Repeated mass testing with rapid antigen tests can effectively reduce SARS-CoV-2 transmission in defined populations

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Summary

There is significant interest in the use of repeated testing - particularly using rapid tests - to help rapidly identify positive cases of COVID-19. We used data from high frequency testing of London healthcare workers in Spring 2020 to estimate the probability of detection over time, post-infection. We then combined these estimates with a model of onwards transmission to estimate the transmission reduction that would result from frequent testing of pre/asymptomatic individuals in a defined population with lateral flow tests and/or PCR, incorporating data on current delays from test-to-result (and hence isolation). We found that the use of frequent lateral flow testing detects a comparable number of infections to frequent PCR, and can avert more transmission than PCR if they can be used more frequently. Lateral flow tests taken every 3 days may prevent 54% (95% Uncertainty Interval: 47%, 61%) of transmission compared to 52% (95% UI: 45%, 59%) with PCR swabs taken every 5 days, assuming that all symptomatic persons self-isolate upon onset. Requiring a confirmatory PCR test upon receipt of a positive lateral flow result substantially decreases the number of unnecessary isolations due to LFA false positives, and may increase in utility if COVID-19 prevalence is reduced. Frequent lateral flow testing may present a viable strategy to detect infections, avert transmission and prevent mortality in defined populations.

Introduction

In order to detect infections and prevent transmission of SARS-CoV-2, a strategy of testing and isolation of symptomatic persons and their contacts using polymerase chain reaction (PCR) swab tests has been employed in most countries. However in the UK, these efforts have been limited in their effect by asymptomatic and pre-symptomatic transmission (1), limited involvement in contact tracing by the public (2), delays in contact tracing (3) and delays in receiving test results (4). In contrast to the current PCR testing used by the National Health Service, the UK government is currently considering the use of alternative tests which may cut delays to receiving a test result from days down to hours or even minutes (5). While such rapid tests may have lower sensitivity than PCR, the speed at which results are available may, with costs permitting, allow for repeated testing of individuals that enables faster isolation of cases and reduced transmission potential even if the ability to detect infections is reduced somewhat.

Here we consider the regular testing of individuals in defined populations of interest, e.g. in residents or staff in a long-term care facility, or children and teachers in a school. As the population of interest are not transient, as in airport testing, we consider regular testing in order to detect the presence of an infection which is either pre- or asymptomatic and isolate those testing positive (and hence presumed infected). Two tests are considered - the current gold-standard PCR and a newer lateral flow-type antigen test (LFA), with the option of a confirmatory, follow-up PCR test after a positive LFA test.

Method

We used a stochastic, individual-based model (based on previous work by the authors (6,7)) to evaluate different strategies for frequent testing. We compared the probability of detection and transmission potential averted by lateral-flow type antigen (LFA) tests and PCR testing at intervals of 1, 3, 5, 7 and 14 days.

We simulated populations of 50 infected persons (based on the average number of long-term care home beds in 2016/17 (8)) who are tested at regular intervals over the course of 30 days from the time of their infection. We do not consider transmission between individuals in this model and so all individuals' disease progression is relative to the time of their infection. The populations are simulated 1000 times. We assume that the individual is first tested with uniform probability between 0 days (exposure) and the screening interval (i.e, they were exposed some time after the last test and before the next scheduled test), with subsequent tests occurring at regular intervals after the initial test. If a positive test is returned, the individual enters a period of self-isolation, where all subsequent transmission is prevented. If a confirmatory follow-up test is required, individuals self-isolate from the point of their first test, leaving self-isolation if their confirmatory test is negative. We assume that a proportion of individuals developing symptoms will also self-isolate from that time and that individuals who remain asymptomatic throughout the course of their infection do not self-isolate unless they

receive a positive test result. We also provide a sensitivity analysis of the proportion of individuals who do indeed self-isolate upon developing symptoms, with values of 0%, 50% and 100%.

Estimation of PCR positivity

We use PCR, serology and symptom data for 200 front-line staff at UCLH from the SAFER study and Crick Covid Consortium (9) to estimate the probability of detection by PCR over time. In this preliminary analysis, we concentrate on those individuals who seroconverted and reported symptoms at some point during the study. Once we apply these conditions to the dataset, we are left with a subset of 27 individuals (Figure A2).

We developed a Bayesian model (see Appendix) that first estimates exposure times for individuals based on the timing of their symptom onset (Figure A3). The model accounts for the fact that the true onset time is censored because the data contains the date of last asymptomatic report and the date of first symptomatic report. It then estimates the probability of testing positive by PCR test depending on the time since exposure using each person's inferred exposure time and their subsequent test results (Figure 1A).

We then sample a fitted posterior curve from this model for each individual. To account for differences in PCR and LFA in detecting an infection, we scale the PCR positivity curve by 0.739 (Figure 1A). This value is derived by integrating the PCR positivity curve from 5-10 days (the time around the peak detectability) and finding the value which, when multiplied by this area under the curve (0.622), matches the mean reported sensitivity of the LFA (46.0%, reported to SPI-M on 18 October 2020). The same approach is used to scale the PCR (and, hence, LFA) positivity curve by 0.62 to obtain the time-varying sensitivity for detecting asymptomatic infections (10), which we assume represents 31% (95% CI 26%, 37%) of infected individuals (11). We assume that the probability of detection by PCR after 30 days is 0.

