Department of Health & Social Care

NHS

From the Chief Medical Officer & Chief Scientific Adviser
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Rt Hon. Jeremy Hunt MP
House of Commons
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03 November 2020

Dear Mr Hunt

Following the publication on September 24th of the Health and Social Care Select Committee report *Delivering core NHS and care services during the pandemic and beyond,* we are writing to update you on covid-19 antigen testing in NHS staff.

We agree with the general principle that regular testing of asymptomatic staff who may have patient contact can be a valuable tool. The value of regular asymptomatic testing to reduce nosocomial transmission is likely to increase as incidence increases, as previously laid out to the Committee. As such, advice has for some time been that asymptomatic testing of healthcare staff should be used during hospital outbreaks and in high incidence settings. In addition, NHS staff have been recruited into the SIREN study and SIREN-associated studies, which we anticipate will provide further evidence on the impact of seropositivity and the optimum frequency of testing.

Testing capacity has of course practically limited what is achievable at any point in time. There are a number of different demands on testing capacity and prioritisation amongst these given capacity at any one time has been complex. These include clinical management (the top priority), testing of symptomatic people, asymptomatic testing in social care settings, asymptomatic testing of elective patients and other uses. DHSC's published testing prioritisation hierarchy, dated 21st September, can be accessed at: https://www.gov.uk/government/publications/allocation-of-covid-19-swab-tests-in-england/allocation-of-covid-19-swab-tests-in-england.

Nevertheless, as testing capacity increases it is becoming possible to extend regular NHS staff testing. On 12 October we announced the commencement of regular staff testing in geographical areas designated by the government as very high risk (tier 3) and this programme has now begun. Testing capacity has been initially provided by the NHS ('pillar 1') and by the government Test & Trace laboratories ('pillar 2').

Furthermore, with the arrival of new testing technologies we are now in a position to expand asymptomatic staff testing further. We have successfully piloted the use of saliva-based testing using Loop Mediated Isothermal Amplification (LAMP). Our aim

is to use this technology, which is less intrusive than swab testing, to become the main form of testing for NHS staff. This technology has already been introduced in several laboratories and our aim is to establish sufficient hubs through NHS Labs and the 'Test and Trace' programme around the country by December 2020 for routine weekly testing of all patient facing clinical staff in the NHS. We attach a report on this technology from the Chief Scientific Officer, Prof. Dame Sue Hill, which we hope will be of interest to the Committee.

We hope this and the attachment are helpful.

Yours sincerely

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Technical summary of NHS asymptomatic staff testing pilot

Introduction. Recent studies[1, 2] have shown that viral loads in saliva tend to be higher than those in oropharyngeal and nasopharyngeal swabs (ONS) in the early infection cycle, prior to symptoms, making it a powerful method of testing individuals who may be asymptomatic or pre-symptomatic. With the general aim of supporting containment of outbreaks and enabling the continued provision of elective care, this pilot was designed as an NHS service evaluation to explore the feasibility of implementing regular saliva testing amongst NHS staff and to cross validate tests for SARS-CoV-2 infection.

Pilot Overview: The pilot was developed as a multi-centre and multi-assay comparison (**see Annex A**); with 1201 participants across five NHS Trusts, providing daily saliva and weekly matched ONS samples for a 21-day period. Four representative laboratories[3] undertook comparative tests on two LAMP based technologies, which were evaluated using site specific workflows and matched against their own standard of care tests (Reverse Transcriptase-Quantitative Polymerase Chain Reaction {RT-qPCR}) to further evaluate the technologies in these real-world settings.

The objectives were to:

- Build a body of evidence around regular asymptomatic testing of NHS staff using saliva.
- Conduct real-world validation of OptiGene LAMP and Oxford Nanopore LamPORE technology.
- Develop a blueprint for whole-hospital NHS staff testing.
- Collate findings from comparable independent pilots that had evaluated these LAMP based technologies.

