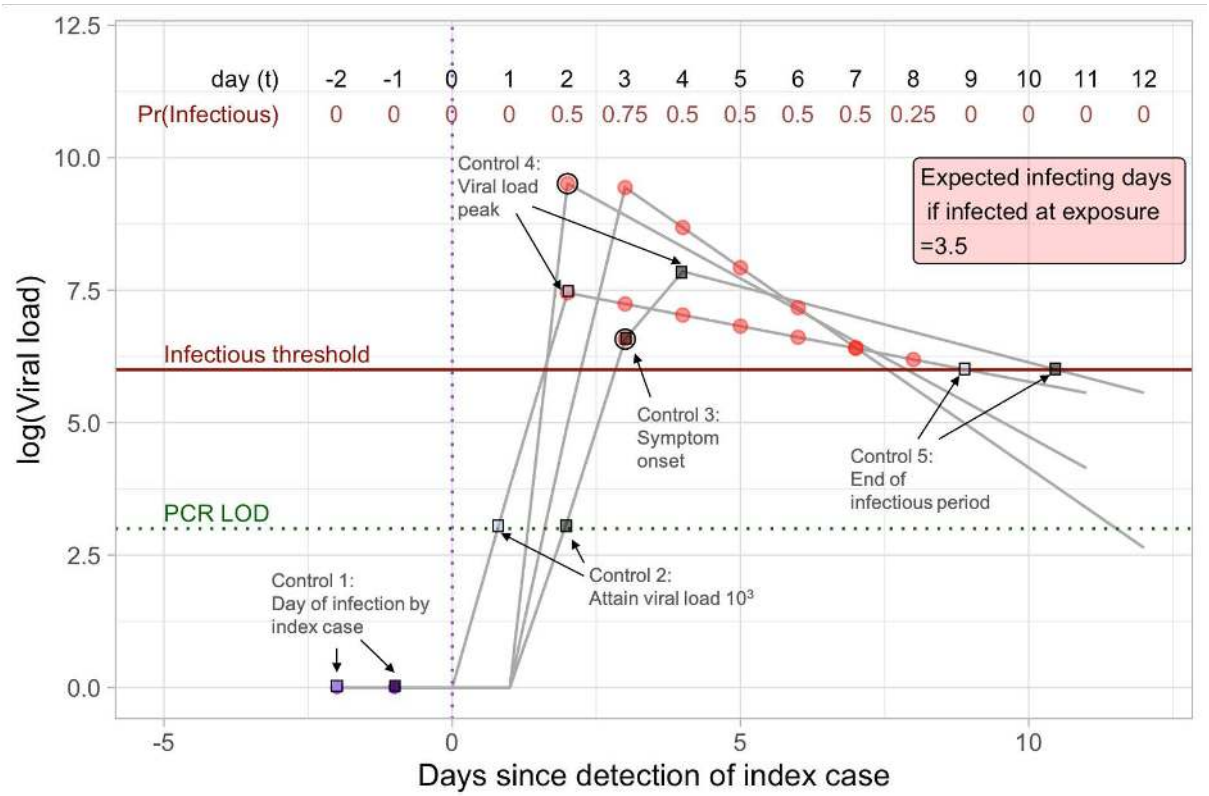

Figure 1: Description of the simulation of viral load paths. The horizontal axis represents a timeline, with $t = 0$ representing the date of detection of the index case and its contact. Each gray line indicates one simulated viral load path of the infected contact, which is generated randomly using 5 control points shown with squares for 2 independent paths (with light and dark colors). Control 1 is the day of infection, which in the example includes days -1 and -2 for each respective path. Control point 2 is the day on which a viral load is detectable by PCR. Control 3 is generated only for symptomatic cases and corresponds to the day of symptom onset (represented with a dark circle). Control 4 is the peak viral load and the day it is attained. Control 5 is the day at which the infectious period ends and indicates the slope of the viral load decline. Red dots indicate the infectious days on each viral path; individuals self-isolate the day after presenting symptoms; therefore infecting days post-symptoms are averted. The top part of the figure shows the probability that the infected contact is contagious on that day (excluding days where infection is averted). Expected infecting days, which are conditional on the contact being infected, are equal to the sum of these probabilities.

individual is identified as contact. Exposure dates of the contact occur during or before the confirmation date ($t \leq 0$). Further details on the simulation, including the probability distributions used to simulate the control points, are described in the Appendix B.

The red points in Figure 1 show the days on each path in which the individual was infectious, i.e., when the viral load exceeds the level of infectiousness (10^6 cp/ml). Symptomatic cases are assumed to self-isolate after symptom onset, whereas asymptomatic cases are not isolated and therefore continue to infect throughout the infectious period. Conditional on being infected at exposure, the probability that the individual is infecting others on a given day is the fraction of sample paths that are above the infectiousness threshold on that day. The expected number of infecting days is the sum of these probabilities across all days after the first exposure date. An example of these calculations is provided in Figure 1 for the illustrative sample paths that were simulated. In the actual simulation, we consider 200,000 sample paths for each exposure date. The probability distribution of the exposure data is described next.

