JS Medical

INFORMATION UPDATE – DECEMBER 2020

A Practical Guide To COVID-19 Testing

Pandemic Perspective and Overview

1. At the start of the SARS-CoV-2 viral pandemic in February 2020, the World Health Organisation (WHO) alerted the world to an outbreak of a severe respiratory illness which was later to be called COVID-19, as this novel virus first emerged in Wuhan, China in late 2019 where at the time it was just a local epidemic.

2. Infected individuals often presented with a high temperature, a new persistent cough and severe breathing difficulties with low blood oxygen levels. We later became aware of other obscure symptoms such as loss of taste and smell (anosmia), fatigue, neurological symptoms, diarrhoea, visual disturbances, muscular and body aches, nausea, vomiting and a runny nose, in fact, symptoms that could easily be mistaken for the season flu that we are all too familiar with each year. Many COVID patients end up in hospital on ventilators in an intensive care unit. The main threat was from a phenomenon called "cytokine storm", an overwhelming immune inflammatory reaction that can cause multi-organ failure with devastating outcomes.

3. The mantra from the WHO surrounding COVID-19 was "Test, Test, Test" in order to identify those subjects carrying the virus in an attempt to isolate them to prevent onward transmission to healthy people. The incubation period is usually 2-14 days but may be longer in some individuals. Not everyone who is carrying the COVID-19 virus develops symptoms, which for most people are mild and fleeting. However, it is now known that asymptomatic carriers can infect others. Due to the severity of COVID disease in a small, but significant number of people, and the transmission dynamics modelling undertaken by world leading academic institutions such as Imperial College, London (ICL), University College London (UCL) University of Oxford, the US Center for Disease Control (CDC), Johns Hopkins University (JHU) and the Robert Koch Institute in Berlin (RKI), the WHO advised governments to adopt strict guidelines to manage and contain the virus to prevent overwhelming healthcare systems and mitigate the loss of life. Just imagine that in 2014 and 2018 close to 50,000 people died from seasonal influenza in the UK alone. The same biostatistical modelling was used to predict the potential deaths from this even more lethal COVID-19 virus.

4. These guidelines included the use of PPE, viral testing, social distancing, self-isolation, hand hygiene and the use of face masks. Measures taken by the

United Kingdom government resulted in a full lockdown followed by numerous regional lockdowns where the R-rate began to rise from time to time. The idea was to keep the R-rate to below 1.0 which is an index of contagion rates, or how many people 1 infected person transmits the virus to.

5. What rapidly followed the WHO alert to the world, was a rush to procure personal protective equipment (PPE), ventilators and COVID viral testing products on the open market with China dominating the supply chain.

6. In the mayhem surrounding the fight to secure these products, many of the products purchased, were often at inflated prices and were of poor quality and often unfit and not effective for clinical use. Many of the normal regulatory and quality control measures used to assess fitness for clinical use were bypassed in order to expedite supplies to front-line staff with what they needed to fight the virus and protect themselves.

Testing Program Overview

1. Following on from the cry of "Test, Test, Test", the only test available at the beginning of the outbreak was the so-called laboratory-based RT-PCR swab test, a molecular or genetic test. This requires a throat & nose (nasopharyngeal) swab to be taken by a healthcare professional and sent to a specialised laboratory for processing with turnaround times (TAT) of up to 4 days. There are limitations associated with the PCR test, as there are with all tests. In March 2020, the NHS and Public Health England were only capable of processing about 2,000 PCR tests per day. Remarkably, this was increased to over 600,000 per day by November, and the British government is now planning to perform 1 million tests per day by the end of 2020, often focussed on areas with high or rising infection rates.

2. The PCR test is a molecular or genetic test that looks specifically at the presence of the virus by identifying its RNA by a process called Reverse Transcription Polymerase Chain Reaction (RT-PCR). In other words, viral antigen testing is designed to look at where the infections are in the community in real time, or "WHO HAS THE VIRUS NOW"? The antigen is the protein material that causes the infection and attacks the body, usually the lungs, kidney, brain, heart and blood vessels.

