IRAS Project ID:311842

Covid-SMART Release & Return:
Urgent NHS Pilot of Dynamic Quarantine & Isolation

Version 4.7; 26th July 2022 (updated figures to reflect cumulative data)

Version 4.4; 11th March 2022 (updated figures to reflect cumulative data)

Version 4.3; 11th February 2022 (updated figures to reflect cumulative data, more detail on viral culture nested study added)

Version 3.9; 24th January 2022 (finalised, approved pre-recruitment protocol)

No other versions were circulated, actioned or published – incremental version numbers reflect frequent updates of the figures with cumulative data

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Version 4.7; 26th July 2022

Purpose

Study protocol developed with Testing Initiatives Evaluation Board and requested originally by Merseyside Resilience Forum in response to extreme staffing pressures exacerbated by Omicron in December 2021.

Problem

Essential services can face staffing pressures if large proportions of workers are quarantined after close contact with Covid-19 cases before they return to work on daily contact testing (test-to-release). Similar avoidable pressures arise from isolation of asymptomatic cases after they have ceased to be infectious. The civic risk from essential service loss can at times be greater than the direct health risks posed by SARS-CoV-2. There is a requirement[1] for health and social care workers to have a negative nucleic acid test before they are released from quarantine on 10 days (from exposure) of certification with daily negative lateral flow tests (LFTs). However, at times, access to Pillar 2 PCR testing can be difficult and slow (~48hours to results), adding further risk to essential service continuity.

In Cheshire & Merseyside a quarter of NHS staff were absent from work over Christmas and New Year 2021 and staffing pressures exceeded those at the height of the Alpha wave as shown in Figure 1, concurrent with high/rising non-Covid pressures on acute trusts as shown in Figure 2. This population has the world's longest running cohort of SARS-CoV-2 rapid antigen community testing,[2] with the time course reflected in Figure 3.

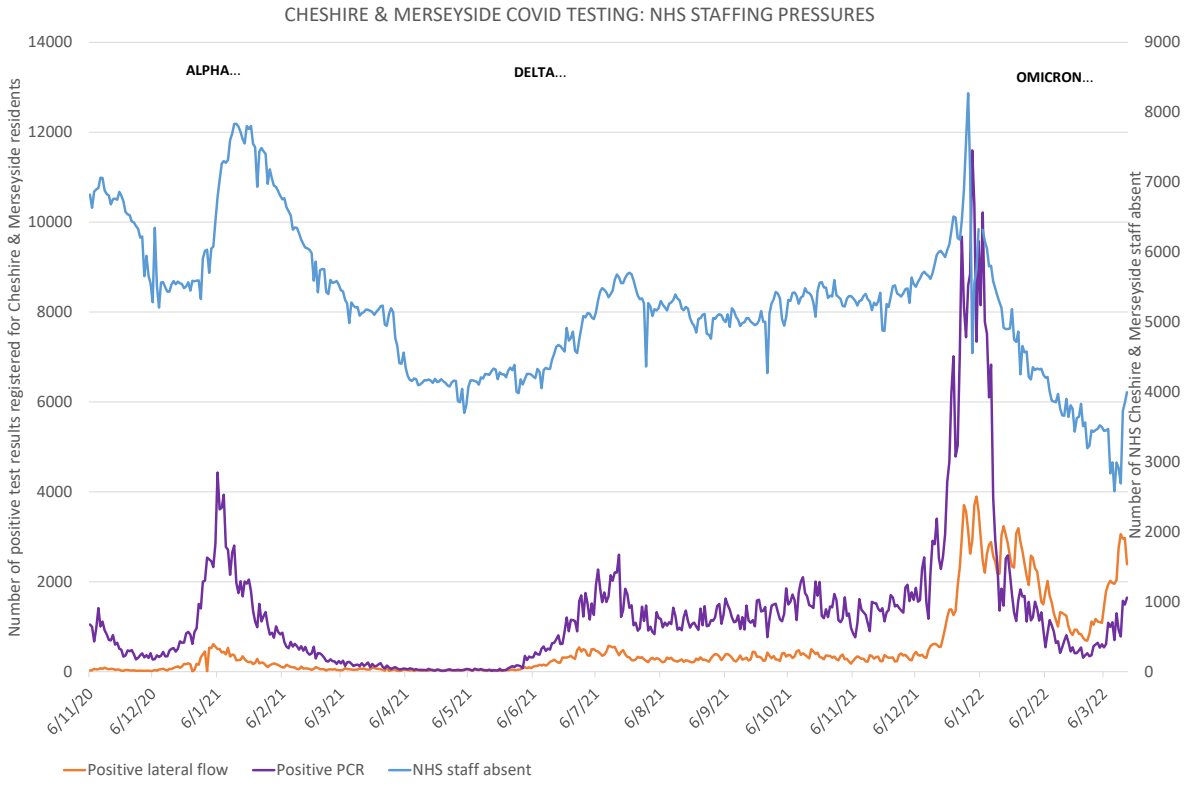

Figure 1: Timeline of Pillar 2 positive test numbers by PCR and lateral flow along with staff absence numbers since Liverpool community testing began 6th Nov 2020.