2.1 Modeling uncertainty in the exposure time

Our methodology incorporates uncertainty on the day in which the contact has been infected, considering a range of possible exposure days of index case with the traced contact. This modeling approach is more realistic in settings with structured contact networks that interact frequently (e.g. school and workplace).

The uncertainty in the exposure time is modeled using a probabilistic approach, deriving the probability distribution for the days in which the transmission from the index case to the contact may have occurred; this probability distribution is used to simulate the contact's viral load. Specifically, let $t \in \{0, -1, \ldots, -14\}$ represent the set of possible exposure days, where $t = 0$ is the day of index case confirmation (we consider up to two weeks before confirmation as possible exposure dates). Infection occurs on day t when: (i) the index case is during the infectious period on that day, which is presented by the probability p_t; and (ii) the contact was not previously infected and transmission from the infectious index to the susceptible contact. The latter is represented by the *infectivity* parameter β, which represents the transmission probability, conditional on the index case been infectious.

The probability distribution p_t (index case is infectious on day t) depends on how the index case was detected at $t = 0$. The model considers three types of index case detection: (1) symptomatic index case detected at symptom onset; (2) asymptomatic index case detected by a randomly performed LFA test; and (3) asymptomatic index case detected by a weekly surveillance screening with LFA test. To compute p_t on each of these three scenarios, we simulate a large sample of viral load paths of the index case starting on each possible infection date $t \in [-14, -1]$. From this large sample, we select the paths that are feasible with the index case detection on t. For example, for the scenario where the index case is detected at symptom onset, only the simulated paths that present symptoms on day $t = 0$ are selected. For the scenario detected by a random LFA, the selected paths include the simulations with viral load above the LOD ($10^5 cp/ml$)) on day $t = 0$. Using this selected sample, p_t is computed as the fraction of selected paths that exceed the infectious threshold (10^6) on day t. The top panel of Figure 2 shows the calculations of p_t for the three scenarios considered in the model. The area under the curve represents the average number of days in which the index case was infectious previous to detection.

Conditional on been infectious, the probability that the index case infects the contact on a given day is given by the infectivity parameter β (we assume that the infectivity is constant during the infectious period, that is, when the viral load is above 10^6). Define the events: (i) S_t= the contact has not been infected up to time t; and (ii) I_t= index case is infectious at time t. The probability that the contact is infected at day t can be expressed as:

$$r_t = \beta \Pr(I_t|S_t) \cdot \prod_{j \leq t-1} (1 - \beta \Pr(I_j|S_j)),$$

where the term in the product represents the probability that the contact was not infected up to time t (i.e. $\Pr(S_t)$). Appendix B provides further details on how to compute r_t using simulation methods. Conditioning on the event that the contact was infected, the probability that the exposure occured in day t is obtained by normalization, $r_t / \sum_{j=0}^{-14} r_j$. Note that this exposure time distribution depends on the infectivity parameter β. The bottom panel of Figure 2 shows the (normalized) probability distribution of the exposure date for an infected contact for two values of β equal to 0.1 and 1.0 (Low and High) under the different scenarios of index case confirmation. As the figure illustrates, increasing the infectivity parameter β moves the distribution of the infection time to the left, because the the exposure time is more likely to occur during the first interactions of the index case with the contact. This effect is larger for the scenario where the index case is detected at symptom onset, which has a narrower range of possible exposure days. The figure suggests that for the other two scenarios (random LFA test and weekly LFA test), the exposure time distribution is not very sensitive to the infectivity parameter.

The simulations were generated using multiple values of β (0.01, 0.1, 0.5 and 1.0) to assess whether the efficiency of the testing schedules are sensitive to the infectivity profile. This is important because infectivity may vary depending on the context, including the usage of personal protective equipment,

