Isolation and testing combinations for Test and Trace

A comparison between number, timing and types of tests

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Summary

The modelling of use of LFDs and PCR for isolation-test-release planning is complicated by the different expected characteristics of LFDs compared to PCR, principally that the window of detection for infections with LFDs is expected to be narrower than that for PCR.

The standard we have used to compare performance against is whether a test with a PCR or LFD device can shorten isolation periods with no detriment to the protection of the public.

These analyses are constrained by the direction that we have been given by DHSC that we consider that infection in a contact occurred at the point of last contact with an established case. This assumption will give an artificially high apparent risk of releasing a person from isolation, with or without testing, that is unlikely to translate to actual practice. We have previously modelled the protective effects of isolation +/- testing programmes using a more realistic distribution of infections occurring around the time of last contact with a case and these show that the effects of isolation of contacts is in practice likely to be significantly better than suggested by these analyses. In other words, these calculations should be used to show the relative strength of effects between the different regimes, and the absolute effects (dependent on compliance) are likely to be substantially better.

Key findings

(1) An isolate-test-release system always improves the protective effect when compared to a simple isolate only programme for the same length of isolation;
(2) All combinations of isolate-test-release in the range 7-10 days isolation (using either PCR or LFD tests) perform as least as well and often better than 14-days of isolation alone;
(3) Where a single test PCR test is used to support a 10-day isolation period then the optimal point for administration is at days 8-10;
(4) Where a single LFD test is used to support a 10-day isolation period then the optimal point for administration is likely to be at an earlier point in the isolation period, probably at days 6-8;
(5) Where a single test is used then PCR outperforms LFD, however both types of test offer significant improvements to current isolate only systems by reducing the length of isolation needed and reducing the proportion of people released from isolation still infected;
(6) Double-testing with PCR does not improve effectiveness of any isolate-test-release regimes;
(7) Double-testing with LFD may improve effectiveness of a single testing regime with LFDs, however, our calculations on this point are very sensitive to the assumptions that we have made on the performance window for LFDs and is not likely to be reproducible in practice as it would be dependent on some very exacting timings of these tests aligned to a reasonably certain point of exposure that cannot be known with the necessary certainty.

[1] Bi Q et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. The Lancet Infectious Diseases¸2020; 20(8):911-919
[2] Singanayagam A et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill. 2020;25(32):2001483

Recommendations

(1) Reducing isolation periods, supported by a single LFD or PCR test at a suitable point before release, can be expected to be effective, and not increase risk to the general public;
(2) PCR will outperform LFDs for this purpose;
(3) There is an optimisation for timings of these tests, with PCR best done close to the end of the isolation period, and LFDs performed around day 6-8 after presumed exposure.

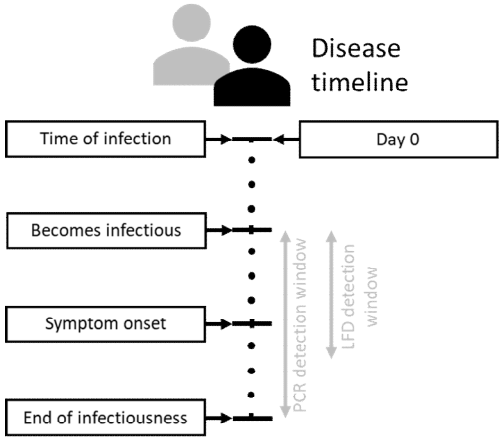
Caveat

These findings are dependent on the early characterisation of LFDs that were available at the time of developing these calculations. We have been conservative in our estimation of the window of detection that can be achieved by these devices and in practice better protective performance may be achieved.

Assumptions

Disease course

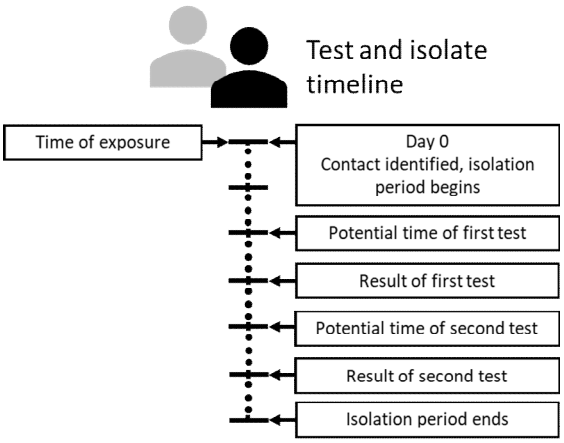
- Simulated individuals are infected by the index case at the last point of contact and so all individuals have a known infectious time.
- The period for isolation starts at this infection point. This implies that individuals do not become infectious prior to beginning their isolation period.
- Distribution of time between infection and onset of symptoms follows [1].
- 60% of the population will present with symptoms.
- Simulated individuals can be infectious up to one day prior to symptom onset.*