Transmission potential

We assume that the infectiousness of an individual varies over time. We use the infectivity profile from (1) combined with a sampled incubation period from (12) to create a transmission potential distribution (Figure 1B) for each individual. We then calculate the proportion of this transmission potential averted in isolation (after a positive test), with the remainder being that realised within the population. If individuals are required to have a follow-up PCR test upon receipt of a positive initial LFA test, and the follow-up PCR test is negative, we assume individuals leave self-isolation after the negative PCR result. Transmission potential is assumed to be the same for asymptomatic and symptomatic infections. Note that we do not explicitly model transmission events, but the potential of an infected person to cause further infection over the course of their infection. As such, there is no need to consider estimates of R and its overdispersion in a branching process (13), nor transmission rates in an SEIR model (14).

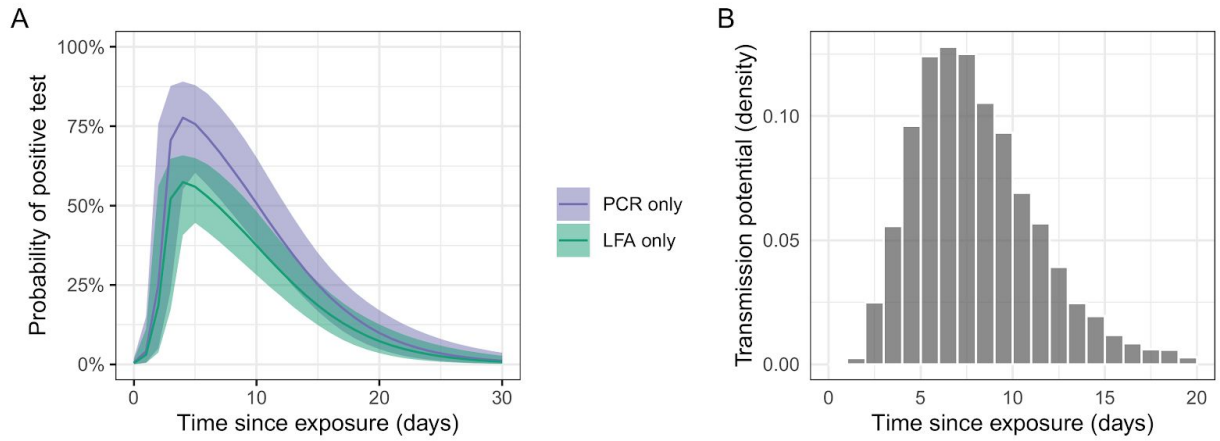

Figure 1 - A: Posterior medians and 95% credible intervals for probability of a positive test for an individual infected with SARS-CoV-2 as a function of the length of time since infecting exposure event for PCR, and the inferred detection curve for LFA using a scaling factor of 0.739. B: Transmission potential of persons infected with SARS-CoV-2, generated from the incubation period from McAloon et al. (2020) (15) and infectivity profile from He et al. (2020) (1). Sampled sum of log-normally distributed onset of symptoms, with location parameter 1.63 and scale parameter 0.41, and Gamma-distributed infectivity from onset, with shape 97.19, rate 3.71, and shifted by 25.62 days.

Testing delays

We parameterise the delays from having a PCR test to receiving the result using Pillar 2 testing data from 1 October 2020 to 7 October 2020 (4). We fit a Gamma distribution to this data, treated as doubly-censored observations of the reported 24 hour intervals using the fitdistcens function from the fitdistrplus package in R (16), then sampled a testing delay for each individual in the model. We also investigate fixed PCR testing delays of 0, 1, 2 and 3 days for sensitivity. For LFA tests we assume a fixed delay of 15 minutes as the test does not require processing in a laboratory off-site. We assume that self-isolation occurs immediately on receipt of a positive test result.

Proportion of infections detected over time

For each case we record the time from exposure until they were detected by testing. Where a case was never detected, it was recorded as a censored failure to detect during the 30 day period of testing. Survival analysis (17) was then used to determine the proportion of remaining undetected infections at days 0 to 30; here we present the complement, namely, the proportion of detected infections by a given time for each testing frequency and test sensitivity (Figure 3).

Specificity, NPV, and PPV

We estimate positive and negative predictive values (PPV and NPV), i.e, the probability that someone who has a positive test truly has contracted the virus, or someone who has a negative test truly has not contracted the virus,

respectively, for both LFA and PCR, as well for confirmatory PCR testing upon receipt of a positive LFA result. Based on provided LFA test data, we assume that the lateral flow test has a specificity of 99.5%. We assume PCR testing has a specificity of 99.9%, with a sensitivity analysis of 100% and 99.5%. We investigate PPV and NPV for COVID-19 prevalence ranging from 0.001% to 10%.

Results

We find that frequent LFA testing performs comparably to frequent PCR testing at detecting infections (Figure 2A) and may avert a greater proportion of transmission than PCR if testing can be conducted more frequently, as is their use case (Figure 2B). For example, lateral flow tests taken every 3 days may prevent 54% (95% Uncertainty Interval: 47%, 61%) of transmission compared to 52% (95% UI: 45%, 59%) with PCR swabs taken every 5 days. As the time between tests increases, repeated testing is less likely to detect infections; this is likely a combination of a reduced number of tests and a failure to test around the time of peak detectability (Figure 1A).