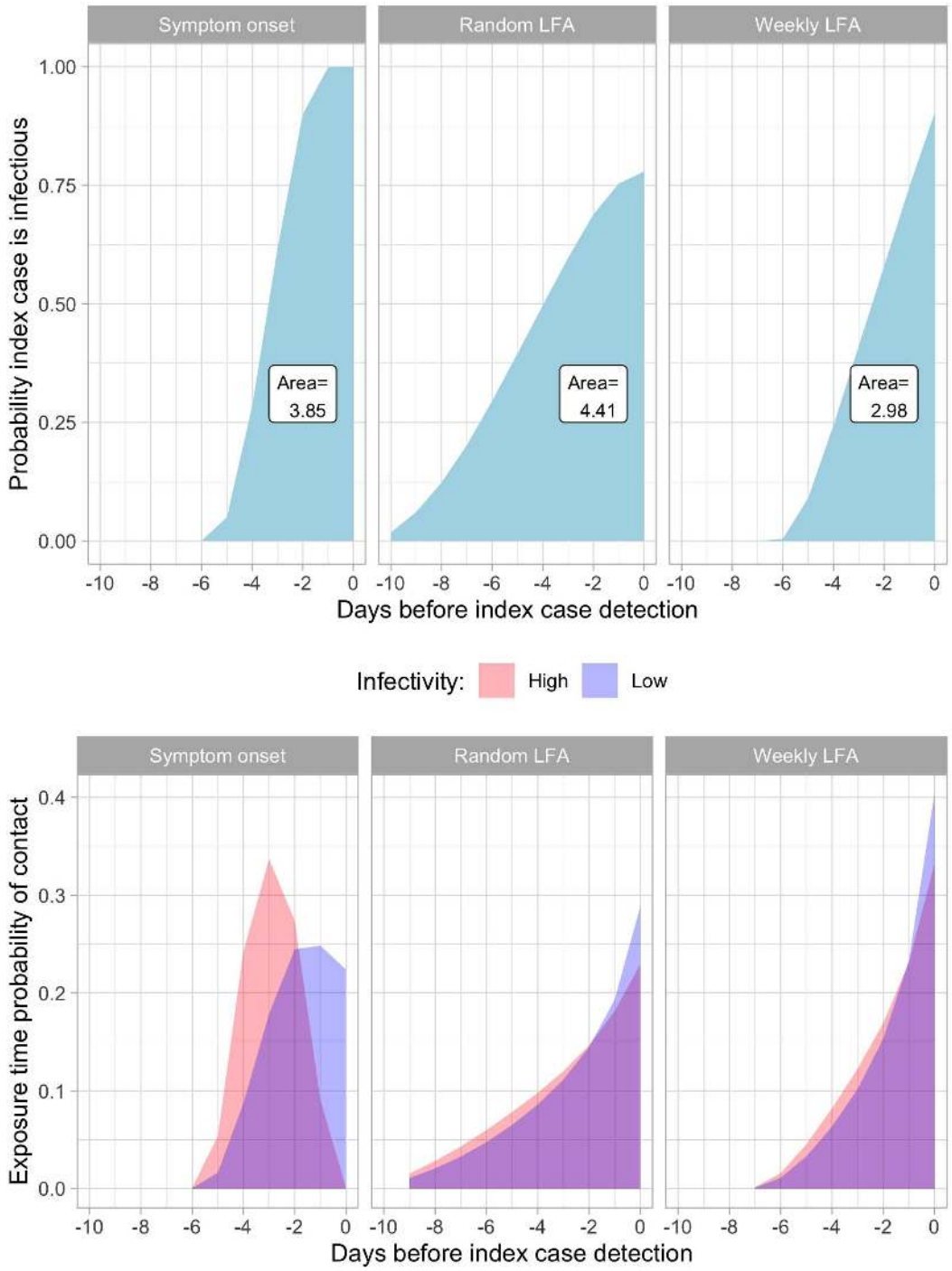

Figure 2: The top panel shows the probability of the index case been infectious on each day prior to the confirmation date ($t = 0$). Each facet describes a different scenario on how the index case was detected: (i) at symptom onset; (ii) asymptomatic detected with a random LFA test; (iii) asymptomatic detected with a weekly surveillance LFA test. The bottom panel shows the distribution of the exposure time of a contact that was infected on or before the index confirmation date, for each scenario. The distribution is calculated using two infectivity parameter values, Low (0.1) and High (1.0). The overlap between these distributions is shown in purple color.

indoor ventilation, vaccine adoption, type of contact (e.g. household) and potential risk factors (Hu et al. 2021).

2.2 Modeling testing strategies

Expected infecting days can be reduced with contact tracing and immediate quarantine. Note that quarantine at $t = 1$ does not fully mitigate the contact's infecting days because the infectious period of the contact may start before the index case was detected. As an alternative to quarantine, identified contacts may continue with active circulation with a test schedule to detect a potential infection, thereby reducing the costs of unnecessary quarantines when the contact case has not been infected. A test schedule is defined as a set of test interventions on specified dates, where each test performed has an associated LOD and delay to inform the test result. Two types of tests were considered for this analysis: (1) PCR test, with LOD=10^3 and a one-day delay to report results; and (2) LFA test, with LOD=10^5 and immediate reporting (zero delay).

The sensitivity of the test depends on the scheduled date and its LOD. The false negative rate (FNR) of a test is defined as the probability of obtaining a negative test result on an infected subject. In our simulation, the FNR can be calculated as the fraction of sample paths with viral load below the LOD of the test. The panel of Figure 3 illustrates an example of a test schedule with one LFA test implemented one day after the index case detection ($t = 1$). When obtaining a positive test, the contact is immediately isolated, and the identified infecting days correspond to the purple dots shown in the figure. Negative results filter out all the sample paths with viral loads above LOD=10^5 on day $t = 1$: all of these paths are discarded; therefore, an infected individual could evolve on only one of the remaining paths with viral loads below the LOD on the test date. The discarded paths are "grayed-out" in the figure, and their infection days are eliminated.

If the contact was infected at exposure with the index case, the red dots in Figure 3 represent the possible infecting days when the contact remained active in the community after a false negative test result. The fraction of paths above the infectious threshold that have not been isolated represents the probability that the individual is infectious on that day. These infecting days, which are referred to as the *residual risk* (van der Toorn et al. 2021), are generated by the paths that were not filtered out by the LFA test on day 1. Considering both scenarios, namely, a true positive and false negative test result, the expected infecting days (conditional on infection at exposure) is equal to 3.07 in this example (shown in the bottom-right of the top panel).