- Distribution of time between infection and recovery follows [2].
- Infected persons are detectable by PCR for the entirety of their infectious period. The PCR test has 100% sensitivity during this period, and 0% sensitivity otherwise.
- The LFD detectability period begins at the onset of infectiousness and ends 5 days after. If an infected person is allocated an infectious period of less than 5 days, the LFD detectability period is capped to match the end of the infectious period. The LFD test has 100% sensitivity during this period, and 0% sensitivity otherwise. It is understood that the LFD sensitivity is extremely good within a small window of high viral load (personal communication with PHE LFD evaluation team) and that taking a sweeping 50% sensitivity across the whole detection window may not be valid since this will have an effect on the time of the test. This requires proper quantification, which has led to this basic assumption to start with.
- The symptomatic individuals' transmission risk period is taken to be the pre-symptomatic infectious period, as it is assumed once symptoms are displayed individuals will take steps to avoid further contact with other members of the population. All calculations based on transmission risk use this period, not the total infectious window of the symptomatic individuals.

*Symptom onset time is allocated to all individuals. Forty percent are then randomly selected to be labelled as asymptomatic. Their symptom onset time is then removed. The prior infectious period is then simply an extension of up to 1 additional day on their infectious period.

Isolation and testing regime



- It takes 2 days for a PCR test to be returned. Therefore, sequential PCR tests are spaced at least 2 days apart; if PCR tests are being administered prior to release, there are no fewer than 2 days between this test and the end of isolation.
- LFD tests return results instantly.
- If symptomatic individuals are released undetected, they are re-captured by the system when their symptoms begin.
- This work is for non-household contacts. The timeline for infected household contacts is likely to be different.
- Specificity is not considered. Percentages presented are those expected from truly infected individuals who enter the T&T system. Therefore, estimates for population prevalence and false positives are also not presented.
- Non-compliance is not considered.

Questions

- If contacts after 10 days isolation with no test, what proportion of people will be undetected and present a transmission risk after release? What proportion of those released will develop symptoms (get a test and isolate for an additional 10 days) and what proportion will be asymptomatic? (SH)
- For a PCR test on day 8 and release on day 10 if negative, what proportion of people will be undetected and present a transmission risk after release? What proportion of those released will develop symptoms (get a test and isolate for an additional 10 days) and what proportion will be asymptomatic? (SH, SPI-M)
- What is the comparison between a 14 day isolation period and a 10 day isolation period with an LFD test at the end? (SPI-M)
- What happens to the proportion of releases if a lateral flow test is given every day for 10-14 days and only isolate if is positive? (SPI-M) (*Is this for after a 10 day isolation period, and is this with or without previous tests?) Not considered here, but could be calculated from accompanying xlsx file. Under the assumptions presented here, I suspect that the shorter LFD window will not be helpful because individuals will be sufficiently into their infectious period that they will not be detectable by LFD test.*

Results

The assumption that an LFD test will return a positive result when the test is administered with the first 5 days of infectiousness (which is capped at the end of the infectious period if this is longer than 5 days), leads to a detectability window of approximately 43% of the PCR detectability window.

PCR test (2 days for results)			LFD test (instant result)		
Isolation period (days)	Day of test(s)	Undetected proportion of infected population with some/all of their infectious period falling outside of the isolation window	Isolation period (days)	Day of test(s)	Undetected proportion of infected population with some/all of their infectious period falling outside of the isolation window
7	5	0.34	7	7	0.31
8	6	0.26	8	8	0.32
9	7	0.20	9	9	0.33
10	8	0.15	10	8	0.28
10	0, 8	0.15	10	9	0.32
10	5, 8	0.15	10	10	0.35
			10	0, 10	0.35
			10	5, 10	0.12
			10	8, 10	0.24
14	8	0.11	14	10	0.23
14	10	0.08	14	11	0.26
14	12	0.06	14	12	0.28
14	0, 12	0.06	14	13	0.30
14	5, 12	0.06	14	14	0.31
			14	0, 14	0.31
			14	5, 14	0.15
			14	10, 14	0.20