The reliability of PCR testing to avert transmission is diminished slightly by the longer delays from test to result for PCR testing compared to that of LFA testing (median 1 day, mean 1.3 days for PCR testing in England in early October 2020 (4), reported 15 minutes for lateral flow-type antigen testing). We provide a sensitivity analysis for these delays in Figure A1. Requiring a confirmatory PCR test after a positive LFA test does not increase the ability of testing to detect infections, although this may have utility in reducing the false positive rate; this, in turn has implications for the number of people required to isolate despite not being infected (18). Multiple tests increase the overall sensitivity of testing to detect infections (Figure 2A), with higher frequency of testing resulting in increased ability to detect a pre-symptomatic or asymptomatic infection. Most importantly, more frequent testing detects more infections earlier (Figure 3), hence averting more transmission (Figure 2B). If we relax the assumption of all individuals self-isolating from the point of onset (due to a lack of specific symptoms, willingness, or ability), the utility of shorter screening intervals to avert transmission remains high, whereas the utility of longer screening intervals to avert transmission is lessened further as persons spend a smaller proportion of their infectious period inside of either post-positive test or post-symptom self-isolation (Figure 2B).

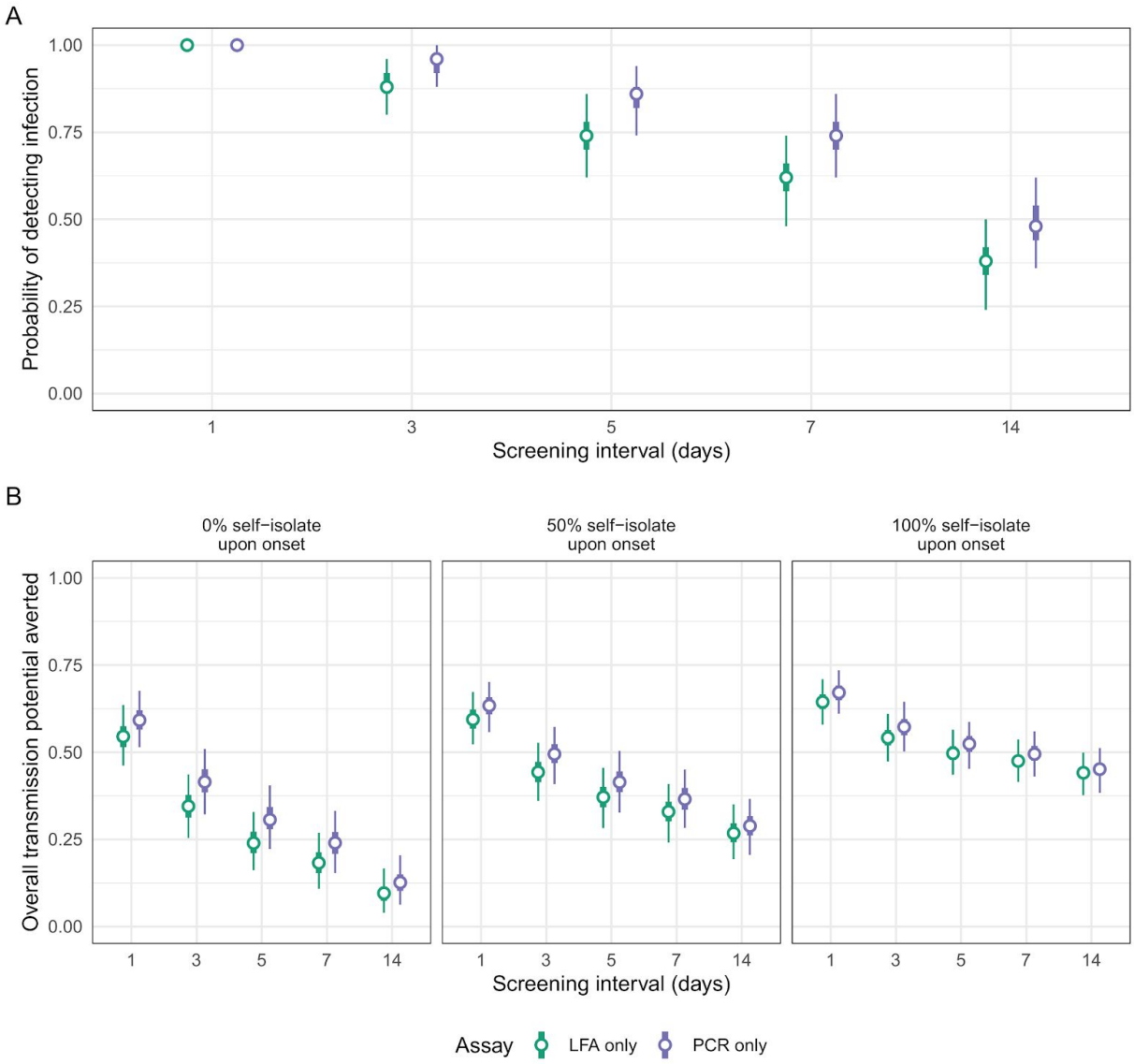

Figure 2 - A: Probability of detecting an infection with 1, 3, 5, 7 and 14 days between tests, with lateral flow antigen (LFA) testing only and PCR testing only. Median probability of detection with 50% and 95% uncertainty intervals as thicker and thinner lines respectively. B: Overall transmission potential averted with 1, 3, 5, 7 and 14 days between tests, with lateral flow antigen (LFA) testing only and PCR testing only, with 0%, 50% and 100% of cases self-isolating upon developing symptoms. Median overall transmission potential shown with 50% and 95% uncertainty intervals as thicker and thinner lines respectively.