The middle panel of Figure 3 shows a test schedule with an LFA test performed at day $t = 3$. Note that the FNR drops (relative to a test on day 1) because a larger fraction of sample paths exceeds the LOD on day 3, thus implying a higher test sensitivity. The expected infection days for individuals with positive test results increase for this test schedule; however, this increase is compensated with a large reduction in the residual risk of false negative results. The overall effect is that delaying the LFA test from day 1 to day 3 reduces the overall expected infection days from 3.07 to 2.24.

The bottom panel of Figure 3 illustrates a test schedule with two sequential LFA tests conducted on days 1 and 3. A comparison of this strategy with the previous one with a single LFA test on day 3 showed that the remaining paths after a negative test result on day 3 are the same in both cases (hence their residual risk is the same). However, the first test on day 1 was capable of detecting infected contact in scenarios where infection occurred on earlier exposure dates, which reduces the infection days for the scenarios that are detected with the LFA test on day 3. This initial "filtering" of cases at day 1 also increases the FNR of the LFA test on day 3. Altogether, incorporating an additional LFA test on day 1 to a test scheduled on day 3 reduces the expected infecting days from 2.24 to 1.55.

The above examples are provided to illustrate our modeling approach, which can also be applied to PCR tests by adjusting the LOD and delaying case isolation by one day after a positive result. We applied this methodology to study all possible test combinations that can be generated with up to two PCR tests and five LFA tests within the 8 days following the index case detection date, considering different numbers

of tests and testing dates.

The results of the analysis are presented next. All the data used in this analysis is synthetic and generated via simulation using Python and R code, to be made publicly available.

3 Results

We evaluated all testing policies considering a maximum of 2 PCR and 5 LFA tests. Figure 4 shows the results for the scenario where the contact was exposed to an index case detected at symptom onset. The top panel shows the performance of different numbers and combinations of tests, thus allowing two tests of different types on the same day, and different values of the infectivity parameter β (0.01, 0.1, 0.5 and 1.0). Each dot in the plot shows the expected infecting days of a feasible testing policy for a fixed infectivity parameter. The dispersion across testing policies is illustrated with dot plots and box plots, and the policies are grouped by the number of PCR and LFA tests used, with each pair (#PCR,#LFA) indicating the number of tests of each type. Dot plots with higher densities represent clusters of policies that achieve similar performance. Testing policies are ordered from lower to higher costs on the horizontal axis; because PCR tests are typically more costly, policies within the same group are reported in increasing order of PCR tests. We notice that the costs of PCR testing can be lowered by pooling specimens from multiple samples; however, this cost reduction is less effective when prevalence is high, as would be expected with effective contact tracing (Cherif et al. 2020).

The horizontal red line shows the expected number of infecting days of the traced contact when he/she remains active in the community until self-isolation only at symptom onset (for asymptomatic cases, there is no isolation), giving an upper bound of 5.44 expected infecting days when neither testing nor quarantine are used. The horizontal blue line shows the lowest expected number of infecting days of the traced contact if he/she is *immediately* quarantined upon confirmation of the index case (with 100% adherence), and it is equal to 0.26 expected infecting days, which represents a lower bound on the performance of all possible testing policies. The analysis suggests that with four tests, the averted risk reaches this lower bound; therefore, all reported results are limited to 4 tests or fewer (LFA and PCR combined).

For each pair (#PCR,#LFA), we identified the *optimal policy* by selecting the testing schedule that minimizes the expected infecting days; we found that the optimal testing schedule was similar across all the parameter values of infectivity (β) that were used to simulate the exposure time distribution, with some exceptions. An example where the optimal policy changes with β is when a single test is available: the simulations using a higher infectivity parameter suggest that earlier testing is more efficient to avert risk, because it is more likely that the contact was exposed earlier (see Figure 2). When the optimal testing schedule changes depending on the infectivity parameter, we also identify the policy that minimizes the worst-case scenario (i.e. highest expected infecting days) across all values of β, hereon referred to as the *robust testing policy.*

The middle panel of Figure 4 shows in further detail the performance of the robust testing policy for each pair (#PCR,#LFA). The small squares represents the average expected infecting days and the gray rectangles the range of expected infecting days, across all the values of the infectivity parameters used in the simulation. The error bars indicate the 10% and 90% percentiles of the number of infecting days across all the simulated sample paths for the selected policy. This graph also includes two additional benchmarks indicated by the light blue and purple horizontal lines, which correspond to a 14-day quarantine with 90% and 80% adherence (with full isolation at symptom onset).

The bottom panel shows in further detail the days in which the tests are performed for the robust testing policies (black squares represent the days when the PCR/LFA tests should be performed). For visualization purposes, this detailed testing schedules are only shown for the policies with the lowest expected infecting days for a given number of tests (In Appendix D, Tables 1, 2, and 3 show the detailed testing schedules for all the policies).

