Department of Health & Social Care

COVID-19 Self-Test Kit- Rapid Antigen Test Device Exceptional Use Authorisation Request Technical Summary

Version: 2

Date: 14th December 2020

15th of December 2020

Medicines & Healthcare Products Regulatory Agency
10 South Colonnade
Canary Wharf
London
E14 4PU

Subject: Exemptions from Devices regulations during the coronavirus (COVID-19) outbreak

The Department of Health and Social Care (DHSC) has issued a policy paper about the scaling up of coronavirus (COVID-19) testing programmes. Testing is a key pillar of our strategy to protect the NHS and save lives. DHSC is focusing on 2 types of tests:

- 'swab tests' for people with symptoms to see if they have coronavirus, and
- 'antibody tests', which test for the presence of antibodies that will demonstrate whether you have had the disease

This submission is for an antigen based self-test swab kit which we believe is critical for the National Testing Programme in order to scale up our testing capability and bring testing to communities and groups without current easy access to testing to identify individuals that are infectious with COVID-19. Reference is made to the DHSC COVID-19 Self-Test (rapid antigen test), in both its 3 test and 7 test kit variants.

DHSC herein requests an exemption under the UK Medical Devices Regulations of 2002 for the DHSC COVID-19 Self-Test (rapid antigen test).

Should you have any questions during the review period, please let us know via email and we will respond as a matter of urgency.

Kind regards,

Department of Health and Social Care

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1.03 List of Terms/Acronyms

Acronym	Meaning
CMMID	Centre for the Mathematical Modelling of Infectious Diseases
DEUA	Device Exceptional Use Authorization
DHSC	Department of Health and Social Care
IFU	Instructions for Use
IVD	In Vitro Diagnostic Medical Device
LFD	Lateral Flow Device
RT-PCR	Real Time Polymerase chain reaction
PHE	Public Health England
SPI - M	Scientific Pandemic Influenza Group on Modelling

1.04 Administrative Information

The Department of Health and Social Care (DHSC) herein requests an exemption under the UK Medical Devices Regulations of 2002 for the DHSC COVID-19 Self-Test Kit (3 and 7 test variants).

A self-test kit is critical for the National Testing Programme in order to better control the person-to-person spread of COVID-19. As it is intended to be used by lay persons in a home, office or school environment and has a swift turnaround of 15-20 minutes it can effectively intervene in the dissemination of the virus.

This document follows the internationally harmonized, modular format for use created by the International Medical Device Regulators Forum (IMDRF) for the filing of medical device submissions to regulatory authorities for market authorization. As such section numbering follows that standard and section are present where information is provided.

1.04.01 Administrative Data of the Manufacturer

Under the In Vitro Diagnostic Medical Devices Directive (98/79/EC), the Department of Health and Social Care (DHSC) will be the legal manufacturer and responsible for the design, manufacture, packaging, and labelling of the finished device.

- Department of Health and Social Care (DHSC)
  39 Victoria Street, Westminster
  London, SW1 0EU

The DHSC COVID-19 Self-Test Kit (3 and 7 test variants) will be manufactured by:

- Xiamen Biotime Biotechnology Co., Ltd.
  3F/4F, No. 188, Pingcheng South Road
  Haicang, Street, Haicang District
  Xiamen, Fujian, 361026, P.R. China

2.02 General Summary of Submission

The UK remains in the grip of the coronavirus pandemic and according to Office of the National Statistics (ONS) with an estimated population prevalence of 1.12%.

Current testing modalities are inadequate for decentralised testing of the population. The primary method of COVID-19 testing is through centralised laboratories using RT-PCR. The scale of testing is limited and only a small minority of the UK population can be offered a test (approximately 500k per day) and predominantly prioritised for those with symptoms in the community. Currently about 40% of the estimated new cases occurring each day in the UK are identified through PCR testing. Notably 60% of infected people are not tested. There is also no routine approach for testing asymptomatic people who may represent most of the infected population who are unwittingly contributing to large-scale cryptic transmission in the community. Furthermore, the semi-quantitative PCR test has a slow turnaround between 2 to 3 days and is too slow to effectively intervene to control person-to-person spread of COVID.

A rapid self-administered COVID-19 test can change this scenario and it is critical for the National Testing Programme.

The Innova antigen lateral flow device (LFD) test is the optimal candidate as it offers a paradigm shift to testing. LFDs offer the way to decentralised community testing and approaches for better controlling spread of COVID-19. In order to effectively deploy these LFDs in the community (including workplaces and at home), sufficient performance for self-use of these LFDs is important.

The objective of the DHSC testing strategy is to detect and quarantine sufficient cases with transmissible virus infection to reduce R and control the pandemic and protect the vulnerable, enable return to work and restore the economy and society to near normal. This requires a test to identify people with transmissible virus for quarantine and, thereby, interrupt viral transmission. At present, between 20% and 70% (median 50%) of those infected are asymptomatic at some point, with 25% never developing symptoms. (Attachment 1). NHS Test & Trace is currently identifying up to 40% of all infected cases in the population. To reduce R by 40%, we estimate that we need to identify 70% of those infected (and persuade 80% of these people to isolate). Crucially at least 60% of infected people are not tested and are unwittingly spreading the virus.

This objective requires a significant increase in the scale of testing to include asymptomatic people. Distributed self-testing is likely the only approach that will achieve this. To deliver this scale, we need to deploy a test that is simple for a person themselves to perform, swift and low cost. There are tests that can be undertaken in centralised laboratories that could achieve this massive capacity. However, the logistics of sourcing, electronically tracking, couriering, receipting, and robotically processing the large flow of swabs makes these options impractical for mass population and, therefore, asymptomatic testing. Lateral flow devices are the only

validated diagnostic tool that can deliver such distributed mass testing capacity. They have the advantages of ease of use, rapid processing, and can be done anywhere. Thus, they offer the potential for mass and repeated, even serial, testing by the general populace themselves. They are the only viable option for finding infectious cases and, thus, controlling the spread of disease across the whole country.

Validation work by PHE [redacted] and the University of Oxford, so far, demonstrates that there are four lateral flow devices meeting our testing criteria for reliability and performance; they are: Innova, Abbott, Deepblue, Orient Gene.

The Innova SARS-CoV-2 Antigen Rapid Qualitative Test is available in sufficient quantities to meet urgent operational requirements, thus the DHSC intends herein to present information and key supporting evidence to ensure approval of the device to gain approval to the request for a Device Exceptional Use Authorisation.

The following are the details on the DHSC's COVID-19 Self-Test Device:

- **Device type:** COVID-19 Self-Test Kit
- **Trade Name:** DHSC's COVID-19 Self-Test - Rapid Antigen Test
- **General Purpose:** the DHSC's COVID-19 Self-Test (Rapid Antigen Test) is a swab test to check for transmissible coronavirus (COVID-19) in symptomatic or asymptomatic people.
- **Intended Use:** The kit is intended for self-test use by lay individuals aged 18+, self-test under adult supervision by adolescents aged 11-17, or administered by adult guardians of children under 12 years of age.

Central to the case for their wide deployment are three principles for which the evidence is laid out in this submission.

1. The first principle is that qPCR positive testing offers the inappropriate gold standard for a test to identify infectious individuals in the population. Identification of viral RNA in the nose and throat including at very low viral copy numbers is sensitive, but not specific for infectiousness, as it is only those with higher viral copy numbers that spread the virus. Namely, many people will be falsely labelled as infections as set out in 3.05 Analytical Performance and, 4.06 Modelling and simulations, using LFD performance and Infectiousness data, for real-world use.
2. The second crucial issue is that mass population testing needs to include the 60% of infectious people currently missed using available PRC testing resources. Thus, most infected people are unaware of their status and have no reason to modify their behaviour. This has ramifications as set out below.
3. Repeated sampling with a throat or nasopharyngeal swab is unacceptable for most people. A simple more acceptable type of swabbing approach has not been addressed

and validated so far. A self-administered external nasal swab has been found to be acceptable and effective for viral detection as also set out below.

4. Laboratory and Field-Testing Performance of the Innova Lateral Flow Device and Definition of Infectiousness as a Target for Mass Testing.

2.04 Device Description

2.04.01 Comprehensive Device Description and Principle of Operation

The following section outlines in detail the changes from Innova's SARS-CoV-2 Antigen Rapid Qualitative Test components to the DHSC COVID-19 Self-Test (Rapid Antigen Test) product.

The current Innova product, the SARS-CoV-2 Antigen Rapid Qualitative Test, is indicated for professional use and is provided in a kit with materials sufficient to conduct 25 tests.

In moving to a product suitable for self-test the following primary alterations were identified as necessary:

- Provision of a suitable number of kits for the lay user based on the programs current understanding of government policy and ensuring that the product could be easily mailed to individuals requiring the test
- Provision of instructions for use that are suitable to enable the lay user to utilize the kit in a safe and performant manner
- Provision of all elements of the test in a 'single use' format that allows the user to utilize a set of items for a test and then safely dispose of them. This requires an alteration to the extraction buffer solution, provided in the form of two 6mg bottles in the professionally marked Innova kit

Based upon these inputs, this submission covers two versions of the proposed DHSC COVID-19 Self-Test Kit (Rapid Antigen Test), a 7-test version and 3-test version. The content of each of these kits, compared to the professionally market 25-test kit is summarized in Table 1.

Table 1: Summary of Differences Between Innova's SARS-CoV-2 Test Kit and DHSC COVID-19 Self-Test Kit (Rapid Antigen Test)

Innova SARS-CoV-2 Antigen Rapid Qualitative Test	DHSC COVID-19 Self-Test (Rapid Antigen Test) Pack of 3	DHSC COVID-19 Self-Test (Rapid Antigen Test) Pack of 7	Change Between Innova and DHSC Products (other than no. of units)
25 x lateral flow test strips sealed in foil pouch	3 x lateral flow test strips sealed in foil pouch	7 x lateral flow test strips sealed in foil pouch	Labelling Change Only

25 x extraction tubes	3 x extraction tubes	7 x extraction tubes	No Change
2 x 6ml bottles of extraction buffer solution	3 x single use extraction buffer sachets, each one 180 microlitres	7 x single use extraction buffer sachets, 180 µl microlitres	Altered Component
25 x throat or nasal swabs	3 x nasal swabs	7 x nasal swabs	No Change
1 x IFU	1 X IFU	1 x IFU	Altered Component
Carton for 25 kits	Carton for 3 test kits Integrating extraction tube holder	Carton for 7 test kits Integrating extraction tube holder	Altered Component

In addition to the alterations to the physical components of the product a review has been conducted of the alterations between the current Innova SARS-CoV-2 Antigen Rapid Qualitative Test and the proposed DHSC COVID-19 Self-Test. The analysis is summarized in Table 2.

Please see attachment 2 for the Innova SARS-CoV-2 Antigen Rapid Qualitative Test IFU and attachment 3 for the proposed DHSC COVID-19 Self-Test (Rapid Antigen Test) IFU.