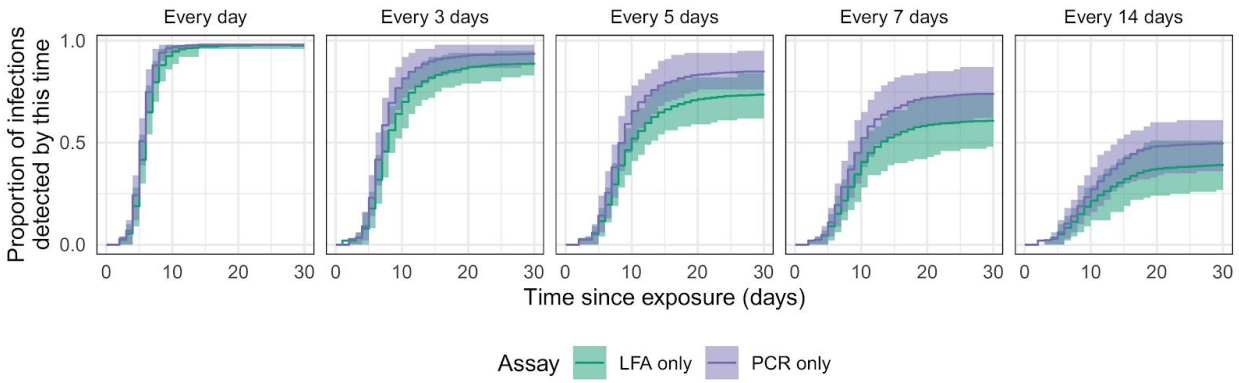

Figure 3 - Proportion of infections detected over time by multiple testing. Columns indicate the number of days between two subsequent tests, out to a maximum of 30 days since exposure. The solid line represents the complement of the average survival curve across 100 simulations, with the shaded region the 95% interval across survival curves.

Negative and positive predictive values (NPV and PPV) vary with prevalence and the testing strategy used, with confirmatory PCR testing upon a positive LFA test acting to substantially increase the probability of a positive predictive test (Figure 4). Assuming LFA test specificity is 99.5%, PCR testing specificity is 99.9% and COVID-19 prevalence is 1%, the median PPV for LFA + confirmatory testing is 0.998 compared to 0.328 with LFA only and 0.710 with PCR only. This difference persists at much lower prevalences, i.e for a prevalence of 0.01% LFA + confirmatory testing has a PPV of 0.980, compared to 0.045 with LFA only and 0.192 for PCR only. This indicates that rapid LFA testing with confirmatory PCR testing may represent a viable strategy to detect and isolate infected persons while reducing the number of healthy persons instructed to self-isolate with greater benefit observed at lower prevalence. There are only minor changes in PPV and NPV attributable to testing frequency (Figure A2). NPV remains high (>0.995) for prevalence below 1%, but decreases to 0.915 at 10% prevalence. If the real-world test specificity of PCR is lower, i.e 99.5%, then the PPV performance of LFA + confirmatory PCR testing decreases, however still exceeds 0.99 (Figure A2). The high NPV for LFA testing indicates that if it is used to test new arrivals to the defined population (e.g. visitors or new residents in a long-term care facility) the risk of a false negative that will trigger a new outbreak is low.

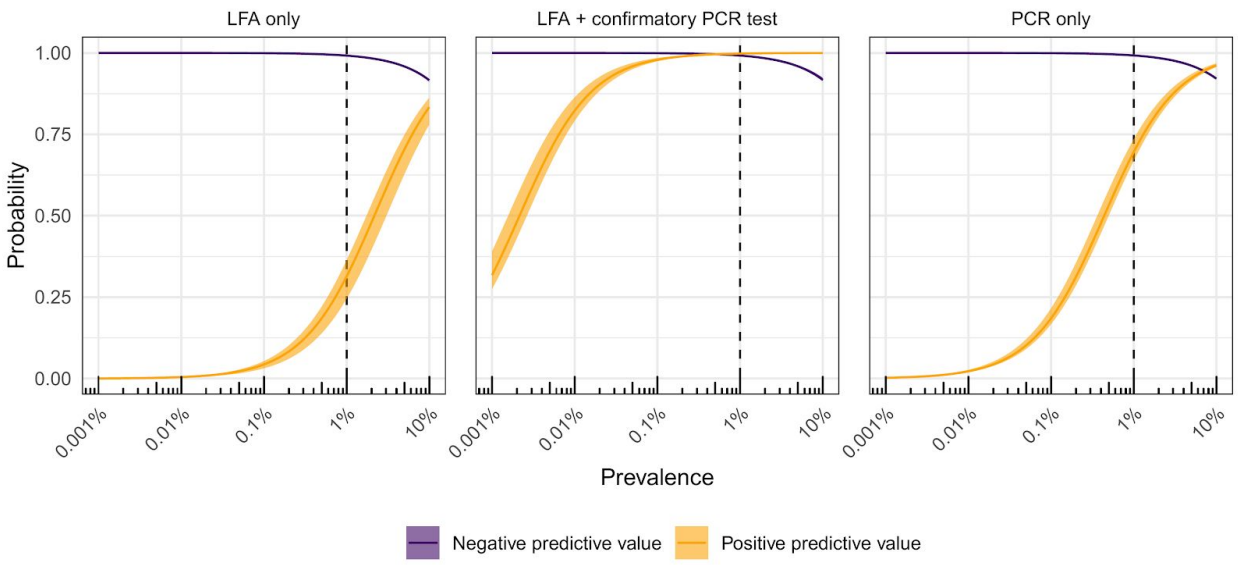

Figure 4: Negative Predictive Value (NPV) and Positive Predictive Value (PPV) vary with prevalence and testing strategy used, assuming a specificity of 99.5% for LFA testing and 99.9% for PCR testing. Vertical dashed lines indicate current COVID-19 prevalence in the UK . Results are for a single test.