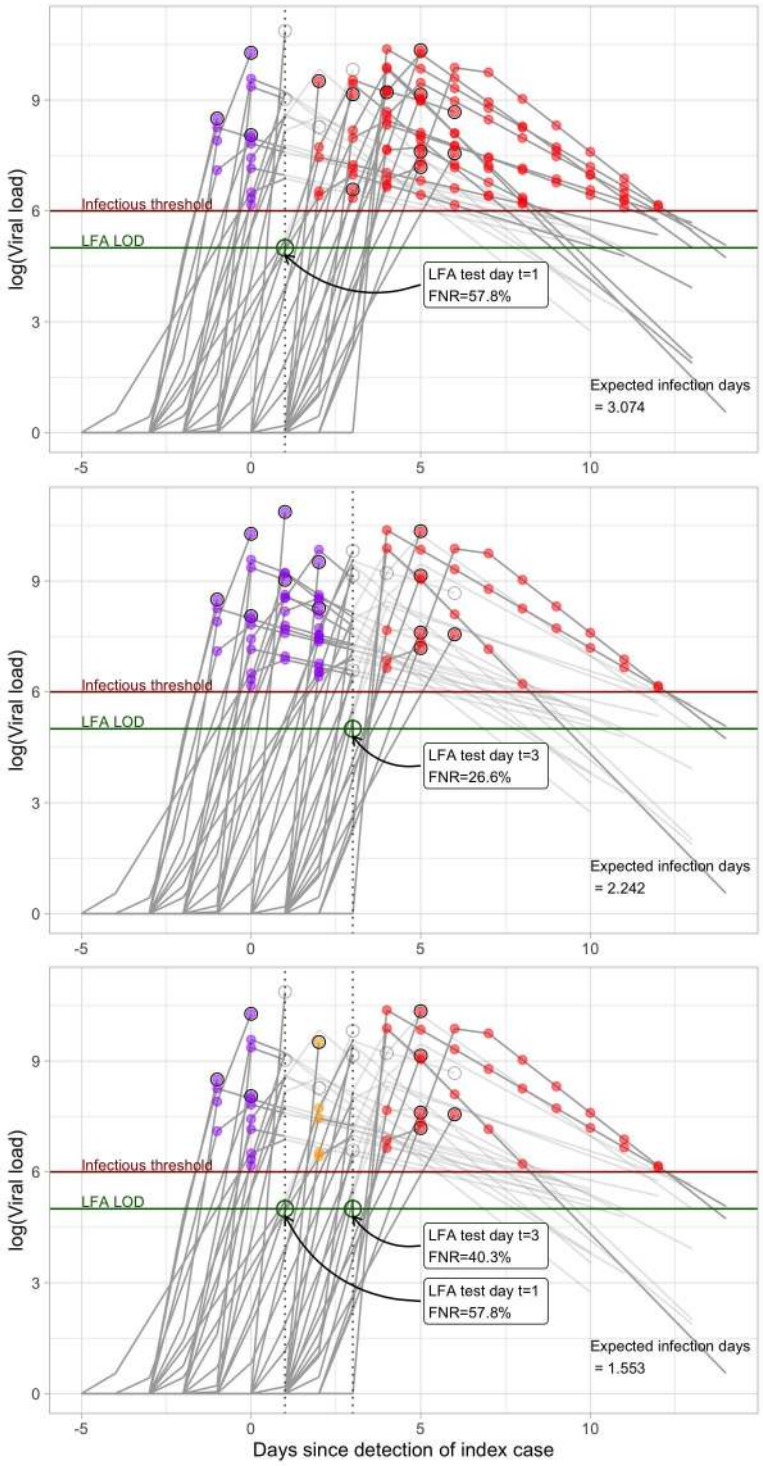

Figure 3: Examples of test schedules for an infected contact and their impacts on the infecting days. The top panel shows a schedule with the LFA test on day 1 after index case confirmation. Purple dots indicate infecting days for the contact when detected by the test; and red dots show the infecting days for undetected cases. Viral paths are shown in light gray after they are detected by the corresponding test. The middle panel shows the performance of an LFA test on day 3. The bottom panel shows the performance of two sequential LFA tests on days 1 and day 3, with the yellow dots representing the infection days for the scenarios that are detected with the second test.