Table 2: Summary of key IFU alterations

IFU Area	Innova SARS-CoV-2 Antigen Rapid Qualitative Test	DHSC COVID-19 Self-Test	Comment / Justification
Subject	Individuals who are suspected of COVID-19 by their HCP within the first 5 days of the onset of symptoms	The DHSC's COVID-19 Self-Test (Rapid Antigen Test) is a swab test to check for transmissible coronavirus (COVID-19). Positive results mean the device has detected viral antigens predicting the presence of transmissible virus. Negative results mean antigens have not been detected, indicating it is	

		unlikely that an individual has transmissible COVID infection.	
Subject Age Range	Not specified	Adults aged 18+ (self-test and report with assistance if needed) Adolescents aged 11-17 (self-test and report with adult supervision) Children should be tested by an adult	Further detail provided in IFU to support self-test. This aligns with the national testing approach for RT-PCR self-swabbing that has been successfully and safely implemented.
Test Users	Trained clinical laboratory personnel…… and individuals similarly trained in point of care settings.	Adults aged 18+ Adolescents aged 11-17 under supervision	To support mass testing in a variety of scenarios self-test is See usability testing conducted in section 5.4.4
Pre-Test Preparation	Not specified	Before opening the kit, handwashing is directed Gentle nose blowing with clean tissue directed Clearing and cleaning an area for the test directed Final wash and hand sanitization directed	Trained staff are expected to be aware of infection control and contamination issues and have in place processes to address these. Part of the alterations to enable the move to self-test and ensure false positives (due to contamination from other sources) or false negatives (due to poor sampling) are controlled is to provide specific instructions on use
Sampling	Innova IFU covers nose, throat and sputum sampling: Throat sampling instructs wiping the pharyngeal tonsils on both sides at least 3 times OR Nasal swabbing instructs the rolling of the swab 5 times around the inside of the nostril	The proposed DHSC product utilized combined throat AND nose swabbing, similar to that employed in the RT-PCR home testing kit. Throat sampling instructs wiping the pharyngeal tonsils on both sides at least 4 times Nasal swabbing instructs the rolling of the swab 10 times around the inside of the nostril	Updates to both align with RT-PCR sampling approach and to ensure that parties using the test are provided sufficient direction to gather an appropriate sample
Test Use	6 Drops of fluid are dispensed from a bottle (6 ml) into the extraction tube	Individual sachet provided for each test (180 µl) with the complete volume	Updates to sample processing methods and instructions (including improved diagrams) are aimed at ensuring the lay user can understand the

	Extraction tubes have separate tip to be added onto tube to allow for test sample to be dispensed onto the test strip Sampled processing directs rotating and pressing swab head into extraction tube wall for 10 seconds. Squeezing fluid out of swab head on removal	dosed into the extraction tube Extraction tubes have an integrated lid Sampled processing time follows similar procedure but altered to 15 seconds.	preparation process required as well as Also see usability study conducted in section 5.4.3
Disposal	Disposal of used test kits as biohazardous waste in accordance with federal, state and local requirements	The proposed DHSC product directs test components to be placed in one of the provided waste bags. Bag to be sealed and placed in household waste.	See section 5.3 for further discussion of test disposal
Reporting results	No instructions provided	Instructions provided on digital and telephone reporting of results. to align with current digital and telephone reporting routes.	In alignment with current government policy.
Quality Control	Potential use of positive and negative controls noted. These are purchased separately and not part of the test kit	Control use is not planned for the DHSA COVID-19 Self-Test (Rapid Antigen Test)	In addition to quality control activities conducted at Innova the DHSC plans to conduct sample testing of the product on arrival in the UK. Testing will confirm test strip functionality, based on the appearance of the control line. Samples will also be tested with positive and negative control solutions.

The proposed DHSC COVID-19 Self-Test (Rapid Antigen Test) IFU also includes references to an on-line demonstration video utilizing the product and IFU. This is currently under development for early December availability. The DHSC will provide this to the agency as soon as it becomes available.

2.04.03 Description of Device Packaging

The following section outlines in detail the components of the DHSC COVID-19 Self-Test (Rapid Antigen Test) product.

2.04.03.01 Secondary Packaging

The secondary packaging has been modified from the original

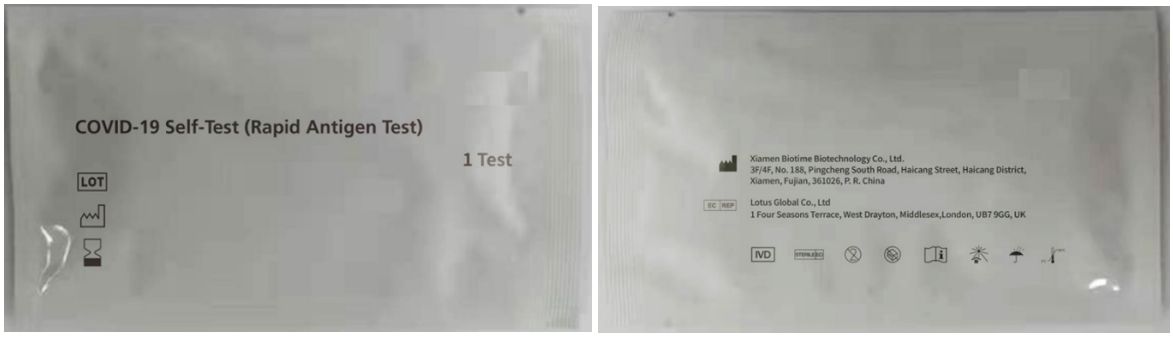
- Carton packaging sized reduced to accommodate the required 3 or 7 sets of tests (vs. 25 in the Innova test kit).
- Carton altered to more rigid cardboard to increase protection for the device.
- An extraction tube holder is now integrated based on feedback from the usability study conducted (see section 5.4.4)
- Labelling updated to reflect NHS branding and new legal manufacturer

Secondary packaging images can be found in attachment 4 (3-pack) and attachment 5 (7-pack).

2.04.03.02 IVD Test Strip Primary Packaging

No alteration to physical aspects of primary packaging, a metalized paunch with tear points, including a desiccant bag, has been made.

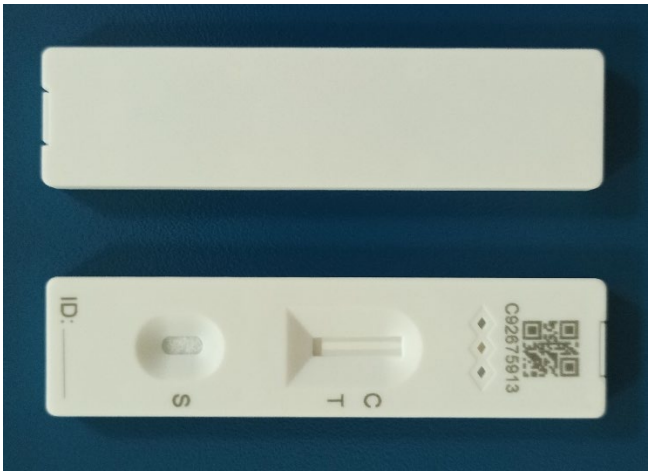
Figure 1: Image of primary packaging



2.04.03.03 Test Strip

Innova currently utilize four different outer body slivers in their professional use product. The proposed DHSC COVID-19 Self-Test (Rapid Antigen Test) will utilize only a single sliver shape (80mm x 20mm x 5mm) from this set as per Figure 2.

Figure 2: Imaged of test strip body (note data format in barcode is still to be updated)



The barcode on the test strip will be updated to encode the information required by the Mass Testing Program Digital solution. This takes the form of a device identifier in the format AAAnnnnnnn, where 'A' represents a letter and 'n' a number. The encoded data will also be printed in a human readable format below the barcode.

2.04.03.04 Extraction Buffer Solution

The buffer solution provided in the DHSC COIVD-19 Self-Test Kit will be in the format of individual sachets, with one provided for each test. The entire 180 µL contents of the sachet are used in the self-test removing the need for precision dosing activity.

Figure 3: Individual extraction buffer sachet and package from 3 test product

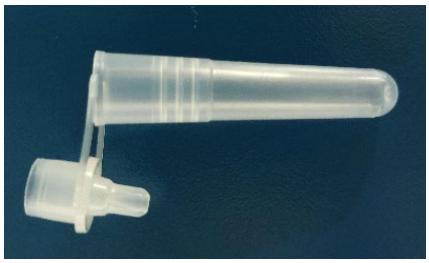
The use of this sachet was investigated in our usability trial for the self-test kit, 4.02.02 Usability Testing.

The buffer solution itself is manufactured by Innova/Biotime and remains unchanged from that supplied in the current Innova SARS-CoV-2 Antigen Rapid Qualitative Test. Technical drawings for the buffer sachet are provided (attachment 06) and validation information is provided in 3.06.05 Stability of the IVD.

2.04.03.05 Extraction Tube

Innova currently utilize four different extraction tubes for their professional use product. The proposed DHSC COIVD-19 Self-Test Kit will utilize a single extraction tube design from this set. See Figure 4.

Figure 4: Extraction tube



2.04.03.06 Sampling Swabs

Innova currently utilize four nasal swabs for their professional use product. The proposed DHSC COIVD-19 Self-Test Kit will utilize two of these swabs.

Data relating to these two swaps can be found in attachment 07 (a, b, c, d) and attachment 08 (a, b, c, d) Individual manufacturing lots will consist of swabs from a single supplier.

2.04.03.07 Waste Bags

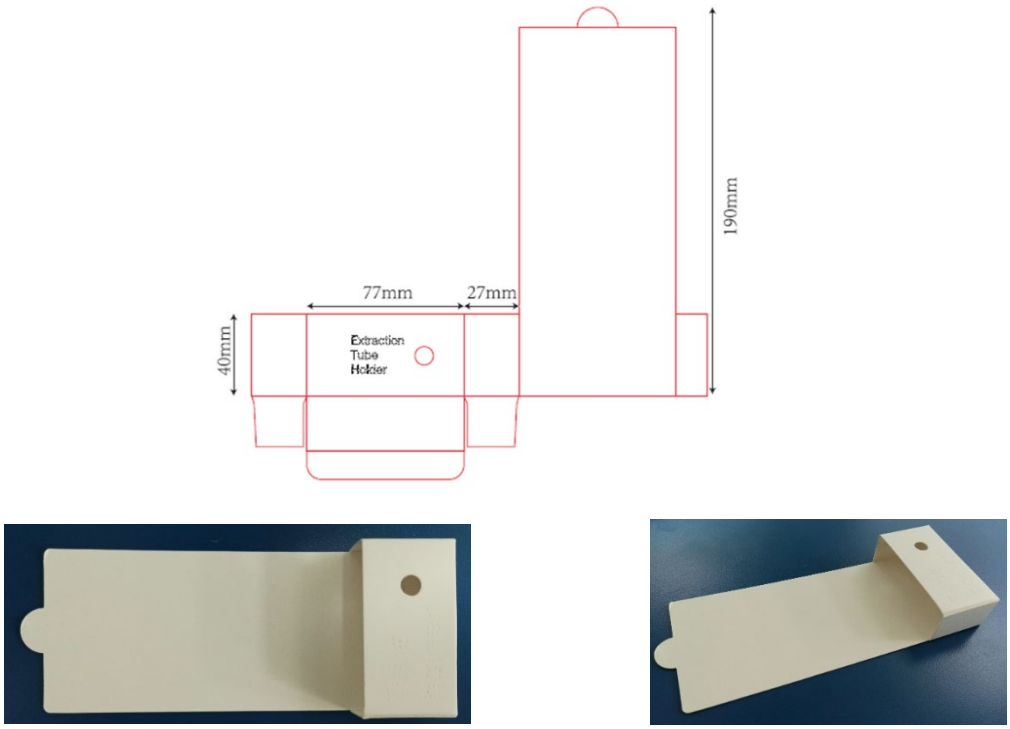
A new component in the proposed DHSC COVID-19 Self-Test. A transparent sealable waste bag is included for each test strip (3 or 7), to allow the user to place all waste from the test in a sealed bag for disposal in the household waste.