No test	
Isolation period (days)	Undetected proportion of infected population with some/all of their infectious period falling outside of the isolation window
7	0.57
8	0.53
9	0.50
10	0.48
14	0.35

Summary

Purely considering the infectious risk of different testing scenarios (irrespective of compliance, implications of isolation periods regarding time off work etc), under these assumptions we find that:

- Taking day 0 as the known last time of contact means that any test on time of entry will not detect any infected individual. In future, we would like to consider a set-up with uncertainty on the time of infection, and a delay period before the individual is placed into isolation. This will alter the definition of day 0.
- The best performing regime is for an isolation period of 14 days, with a PCR test administered on day 12.
- When no test is used, a longer isolation period is more protective. The proportion of identified symptomatic individuals is similar between 10 and 14 days, but the longer isolation period minimisation the infectious period of asymptomatic infections that occurs outside of isolation. (Note that under this assumption for day 0, the proportion of infective released individuals is significantly higher when compared to the border screening work. This is to be expected.)
- For the same isolation period, a regime which includes testing lowers the number of infective releases when compared to an isolation period without testing. When considering infective releases, a PCR test on day 5 with 7 days of isolation achieves a similar result to isolating for 14 days. However, the proportion of transmission days is higher from the PCR regime.
- The number of PCR tests (one or two) performed does not make a difference to the proportion of released infectives. However, the correct placement of the first PCR test can enable the detection of additional individuals.
- If an LFD test is to be administered at the end of the isolation period, there will be a trade-off between the narrower detection window and the protective effect of isolation. This is because fewer people will be identified by a later test, but more there is more time to begin displaying symptoms.
- If an LFD test is to be administered at the end of isolation, an additional test part way into the isolation period will prevent infectious individuals from escaping the system.
- When a single test is administered at the maximum time point (2 days before for PCR, and on release for LFD), the PCR test outperforms the LFD test, due to the assumption on the detection window. The discrepancy between these will reduce as the time of PCR test gets closer to the LFD detection window.

Further work

Can the LFD detection window be scaled to better achieve 50% or 70% sensitivity?

How will test sensitivity that depends on a viral load alter the effect of these tests?

What is the optimal strategy for the use of multiple LFD tests?

Are there combinations of PCR and LFD tests that optimise the proportion of detected individuals?

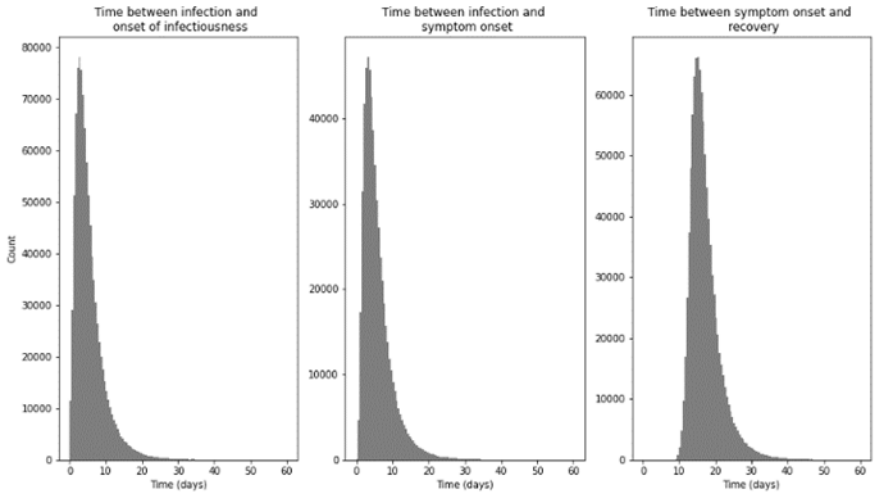
If contact tracing of the contacts is required (possibly due to delays for test returns and contact tracing or concerns about compliance), is it better to use an LFD test at the beginning with an instant return?

Can we capture transmission time prior to commencing an isolation period (due to delayed test result of contact, contact tracing, mis-identifying the time of contact)?