3. The government has just started using a new-style **antigen** test called a lateral-flow rapid test (LFT) which is designed for use at the point-of-care (POC) with a turnaround time of under 30 minutes. These types of antigen tests also identify the virus by an immunochemistry process linked to a colloidal gold chromatographic process. The accuracy of the current LFT selected by Her Majesty's Government (DHSC/PHE) has been called in to question by a number of academic sources as being only 50% accurate and described as "not fit for purpose". Fortunately, there are now more accurate versions of the LFT available with results produced in 10-15 minutes.

4. If we return to the start of the pandemic and the desperation for testing devices across the world, a large number of manufacturers, mainly from Shenzhen China, rushed to develop and bring to market a host of these so-called **antibody** rapid tests. These devices were also called lateral-flow tests and required a tiny finger-prick of blood for result in 10 minutes. The key issue

related to the use of antibody tests at the beginning of the pandemic was flawed for two reasons. The main reason was that the antibody test was used for the wrong reason at the wrong time. When people first become infected with the virus, they do not necessarily develop the memory antibody IgG for some time after the infection subsides. Secondly, many people do start to develop the acute-phase antibody IgM, but at such low levels as to be below the detection limits of the rapid-style test. It may only be possible to use a laboratory method of analysis to test for low levels on antibody. It was used blindly instead of a viral antigen test to look a COVID positivity in the community.

5. In general, the quality of the early antibody tests was poor, often developed in a rush by Chinese manufacturers of food and industrial testing devices with no experience in medical diagnostic devices.

6. Still today, the NHS Test & Trace service rely on the RT-PCR method with drive-in, mobile and home test kits, although there is a move towards using more community-based lateral-flow rapid tests now that the devices are more reliable and accurate with high specificity and sensitivity to the SARS-CoV-2 antigen.

7. The use of antigen tests is going to increase and be around for a long time as the virus will remain a threat for several years to come. Viral antigen tests will be used by NHS Test & Trace, Public Health England, airports, the education sector and industry as we strive to reopen our economy by getting people back to work and students back into full-time education. Many countries demand a recent antigen test prior to entry into their country. There is now a dual or "combi test" that can discriminate between COVID and flu, useful during the winter flu season.

8. Antibody tests are going to be crucial once a widespread vaccination program is rolled-out to check that the vaccine has stimulated the immune system in to developing protective antibodies to the SARS-CoV-2 virus. It is worth keeping in mind that having antibodies does not necessarily guarantee immunogenicity in everyone, but also, if immunity is created, the big question is for how long it will last. There is evidence that immunisation may reduce the severity of symptoms if a person goes on to contract the virus and provide protection against some of the pro-morbidities that we are used to seeing.

9. Over the last 9 months, we have seen significant improvements in clinical care that are beginning to reduce morbidity. Patients are not rushed to be intubated and ventilated as they were in the beginning. There is wider use of CPAP oxygenation, anticoagulation, kidney protection, hydration, high-dose dexamethasone, antiviral drugs and better nursing techniques. We are still trying to understand why certain ethnic minority groups generally have poorer outcomes from COVID disease, which may be due to underlying genetic factors. While we are also trying to understand more about the causes of so-called Long COVID Syndrome.

Test Sensitivity and Specificity

1. **Specificity** is defined as the number of individuals without the disease that test negative. If the test was 100% specific, there would be no false positives.

2. **Sensitivity** is defined as the number of individuals with the disease that test positive. If the test was 100% sensitive, there would be no false negatives.

3. **Cross-reactivity** is defined as a specific test also picking up interference from other similar viruses or substances. There are over 300 know varieties of coronavirus.

4. **Limit of detection** is defined as the lowest level or concentration of the virus in the sample that a specific test can accurately detect and measure.

What test to choose?

1. **Antigen tests (Ag)** – are for individuals who wish to know if they are currently carrying the COVID-19 virus. Useful prior to travel or returning to the workplace or education. Rapid lateral-flow tests can be used as a convenient point-of-care device. Useful for care homes to test both residents and visitors and school/university/college students. Useful if an individual has been in close proximity to someone know to be COVID positive. WHO HAS THE VIRUS?