See 3.02.03 Disposal of the Test for further details on the approach to disposal.

2.04.03.08 Extraction Tube Holder

A new component in the proposed DHSC COVID-19 Self-Test. A cardboard component integrated into the secondary packaging carton to provide the user a stable location to place the filled extraction tube whilst they are taking their swab sample. See the IFU (attachment 03) for details of its use within the testing process. The design for the extraction tube holder is provided in Figure 5.

Figure 5: Design of the extraction tube holder (3 pack illustrated)



2.04.03.09 Instructions for Use

A new IFU had been created based upon both the original Innova IFU and the validation and usability work conducted by the Test and trace program.

The IFU is in A5 booklet format, please see attachment 03 for details of the IFU.

2.05 Indications for Use and/or Intended Use

The DHSC's COVID-19 Self-Test (Rapid Antigen Test) is a swab test to check for transmissible coronavirus (COVID-19). Positive results mean the device has detected viral antigens

predicting the presence of transmissible virus. Negative results mean antigens have not been detected, indicating it is unlikely that an individual has transmissible COVID infection.

The kit is intended for use by lay individuals such as:

- Self-test by adults aged 18+
- Self-test under adult supervision by adolescents aged 11-17
- Children under 12 years of age should be tested by an adult.

2.05.01 Usage Scenarios and Product Options

As covered in the statement of intended use the DHSC Self-Test (rapid antigen test) will be used in scenarios where there is a need to detect individuals who are presenting a risk of transmitting the COVID-19 virus.

The kits are intended for intermittent and the regular testing of individuals to support the following objectives:

- Identification of positive infectious cases in asymptomatic individuals e.g., as part of mass testing in high prevalence areas.
- Further enabling the regular, repeated testing of groups and key workers e.g., health care workers
- Workplace settings e.g., educational institutions, factories, businesses.
- Pre-event testing in low prevalence populations
- Serial testing of asymptomatic index/close contact cases as an alternative to quarantine

If a person tests positive they will report to Test and Trace and follow national guidance with respect to self-isolation procedures. Individuals with a void test will repeat the test. Failure to perform a test successfully will be reported to Test and Trace – this should be a low frequency problem.

Due to the different usage scenarios flexibility in the provision of the test kits is paramount. Therefore, kits of two different sizes, one consisting of the components for 3 tests and another for 7 tests. The secondary packaging has also been made more robust and resized to enable postage through a standard UK letterbox if that is required as use cases and usage evidence develops. This flexibility is intended to support a range of scenarios depending upon the strategic direction in which the government decides to pursue mass testing. Thus, the size of kits may be adjusted to new requirements.

A kit of 3 tests is envisaged as useful in scenarios where an individual is looking to understand their potential infectiousness before an event, or as a one-off need. Whereas 3 and 7 kit may be combined to provide 10 tests to people who are contacts and wish to test daily to avoid being placed in quarantine – "test and enable".

At the point of submission, the initial specific use cases being targeted are:

- Distribution to NHS staff to conduct self-tests
- Organisation based testing, enabling businesses to distribute kits to their employees and/or customers to reduce the risk of workplace return and institutional based testing (e.g. prisons, universities and schools) to reduce risk within specific settings.
- Testing at asymptomatic testing sites (ATSs), potential coupled with local initiatives to actively deliver door to door and/or outbreak responses

Approaches to distribution will require flexibility. For example, NHS England is already distributing LFD tests to staff for asymptomatic testing and piloting of self-swab-based testing is well advanced with both universities and employers.

Attachment 12 outlines the process currently being created for use of self-testing in education.

2.05.01.1 Limitations to the clinical applicability of LFD's

There are a number of device related limitations to consider in terms of the use of the device in the scenarios outlined above.

Sensitivity

We are aware that questions have been raised about the appropriateness of using lateral flow devices for mass testing, in particular, around the sensitivity of the test and the risks associated with false-negative results (attachment 09). This concern has been carefully considered. Critically, this view assumes that the current categorical RT-PCR test is a gold standard for infectiousness. As argued above, there is good evidence this is not the case. Using categorical RT-PCR as a gold standard for assessing infectiousness is inappropriate. We recognise a negative PCR test is a good rule out for infectiousness on the day of the test, which is often 2 to 3 days before getting the result. By which time, an individual could have become infectious. In addition, The PCR test's specificity for infectiousness is lower with positive predictive values for infectiousness of less than 50%. In contrast to PCR, results of LFD are a good rule-in test and is available within 30 minutes.

The preliminary report from Joint PHE [redacted] & University of Oxford (see section 5.4) indicated that the sensitivity of the test for infectiousness ranges from

67% to over 90% depending on the experience of the user, thus, at least two thirds of the possible transmission events can be avoided.

Specificity

There is a clear public health need to quarantine individuals who are likely to be infectious. The current public health strategy is to use indirect clinical methods to identify possible infectious people. These include isolating individuals self-identifying with symptoms 'typical' of COVID-19 sometimes supported by PCR tests or by isolating asymptomatic contacts of known individuals without the support of PCR testing. Each of these methods have a high false positive rate leading to much unnecessary isolation of people. We estimate that symptomatic individuals have about a 20% chance of being PCR+ during the March outbreak (reference Eyre et al (attachment 10)), while close contacts of known positive individuals may, at most, have a 40% chance of being PCR+. Given the known slow time course of clearance of PCR positive RNA and the current work on infectiousness, we estimate that individuals who are PCR+ have less than a 50% chance of being infectious. Moreover, the slow turnround time for the result will make this even lower. This means that the specificity value of symptom-based labelling for quarantine is at best 10% (dependent of background prevalence of COVID) and for contacts is 20%. RT-PCR has a high specificity for detecting COVID RNA. This means that the positive predicted value of a positive PCR test for infectiousness is about 50%, regardless of the disease prevalence.

In contrast the specificity of lateral flow tests for infectiousness is 99.7%. Assuming that only 80% of individuals with a positive lateral flow test are infectious, we have estimated its positive prediction for different levels of prevalence (see Table 3) and, as expected, its positive prediction values vary with disease prevalence as shown in the table below.

Table 3: Lateral flow tests vs. PCR performance in minimizing unnecessary quarantine

Disease prevalence	PCR		Lateral Flow Test	
	Specificity	Pos Pred Value	Specificity	Pos Pred Value
0.3%	99.85%	50%	99.7%	40%
1%	99.5%	50%	99.7%	61.54%
2%	99%	50%	99.7%	69.57%
5%	97.5%	50%	99.7%	75%
10%	95%	50%	99.7%	78%
20%	90%	50%	99.7%	79%

As the table shows, Lateral Flow Tests performs better than PCR in minimizing unnecessary instruction to quarantine, except in low prevalence setting. In this situation, confirmatory PCR testing is desirable.

Behaviour-change in false negatives

This issue has been much discussed, as there is a concern that in the presence of a false negative test, individuals will undertake riskier behaviour and could, therefore, cause more onward infections. This concern is mitigated by several factors. Firstly, much of this worry stems from the belief that a false negative should be judged by PCR positivity. This is clearly not true, as these LFD tests are effective at identifying individual risks of infectiousness and the sensitivity figures that create anxiety are all based on comparison to categorical PCR positivity. A negative lateral flow test is likely to be a good indicator that individuals are unlikely to spread disease in the next 24 hours. Secondly, it is important that subjects are instructed at the time of testing that these tests are, like most tests, not 100% accurate and hence they should not reduce their attention to social distancing. Finally, in the presence of self-testing would move to repeat testing. As described above and in the modelling section, repeat testing is a very robust and effective method for strengthening the performance of these tests. This would, in a self-testing setting, be almost universally used at two- or three-day intervals for most use cases. This should mitigate the risk associated with poor behaviour in the presence of a negative test.

Cost

An important public health consideration is the overall balance of costs and benefits of the testing regime across the population. Although large scale mass testing using LFDs is likely to generate considerable device costs as many hundreds of millions will be used, it is nevertheless the most cost-effective testing methodology as it requires no lab infrastructure costs, no logistics for sample flow and a small workforce to train and distribute tests. In addition, the test at scale is inexpensive, between £3-5 per test. Therefore, the lower costs associated with self-testing using the lateral flow device compared to RT-PCR are important to note, insofar as they reduce the opportunity cost of the testing programme as a whole. In addition, the reduction in costs to the programme through reducing the levels of swabbing assistance required, and the reduction in costs borne by members of the public associated with the need to attend a testing site are important factors to consider.

2.06 Global Market History

The DHSC's COVID-19 Self-Test (Rapid Antigen Test) has not been approved in any other region. However, the Innova SARS-CoV-2 Antigen Rapid Qualitative Test is currently approved for use in Mexico, UAE, Saudi Arabia, Philippines and CE marked in the European Union. There

are pending applications in United States, Israel, Jordan, Australia, Singapore, Thailand, Canada.

Non-UK sales of the Innova test kit have exceeded 13 million units.

2.07 Post Market Surveillance Plan

The DHSC is currently developing a Quality Management System (QMS) to support the manufacture of the RT-PCR home testing kit which will include all SOPs and Policies related to Post Market Surveillance. It is important to note that for all quality related issues the DHSC is utilizing the Biotime's QMS. Our proposed PMS approach, summarized in Figure 6, will link into the Biotime QMS for this purpose

The following sections outline our PMS approach and note initial risk assessment and validation activities where appropriate.

1 Risk Assessment:

A baseline risk assessment for the Innova SARS-CoV-2 Antigen Rapid Qualitative Test is included as attachment 11 and the baseline DHSC risk assessment for the COVID-19 Self-Test kit (rapid antigen test) is included as attachment 13 . The primary areas of risk, as seen by the DHSC, are also summarized in 5.3.

As part of PMS we will maintain an ongoing risk assessment of the proposed DHSC COVID-19 Self-Test (Rapid Antigen Test) product.

2. Device and Manufacturing Process Development:

In response to initial development needs and post market issues identified additional product development or manufacturing improvement may be required.

The DHSC propose to notify the MHRA, in advance, of any product alterations planned as part of periodic reporting and to have these alterations agreed (or confirmed as not objected to) by the agency.

3. Validation (including usability):

Alteration to product design or manufacturing process to be validated as required. In the context of a self-test significant focus will be on the usability and performance of the test in the hands of lay users.

The DHSC has already conducted a range of assessments and usability studies related to self-test (see section 5.4.3 and 5.4.4) and will be conducting further clinical studies related to the use of self-test kits during December.

4. Proactive Post Market Surveillance:

Proactive PMS activities will be conducted including:

- Surveys of user experience from each of the deployment channels operationalized (as discussed in section 3.1)
- Post DEUA clinical surveillance options for consideration:
    - Studies conducting RT-PCR on samples can be considered for selected new deployments, outbreak locations or high prevalence areas to provide data on the performance of the LFD vs historical performance and assess any performance drift over time
    - Survey by a sentinel group of self-testers to undertake RT-PCR of all their samples to assess kit failure, specificity, sensitivity and usability over time. New kit batches could also be evaluated by this group.
- Monitoring and analysis of test results captured on the governmental digital portal and 119 service:
    - Number of tests reported
    - Positive, negative and void results

5. Reactive Post Market Surveillance:

Proactive PMS activities will be conducted including:

- Routine quality testing of manufacturing batches on arrival in the UK
- Monitoring of news and social media
- Collation of user feedback and complaints from the incident management processes running in each area of the program as well as the 119-service referenced on the IFU and the digital platform, once available. Where possible incidents will be categorized, including topics outlined below:
    - Material break (if something breaks during use)
    - Detachment of device component (for example, if the swab head of the swab falls off)
    - Component missing (if something in the kit is missing)
    - Packaging problem
    - Unable to obtain readings (e.g. failure of control line or if the user is unsure of the result)

- Failure to obtain sample
- Inadequate instructions
- Device handling problem
- Negative clinical effect associated to the test, e.g. cuts, nose bleeds etc.