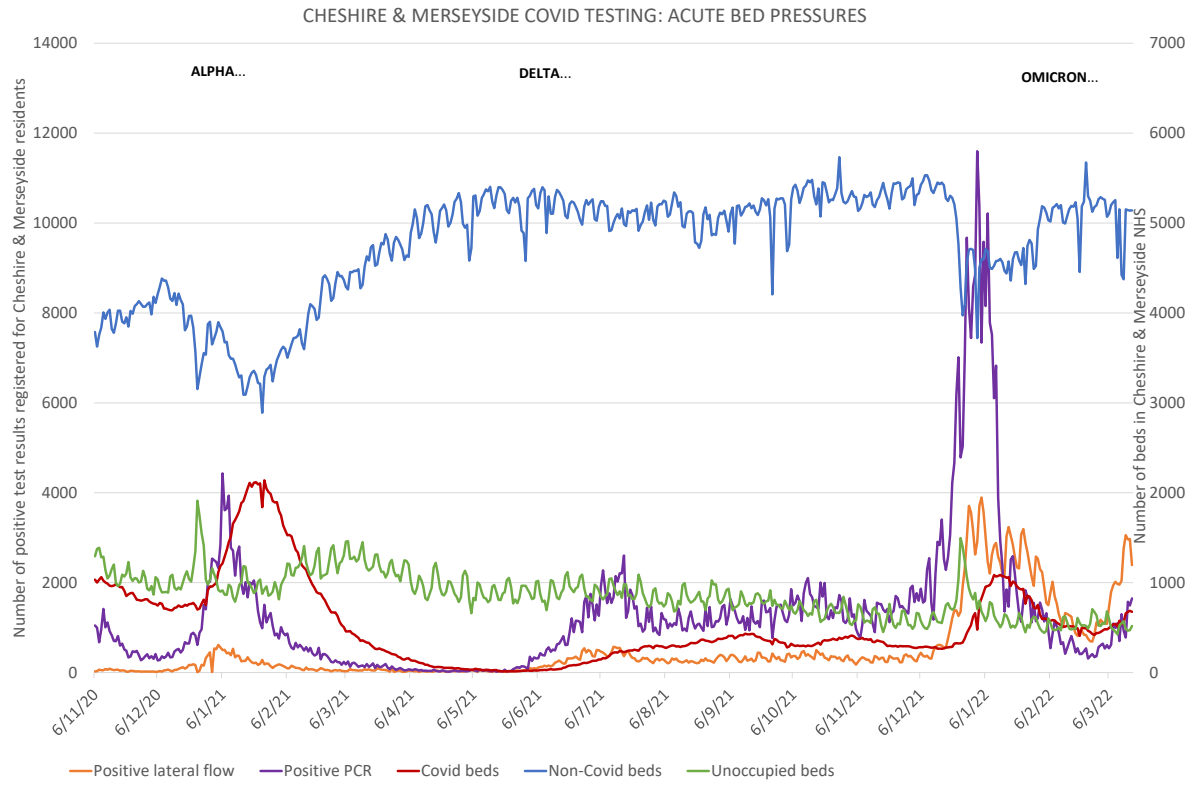

Figure 2: Timeline of Pillar 2 positive test numbers by PCR and lateral flow along with NHS acute bed occupancy (Covid and Non-Covid) since Liverpool community testing began 6th Nov 2020.