Discussion

Our results indicate that frequent testing, i.e every 1 or 3 days, is likely to detect a substantial proportion of asymptomatic and pre-symptomatic infections and avert the majority of onwards transmission, whether using LFA or PCR testing. As LFA tests results can be returned in a fraction of the time required to return PCR test results, infected individuals may be identified and isolated much more quickly, counteracting the loss in sensitivity of LFA tests and averting a similar amount of transmission. For example, the proportion of infections detected by LFA testing every 3 days matches the proportion detected by PCR testing every 5 days (Figure 3). Furthermore, if LFA testing can be used on a more frequent basis than PCR testing due to logistical and cost advantages, then an even greater proportion of transmission may be prevented. It is worth noting that should the proportion of persons self-isolating upon symptom onset be less than perfect, the ability of longer screening intervals to avert transmission is much decreased, indicating that infrequent testing should not be used to replace the current advice to isolate upon symptom onset. Due to the lower specificity of LFA compared to PCR testing, it may be advantageous to require a confirmatory PCR test upon receipt of a positive LFA test in order to substantially reduce the proportion of false positive tests, with greater benefit when COVID-19 prevalence is low.

This work has several limitations. In our estimation of probability of detection and averted transmission potential, we consider only a closed population and do not model persons entering or exiting the population, for example new residents, visitors, or staff who may reintroduce SARS-CoV-2; however, testing and/or quarantine of entries is likely to reduce transmission in an analogous way to that of quarantine and testing for

international air travellers (7). We use the example of long-term care facilities and nursing homes, however the results of this model may be generalised to other defined settings and closed populations, for example schools, non-customer facing workplaces, prisons, and cruise ships. We also do not explicitly model transmission events nor a depletion of susceptibles within the closed population, but simply the likely times of potential transmission from infected persons over the course of their infection. We assess a time period of 30 days post-exposure, as our analysis indicates that after this point, the average probability of detection by PCR is extremely low and individuals are very unlikely to be infectious after this point.

One of the key reasons for investigating the use of LFA tests as an alternative to PCR tests is the delay inherent in the use of PCR testing. We have assumed here that upon receiving a positive test an individual who will isolate does so immediately. It may be the case that a recently notified individual cannot immediately self-isolate, and this will likely be dependent on the type of population of interest. We suggest that any assumptions about delaying self-isolation should be encoded in the distribution representing testing delays.

We consider infectivity to be centred around symptom onset; however, as it is yet not fully understood how infectiousness, viral load, symptom onset and probability of detection correlate, we do not correlate the timing of onset with the probability of detection by PCR; hence, in a small number of cases in our model, individuals may experience peak infectiousness late compared to the average probability of detection by PCR. We estimate a scaling factor for LFA applied to the probability of detection curve by PCR, however it is possible that the probability of detection curve for antigen is a different shape to that of the viral RNA detected by PCR, for example, the probability of detection may be shorter if antigen is more rapidly cleared from the body. For the analysis of specificity, NPV and PPV, we consider broadly indicative values for the specificity of LFA and PCR, however it is likely that real-world values are lower than that observed in lab conditions.

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Appendix data & methods

Table A1: Data from Figure 2B.

Assay	Proportion who self-isolate upon developing symptoms	Screening interval (days)	Overall transmission potential averted (median)	50% UI	95% UI
LFA only	0%	1	55%	(51%, 58%)	(46%, 64%)
		3	35%	(31%, 38%)	(25%, 44%)
		5	24%	(21%, 27%)	(16%, 33%)
		7	18%	(15%, 21%)	(11%, 27%)
		14	10%	(7%, 12%)	(4%, 17%)
	50%	1	59%	(57%, 62%)	(52%, 67%)
		3	44%	(41%, 47%)	(36%, 53%)
		5	37%	(34%, 40%)	(28%, 46%)
		7	33%	(30%, 36%)	(24%, 41%)
		14	27%	(24%, 30%)	(19%, 35%)
	100%	1	64%	(62%, 67%)	(58%, 71%)
		3	54%	(52%, 56%)	(47%, 61%)
		5	50%	(48%, 52%)	(44%, 56%)
		7	47%	(46%, 49%)	(41%, 54%)
		14	44%	(43%, 46%)	(38%, 50%)
PCR only	0%	1	59%	(56%, 62%)	(51%, 68%)
		3	41%	(38%, 45%)	(32%, 51%)
		5	31%	(28%, 34%)	(22%, 40%)
		7	24%	(21%, 27%)	(15%, 33%)

		14	13%	(10%, 15%)	(6%, 20%)
	50%	1	63%	(61%, 66%)	(56%, 70%)
		3	49%	(47%, 52%)	(41%, 57%)
		5	41%	(39%, 44%)	(33%, 50%)
		7	37%	(34%, 40%)	(28%, 45%)
		14	29%	(26%, 32%)	(21%, 37%)
	100%	1	67%	(65%, 69%)	(61%, 74%)
		3	57%	(55%, 60%)	(50%, 64%)
		5	52%	(50%, 55%)	(45%, 59%)
		7	49%	(48%, 52%)	(43%, 56%)
		14	45%	(44%, 47%)	(38%, 51%)