6. PMS Data Collation and Clinical Risk Evaluation:

Data from PMS activities will be collated and initially assessed for clinical risk and recommendation. Regular data will include anonymized reporting of number of tests, results and issues reported (as referenced in stages 4 and 5)

7. PMS Risk Evaluation and Action Review:

Clinically assessed data and recommendations will be reviewed for necessary action.

8. Periodic MHRA Reporting:

The DHSC proposes to provide the agency pooled PMS data every 2 weeks.

The DHSC will also follow regulatory timelines for reporting of any adverse event or malfunction / deterioration in the characteristics or performance of the device which might lead to the death of a user or serious deterioration in his/her state of health. Reporting of such incidents will be via the MORE reporting system.

9a and 9b. DHSC Quality Event Management:

Based on the PMS Risk Evaluation and Actions Review DHSC Quality Events will be raised and tracked as necessary.

10. and 11. DHSC and Contract Manufacturer Product Investigation(s):

Depending on the PMS data gathered, and Quality Event raised investigations may be needed by both the DHSC and Biotime (within their QMS). Corrective Actions' and Preventative Actions (CAPA's) will be raised and resolved as required.

12. Material Vigilance (Biotime):

In accordance with Biotime's QMS they will continue to monitor and report any quality issues to their supply chain.

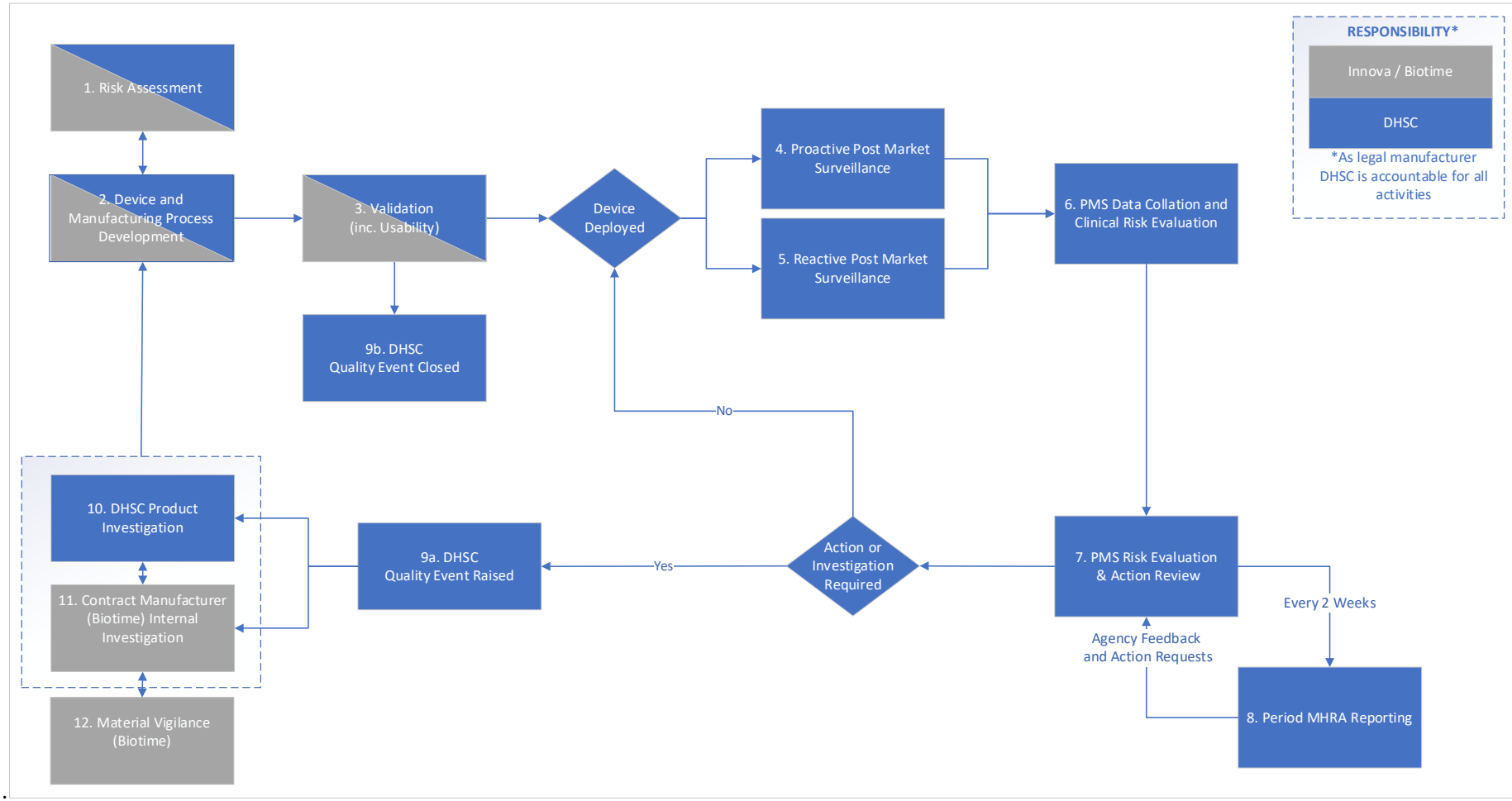


Figure 6: Post Market Surveillance Overview

2.08 Approach to Gaining CE Marking

Further to the DEUA it is the intent of DHSC to work with Innova and provide all of the sharable information the DHSC owns in support of their being able to progress with UK regulatory approval of a product based on the DHSC submission. This will be on the basis of revised branding and without providing Innova undue competitive advantage (for example by sharing materials such as the IFU with other parties).

DHSC will also explore the possibility of issuing contractual obligations with Innova, linking any additional procured volume to the guarantee that Innova will pursue a self-test submission.

2.08.01 Product Volumes and Withdrawal Plan

It is currently projected that 60 million DHSC COVID-19 Self-Test (Rapid Antigen Test) kits will be manufactured during 2020 (with a 50:50 split between 3 and 7 sized packs).

Looking forward into 2021 the intention is to continue to manufacture further volumes in excess of 10 million per month, on the basis that there are no other viable alternatives for the provision of mass self-testing. As noted previously the supply route for these is primarily intended to be via institutions and existing healthcare locations (see section 3.1).

We ask that the agency considers a DEUA approval sufficient to allow for the UK regulatory approval of this product to be achieved. We will also be monitoring the epidemiological situation as it develops, with the passage of winter passes and deployment of vaccines, which may also reduce the need for mass self-testing.

3.02 Risk Management

In considering the incremental risk assessment for the proposed product three areas were identified for consideration:

- The swabbing activity being conducted by the lay user
- The use of the device by the lay user
- Consideration of disposal of the device in a domestic setting

The following sections consider each of these in turn. The original risk assessment conducted by Innova for the SARS-CoV-2 Antigen Rapid Qualitative Test is also provided (attachment 11). The DHSC has conducted its own risk assessment for the DHSC COVID-19 Self-Test (Rapid Antigen Test), see attachment 13.

3.02.01 Collection of Swab Sample

The collection of the swab sample has been assessed as the most hazardous aspect of utilization of the test kit, as well as having implications for the potential sensitivity of the test due to variation in swabbing technique.

In considering the safety implications of swabbing the most relevant dataset available relates to the swabbing activities conducted as part of the home RT-PCR self-test kit. This kit uses the same nose and throat swabbing technique as proposed in the DHSC COVID-19 Self-Test (Rapid Antigen Test) product.

Over 6 million RT-PCR self-test kits have been issued to households with over 10 million further tests conducted at test sites using a similar technique (by either trained parties or under observation). Based on data captured through the 119 service 17 incidents of swallowing or choking on a swab or swab part being recorded via 119 (no deaths). This represents an incident rate of less than 1 in 1,000,000. The program has submitted 3 MORE reports regarding swab related events as of 23rd November 2020.

3.02.02 Sample Preparation and Use of the Test Strip

Once the user has conducted the swabbing operation, they must prepare their sample, by using the buffer solution and extraction tube to remove their gathered sample from the swab head, and then place two drops of the prepared fluid onto the test strip. Final results develop in 30 minutes and the user must read and interpret the result as directed by the IFU (attachment 03).

The bulk of test data gathered to date relates to device use by trained laboratory personal, healthcare professionals and trained individuals. The analysis of these results is covered in section 5.4. and is based on operators either using the Innova IFU or Test and Trace documentation based closely on it. This includes the most recent self-test operational evaluation study whose interim results are discussed in section 5.4.5

In order to address concerns around usability of the test (and its associated impacts on performance) modification have been made to:

- Provide clear user instructions highlighting critical activities
- Provide a training video aligned to the IFU (as this was the top request from parties when surveyed)
- Improve the test format to increase usability (single dose buffer container and extraction tube holder integrated into packaging)

The results of usability testing conducted with a mature draft (attachment 4) of the proposed IFU (attachment 23) are summarized in section 5.4.4.

The DHSC will, as part of proactive post market surveillance, to conduct additional post DEUA clinical surveillance to assess the ongoing performance of the device. See 2.07 Post Market Surveillance Plan for further details.

3.02.03 Disposal of the Test

The Test and Trace program has assessed that self-administration of the Innova LFD antigen test can broadly fit into three scenarios a) within the context of large scale roll out of testing which occurs at a specific location for example in:

- At a regional testing site
- Within a work placed setting
- In a domestic setting

For the first scenario Test and Trace has been working to classify the wastes arising from the roll out of the LFD. This has taken into account that there are small quantities of chemical used to extract any biological material present on the swab used to perform the test.

Discussions have been held with a number of parties including PHE, DHSC, MRHA, EA, the Army, and an experienced healthcare waste consultant to develop consensus on the position, summarized in Table 4, in the context of the current non-domestic deployments.

Table 4: Waste at regional testing sites

Item	Waste categorisation	EWCs	Likely Management Route / Waste Hierarchy	HTM 07.01 Packaging
General waste	Domestic / Recycling	20 03 01	1. Materials Recycling Facility 2. Energy from Waste plant 3. Landfill	
All packaging	Packaging	Eg. 15 01 01, 15 01 02, 15 01 05, 15 01 06	1. Materials Recycling Facility 2. Energy from Waste plant 3. Landfill	Use existing municipal route
Swabs	Chemical	18 01 04 +18 01 07	1. Energy from Waste plant 2. Municipal Waste Incinerator Hazardous or Clinical Waste Incinerator	Unmarked yellow neutral container > white / clear > last resort tiger - Do not use hazardous waste packaging
Cartridges/Devices	Chemical	18 01 04 + 18 01 07	1. Energy from Waste plant 2. Municipal Waste Incinerator Hazardous or Clinical Waste Incinerator	
PPE	Offensive	18 01 04	1. Energy from Waste plant 2. Last resort Landfill	Yellow bag with black stripe = Tiger bag

Where these may be supplied commercially to large organisations for testing in the work place environment then these would be classed as commercial waste and would require an accurate description of the waste to be made for the waste collector on a waste transfer note. As there would be no healthcare professional involved in this process, the waste would not be a Chapter 18 healthcare waste. An unmarked bag is supplied as part of the proposed test kit to bag all components. Such an approach ensures that any virus within or on the device would be contained for the short period of time (24hrs or less) that the virus may remain viable. On this topic expert advice has been sought from two clinical virology advisors to the Test and Trace Lighthouse laboratories. As the buffer solution dries quickly, quantities of virus in the buffer and on the swab will rapidly inactive, virus on the surface of the device will decay

rapidly as there is limited viability of the virus on plastic and any virus within the device will be contained by the device and also likely to inactivate quickly

For the third scenario if these tests are used by a householder to self-test, the waste falls into a different classification under the Controlled Waste (England and Wales) Regulations 2012. Wastes from a householder is classed as household waste regardless of its properties and falls under 20 03 01 mixed municipal wastes.

