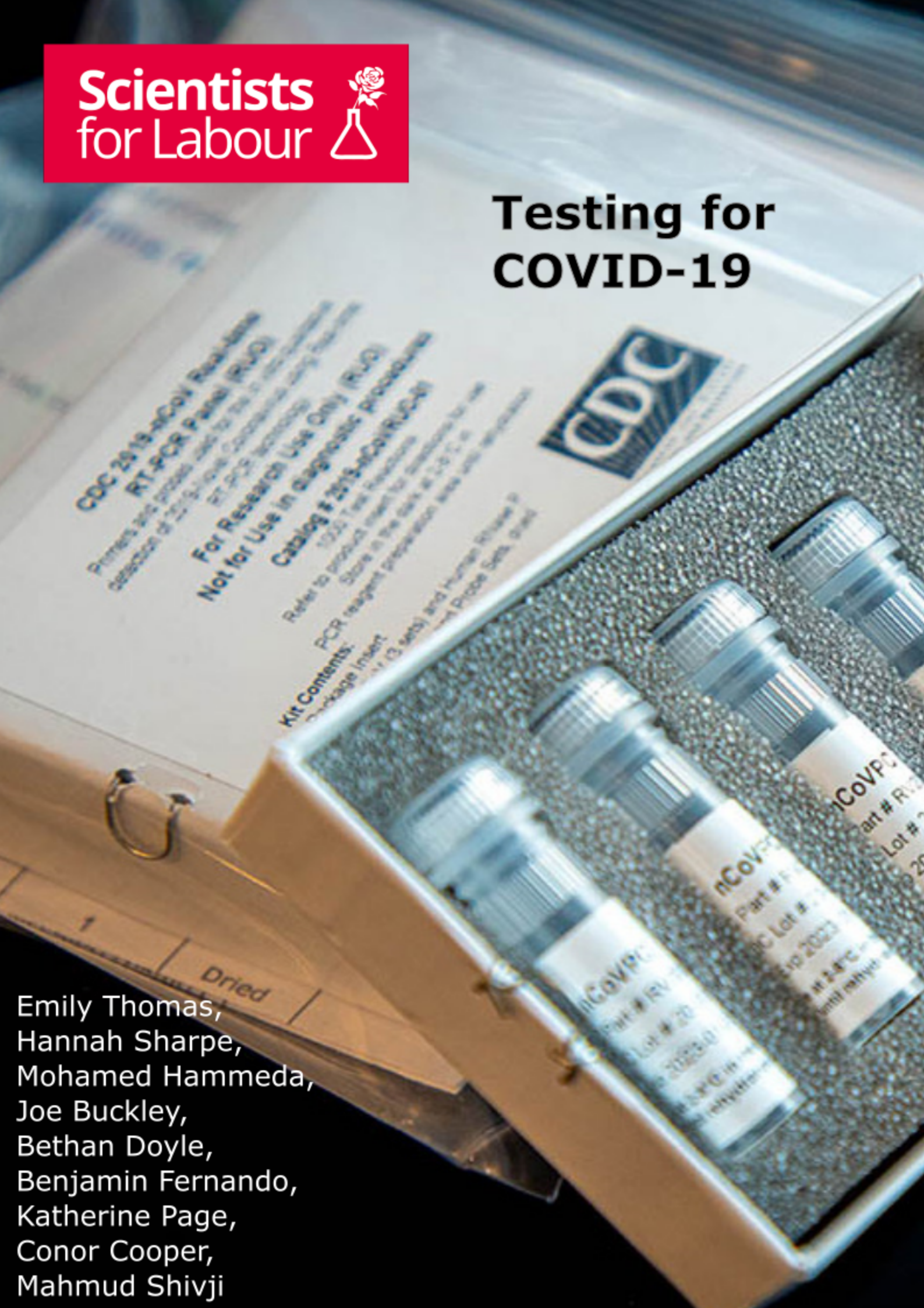
Scientists for Labour

Testing for COVID-19



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Scientists for Labour

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Throughout the COVID-19 crisis, Scientists for Labour are preparing briefings and summaries of the latest research into coronavirus for Labour Party representatives and their staff. If you would like to receive these briefings or have any other queries, please contact Benjamin Fernando: chair@sfl.org.uk.

Aims and Scope

This report details the current state of testing in the United Kingdom for current or past infection by SARS-CoV-2, the virus responsible for causing COVID-19. Important policy questions are also raised.

Whilst every effort has been made to validate the statements made in this report and an expert fact-check has been performed by the Boyd Orr Centre for Population and Ecosystem Health at the University of Glasgow, we cannot claim that the report is accurate in every regard. Care should be taken when extrapolating from the questions posed here to actual policy, and it should be noted that the situation is changing very rapidly.