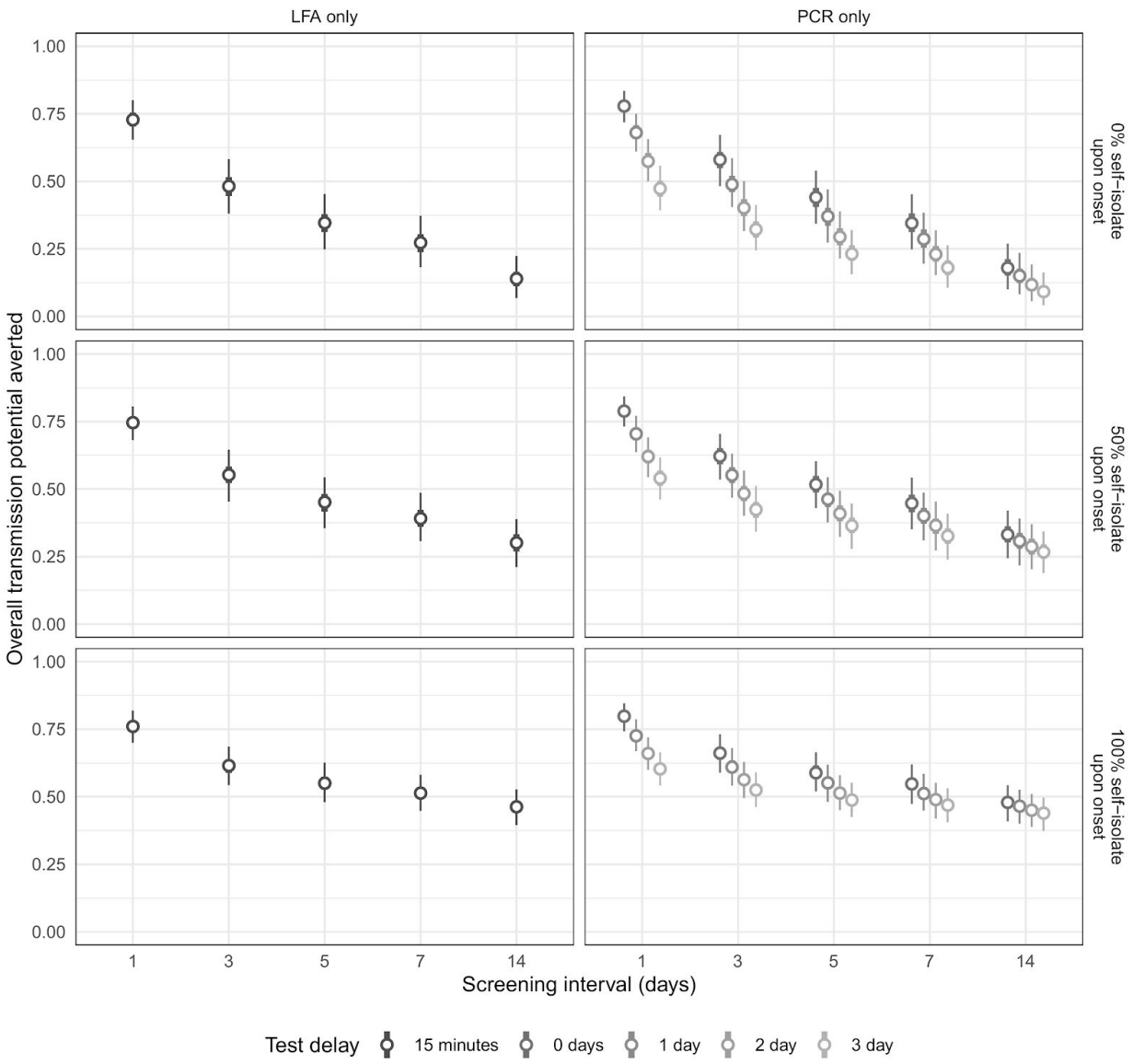

Figure A1 - Overall transmission potential averted with 1,3, 5, 7 and 14 days between tests, with lateral flow antigen (LFA) testing only and PCR testing only, with a sensitivity analysis of PCR test-to-result delays. Rows indicate different assumptions of self-isolation upon developing symptoms. Overall transmission potential per simulation shown as jittered points, with median and 50%, 95% uncertainty intervals overlaid.