Based on the reviews conducted for the test centres and the fact that each test only weighs a few grams and utilizes only 180µL of non-hazardous liquid (most of which will be absorbed onto the swab or used for the actual test where it will be retained). The risk of any contamination, including that of infection control risk from a positive test, of any other waste is minimal. As noted previously an unmarked bag will be supplied with the kit to bag all components of the kit prior to placement in the household waste stream.

3.05 Analytical Performance

For any test, sensitivity and specificity is assessed against a gold standard.

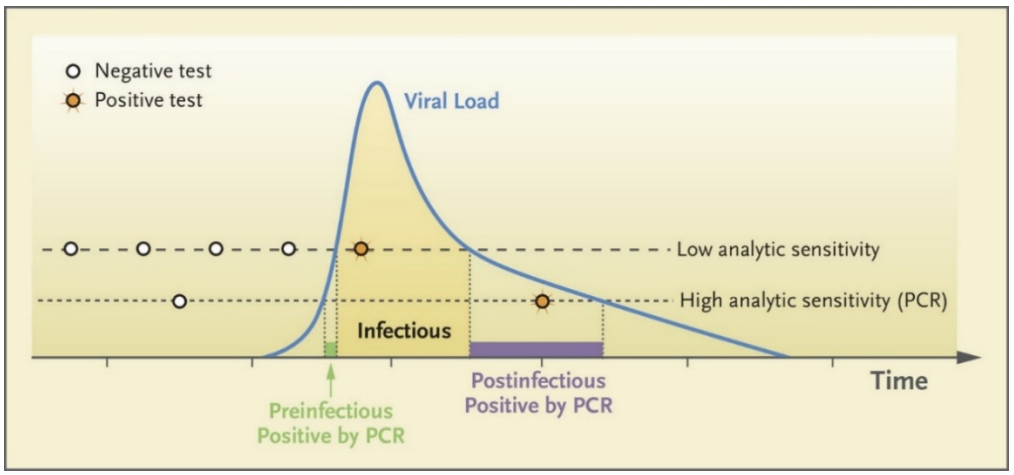
The question for a test which is aiming to identify subjects who transmit virus, the standard should be the capacity to detect people with replicating, and, therefore, transmittable infectious virus. This concept is critical to this submission, which clarifies the characteristics and performance of the Innova LFD that tests for transmissible virus rather than a test which detects viral nucleic acid whether associated with replicating and infective virus or not.

Typically, an evaluation of a test uses a truth set of true positives and true negatives. However, there is no simple binary differentiation for categorising people as having transmissible/infective virus and non-transmissible virus. Therefore, there is no gold standard test for replicating and transmissible virus available.

The challenge for a test of infectivity for SARS-CoV-2 is identifying the relevant viral status, which represents transmissible virus. However, for every replicating virus, which possesses a capsid around it, there are about 500 - 1000 equivalent non-functional, non-intact, non-replicating viral RNA fragments which cannot transmit infection; see Table 5 and attachment 14

Over the course of infection, total detectable viral genomic RNA increases substantially to a peak that then declines more slowly see Figure 7 below from the NEJM (attachment 15). It is during the first part of this increase that replicating virus is prevalent. Once the viral load is reducing, non-replicating virus begins to dominate, and persists, with substantial variation in decay between individuals, for up to, at least, 104 days, although, less than 28 days in the majority.

Figure 7: High frequency testing with low analytical sensitivity vs. low frequency testing with high analytical sensitivity (attachment 15, Rethinking COVID-19 Test Sensitivity)



Current RT-PCR tests detect the total viral burden because they directly assay viral RNA fragments, whether part of infective virus or not. This presence of detectable viral RNA is for longer than clinical illness. For clinical diagnostics, qPCR has been optimised to detect even very small quantities of viral RNA, reflecting either current or recent infection. This is essential for clinical diagnostic or surveillance purposes. However, it is less relevant for an assay of current replicating infectious virus which is critical for predicting infectivity. As antigens form part of the capsid, the antigen test provides a method for better detecting infectious virus.

Therefore, for antigen tests, it is not relevant to consider overall RT-PCR positivity as a single gold standard. However, whilst PCR tests are generally reported as binary (negative vs positive), underpinning this binary result is a semi-quantitative measure of viral load, specifically the cycle threshold value (low Ct means virus detected by fewer cycles, i.e., higher viral load). There is a relationship between (Ct) quantified viral load and a measure of infectivity (see next section); however, this is a continuum and there is no clear threshold, reflecting the varying balance between replicating and non-replicating virus (above). Because higher viral loads correspond to the more infectious periods, we can use viral load as a metric to stratify PCR positivity into groups where antigen tests should perform poorly (because they are not measuring the same thing) and where they should perform well because replicating infective virus is dominating.

3.05.05 Analytical Sensitivity and Limit of Detection

The first step in validation of the Innova lateral flow device was to determine limits of detection (LOD) against infective virus measured by plaque forming units (PFU), which are a direct measure of intact replicating virus. The Innova and other three devices evaluated and selected reliably detect 100 PFU/ml of sample. The viral loads of the samples were assayed and demonstrated an approximate ratio of 1: 500-1000 infective viruses to the total RNA copy

number, indicating that for every infective virus there are approximately 500-1000 non-infective viral RNA copies. See table 3.05.1 below:

Table 5: Limit of Detection – Saliva spiked with virions

Limit of Detection
saliva spiked with virions (plaque forming units)

PFU/ml	Estimated Viral Load*	Positive LFD /total LFD tests	% positive
100000	46,000,000	20/20	100.0
10000	5,600,000	25/25	100.0
1000	210,000	65/65	100.0
390	74,000	5/5	100.0
100	60,000	63/65	95.5
40	7300	3/5	60.0
20	4200	0/5	0.0
10	2200	0/5	0.0
5	1300	0/5	0.0
2.5	800	0/5	0.0
1.2	400	0/5	0.0

* Measured by qPCR (Cobas Machine [redacted]). CT values converted to viral load.

The second step was to determine sensitivity measured by retrospectively processing 200 thawed RT-PCR positive samples from the first wave of COVID-19. Of which, 173 had usable results; see Table 6 below.

Table 6: Innova test sensitivity of against conventional qPCR

Log viral load RNA copies/ml	LFD Pos	Prop Pos	(95% CI)
<1000	0/11	0%	(0-28.5)
1000-10,000	11/62	17.7%	(9.2-29.5)
10,000-100,000	25/39	64.1%	(47.2-78.8)
100,000-1,000,000	30/32	93.8%	(79.2-99.2)
>1,000,000	29/29	100%	(88.1-100)

Prop Pos = proportion positive

3.05.06 Analytical Specify

Specificity of the Kit was assayed by processing 1000 RT-PCR negative samples in viral transport medium (Phase 3a evaluation -negative samples); see Table 7 below

Table 7: Innova test strip false positive (specificity) against conventional PCR

Evaluation Phase	Test Center	False positives/total PCR negatives	False positives 95% CI (1-Specificity)
Phase 2 evaluation	[redacted]	0/72	0.00% (0.00-5.00)
Phase 3a evaluation- negative samples	[redacted]	0/940	0.00% (0.00-0.39)
Phase 4 evaluation- armed forces	[redacted]	0/105	0.00% (0.00-3.45)
Phase 4 evaluation- PHE staff	[redacted]	0/209	0.00% (0.00-1.75)
Phase 4 evaluation- hospitalstaff	[redacted]	1/329	0.30% (0.07-1.68)
Subtotal (Experienced laboratory workers)		*1/1655*	*0.06% (0.02-0.34)*
Phase 4 evaluation- school 1	Local	9/1855	0.49% (0.22-0.92)
Phase 4 evaluation- school 2 + 3 + 4	Local	7/2130	0.33% (0.13-0.68)
Phase 4 evaluation- Regional testing Site (RTS)	Local	5/1314	0.38% (0.12-0.89)
Manchester RTS	Local	4/314	1.3% (0.35-3.22)
York	Local	9/480	1.9% (0.86-0.35)
Liverpool	Local	3/5402	0.06% (0.01-0.16)
Subtotal (Field Workers)		*37/11495*	*0.32% (0.23-0.44)*
TOTAL		**38/13150**	**0.29% (0.20-0.40)**

There is clear heterogeneity between the different studies: chi(2)10=69.5 P<0.0001
Many false positives had 'weak' bands which looked different and were negative with retesting with LFD

4.06.04 Usability Testing

Usability testing has been conducted on a COVID-19 Self-Test (Rapid Antigen Test) sample, representative of the intended final product (see protocol, attachment 16) . A number of differences between the test used in the study and the final product are noted below, however the alterations will enhance the overall usability of the kit.

The variations major from the final product were:

- Final packaging was not available
- Version 0.92 (attachment 4) was utilized, this has subsequently developed to the proposed version 1.06 (attachment 23)
- An alternative extraction tube was utilized, without an integrated cap
- The IFU instructed users to utilize a small cup to hold the extraction tube. This has now been replaced with directions to use an integrated extraction tube holder provided as part of the secondary packaging, based on feedback from this study

The study's conclusions are provided in attachments 17 and 18 and changes integrated into the proposed product IFU.

Whilst the clinical and usability work conducted supports the performance of the device in the hands of lay users the DHSC has also conducting surveys with parties who have been using the existing Innova SARS-CoV-2 Antigen Rapid Qualitative Test (attachment 19).

The survey concluded that participants (university student and army users) were confident in the use of the device (88% agreeing or strongly agreeing it was acceptable to use) and would agree with daily testing if offered as an alternative to isolation (90% agreeing or strongly agreeing).

Self-Swab User Feedback

The low number of incidents logged against swabbing with the home testing kit (see 3.02.01 Collection of Swab Sample) provides evidence that users can safely conduct self-swabbing.

A further service evaluation of 1405 people who undertook two self-swabs, one for RT-PCR test and one for Innova LFD test was conducted in November 2020. Although 48% of subjects reported the self-swabbing to be uncomfortable there were only a limited number of more specific concerns raised, captured in Table 9.

Table 8: User survey on self-swabbing (1405 participants)

Comment	Count
Instructions too difficult/too long	13
Too much liquid	11
Appeared to not swab long/deep enough	9
Blood on swab	7
Multiple swab attempts required	6
Dropped swab/spilt fluid	5
Gagged	4

Overall, the initial formative data indicates that the self-use LFD device was usable for both swabbing and testing and did not create insurmountable obstacles for most subjects. There were recommendations for improvements which arose, and these are being addressed with new instructions for use to inform better training e.g., videos and instructions in a number of different languages. The specific issue with too much liquid being used is being addressed by production of single dose containers for the proposed product

3.06.05 Stability of the IVD

Device storage and transport stability validation for the Innova SARS-CoV-2 Antigen Rapid Qualitative Test is provided in attachments 20 and 21.