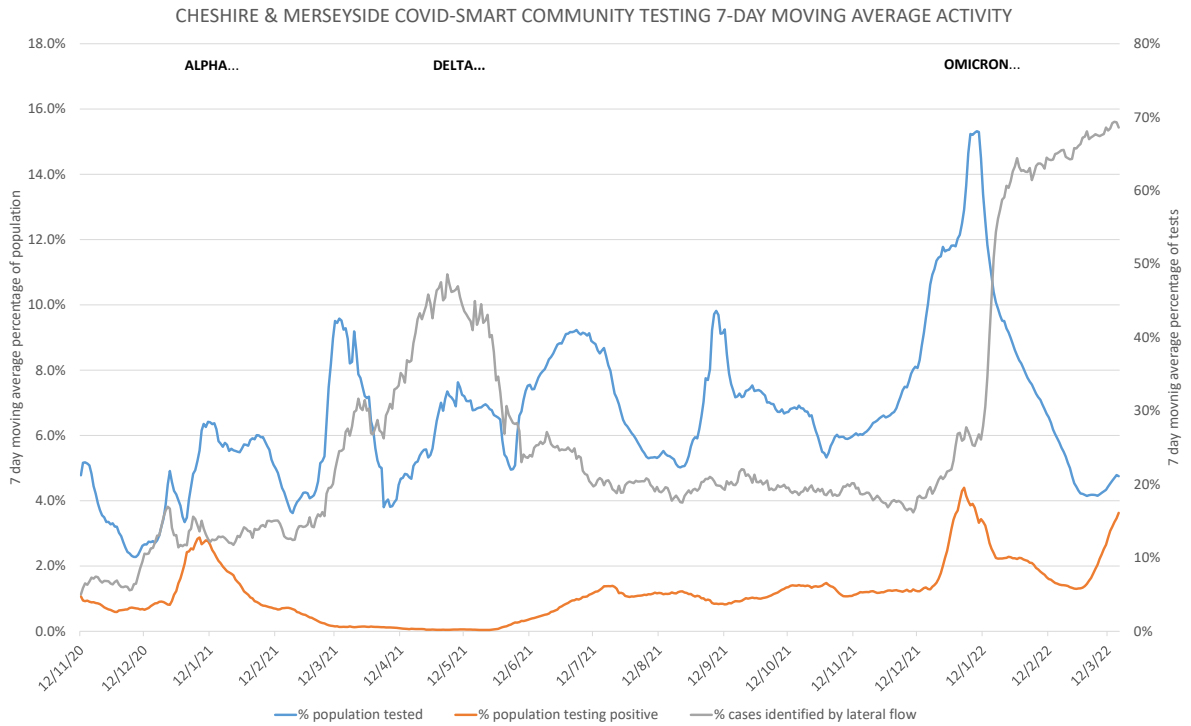

Figure 3: Cheshire and Merseyside population registered reporting of tests and positivity since Liverpool community testing began 6th Nov 2020.

Although NHS staffing pressures have now subsided, Omicron cases are rising again. NHS and social care services also face a long tail of displaced care demand, winter pressures and staff burnout. Covid testing regimes in some cases are counterproductive. For example, twice weekly LAMP for hospital staff is unpopular and compliance is around 25%. If notified positive, the staff member is already on site, when an alternative LFT could have been taken at home avoiding onward transmission that day if the positive staff member stays at home. As evidence builds that LFT better reflects infectiousness than PCR/LAMP, staff trust (and compliance) in testing will be lost if policies don't keep up with evidence.

There are reports of delayed Omicron detection if using nasal only swabbing for rapid testing.[3] Larger studies are needed to confirm this and the proposes study can.

It is widely reported on social media and via Covid monitoring apps that since the emergence of Omicron, substantial numbers of people test positive with LFTs for more than five days, running past 10 days post-exposure, but the extent is unclear given likely reporting bias. Guidance[1] for NHS staff testing was updated 7/1/22 to advise local risk assessments for those testing positive days 10-14.

Potential Solution

Liverpool piloted SMART Release,[2] which became Daily Contact Testing (DCT) and is well-placed to study dynamic, data-driven return from quarantine/isolation of key workers, aiming to reduce avoidable worker days lost to fixed periods of quarantine and isolation, while maintaining sufficient control of viral transmission. SMART = Specific, Meaningful, Adaptive, Realistic and Timely.

National policies changed in January 2022 to allow early return from 10-day isolation after two consecutive days (5 and 6) of negative lateral flow tests. The findings of this study will reveal the implications of this policy for the NHS in terms of SARS-CoV-2 transmission risks and managing staff shortages.

Convenient home testing with lateral flow devices (LFD) will be used, with the added risk mitigation of using two LFDs from different manufacturers (Orient Gene or Innova) at the same time, and within an hour of leaving for work (if on a daily contact testing regimen). The Orient Gene kit uses a nose only swab whereas the Innova kit uses a nose and throat swab. Compliance with nose only swabbing is assumed to be higher, but Omicron may be shed from the throat several days before the nose.[3]

For contacts, return to work on DCT currently requires a negative nucleic acid test,[1] for which we will deploy rapid results turnaround (< 8-hours) PCR via usual Pillar 1 hospital facilities, and as needed, we can deploy mobile RT-LAMP units (< 6-hour turnaround). The Pillar 1 PCRs are not quantitative, therefore, to gather proxy viral load trajectories we will add two home Q-RT-PCR Pillar 2 test kits.

Serial negative LFTs informing return to work is based on modelling[4] by SPI-M and UKHSA[5] and unpublished work reported on to NERVTAG by the Virology Cell. These models will be updated as Omicron viral load trajectories become clearer. We note that the main target of testing is identification of asymptomatic high shedders who are likely to have had high load exposures and experience shorter incubation periods, therefore any future shortening of the isolation period enabled with dual LFT testing is very unlikely to add more risk than that removed by relieving staffing pressures.