LAMP Overview: Loop Mediated Isothermal Amplification (LAMP) is a rapid (<20 mins) nucleic acid amplification technique performed under isothermal conditions to create double stranded amplicons which melt at a specific temperature. The size of the genomic region involved in the amplification (~150-300bp) is typically larger than that targeted in the RT-qPCR amplification assay. The OptiGene RT-LAMP assay targets the Orf1ab region and includes 6 primers, targeting 8 genomic regions. The assay has two formats, RNA RT-LAMP which uses extracted RNA and Direct RT-LAMP which uses crude clinical samples.

RT-LAMP assays amplify larger genomic regions than RT-qPCR and this performance characteristic may influence the types of viral RNA that are detected during each stage of a CoV2 infection. During the asymptomatic phase of infection, the viral load increases rapidly, becoming detectable by the molecular methods deployed in this pilot at an early stage. A graphical representation of such changes may be found in **Annex B.** The interim results data set for Optigene RT-LAMP is shown in **Annex C**. The main observations made with Optigene RT-LAMP are:

- RNA RT-LAMP has comparable technical performance (97.83% Sensitivity (swabs) and 88.23% Sensitivity (saliva); 100% Specificity for both) to RT-qPCR and can detect viral loads over a similar dynamic range.

[1] https://www.medrxiv.org/content/10.1101/2020.04.16.20067835v1

[2] https://www.journalofinfection.com/article/S0163-4453(20)30440-0/pdf

[3] An active virology laboratory within a District General Hospital, a regional reference laboratory, a university laboratory and a large hospital diagnostic laboratory.

- Direct RT-LAMP has a lower overall Technical Sensitivity (82.30%) when considering the full dynamic range of "positive" samples (RT-qPCR of C_T <45), improving to 96.15% in the cohort with a higher viral load (RT-qPCR of C_T <25), on saliva samples.
- Direct RT LAMP has a comparable specificity to RT-qPCR (100% for both swabs and saliva).

LamPORE Overview: LamPORE is a technology that combines LAMP methodology with Oxford Nanopore sequencing technology. Nanopore sequencing is a nucleic acid sequencing technology which utilises detection of voltage perturbation as nucleic acids transit through a protein pore embedded in a resistive membrane. This allows identification of the bases that transit through the nanopore. A key advantage of nanopore sequencing is that data is produced continuously, so the system can be run until sufficient data is produced, rather than wait for a sequencing run to complete (e.g. for Illumina SBS technology which can between 12-24 hours to complete). The technology also allows multiplexing of samples using "barcodes" which are short stretches of nucleic acids that act to uniquely identify each sample within the assay, allowing high multiplexing of up to 96 samples per run, with a capability of 5 runs per machine per hour. Ongoing work suggests multiplexing up to 768 samples per individual run is possible, allowing an analytical scale up that would need to be matched by other parts of the testing process for full deployment. The implementation of a more automated workflow (i.e. liquid handling robots) would need to be evaluated in this evolved model of mass testing.

The main observations made with Oxford Nanopore RNA LamPORE are:

- For swab samples, LamPORE had a comparable technical performance {Sensitivity = 98.31% (CI 95% 90.91-99.9%), Specificity 99.97% (CI 95% 99.7-100%)} to RT -qPCR
- For saliva samples, LamPORE had a comparable technical performance {Sensitivity = 99.39% (CI 95% 96.6-99.9%) and Specificity 99.77% (CI 95% 99.7-99.8%)} to RT -qPCR
- The results were consistent across the full dynamic range of positive samples (CT threshold <38 as per RT-qPCR IFU)

Work continues on the application of LamPORE for Direct assays across the pilot sites, but a summary of the early results is shown in **Annex D**.

Results: Whole hospital testing of NHS staff using LAMP technologies for interval testing (i.e. 1-7 days) is feasible and RNA and Direct RT-LAMP technologies on saliva samples may now be considered as effective tools for defined use case scenarios, as a public health intervention. Participant feedback emphasised that saliva testing was significantly more tolerable than swab testing for staff, potentially improving the compliance of any long-term testing strategy. Whilst Direct LAMP on saliva is not as sensitive as RT-qPCR on swabs, interim results from this pilot has demonstrated that the technology has a comparable performance at higher viral loads. Within a whole hospital testing strategy of repeat sampling, the Direct LAMP performance would contribute substantially to the identification and isolation of infectious members of staff. This system takes into account the frequency of testing, the population tested and the speed at which results are returned; and underscores the concept4 that the sensitivity of the testing system is not constrained by the sensitivity of the individual test but is context, or use case, specific.