Validation has also been conducted on the individual buffer sachet utilized in the DHSC COVID-19 Self-Test (Rapid Antigen Test) and provided under attachments 22 and 23. Further stability validation is ongoing for the DHSC COVID-19 Self-Test kit (attachment 24 and 25).

4.02 Overall Clinical Evidence Summary

The test was used in 6 different groups all done with self-swabbing. In two groups the tests were sourced in a regional test site (RTS) and one set was processed in [redacted] by a Laboratory scientist and the other set was processed on site at an RTS by a health care worker; see table 3. The other four field sites are listed in Table 9.

Table 9: Clinical performance assessment locations

	Health Care Workers		Field Sites including Self Users			
	Lab Scientist	HCW	RTS	[redacted]	[redacted]	[redacted]
All cases	199	242	1737	5841	412	637
Total PCR+	199	242	373	73	88	125
Setting of sample	RTS sites	RTS sites	RTS sites	Community	RTS	RTS
Self swabbing	+	+	+	+	+	+
Site of LFD use	Swab sent to [redacted]	Local at RTS site	Local at RTS site	Local at Community test centre	in car at RTS site	In car at RTS site
Personel using LFD	Clinical Scientist	Research Nurse	RTS helper	Armed Forces	self use	self use
Training	Intensive and assured	Intensive and assured	Simple information leaflet	Training video	Training VIdeo	

HCW = health care worker
RTS = regional test site
[redacted] = [redacted]

The field studies highlight that many of these evaluations were conducted under sub-optimal conditions (e.g., handling the kits in a car without a stable working surface). When performed by an expert under ideal conditions i.e., a clear workspace e.g., a flat worktop; see Table 10. In the future, we would intend to deploy these tests for self-swabbing at home with guidance on where and how to perform the test, which will not be unlike [redacted] and [redacted]. Improved performance with good instruction/training and practice has unsurprisingly been shown(attachment 26), so is likely to perform better than this worst-case scenario.

Table 10: Clinical performance at assessment locations

	Health Care Workers		Field Sites including Self Users			
	Lab	HCW	RTS	[redacted]	[redacted]	[redacted]
All cases (LFD Void)	199 (9)	242 (23)	1737 (33)	5841 (22)	412 (9)	637 (38)
PCR void (LFD Void)	*n/a*	*n/a*	*28 (1)*	*348 (0)*	*3 (0)*	*4 (1)*
PCR neg (LFD Void)	*n/a*	*n/a*	*1336 (22)*	*5420 (18)*	*321 (7)*	*508 (28)*
PCR pos (LFD Void)	199 (8)	242 (23)	373 (10)	73(4)	88 (2)	*125 (9)*
Median Log viral load (RNA copies/ml) (interquartile range)	4.6 (3.5-5.7)	4.6 (3.5-5.7)	5.8 (4.6-6.5)	4.5 (2.5-5.5)	4.7 (3.4-5.9)	5.1 (4.0-6.0)
LFD readable	191	219	363	69	86	116
LFD pos	156	158	214	28	34	63
Results of cases above median infectiousness						
PCR>1,000,000	32	45	155	11	20	33
LFD void	2	6	2	0	0	0
LFD readable	30	39	153	11	20	33
LFD pos	30	36	129	10	16	27
LFD Pos % (95% CI)	100% (88.4-100)	92.3 (79.1-98.4)	84.3 (77.6-89.7)	90.9 (58.7-99.8)	80.0 (56.3-94.3)	81.8 (64.5-93.0)

Lab = laboratory scientist
HCW = health care worker
LFD = lateral flow device
RTS = regional test site
[redacted] = [redacted]

For the subset of subjects tested with the swab processed by an expert health care worker, the proportion of individuals testing Innova antigen positive as a function of their viral load is represented in Figure 8 Panel A below. This data was also analysed using logistic regression, see Panel B below.

To assess sensitivity, we have stratified the RT-PCR positive results according to viral load; see Figure 9 below. This shows that 182/217 (83.8% [95% CI 78.3%-88.5%]) individuals are identified (equivalent to sensitivity in this stratum) with viral loads above 1,000,000 copies/ml based on the scenario where inexperienced users processed the samples (RTS [redacted], [redacted] and [redacted]). This is a good proxy for infectiousness (see below for justification of these thresholds). This detection of cases needs to be considered in the context of the intended use for these tests, namely, people without symptoms who would otherwise not be tested. As expected, sensitivity to identify individuals with viral load between 10,000-1,000,000 copies/ml (the majority of whom will have little infective virus) was 132/258 (51.2% [95% CI 44.9-57.4%]), and under 10,000 copies/ml (where the majority will have negligible to zero infectious virus) was 25/159 (15.8% (95% [CI 10.4-22.3%]).

In the best-case scenario, where expertly trained or more experienced users perform the test, the performance is much improved over the scenario involving inexperience users. For people with viral loads above 1,000,000 copies/ml, 66/69, 95.7% (87.9-99.1%) were detected, and for individuals with between 10,000 – 1,000,000 copies/ml 180/195, 92.3% (87.6-95.6%) were detected, and for those with under 10,000 copies/ml, 55/127, 43.3% (34.5-52.4%) were detected.

Figure 8: Device clinical sensitivity with logistic regression

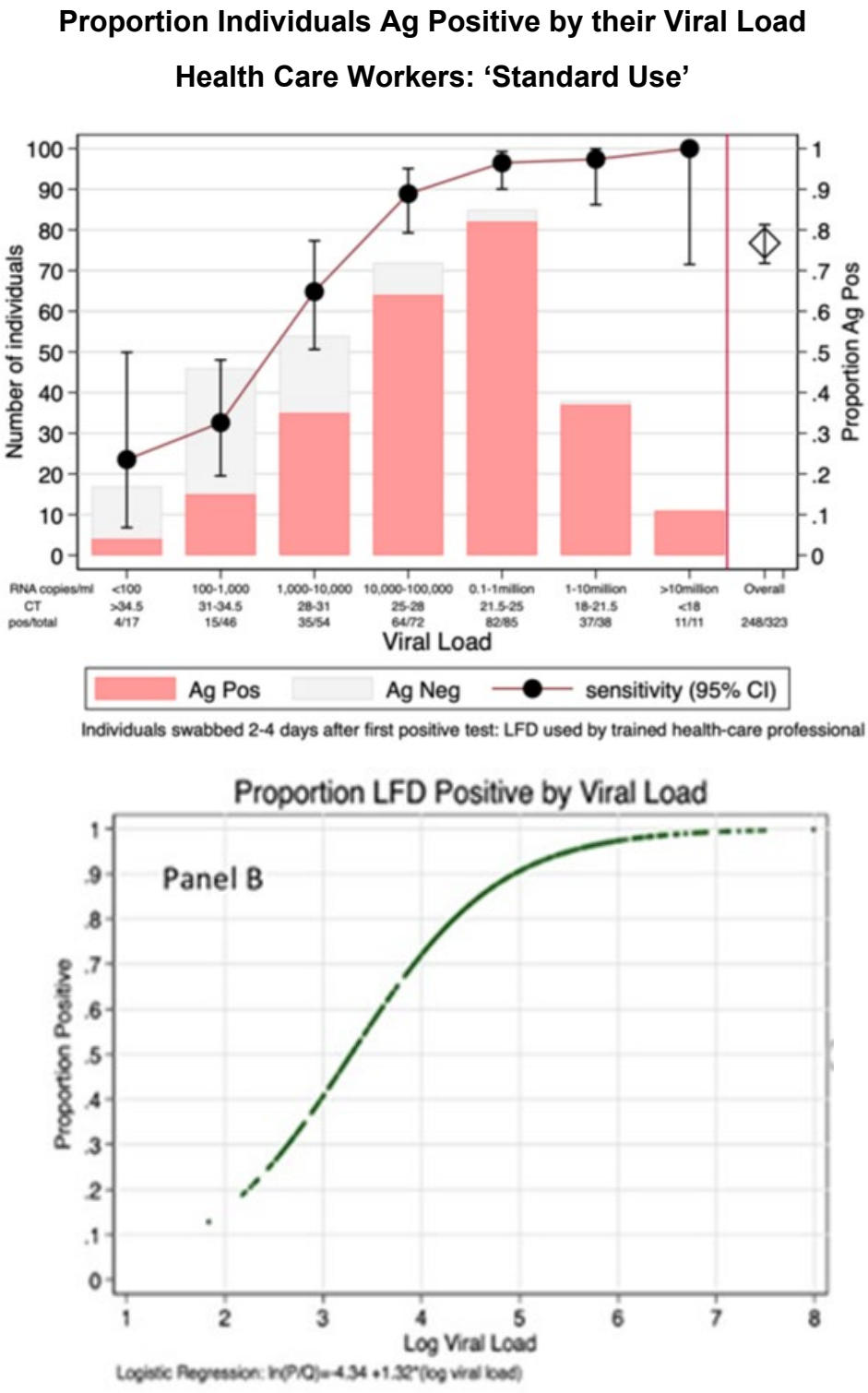
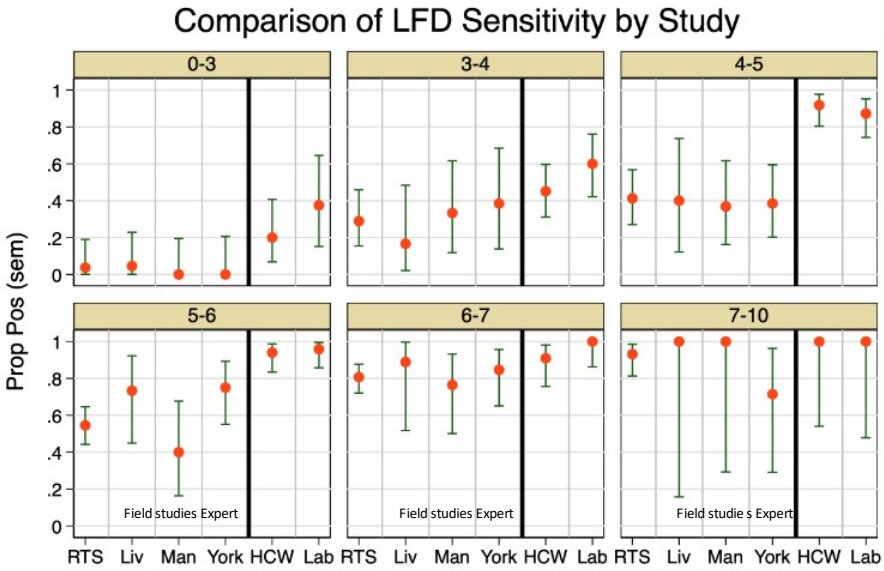


Figure 9: Sensitivity analysis across studies (graphs by log viral load ranges)



The label for each panel is log_{10} viral loads, i.e. 0-3 = 0 to 1,000 RNA copies/mL

Specificity vs PCR ranges from greater than 99% for experienced testers 99.94% (99.7% - 99.98%) and [redacted] 99.94 (99.84% - 99.99 %) to less than 99 % for [redacted] and [redacted] in smaller subsets of subjects (see prior Table 7 in 3.05.06 Analytical Specify) Specificity was also other sets of data including the first and second phase of analytical evaluation, field studies in a hospital, four schools, and a group in the armed services.

The proportion of kit failures was considered. For this all categories of testing were included in the analysis. As with specificity listed above, the sets of investigations where there was no associated RT-PCR data available are included. They consisted of studies of Hospital staff, armed forces and children from four schools. This evaluation also included phase 2 and 3 evaluations of analytical performance. The Falcon studies were focussed on RTS sites around the country and above are referred to as the RTS study. These kit failures ranged from 0.4 % to 14.4 % see Figure 10.