We seek to reduce LFD reading errors and make result reporting easier by implementing AI automated reading which improves accuracy of results (papers.ssrn.com/sol3/papers.cfm?abstract_id=3861638).

Unknowns: The sensitivity gains from repeating LFT at the same time and from using two different devices is unknown. The difference in Omicron early detection between nose only and nose + throat swabbing is unclear. The transmission risk from asymptomatic LFT negative PCR positive individuals is also unknown. Transmission risk from LFT positive individuals beyond nine days post exposure.

Research Questions

1. Does the addition of dual swabbing and use of two different manufacturer's devices at the same time add substantial value (in timely case detection) over a single device?
2. Does nose only swabbing detect Omicron infection as early as nose plus throat swabbing for LFT?
3. Is two consecutive days of negative (dual) LFT results a reliable indicator that an Omicron case will not subsequently revert to (validated) LFT positive/shedding within the same course of infection?
4. Can Omicron be cultured from cases after two consecutive days of negative LFTs by Day 7/8 when they are eligible to return to work from isolation?
5. Will NHS staff cases take up the offer of accelerated return to work given serial negative LFTs when their employer strongly encourages/organises participation?

Design

Urgent pilot service evaluation with randomised order of swabbing (directed by instruction leaflet) and internally controlled comparison of single vs dual LFT results. Observational study of serial dual LFT vs PCR Ct. Quantitative and qualitative (participant and employer survey) observational study of uptake and staffing impacts.

A survey of health & social care system managers will gather operational evidence. Non-randomised controlled comparison of intervention sites (up to 3) and the rest of provider employers in Cheshire & Merseyside where real-time integrated care and daily staffing reports are fed into a combined intelligence system (www.cipha.nhs.uk).

All participants must be fully vaccinated.

A sample of at least 30 participants who have either of their two daily lateral flow tests positive on each day from Day 5 to Day 7 will be invited to have another swab for viral culture on Day 7, or on Day 8, 9 or 10 if they are serially lateral flow positive until then.

In addition, a sample of at least 30 participants who have either of their two daily lateral flow tests negative on each of Days 5 and 6, or 6 and 7, after having at least two consecutive days of either lateral flow test positive between days 1 and 4, will be invited to have another swab for viral culture on Day 7 or Day 8. This coincides with the early return from isolation in current NHS staff Covid policies.

From each of the viral culture's RNA sequencing will be attempted in order to confirm that the virus cultured from the swabs provided is SARs-CoV-2 and will also confirm which variant is present.

Uninfected contact participant pathway (illustrated in Figure 4)

1. Household member of NHS worker is notified they are Covid positive, so their NHS contact starts quarantine and notifies their employer.
2. Employer has adopted SMART Release & Return testing schedule as their local standard policy and directs the staff member to a booking website for the scheme, which provides and information sheet, consent process and directions to the unit/site.
3. Participant receives a 10-day pack of daily dual LFT + 2 PCR home test kits, and if they have not had a positive Covid test in the past 90 days they take a swab for quick turnaround (binary) PCR.
4. Participant receives PCR negative result on Day 0 and returns to work on Day 1 with DCT.
5. Innova (nose/throat) and either Orient Gene (nose only) lateral flow devices are used each morning (or pre-shift) before breakfast in randomised order for 10 days – an information sheet in the pack directs the participant day by day. Either LFD turning positive is an overall positive result.
6. On day 1 the participant also takes a home PCR swab (randomised order with the two LFTs) and returns it by post to Pillar 2 / other (ringfenced) Q-RT-PCR capacity, and the result is not used for any purpose other than research.