The results from the pilot will inform a broader approach to testing of asymptomatic staff across the NHS.

[4] N Engl J Med 2020 Sep 30. doi: 10.1056/NEJMp2025631

Annex A

Mission 2 – Overview of the Asymptomatic NHS Staff Saliva Testing Pilot

Overview

A 21 day pilot to evaluate saliva testing of asymptomatic staff in NHS hospitals in order to facilitate Trust level surveillance. Undertaken as part of DHSC Mass Testing programme (Moonshot).

- 1200 front line NHS staff tested daily
- c. 25,000 saliva samples taken over 21 days; and
- c. 6,000 swab samples from days 1, 7, 14 and 21
- 5 Trusts
- 4 laboratories (3 x NHS and 1 university)
- 3 molecular tests (RT-qPCR, RT LAMP and LamPORE)
- Expect c. 100,000 tests to be completed on these samples
- Blood spots taken at commencement for IgG, A, M
- 2 sample preparation formats (RNA & Direct on both LAMP/LamPORE)
- Utilised COVID-19 Symptom Study App (ZOE) for sample notification and symptom tracking

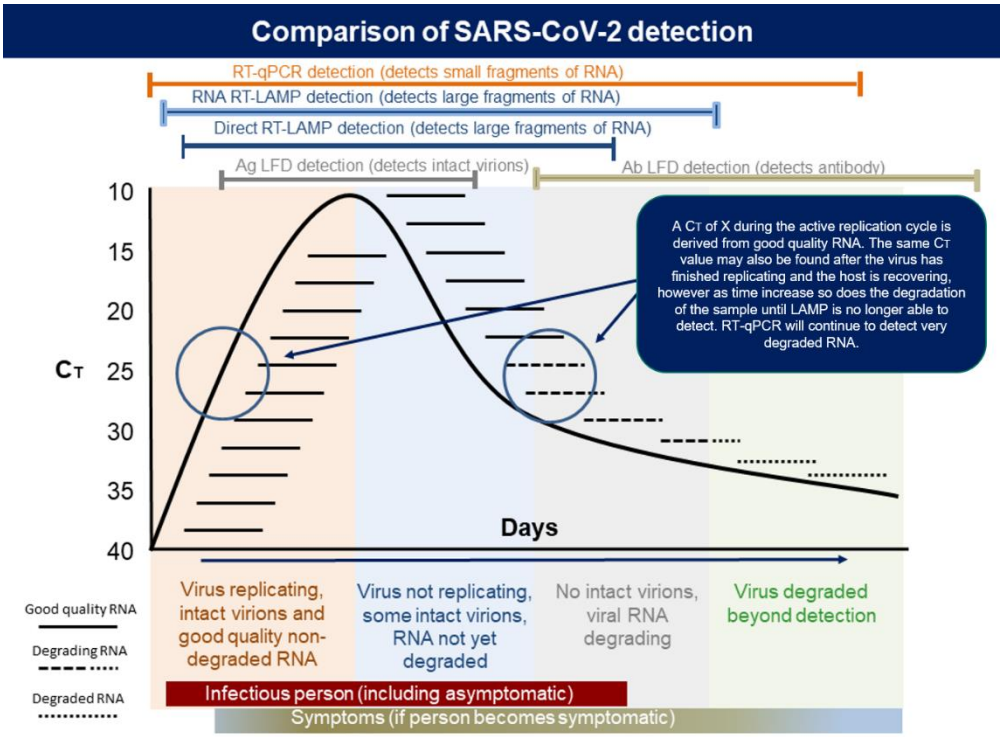
Objectives

- Build a body of evidence around regular asymptomatic testing using saliva
- Conduct real-world validation of Optigene LAMP and Oxford Nanopore LamPORE
- Develop a blueprint for whole-hospital testing
- Collate findings from comparable independent pilots

Critical Path Milestones

Annex B

Hypothetical schematic of CoV2 detection technology tools and potential RNA forms targeted by molecular methods during the viral infection cycle.