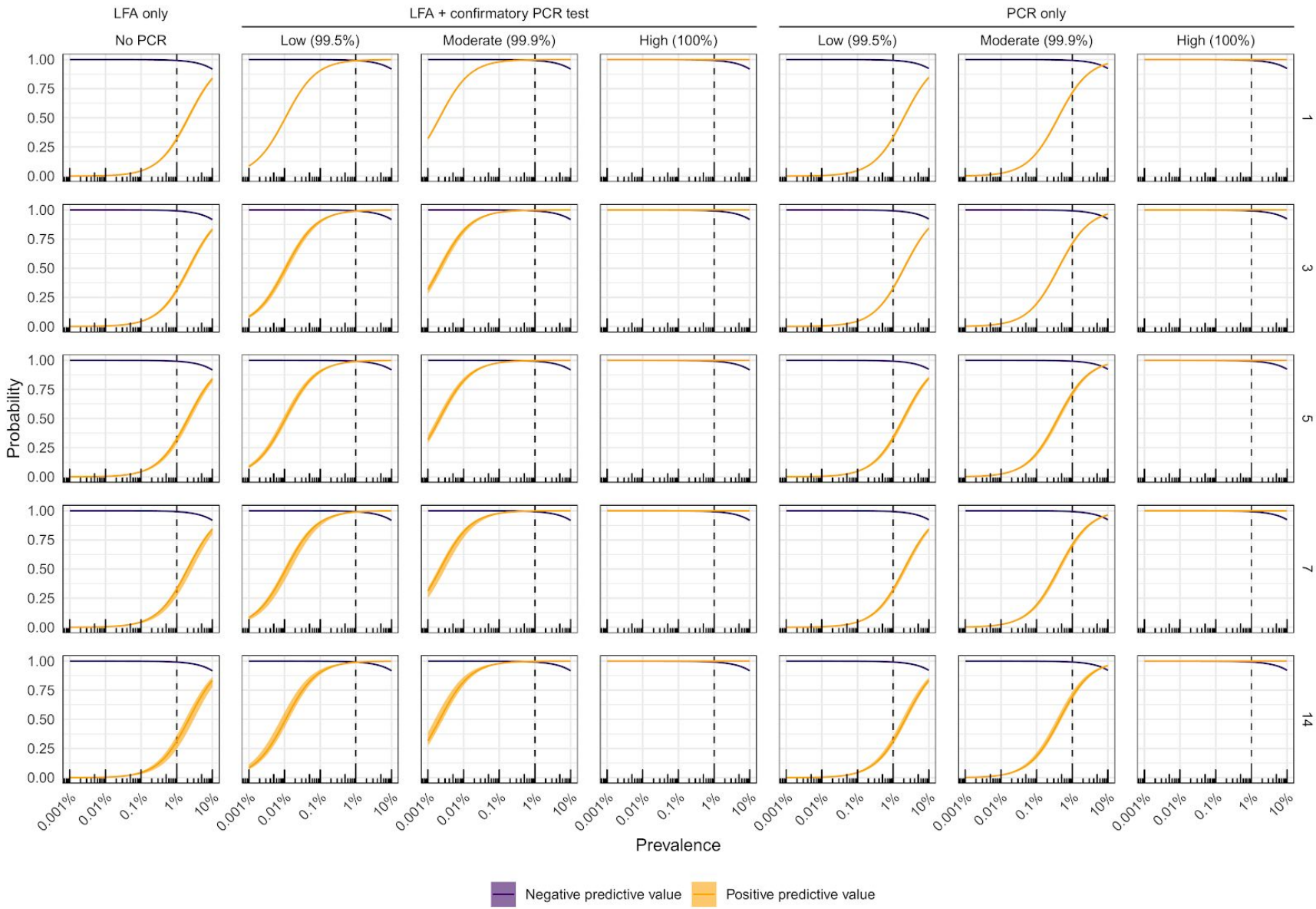
LFA only
No PCR
LFA + confirmatory PCR test
Low (99.5%)
Moderate (99.9%)
High (100%)
PCR only
Low (99.5%)
Moderate (99.9%)
High (100%)
Probability
1.00
0.75
0.50
0.25
0.00
1
3
5
7
14
0.001%
0.01%
0.1%
1%
10%
Prevalence
Negative predictive value
Positive predictive value

Figure A2: Negative Predictive Value (NPV) and Positive Predictive Value (PPV) probabilities against prevalence (x-axis), testing strategy used (top level column grouping) & assumed values of PCR specificity (columns) and screening interval (rows). Current England prevalence shown as a vertical dashed line.

Infection time

Individual i has their likely infection time (T_i) inferred based on the interval between their last asymptomatic report (t_i^{last}) and their first symptomatic report (t_i^{first}). The infection time log-likelihood for the infection time for person i is as follows:

$$L(T_i \mid t_i^{first}, t_i^{last}, \mu, \sigma) = log(F(t_i^{first} - T_e, \mu, \sigma) - F(t_i^{last} - T_e, \mu, \sigma))$$

Where F is the cumulative density function of the lognormal distribution that characterises the incubation period of COVID-19 (12).

PCR positivity

For a given inferred infection time for person i, the relationship between the time since infection and recording a positive nth PCR test on person i ($PCR^{+}_{n,i}$) administered at time $t_{n,i}$ is given by a piecewise logistic regression model with a single breakpoint:

$$PCR^{+}_{n,i} \sim Bernoulli\,(logit\,(\beta_1 + \beta_2(t_{n,i} - T_i - C) + \beta_2\beta_3(t_{n,i} - T_i - C) \times I(t_{n,i} - T_i - C)))$$

Where C is the time of the breakpoint, $I(t_{n,i} - T_i - C))$ is a step function that equals 0 if $t_{n,i} - T_i < C$ or equals 1 if $t_{n,i} - T_i > C$, and β are the regression coefficients fit across all tests and people.