7. A second Q-RT-PCR swab is taken on day 5.
8. Exit questionnaire gathers participant experiences.

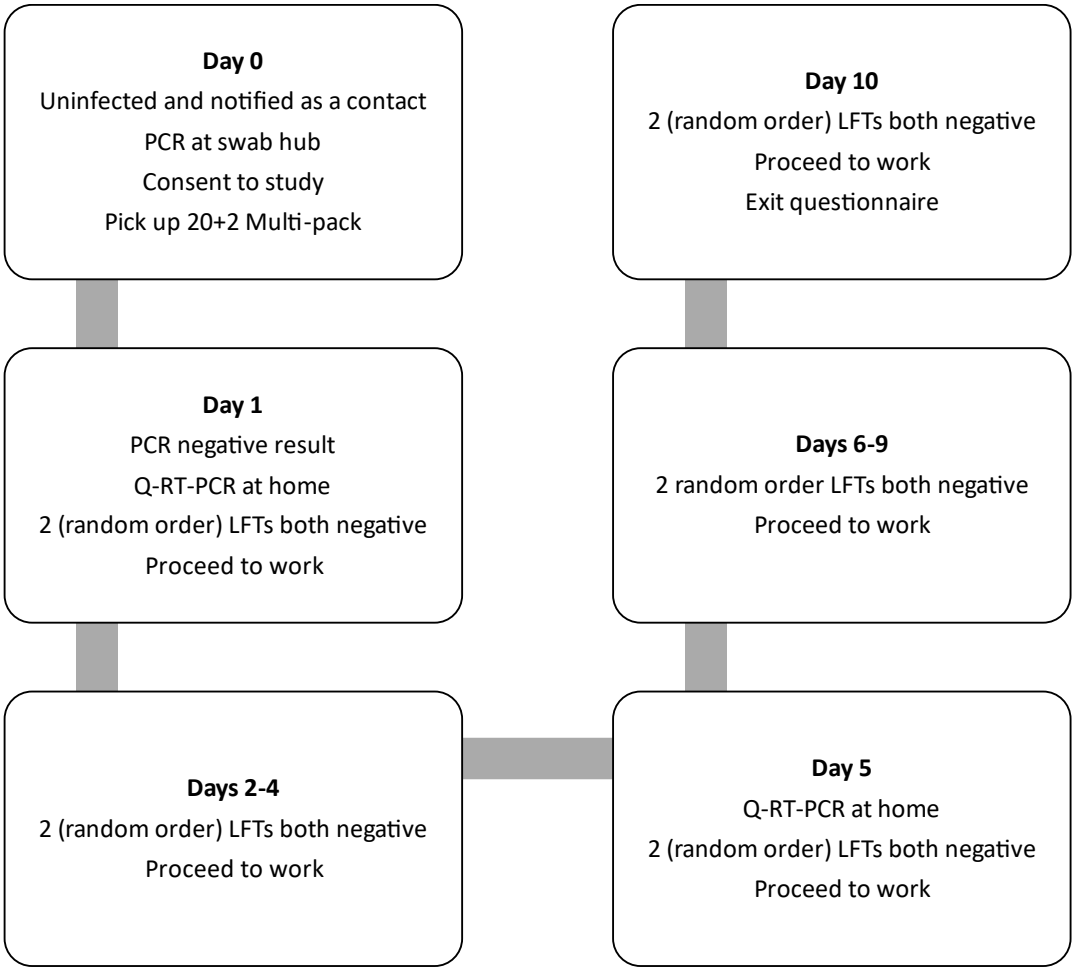

Figure 4: Workflow for participant who tests negative throughout

Asymptomatic infected contact participant pathway (illustrated in Figure 5)

1. Household member of NHS worker is notified they are Covid positive, so their NHS contact starts quarantine and notifies their employer.
2. Employer has adopted SMART Release & Return testing schedule as their local standard policy and directs the staff member to a booking website for the scheme, and directs them to the standard testing/reception site.
3. Consented participant takes quick turnaround (binary) PCR test to return to work from quarantine on DCT and receives a 10-day pack of daily dual LFT + 2 PCR home test kits.
4. Participant receives PCR positive result on Day 0 and stays at home.
5. Innova (nose/throat) and Orient Gene (nose only) lateral flow devices are used each morning before breakfast in randomised order – an information sheet in the pack directs the participant day-by-day.
6. On day 1 the participant also takes a home PCR swab (randomised order with the two LFTs) and returns it by post to Pillar 2 / other (ringfenced) Q-RT-PCR capacity, and the result is not used for any purpose other than research.
7. Second Q-RT-PCR swab is taken on day 5. (Participant is selected to be in the viral culture sample of 30 cases – and their swab in viral transport medium is collected from their home).
8. If day 5 and 6 dual LFT results (4 tests) are negative the participant may return to work.
9. Daily dual LFT testing continues until day 10.
10. If still testing LFT positive at day 7 the participant is advised to call and arrange a RT-Q-PCR swab in viral transport medium for culture.
11. Exit questionnaire gathering participant experiences.