Annex C

Interim LAMP Results[5]

The OptiGene RT-LAMP assay has been validated across nine independent sites using 538 positive and 44,913 negative samples; of which 64 positive and 15,968 negative samples came from the NHS pilot:

- 185 positive and 24503 negative swabs analysed by RNA RT-LAMP (*46 positive and 2071 negatives during the asymptomatic project)*;
- 34 positive and 12359 negative saliva samples analysed by RNA RT-LAMP *(12 positive and 12337 negatives during the asymptomatic project);*
- 189 positive and 356 negative swabs analysed by Direct RT-LAMP *(0 positive and 310 negatives during the asymptomatic project);*
- 130 positive and 7695 negative saliva samples analysed by Direct RT-LAMP *(6 positive and 1250 negatives during the asymptomatic project).*

The sensitivity (Se) and specificity (Sp) of each test format at various RT-qPCR C_T thresholds is as follows:

- <45 RNA RT-LAMP on Swabs: Se 97.83% (CI 0.94-0.99); Sp 99.99% (CI 0.99-1.00)
- <45 RNA RT-LAMP on Saliva: Se 88.23% (CI 0.72-0.96); Sp 100% (CI 0.99-1.00)

- <45 Direct RT-LAMP on Saliva: Se 82.30% (CI 0.74-0.88) Sp 100% (CI 0.99-1.00)
- <33 Direct RT-LAMP on Saliva: Se 84.50% (CI 0.73-0.92) Sp 100% (CI 0.99-1.00)
- <25 Direct RT-LAMP on Saliva: Se 96.15% (CI 0.86-0.99) Sp 100% (CI 0.99-1.00)

- <45 Direct RT-LAMP on Swabs: Se 73.54% (CI 0.66-0.79); Sp 100% (CI 0.98-1.00)
- <33 Direct RT-LAMP on Swabs: Se 84.09% (CI 0.76-0.89); Sp 100% (CI 0.98-1.00)
- <25 Direct RT-LAMP on Swabs: Se 100% (CI 0.96-1.00); Sp 100% (CI 0.98-1.00)

The LOD for the RNA and Direct RT-LAMP assay was evaluated using titrated inactivated virus and titrated synthetic DNA. Primer design Ltd COVID-19 positive control (Primerdesign Ltd COVID-19 genesig® Real-Time PCR assay) was prepared at 1.7 x 10^5 copies per µl starting dilution, followed by a 10-fold decimal dilution series in nuclease free water. This dilution series for both RNA and Direct RT-LAMP assay detected down to 1000 copies/ml in duplicate and 100 copies/ml in single replicates. Additionally, using a synthetic DNA template titrated in nuclease free-water, the RNA-RT-LAMP and Direct-RT-LAMP assays were able to detect $1x10^1$ copies each, in one of two duplicates (detection limit between $1x10^1$ and $1x10^2$ copies).

Analytical Specificity was determined using the NATtrol™ Respiratory Verification Panel 2 (ZeptoMetrix Corporation, New York, United States) containing pathogens causing indistinguishable clinical signs to COVID-19 (n=22). No cross reactivity was observed in either assay (Direct RT-LAMP or RNA RT-LAMP).

[5] These data are interim results and testing is not yet complete, full analysis will follow in a final report.

Annex D

Interim LamPORE Results[6]

The Oxford Nanopore RNA LamPORE assay has been validated across 3 different sites using 709 positive and 15422 negative samples, of which 58 positive and 15422 negative samples came from the NHS pilot.