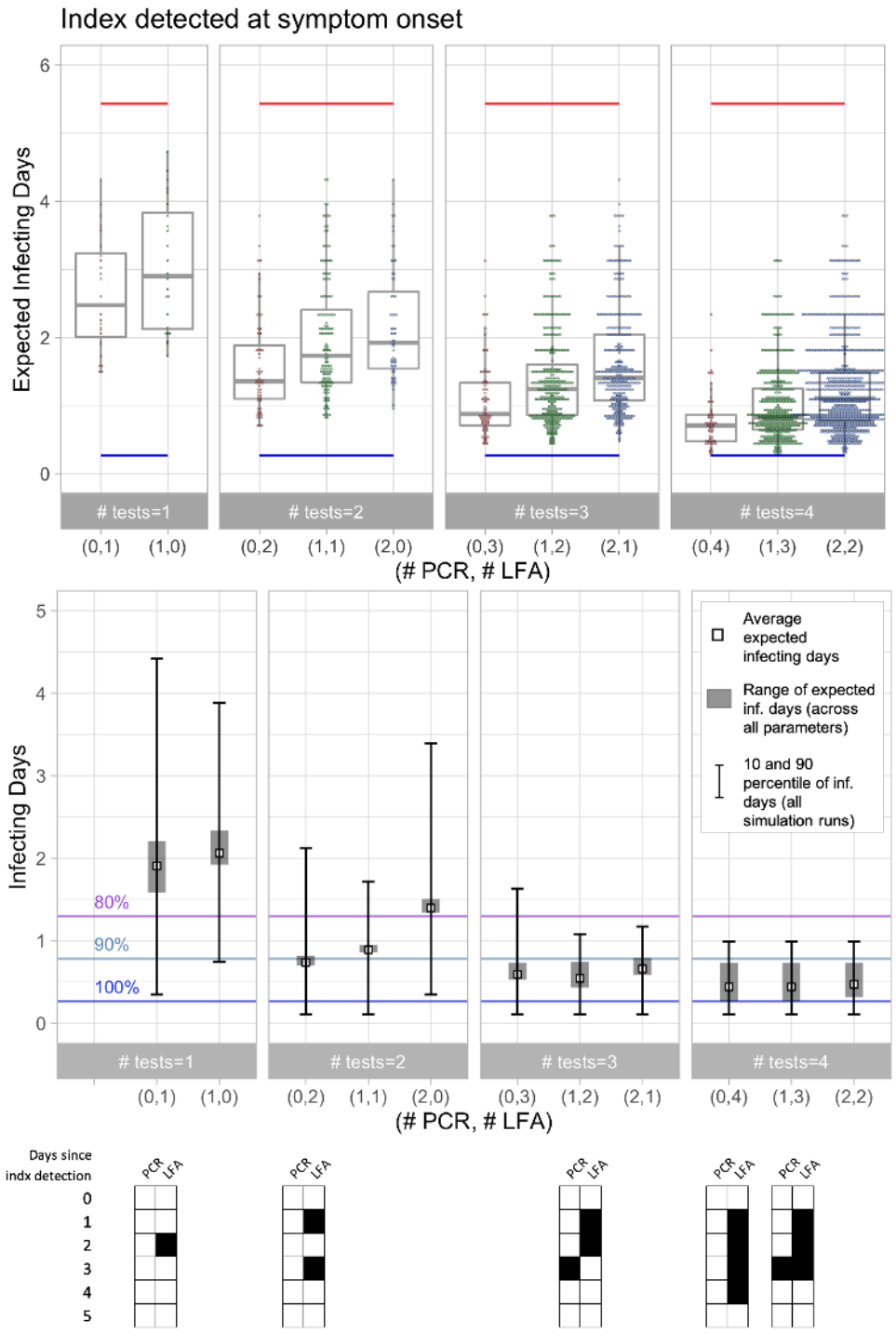

Figure 4: Evaluation of testing policies for a traced contact exposed to an index case identified by symptom onset. In the upper and middle panels, the horizontal axis contains the number of PCR and LFA tests. Blue, green, purple, and red horizontal lines correspond to the average infecting days when traced contact is quarantined for 14 days with adherence of 100%, 90%, 80%, and 0%, respectively. In the upper panel, each dot displays the performance of a testing schedule and infectivity parameter, and the lower and upper limits of boxes are the 25% and 75% quartiles. For the robust testing policies, the middle panel displays the average expected infecting days (small squares), the range of the expected infecting days across all parameters (gray rectangles) and the 10% and 90% percentiles. The lowest panel shows the schedule of the robust testing policy for each group of tests.

Figure 4 suggests that sequential testing strategies can be an effective alternative to quarantines to avert secondary infection risk of traced contacts. For example, two LFA tests can lead to a lower risk relative to a 14-day quarantine with 90% adherence; and three tests (1 PCR combined with 2 LFA) can be as effective as a quarantine with 95% adherence.

However, the results also suggest that the timing of these tests is highly relevant. The optimal schedule of the two LFA tests is on days 1 and 3, thus leading to 0.73 expected infection days. However, changing to a testing schedule on days 1 and 2 deteriorates the performance to 1.38 expected infecting days, thereby almost doubling the risk relative to the optimal strategy. Similarly, when using 2 LFAs and 1 PCR, the optimal schedule on days 1 and 2 for the LFA and day 3 for the PCR leads to an average of 0.54 infection days compared to 1.35 days when using a schedule of LFAs in days 1 and 2 and PCR at day 1 (a 150% increase in the risk of secondary infection). The top panel of Figure 4 shows significant dispersion on the performance across testing strategies using the same number of tests, suggesting that optimizing the dates of the tests matters.

Figure 5 shows the results for the scenario when the contact was exposed to an index case detected by a LFA test. In this scenario, the index case has no symptoms at the moment of detection and hence could be presymptomatic or asymptomatic, which in turn affects the possible dates of exposure. Specifically, since we model an environment where contacts are recurrent, the range of possible dates of infection is longer when the index case is asymptomatic (see Figure 2). This longer time period of exposure increases the likelihood that the contact is already infectious at the time the index case is detected. Consequently, the lower bound represented by the blue horizontal line, which was attained with immediate quarantine of the traced contact at $t = 1$ and 100% adherence, leads to an expected infecting days of 0.78, which is significantly higher than the 0.26 bound attained when the index case is detected at symptom onset, see Figure 4. The upper bound, illustrated by the red line, is the expected infecting days without quarantine or testing, with isolation only at symptom onset. Hence, this upper bound does not depend on the exposure time of the contact.