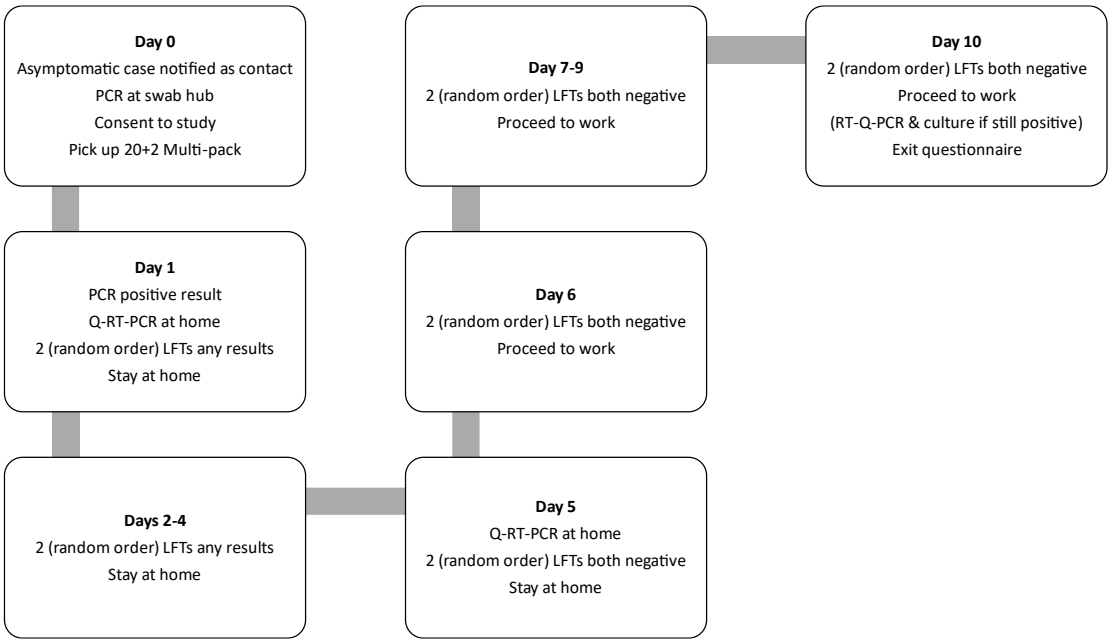

Figure 5: Workflow for contact who tests positive at start

New case referred to the study (illustrated in Figure 6)

1. NHS worker is notified they are Covid positive and notifies their employer.
2. Employer has adopted SMART Release & Return testing schedule as their local standard policy and directs the staff member to a booking website for the scheme, and directs them to the standard testing/reception site.
3. Consented participant receives a 10-day pack of daily dual LFT + 2 PCR home test kits.
4. Innova (nose/throat) and Orient Gene (nose only) lateral flow devices are used each morning before breakfast in randomised order – an information sheet in the pack directs the participant day-by-day.
5. On day 1 the participant also takes a home PCR swab (randomised order with the two LFTs) and returns it by post to Pillar 2 / other (ringfenced) Q-RT-PCR capacity, and the result is not used for any purpose other than research.
6. Second Q-RT-PCR swab is taken on day 5.
7. If day 5 and 6 dual LFT results (4 tests) are negative the participant may return to work.
8. Daily dual LFT testing continues until day 10.
9. If still testing LFT positive at day 7 the participant is advised to call and arrange a RT-Q-PCR swab in viral transport medium for culture.
10. Exit questionnaire gathering participant experiences.