2. **Antibody test (Ab)** – is a serological (blood) test for individuals to know if there is evidence of a past infection, or to monitor treatment after a recent infection. This test depends on the levels of antibodies present to provide useful information. The Ab test looks at levels of IgG and/or IgM depending on the time the test is used post-infection. WHO HAD THE VIRUS?

How often to test?

1. Antigen viral tests should be conducted weekly on staff at work, unless the employee is working from home, and/or when a home worker is returning to work.

2. Antibody tests can used frequently after immunisation to check the body's immune response to the vaccine, optimally a weekly test should be performed in these circumstances.

Who to test?

1. Both symptomatic and asymptomatic people should be regularly tested when the R-rate is on the rise above 1.0 and greater. Also, if exposure to COVID positive persons is suspected.

How to obtain a good sample?

Always read the instruction for use.

1. Wash your hands thoroughly using soap and hot water or use an alcohol-based hand sanitizer.

2. Use appropriate PPE ensuring face is covered. Gloves are essential.

3. Prepare the test including the cassette tray, extraction buffer tube and a swab.

4. Using the swab between the thumb and forefinger, touch the tip on the back of the throat in a swirling circular motion for 10 seconds. Gagging is common and normal.

5. Take the same swab and place it in the nostril and advance it as far as is comfortable with a twisting rotating motion for 10 seconds.

6. Remove the cap from the viral extraction tube, taking care not to spill the solution in the tube.

7. Place the swab tip into the viral extraction medium in the tube and mix well for 10 seconds while rotating the swab.

8. Pinch the tube between the thumb and forefinger and slowly but firmly pull the swab through your pinched thumb/finger. Discard the swab safely.

9. Place the dropper cap on the tube and drop two drops into the sample well of the cassette tray. Start a timer for 15 minutes.

Read the result in 15 minutes.

How to interpret results?

1. Refer to the instructions for use with each antigen test device.

2. There are two test results lines on each cassette. In all cases the C-line must always be displayed, this is the quality control line that shows that the test is valid. The C-line must be always visible whether the test result is positive or negative.

3. For a positive test result, both the C-line and the T-line will be visible.

4. For a negative test result, only the C-line will be visible.

5. An invalid test result will have neither the C-line nor T-line visible.

6. In the event that the T-line is weakly visible, then the test should be repeated.

What if the result is positive?

1. In the event of a positive test, a repeat test should be performed in the first instance.

2. Should the repeat test be positive, an additional test using a different manufacturer's device should be performed.

3. If all tests are positive, the diagnosis should be confirmed using a PCR test as soon as possible.

4. The positive subject must then self-isolate along with anyone that he/she came in to contact with according to the latest government guidelines.

5. Isolation will not be necessary if healthcare professional has used the appropriate personal protective equipment during sample collection.

Important Information

1. Lateral-flow tests are qualitative tests only.

2. All tests have limitations and good clinical judgement must be used in all cases, taking into consideration the clinical and history of the test subject.

3. Lateral-flow tests cannot be sold for home use, based on current guidelines from the UK regulator MHRA.

4. All test should be carried out by suitably trained operators.

5. A negative Ag test only confirms that the test subject was "Negative" to the coronavirus antigen at the time of test. It will not reveal if the subject has been exposed to a past infection. Antibody testing will be required for this purpose.

Useful sources of information?

Visit the following useful websites for more information on COVID testing : -

- Public Health England
  - www.gov.uk/government/organisation/public-health-england
- National Institute for Health and Care Excellence
  - www.nice.org
- UK Government Website – Coronavirus
  - www.gov.uk/coronavirus
- National Health Service
  - www.nhs.uk
- FIND Diagnostics Organisation
  - www.finddx.org
- World Health Organisation
  - www.who.int
- Center for Disease Control and Prevention
  - www.cdc.gov
- Johns Hopkins University Coronavirus Information
  - www.coronavirus.jhu.edu
- Robert Koch Institute Berlin
  - www.rki.de