In qualitative terms, the results of Figure 5 (i.e. index case detected by LFA) are similar to those obtained in Figure 4. Two LFA tests with optimal testing time reduce the secondary infection risk relative to a 14-day quarantine with 90% adherence, and adding a third LFA test attains a lower risk relative to a quarantine with 95% adherence. The optimal testing schedule for each PCR/LFA combination was similar across all the infectivity parameters applied in the simulation.

The two scenarios analyzed in Figures 4 and 5 differ in the probability distribution of the exposure days (presented in Figure 2). An intermediate scenario can be analyzed when the index case is detected by a weekly surveillance LFA test, with a range of 7 exposure days prior to index case detection. The results of this scenario, as reported in Figure 1 in the Appendix, are qualitatively similar to those obtained in the previous two scenarios. The main difference is that the lower bound attained with immediate quarantine with 100% adherence reaches 0.28, which represents a 64% reduction relative to the bound attained when the index case is detected with a random LFA test. Hence, increasing the frequency of a surveillance testing program is useful for improving the case detection rate and simultaneously increasing the efficiency of contact tracing.

4 Discussion

Most countries use quarantines for traced contacts and isolation for confirmed cases of COVID-19, with the purpose of avoiding the further spread of the virus. These strategies are costly, and qualitative studies show that adherence to them is highly dependent on risk perception and the degree of monitoring by the health authority (Reynolds et al. 2008, Saurabh and Ranjan 2020).

In this paper, we propose an alternative to quarantines for traced contacts based on sequential PCR and/or LFA tests (with isolation of confirmed cases) and show that by choosing the appropriate test mix and timing, it is possible to reach the same risks of secondary infections compared to that of strict quar-