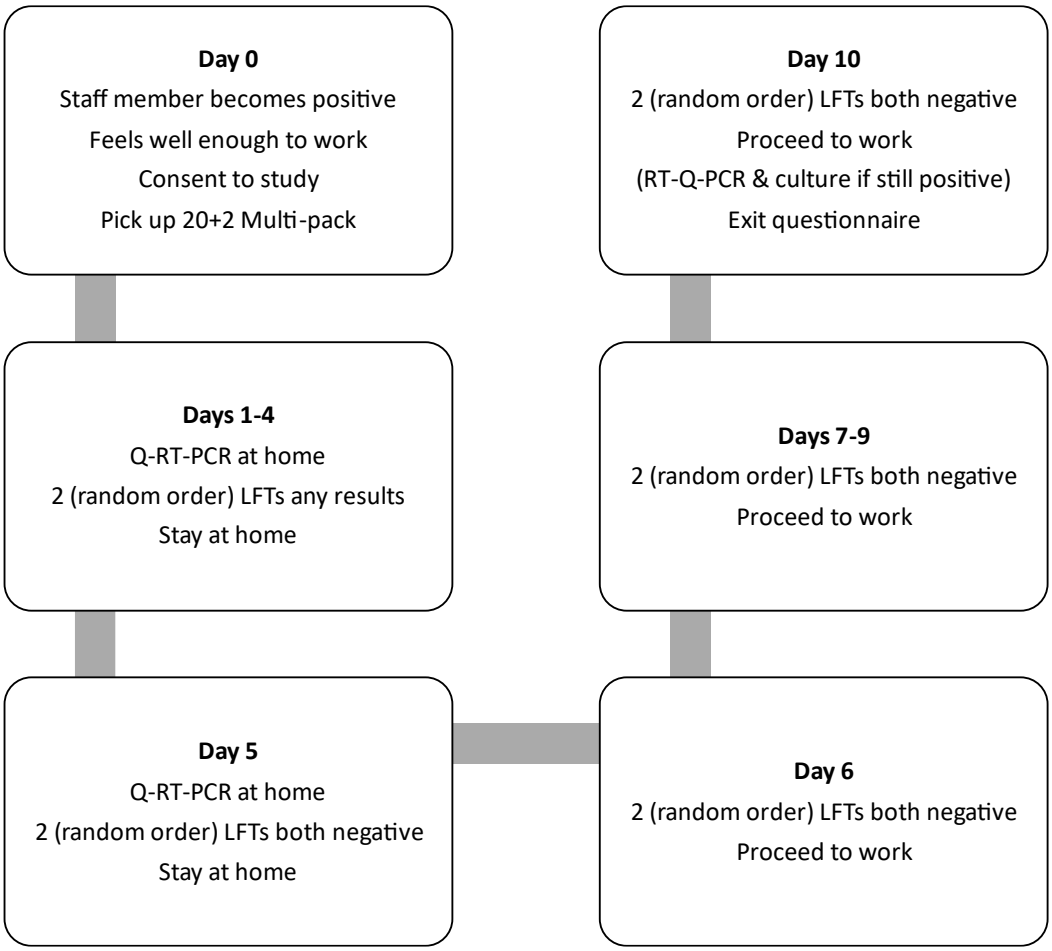

Figure 6: Flow for participant who becomes positive at some point or enters the study as a case

Sample size and time to evidence

For dual testing on the same day, we assume that a result is negative if both tests are negative, and that is positive otherwise (+ve/-ve, -ve/+ve, +ve/+ve). Discordant pairs when assessing single vs dual testing are defined as having a +ve (or -ve) result by single testing and -ve (or +ve) for dual testing.

Assuming a conservative LFD sensitivity of ~0.5 (accepting sensitivity varies as viral load changes over time) for PCR-LFT concordance, the proportion of cases missed on two consecutive days of single LFD testing is then (0.5^2) ~ 0.25 (25%; with the limitation that within-individual physiological and behavioural factors may break independence). With dual testing this proportion over two days is 0.5^4~0.0625, probably higher due to dependence between two consecutive FLT tests done on the same day. We therefore assume this proportion to be higher (e.g., 40% higher: 0.0625*1.4=0.09). So, assuming an LFD sensitivity of 0.5, for every 100 PCR positives, 25 cases are expected to be missed by two consecutive single tests vs approx. 9 cases with dual testing.

The estimated odds ratio for single vs dual testing is then 3.37 = (0.25/0.75)/(0.09/0.91) and the proportion of PCR positives with discordant pairs is ~16/100 positive cases (since the 9 -ve cases by dual testing would be also -ve by single testing).

The number of positive cases required with 80% power at 5% significance to detect a significant difference between the two approaches in the proportion of cases missed is ~164 positive cases. [6] Raised to 200 to account for loss to follow-up. Using only a contact cohort with ~10% case rate this would require a sample of 2000, but more as case rates fall.

Sufficient data for interim analysis should accrue within two to three weeks of operation, producing policy-relevant insights a week later.

Table 1. PCR positive sample size vs LFD sensitivity to detect a significant difference between dual and single LFD testing in the proportion of discordant cases with 80% power and 5% significance level.

LFD Sensitivity	P_single= Prob (-ve LFT based on a single test|+ve PCR)	P_dual=Prob (dual -ve LFTs based on 2 consecutive tests within minutes|+ve PCR)	P1=Prob (-ve LFTs on 2 consecutive days|+ve PCR)=Ps^2	P2=Prob (dual -ve LFTs on 2 consecutive days|+ve PCR)=Pd^2	OR	Proportion of discordant pairs	Number of PCR positives required
Assuming independence (Pdual=Psingle*Psingle)							
0.7	0.3	0.09	0.09	0.0081	12.1	8.2%	131
0.6	0.4	0.16	0.16	0.0256	7.25	13.4%	99
0.5	0.5	0.25	0.25	0.0625	5.0	18.8%	92
0.4	0.6	0.36	0.36	0.1296	3.78	23.0%	98
Assuming some level of dependence between two tests conducted within minutes							
Pdual=Psingle*Psingle*1.2							
0.7	0.3	0.11	0.09	0.0117	8.07	7.8%	159
0.6	0.4	0.192	0.16	0.0369	4.98	12.3%	142
0.5	0.5	0.3	0.25	0.09	3.37	16.0%	164
0.4	0.6	0.432	0.36	0.1866	2.45	17.3%	254
Pdual=Psingle*Psingle*1.4							
0.7	0.3	0.126	0.09	0.0159	6.13	7.4%	202
0.6	0.4	0.192	0.16	0.0502	3.61	11.0%	221
0.5	0.5	0.35	0.25	0.1225	2.39	12.75%	365
0.4	0.6	0.504	0.36	0.2540	1.65	10.1%	1223

Table 1 shows the sample size for various values of sensitivity and for different scenarios regarding the dependence between two consecutive FLT tests done on the same day. Note that the sample size required varies substantially with the within-individual correlation, which is unknown. We assume some level of dependence between two tests conducted between minutes of each other, but not conducted on consecutive days, and have ignored the factor *manufacturer*.