The technical sensitivity and specificity of the RNA format was as follows (C_T threshold <38 as per RT-qPCR IFU):

- Swabs = Sensitivity = 98.31% (CI 95% 90.91-99.9%), Specificity 99.97% (CI 95% 99.7-100%)
- Saliva = Sensitivity = 99.39% (CI 95% 96.6-99.9%) and Specificity 99.77% (CI 95% 99.7-99.8%)

The Limit of Detection (LOD) for the RNA LamPORE assay was evaluated using PHE England reference strain SARS-CoV-2 virus grown on Vero E6 cells and quantified using ddqPCR (digital droplet qPCR) of the E gene of SARS-CoV-2 from an input of 20,000 copies/ml. The dilution series for RNA was able to detect down to 2 copies/ml in duplicate.

Additional specificity assessments had previously been undertaken by PHE Porton Down using a reference panel of pathogens. No cross reactivity was observed in RNA LamPORE.

[6] These data are interim results and testing is not yet complete, full analysis will follow in a final report.

Health and Social Care Committee

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From Rt Hon. Jeremy Hunt MP

5 November 2020

Prof Chris Whitty
Chief Medical Officer and DHSC Chief Scientific Officer

Prof Stephen Powis
National Medical Director, NHS England and NHS Improvement

Letter by email

Dear Professor Whitty and Professor Powis,

Thank you for your letter of 3rd November regarding the asymptomatic COVID-19 testing of NHS staff. I am pleased that the trials of LAMP testing have gone sufficiently well for you to roll these out to clinical staff. It is also good to see that you agree that regular testing of asymptomatic staff can be a valuable tool in tackling this virus. I am though profoundly disappointed that you are only planning to roll this testing out to staff at some point in December given the urgency of the situation we now face.

Nosocomial infection was a leading driver of overall infection rates during the first wave of the virus. The Dynamic CO-CIN report to SAGE and NERVTAG considered by SAGE at its meeting on 15th October showed nosocomial infections peaked during the summer. Figures in this report show that 15% of all patients displayed symptoms a full week after admission to hospital in June. An earlier paper presented to SAGE on 14th April about social distancing highlighted that "nosocomial infection may account for between 10% to 22% of current hospitalised COVID-19 patients, and between 5% and 11% of recent deaths in hospital of COVID-19". The evidence is therefore clear that hospital acquired COVID-19 was a significant factor in thousands of cases and deaths in the first wave. It is for that reason that the Health and Social Care Select Committee recommended regular testing of all NHS staff a full five weeks ago.

I am gravely concerned that we may be about to make the same mistake regarding nosocomial infections and let the virus spread through our healthcare system. Recent NHS figures appear to say that 18% of hospital patients with COVID-19 have become infected after their admission. This has doubled in recent weeks. And the most recent CO-CIN analysis that has been published shows the proportion of patients displaying symptoms a week after admission increased by 50% in early October.

Testing capacity has now expanded significantly and NHS Test and Trace published data shows that since the week commencing 10th September there has been spare swab testing capacity each week. In some weeks this capacity has been over 1 million and the lowest it has been was 740,000. These tests should have been put to use testing NHS staff regularly to give them confidence they aren't spreading the virus and patients confidence that they can use the NHS safely. It is no longer reasonable to say that testing capacity is a constraint in resolving this issue.

In addition any delay goes against both SAGE's own advice and what Professor Whitty has said publicly. SAGE documents from 21st September state that "regular testing of staff should be seen as a priority if infections continue to grow." In July Professor Whitty told the Health and Social Care Select Committee that "If there was a big surge I would be absolutely in favour of going for regular testing, even in advance of knowing the optimal frequency." We are now facing that surge

and yet it appears we will delaying roll out of this vital measure until after the second wave is finished.

I therefore urge the NHS to bring forward these plans and start weekly testing of all staff - or as a minimum all staff who have contact with patients - utilising PCR testing capacity until the LAMP test are ready for full deployment if necessary. Instructions should be issued to all NHS trusts by NHS England to implement routine testing of all staff with immediate effect before any more lives are lost. Whilst people may accept there were reasons we did not know about asymptomatic transmission during the first wave, they would not accept it during a second one and indeed consider it unforgiveable if lives were to be lost during the second wave for an entirely predictable reason.

Yours sincerely,

Rt Hon Jeremy Hunt MP
Chair, Health and Social Care Committee