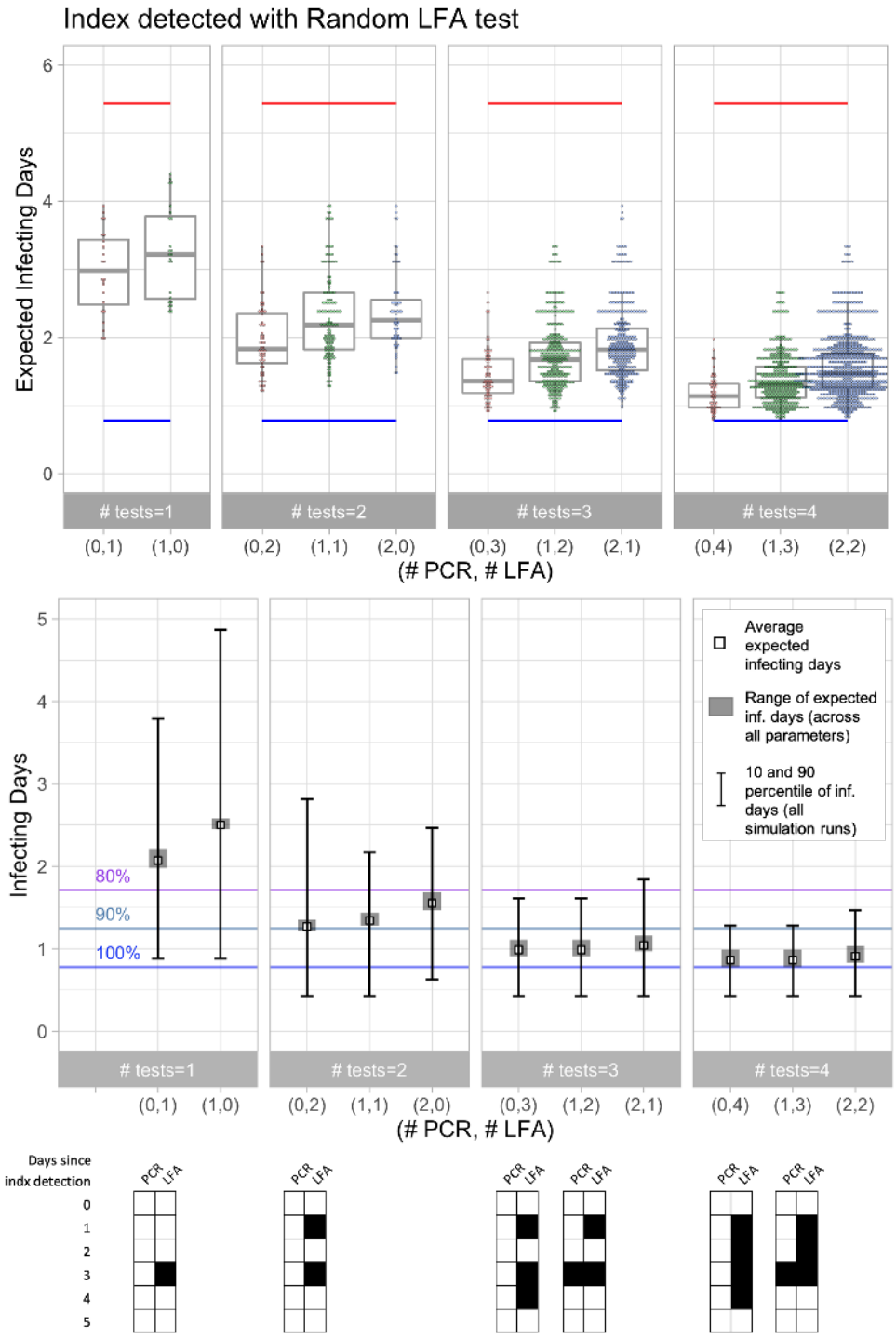

Figure 5: Evaluation of testing policies for a traced contact exposed to an index case detected by random LFA test. In the upper and middle panels, the horizontal axis contains the number of PCR and LFA tests. Blue, green, purple, and red horizontal lines correspond to the average infecting days when traced contact is quarantined for 14 days with adherence of 100%, 90%, 80%, and 0%, respectively. In the upper panel, each dot displays the performance of a testing schedule and infectivity parameter, and the lower and upper limits of boxes are the 25% and 75% quartiles. For the robust testing policies, the middle panel displays the average expected infecting days (small squares), the range of the expected infecting days across all parameters (gray rectangles) and the 10% and 90% percentiles. The lowest panel shows the schedule of the robust testing policy for each group of tests.

antines (100% adherence). For example, the use of 4 consecutive LFAs since notification or 3 consecutive LFAs since notification and 1 PCR on the third day is equivalent to a 100% adherence quarantine.

When considering more realistic adherence to quarantines of 80-90%, a testing approach that consists of two or three LFA tests can actually attain a *lower* risk of secondary infections compared to those with quarantines. We show that the optimal timing of these tests is important to effectively avert infectiousness of the exposed contact. For example, in the case of an index case detected at symptom onset, conducting LFA tests on the first and third days after contact is determined is more effective at averting secondary risk infections relative to a 14-day quarantine with 90% adherence (assuming 100% compliance in the isolation of the contact when confirmed by a positive test).

Our modeling analysis captures three important aspects that determine the effectiveness of sequential testing to reduce the infection risk of traced contacts.

First, for a number of available tests, not all feasible schedules lead to good results; therefore, among all possible test allocations during the contact tracing period, choosing the optimal one leads to significant differences in terms of effectiveness in reducing secondary infection risk.

Second, for a given number of available tests, using LFA tests to avoid quarantines dominates PCR testing (or PCR/LFA combinations). This result extends the conclusions of Larremore et al. 2021 obtained when analyzing surveillance testing strategies. Using PCR is effective to confirm traced contact while maintaining strict quarantine; however, when compliance with quarantine is imperfect, the delay in reporting results increases the risk of secondary infection. This risk can be more effectively managed with a lower-sensitivity LFA test with immediate results, and its cost is usually lower.

Third, our analysis suggests that in environments with structured contact networks with recurrent risk of exposure, the effectiveness of quarantines and post exposure testing of traced contacts depends on how the index case is detected. In this environment, asymptomatic index cases may lead to a wider range of possible exposure dates, thereby increasing the likelihood that the exposed contact is already infectious at the time of case notification. Increasing the frequency of surveillance testing is useful for reducing this risk, thereby improving the efficiency of the contact tracing strategies analyzed in this work. Interestingly, although the effectiveness of post exposure testing varies depending on the range and probability distribution of the exposure days, the optimal testing schedules that should be implemented to avert secondary infection risk are relatively similar across all the scenarios that were analyzed, and their performance relative to quarantines with different levels of adherence was also similar.

Our modeling approach is subject to limitations. First, we assume that confirmed cases fully adhere to strict isolation, which is plausible to implement in environments with stricter control, such as workplaces, healthcare facilities and schools, or where isolation in dedicated facilities is feasible. However, strict isolation may be difficult to implement in other environments, such as households or for social contact networks. Second, our analysis is based on simulated viral load trajectories that have been calibrated in previous work (Larremore et al. 2021). However, recent work in progress by Li et al. 2021 suggests that the viral load of new variants (such as Delta) may exhibit important differences from those reported for the original strains during the initial waves of the COVID-19 pandemic. Hence, our results must be interpreted with caution and may require further analysis with alternative models of viral load evolution. Third, testing strategies may lead to changes in the behavior of the traced contacts on their adoption of complementary prevention measures, such as masking and personal hygiene, which are relevant when the individual is actively in contact with the susceptible population.

Our analysis is focused on improving contact tracing for essential workers, such as medical staff, teachers, and specialized workers, among others, where quarantines might heavily disturb the normal functioning of crucial activities. The proposed sequential testing strategy was implemented in practice at two schools in Chile with teachers that were identified as contacts with students or other school personnel, in environments with low risk of exposure (i.e. wearing mask and with air ventilation). Monitoring teachers through frequent testing during school activities was useful to avoid unnecessary quarantines, increasing in-person teaching hours and controlling anxiety on the school community. No secondary infections were identified from these cases.

Furthermore, as countries are working on finding ways to normalize certain economic activities, foreign travel has been at the center of discussion. Travel has been restricted, and testing at airports and quarantines upon arrival have been implemented in many countries. However, these strategies will become difficult to implement and enforce at a large scale as airport traffic approaches pre-pandemic levels. Therefore, the sequential testing strategies studied in this work might become an effective alternative to complement quarantines for travelers or other settings where adherence to quarantine mandates is low.

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