Table 1 assumes that the two lateral flow devices achieve the same level of sensitivity. Deviation from this assumption (i.e., allowing some degree of differentiation in sensitivities) is not expected to alter the sample size reported in Table 1 significantly. We plan to test this hypothesis as part of a follow-up analysis. The power that can be achieved to detect a 15% drop in sensitivity over a two-day period with nose only swabbing, when compared to nose + throat swabbing, is provided in Table 2 for different sample sizes and values of sensitivity. Both tables use equation (7.1) in Machin et al. (2009)[1] and is based on discordance between results.

Table 2. Power to detect a 15% drop in sensitivity (or higher drop) over a two-day period with nose only swabbing (when compared to nose + throat swabbing) with 5% significance level.

LFD Sensitivity (nose + throat)	LFD sensitivity (nose +throat) over two days	LFD sensitivity (nose) over two days	Number of +ve PCR cases	Power
0.7	0.91	0.77 (=0.91*0.85)	200	96%
0.6	0.84	0.714	200	85%
0.5	0.75	0.638	200	68%
0.4	0.64	0.555	200	50%
0.7	0.91	0.77	250	98%
0.6	0.84	0.714	250	92%
0.5	0.75	0.638	250	77%
0.4	0.64	0.555	250	58%
0.7	0.91	0.77	300	99%
0.6	0.84	0.714	300	96%
0.5	0.75	0.638	300	85%
0.4	0.64	0.555	300	66%

Randomisation

Each of 2000 participants has a randomised testing schedule generated by the research team that will be used by the packing company to generate and individualised day-by-day instruction sheet in the pack they receive. The order in which lateral flow and (on days 1 and 5) PCR tests are instructed to be taken are detailed on the sheet and the participant is asked to upload the results via NHS Test & Trace systems in that order. The enhanced NHS Test & Trace lateral flow reporting link that uses AI reading of photographs of test kits will be provided.

Participant 1926

Day	First test	Second test	Third test
1	Lateral flow "B"	PCR "C"	Lateral flow "A"
2	Lateral flow "B"	Lateral flow "A"	
3	Lateral flow "A"	Lateral flow "B"	
4	Lateral flow "A"	Lateral flow "B"	
5	Lateral flow "A"	Lateral flow "B"	PCR "C"
6	Lateral flow "A"	Lateral flow "B"	
7	Lateral flow "A"	Lateral flow "B"	
8	Lateral flow "A"	Lateral flow "B"	
9	Lateral flow "B"	Lateral flow "A"	
10	Lateral flow "A"	Lateral flow "B"	

Governance and Approvals

Department of Health and Social Care (DHSC) funded, and University of Liverpool sponsored study delivered by NHS Cheshire & Merseyside in concert with UK Health Security Agency (UKHSA). Liverpool City Region and DHSC joint Gold Command as per previous Covid-SMART community testing early roll-out evaluation.[7]

Ethical approval will be processed by UKHSA under urgent public health study arrangements, in concert with HRA and with the full involvement of University of Liverpool Research Ethics Committee.

University of Liverpool holds Indemnity and insurance cover with Newline Insurance Company, which apply to this study.

DHSC/UKHSA/NHS VOC Assurance team will take oversight of the comparison of nasal only with nose and throat swabbing vs questions over Omicron tropism.

Prior SMART Release findings[7] showed that employer ownership of DCT is key to employee uptake. The Royal Liverpool University Hospital NHS Trust has been in daily planning meetings for this study and is ready to deliver it through its Occupational Health and Infection Prevention and Control teams.

End of study is defined as the end of analysis: which is now anticipated to be the end of September 2022

Governance process:

- DHSC Testing Initiatives Evaluation Board oversight and feedback on this protocol
- UKHSA Research Ethics and Governance Group feedback on all documentation
- Liverpool Health Partners Sponsorship Committee: sponsored UoL001685
- University of Liverpool Local Research Ethics Committee: approved
- Liverpool University Hospitals NHS Foundation Trust Executive Oversight Group: weekly feedback

Research and operations team:

- Chief Investigator: Iain Buchan: buchan@liverpool.ac.uk
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- Sponsor lead: Tom Fowler: tom.fowler@dhsc.gov.uk
- Data governance lead: Gary Leeming: gary.leeming@liverpool.ac.uk
- Lead statistician: Marta Garcia-Fiñana martaf@liverpool.ac.uk

References

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[4] Test to release from isolation after testing positive for SARS-CoV-2. www.medrxiv.org/content/10.1101/2022.01.04.21268372v1

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[7] www.liverpool.ac.uk/media/livacuk/coronavirus/Liverpool_City_Region_Covid_SMART_Evaluation.pdf