Figure 10: Summary of in field kit failure rates

Number of evaluations performed. LFD failure rate/ Void

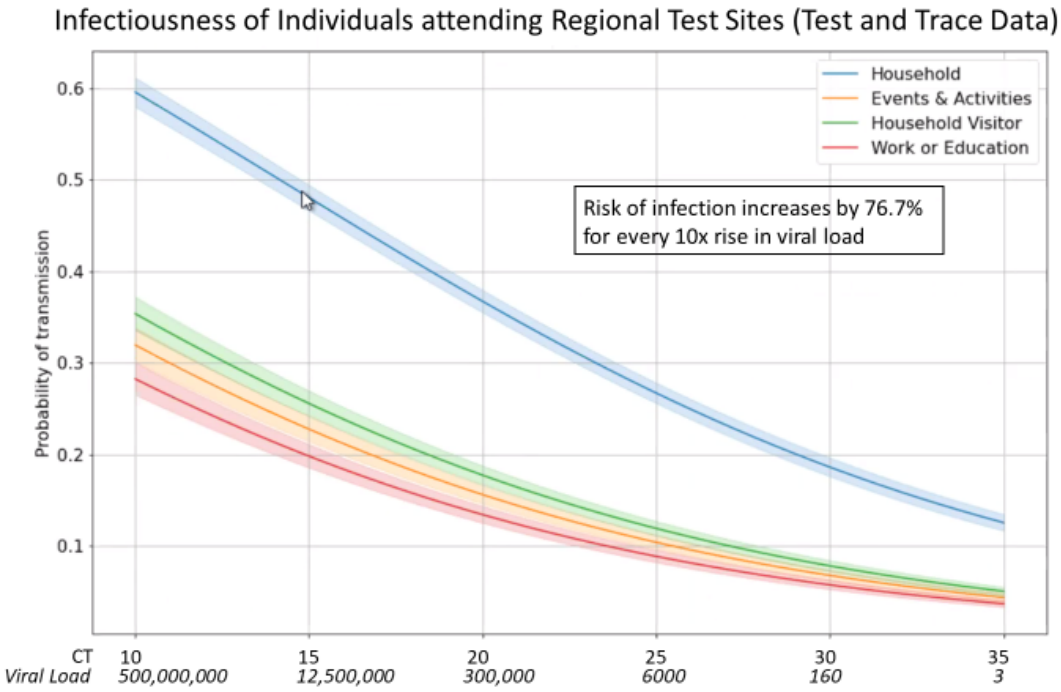
Innova LFD evaluation phase	LFD failures	
	fail/total	%
Phase 2 negatives	0/72	0
Phase 2 positive dilution series	0/215	0
Phase 3a positives	12/212	5.7
Phase 3a negatives	50/1040	4.8
Phase 3b FALCON (Dry swabs - field)	28/296	9.5
Phase 3b FALCON (Dry swabs - lab)	9/221	4.1
Phase 3b FALCON (VTM swabs)	9/166	5.4
Phase 4 hospital staff	17/375	4.5
Phase 4 armed forces	6/163	3.7
Phase 4 PHE staff	19/231	8.2
Phase 4 school 1	311/2166	14.4
Phase 4 school 2 + 3 + 4	14/2146	0.65
Phase 4 Regional Test Site	33/1737	1.9
[redacted]	22/5841	0.4
[redacted]*	9/412	2.2
[redacted]*	38/637	6.3
TOTAL	**579/15868**	**3.7**

Kit failure rates ranged from 0.4% to 14.4% (P<0.0001; chi(15)=1035).
Voids in [redacted] and [redacted] including user failing to complete the procedure.

4.05 Other Clinical Evidence - Justification of virial load thresholds for infectiousness

We have quantified the relationship between viral load in an index case and their infectiousness to transmit to others, using RT-PCR positivity rates in the contacts (with viral load available) in Test and Trace data. Contacts were classified by the degree of closeness, specifically household members, household visitors, work/education, other activities. No other information was available on duration of contact between the index case and contacts. After adjusting for characteristics, including case demographics and disease prevalence (reflecting background rates of transmission), there was a strong relationship between viral load in the index case and the probability of a contact testing positive; see Figure 11 and Figure 12 below:

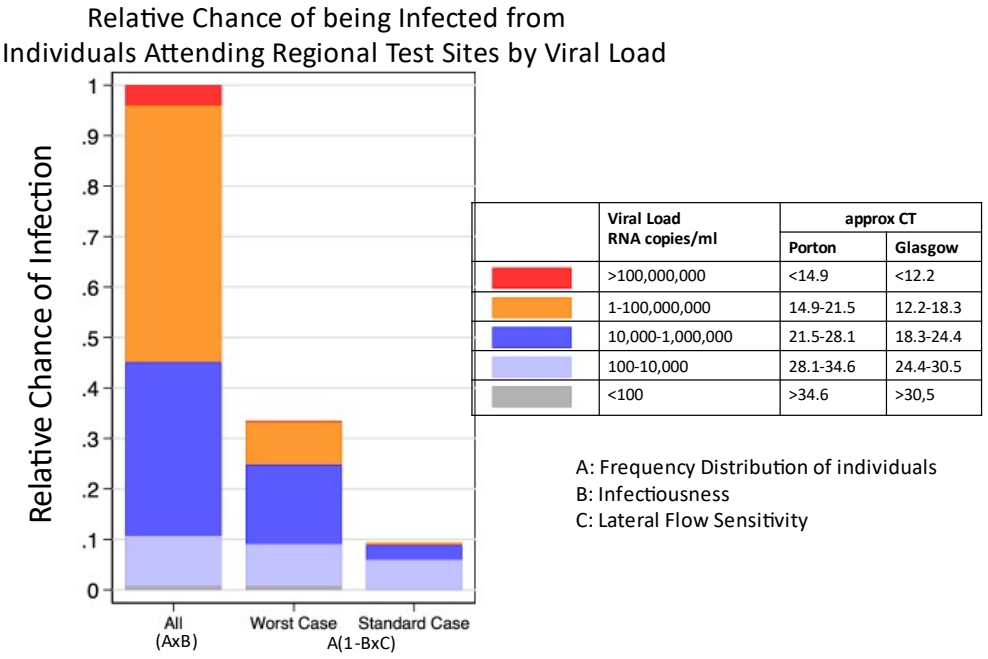
Figure 11: Infectiousness of individuals attending regional testing sites



Of note, these viral load measurements are taken at a single point in time in the index case, and, therefore, the findings above are likely to underestimate the effect of viral load on infectiousness. This is because the measured viral load is at best an imperfect proxy for the true viral load when transmission occurred – that is, the true relationship between viral load and infectiousness is likely to be even stronger than above.

We have combined information about the relationship between observed viral load and infectiousness, the distribution of viral loads in the population testing positive and the performance of the LFD with worst-case / inexperience users (RTS / [redacted] / [redacted] / [redacted]) and standard users ([redacted] / [redacted]). We have calculated that using LFDs to identify and quarantine infectious people would prevent 67% (Worst Case) and 90% (Standard Case) of transmission events respectively versus all of the cases being unquarantined in group "ALL (AxB). See Figure 12.

Figure 12: Relative chance of infection (test and trace data)



Further interpretation and contextualisation of these results is provided in the modelling section below.

4.05.01 Modelling and simulations, using LFD performance and Infectiousness data, for real-world use

Previous studies have assessed the sensitivity of LFA tests as measured against a viral load distribution obtained from many individuals (Grassly et al, Kucharski et al, Hellewell et al, attachments 27, 28, 01]. However, new results show that the peak in viral load is very sharp, but occurs on different days after infection in different individuals (Kissler et al, attachment 29), and models that account for the covariance between viral load, infectiousness (Larremore et al, attachment 30) and test sensitivity suggest that despite their lower sensitivity, LFA tests can be a game changer of several public health use-cases when used appropriately (attachment 31).

In addition, an integrated framework is used as a basis for modelling asymptomatic testing for case-finding with LFD, symptomatic testing, and contact tracing. The model is consistent with:

- Individual viral load trajectories after infection, for asymptomatic and symptomatic cases
- Incubation period (time from infection to onset of COVID-specific symptoms), as a

function of the viral load trajectory
- the distribution of observed infection events as a function of exposure time and onset of symptoms in contact tracing studies.

Figure 13, below, illustrates LFA testing sensitivity throughout the course of the infection, assuming that the first test is taken 3 days after exposure of the contact to their infector. The blue dots show the sensitivity of the individual test, varying the day on which this is taken. The black line shows the overall sensitivity of the full testing strategy until that day. Both sensitivities include 25%

Figure 13: LFA testing sensitivity throughout the course of the infection

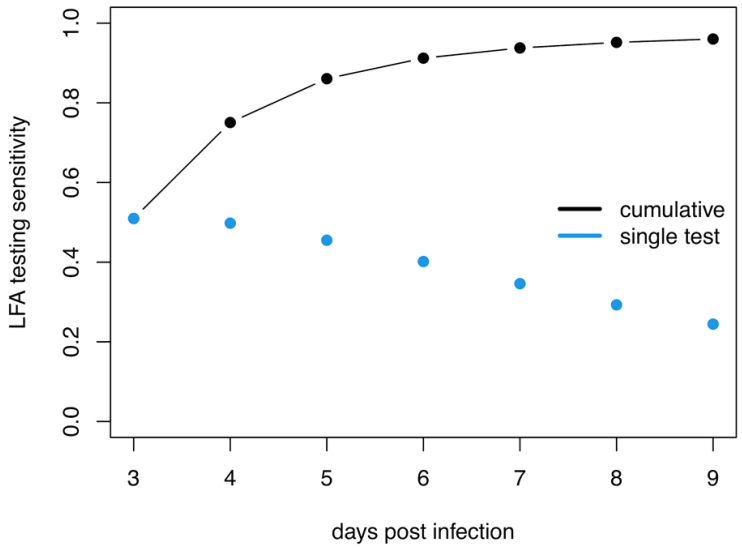
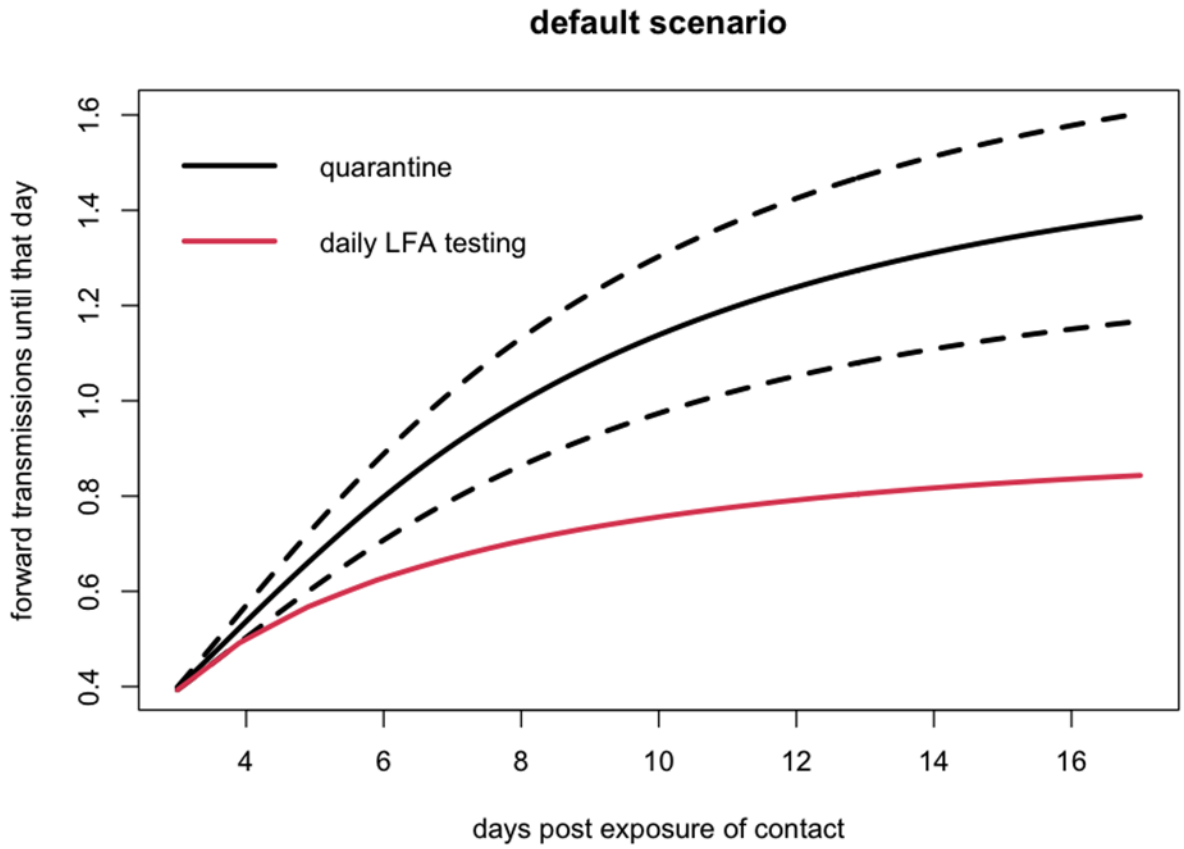