The infectivity of an individual is likely to decline towards the end of the infectious period. Is there a way of quantifying this risk and link it with time of infectious period outside the isolation window?

Method

- A disease course is simulated for a population using the distributions provided. Each individual is allocated an infection time, a time when infectiousness begins, a symptom onset time, and a recovery time.
- Depending on the regime, a set of logical statements are passed to determine the number of individuals captured at each stage.
- Medians are taken over the population.



- The full set of combinations can be found in 20201111_TT_isolation_test_combinations_2_PCRdelay.xlsx. Proportions of individuals are presented with the denominator population of total infected individuals. In the model, we discard individuals from the remaining pool as they are detected by symptoms or test, assuming that on symptom presentation they will get tested and that an individual with a positive first test will not be retested. For example, for a regime with 10 day isolation period and a PCR test on day 8, 47% of individuals will display symptoms before the time of the test. Therefore, only 53% of the population would be tested. Of the total infected population, 34% would return a positive test. These 34% are then excluded from the system. 4% of the total population would display symptoms between day 8 and day 10. This results in the system successfully detecting 85% of infected individuals, with 15% released.

Appendix

Test type	Isolation period days	Test day(s)	Detected proportion	Undetected symptomatic individuals with infectious period falling outside of isolation window	Undetected asymptomatic individuals with infectious period falling outside of isolation window	Proportion of total infectious period outside of isolation
None	7	-	0.43	0.17	0.40	0.75
PCR	7	5	0.66	0.17	0.17	0.39
LFD	7	7	0.69	0.15	0.16	0.32
None	8	-	0.47	0.13	0.40	0.68
PCR	8	6	0.74	0.13	0.13	0.30
LFD	8	8	0.69	0.12	0.20	0.33
None	9	-	0.50	0.10	0.40	0.61
PCR	9	7	0.80	0.10	0.10	0.23
LFD	9	9	0.67	0.09	0.24	0.34
None	10	-	0.52	0.08	0.40	0.54
PCR	10	8	0.85	0.08	0.08	0.18
PCR	10	0, 8	0.85	0.08	0.08	0.18
PCR	10	5, 8	0.85	0.08	0.08	0.18
LFD	10	8	0.72	0.08	0.20	0.27
LFD	10	9	0.68	0.08	0.24	0.30
LFD	10	10	0.65	0.07	0.28	0.33
LFD	10	0, 10	0.65	0.07	0.28	0.33
LFD	10	5, 10	0.88	0.07	0.05	0.11
LFD	10	8, 10	0.76	0.07	0.17	0.21
None	14	-	0.57	0.03	0.32	0.26
PCR	14	8	0.89	0.03	0.08	0.14
PCR	14	10	0.92	0.03	0.05	0.10
PCR	14	12	0.93	0.03	0.03	0.07
PCR	14	0, 12	0.93	0.03	0.03	0.07
PCR	14	5, 12	0.94	0.03	0.03	0.07
LFD	14	10	0.69	0.03	0.20	0.15
LFD	14	11	0.66	0.03	0.23	0.16
LFD	14	12	0.64	0.03	0.25	0.17
LFD	14	13	0.62	0.03	0.27	0.18
LFD	14	14	0.61	0.03	0.28	0.19
LFD	14	0, 14	0.61	0.03	0.28	0.19
LFD	14	5, 14	0.85	0.03	0.13	0.14
LFD	14	10, 14	0.72	0.03	0.17	0.10

The denominator for columns 4, 5 and 6 is the total infected population. Detected individuals are those captured within the system by testing or displaying symptoms. Asymptomatic individuals who complete their infectious period within the isolation period are not detected, and they do not contribute to the asymptomatic transmission risk.

The proportion of infectious period outside of isolation considers both symptomatic and asymptomatic individuals. The transmission risk from symptomatic individuals comes from the pre-

symptomatic infectiousness (under the assumption that they will isolate when symptoms begin), and the full infectious period for asymptomatic individuals.

For example, the first row of the table would read as follows.

With no test and a 7 day isolation period, we would expect to detect 43% of the infected population. (Because no test is used, these detections will purely be due to presentation of symptoms.) 57% of the infected population would escape from the system, posing a transmission risk to the general population because some of their infectious period lies outside the 7 day isolation window. 17% would escape and develop symptoms, and 40% of escapes would have an asymptomatic infection. Finally, 75% of the total transmission window across the infected population occurs outside of the isolation period.