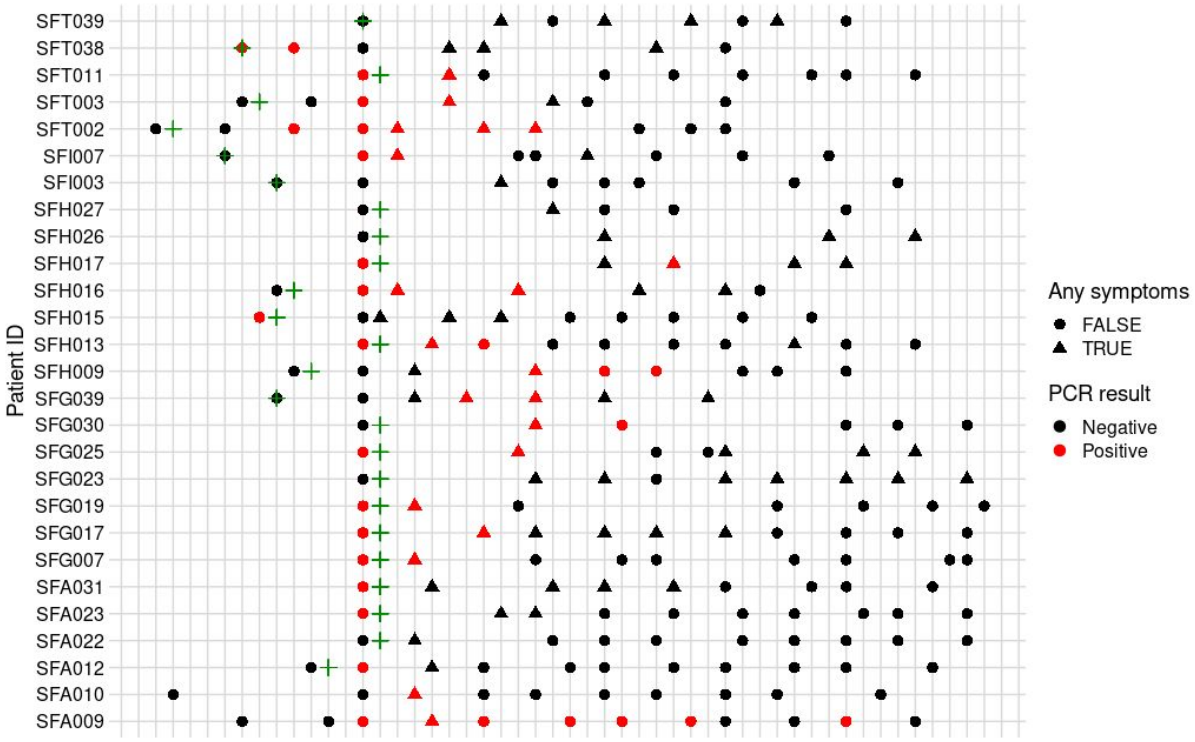

Figure A2: Testing and symptom data for the 27 individuals used in the analysis. Each point represents a symptom report and PCR test result. Red points indicate a positive PCR result while black points indicate a negative PCR result. If any symptoms were reported the point is triangular while if no symptoms were reported the point is circular. Greens crosses show the date of the initial negative serological test. Points are aligned by the day of last asymptomatic report.

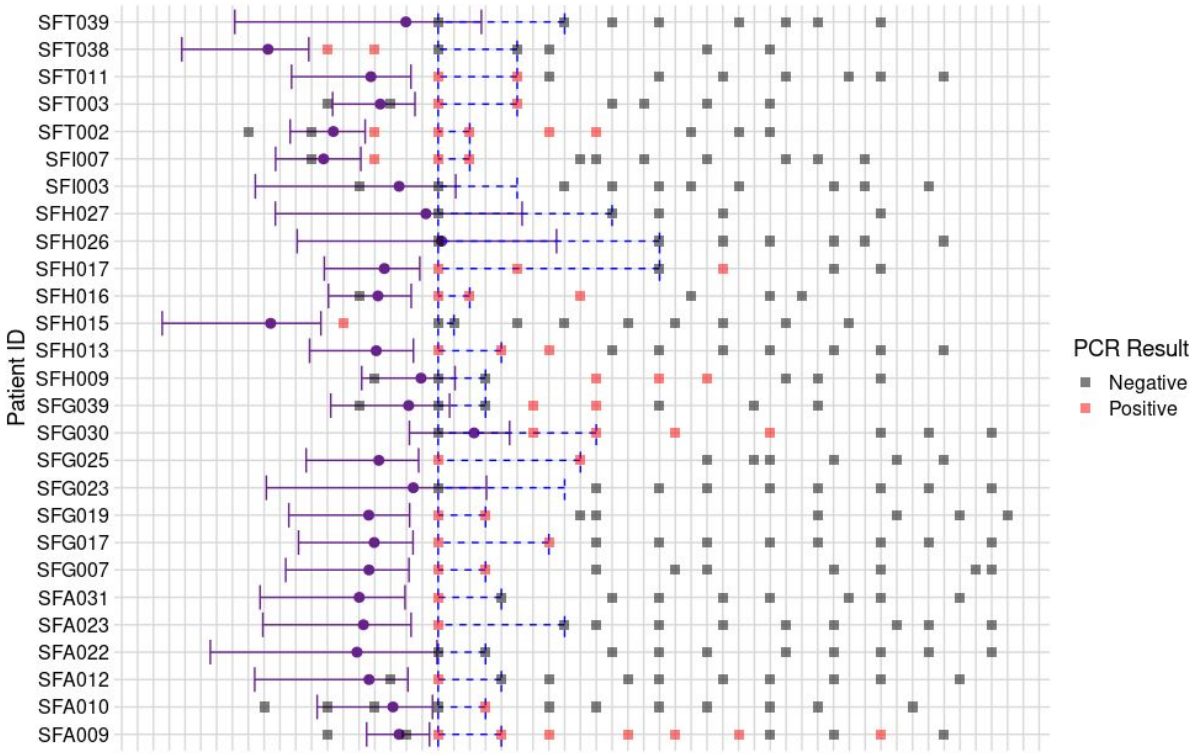

Figure A3: The posterior mean (purple circle) and 95% credible interval (purple lines) for the infection time (T_i) of each person. The interval between the last asymptomatic report and first symptomatic report for each person is shown by the blue dashed lines. Corresponding test results are shown by the square points, positive tests are red and negative tests are black. Points are aligned by the day of last asymptomatic report.