Figure 14, below, illustrates the cumulative number of transmissions a contact-traced infected individual is expected to cause throughout the course of their infection, assuming that they are traced three days after their exposure to their infector. We assume a mean reproduction number of 2 in the absence of contact tracing. The black lines show the scenarios in which they follow quarantine imperfectly, with no testing available (with range 25, 50 and 75% adherence amongst those who intend to adhere but report not adhering). The red line shows an alternative scenario to quarantine, in which they self-administer an LFA test every day, with greater (i.e., riskier) effective contact rates than the quarantine scenario before obtaining any positive test result, but lower (i.e., safer) effective contact rates after obtaining a positive result. This is for the assumption of 75% taking a test every day, with a 5% drop daily dropout rate, 20% reduction in contact during the testing period, and 80% adherence to isolation after a positive test.

Figure 14: *Cumulative number of transmissions expect of a contact-traced infected individuals*



SARS-COV-2 is often transmitted from people before they acquire symptoms, which means that very fast and universal contact tracing after a positive rapid test is important to contain the epidemic. Contact tracing is widespread in many jurisdictions and aims to prevent transmission by finding contact cases before they become infectious. In many instances, contact cases are asked to quarantine, but not tested. Quarantine practiced without testing is characterised by low adherence [Smith et al]. Furthermore, individuals who are contact traced and infected are not themselves tested unless they have distinct COVID-symptoms, such that the opportunity to rapidly contact trace them (potentially reaching the index case of a superspreading event) is missed. Daily LFA testing of traced contacts offers the opportunity to greatly improve the effectiveness of the test and trace system in several ways:

- Greatly improve the effectiveness of the test and trace system compared to quarantine only that is only partially adhered to.
- Add the opportunity of recursive testing which will further stop transmission chains.
- Increase the chance of finding highly connected individuals in the network who could cause a super-spreader event
- Reduce the economic impact of quarantine
- Replace an unpopular policy

4.07 Performance of external nasal swab vs throat + nasal swab

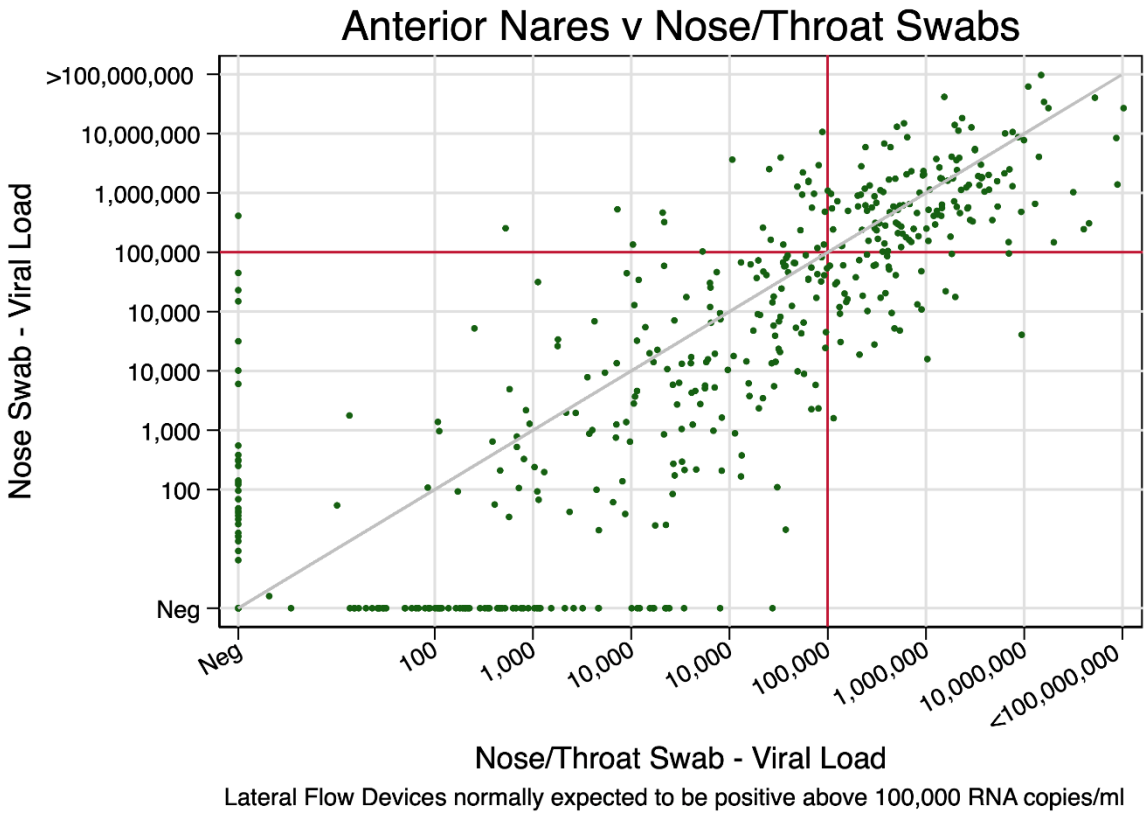
In order to assess a more acceptable swab type for serial and even daily swabbing. External nasal swabbing has been identified as being acceptable by people including in the 20,000-hospital staff, SIREN study led by PHE. Based on this observation, we conducted a literature review and a head-to-head study. The findings are as follows:

From the review of the literature nasopharyngeal swabbing does not appear to provide benefit over anterior nasal swabbing for viral detection. This was reported by three studies (attachments 32, 33, 34) There have been two studies suggesting that the nasal technique might be inferior, however, both these studies was small and therefore of unclear significance (attachments 35 and 36). The most relevant study is that of Lindner et al (attachments 32) Among 289 participants it showed good agreement between nasopharyngeal sampling and anterior nasal sampling using of 79.5% vs 74.4% respectively.

In a large-scale head-to-head evaluation of 2083 subjects, the performance of anterior nares swabs was compared to conventional nose and throat swab.

Individuals attending the regional test sites were asked to provide two swabs. One from the anterior nares and one conventional nose and throat swab. Swabs were sent to the Lighthouse for standard PCR testing. The overall results are shown in Figure 15.

Figure 15: Anterior Nares vs Nose/Throat swabs



To illustrate the performance of anterior nasal swabs the results are presented in 4 different scenarios.

Table 11: Performance of anterior nasal swabs

	T swab positive		T swab negative		At least 1 swab T+ or N+	T+ / T+ or N+	N+/ T+ or N+	N+/T +
Cut off	N+	N-	N+	N-		%	%	prop
PCR pos*	341	46	15	1681	402	96.3	88.6	0.92
VL>10,000	214	44	20	1890	278	92.8	84.2	0.91
VL>100,000	139	38	26	1965	203	87.2	81.3	0.93
VL>1,000,000	48	32	29	1910	109	73.4	70.6	0.96

VL – viral load; T = throat; N = nose
PCR pos* is the categorical result used in reporting result from routine PCR laboratories

Viral Load cut off values of 10,000 and 100,000 are the viral load values above which experienced and inexperienced users can expect the lateral flow device to be give a positive result respectively. Most infectious individuals have viral loads above 1,000,000. Overall, in all the scenarios, the nose swab detects over 90% of the relevant cases compared to the throat swab.

Attachments

Number	File Name
01	Estimating the extent... 2020.05.10.20097543v3.full.pdf
02	Innova IFU.pdf
03	DHSC COVID-19 Self-Test IFU v1.06
04	NHS-COVID-19 Self-Test Kit 3T-195-80-30mm-201212.pdf
05	NHS-COVID-19 Self-Test Kit 7T-195-160-30mm-201212.pdf
06	Single dose buffer Specification drawing.pdf
07 (a, b, c, d)	Swab HH (Packaging, Registration, Certificate, IFU)
08 (a, b, c, d)	Swab MJ (Certificate, Packaging, Registration, IFU)
09	bmj.m4469.full
10	Differential occupational risks to healthcare workers from SARS-CoV-2
11	SAR-R-011 Risk Management Report-Innova A01
12	Test to find at home – schools pilot
13	DHSC Risk Log V1 for LFD device for SARS-Cov-19 - Approved.xlsx
14	Duration of infectiousness and correlation with RT-PCR cycle threshold values
15	Rethinking Covid-19 Test Sensitivity – A Strategy for Containment (footnote 2)
16	LFD IFU STUDY PROTOCOL ASJ-20-1313-D_A.docx
17	Summative Study Report for LFD IFU Remote Based Useability Study
18	IFU recommendation ASJ-20-1317.pdf
19	NHS TandT acceptability and usability survey v1.00.docx
20	SARS-R057 SARS-CoV-2 Antigen Transport and accelerated aging stability-c....docx
21	SARS-R059 SARS-CoV-2 Antigen Transport and realtime and in use Stabili....docx
22	SARS-R050 New buffer model Stability Research Protocol.docx
23	SARS-R051 New buffer model Stability Research Report.docx
24	SARS-R060 COVID-19 Self-Test kit Transport and real time and in use stability.docx

25	SARS-R061 COVID-19 Self-Test Kit Transport and accelerated aging stability.docx
26	At home self-testing of teachers
27	Quantifying SARS-CoV-2 transmission
28	Effectiveness of Isolation, Testing, Contact Tracing, and Physical Distancing
29	SARS-CoV-2 viral dynamics in acute infections
30	Test sensitivity is secondary to frequency
31	Daily_testing_20201124.pdf
32	Head-to-head comparison of self-swabbing (anterior nasal) vs professional-collected nasopharyngeal swab using a rapid test (Linder)
33	140720_EvidenceReport_COMBI021 - BothSigned
34	20200424_EvidenceReport_SE_SWTC001_v5.0BothSigned
35	20200509_EvidenceReport_SE_SWTC003_v3_BothSigned
36	140720_EvidenceReport_TS5_34A - BothSigned