19 April 2020

Executive Summary

Unambiguous diagnoses of COVID-19 can be made in two ways. One requires identification of the SARS-CoV-2 virus which causes it, whilst the other detects the specific antibodies produced by the body's immune response to the virus.

The former method works through detection and identification of RNA (viral genetic material) which is isolated from a nose or throat swab. These tests make use of a technique called a polymerase chain reaction (PCR) and are the current 'gold standard' for testing. PCR tests are generally relatively slow (~24 hours), as they must take place in a laboratory setting and require reagents which are currently in short supply. PCR tests are the only ones currently approved for use in the UK, and are only effective at diagnosing current infection - once the immune system has dealt with the virus, its genetic material is eliminated from the body and further detection is not possible.

The latter method, detecting the proteins produced by the body's response to infection, is known as an 'antibody test'. Antibodies are a class of proteins produced by the immune system when a pathogen (e.g. a virus) is detected in the body. Specific antibodies recognise specific parts of different pathogens, for example the spike (S) protein on SARS-CoV-2.

Antibodies may not appear in the bloodstream until slightly later than the first viral genetic material (as the immune system's action is not instantaneous), and hence antibody tests are not effective at diagnosing infection immediately after it occurs. However, antibodies remain in the bloodstream even once the infection has been dealt with, as they confer some protection against future re-infection.

For this reason, antibody tests are able to diagnose whether or not an individual has been infected in the past (and since recovered), unlike PCR tests. However, antibody tests are much more unrefined technologies than PCR tests, and none are currently licensed for use within the UK (though unauthorised tests can be found online). Those in use abroad, however, have the advantage that they are both faster and more portable than PCR tests.

The reason that no tests have been approved in the UK is that antibody tests are prone to high rates of both false negatives and false positives. These factors are complicated by uncertainty in the degree of protection from further infection conferred by the presence of antibodies in the bloodstream.

As such, whilst widespread testing is valuable for helping to understand the spread of the virus through the population, reliance on antibody tests alone is not currently possible. Care must therefore be taken when formulating policy or developing an exit strategy based on assumptions of infection spread to ensure that the uncertainties associated with the testing procedure, and those in knowing what degree of immunity is conferred by recovery from infection, are understood and the associated risks mitigated against.

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1. INTRODUCTION

1.1 Introduction to Virology

The introductions to virology and antibodies (sections 1.1 and 1.2) are closely related to those included in the our vaccine report of March 30.

Viruses are minute infectious agents capable of infecting living cells, in order to use their internal machinery as a means of replication. Unlike bacteria, or indeed many other parasites, **viruses are unable to replicate outside a host organism**, though they may survive on surfaces and remain infectious for several days (Banerjee et al., 2018).

SARS-CoV-2 is part of the **coronavirus family**, a large group of viruses so-named because of their protruding surface 'spike' proteins which, under microscopic images, appear as a 'crown'. Coronaviruses have, in recent history, been responsible for a number of serious outbreaks including Middle East Respiratory Syndrome (MERS, 2012-onward) and Severe Acute Respiratory Syndrome (SARS, 2003-4). In less serious forms, coronaviruses can also cause variants of the common cold (Li, 2016).

SARS-CoV-2 is so named because of its similarity to the original SARS coronavirus (now called SARS-CoV-1). Its formal name is Severe Acute Respiratory Syndrome Coronavirus 2. When humans are infected, this virus causes the disease known as Coronavirus Disease 2019 or **COVID-19** (World Health Organization, 2020). Coronaviruses are **single-stranded RNA viruses**, meaning that they store their genetic information as single strands of RNA rather than double strands of DNA, which our cells (and indeed all animal, plant and bacterial cells) use to encode the genetic instructions for life. **These genetic codes contain the information needed to make proteins**.

SARS-CoV-2 is a new human pathogen, which emerged in **China in late 2019**. The pathogen likely originated in bats, and may well have had another intermediary host before being transferred to humans (Lam et al., 2020). As viruses replicate rapidly, they have the capability to mutate and evolve on timescales faster than in plants or animals; and **single-stranded RNA viruses like coronaviruses and Influenza are particularly prone to such mutations** (Sanjuan et al., 2010).

One of the most concerning kinds of mutation is to the part of the virus that the human immune system recognises to fight an infection **(the antigen)**. Assuming that infection with SARS-CoV-2 leads to protective immunity in the first place, mutations at these locations have the potential to stop this, allowing for potential reinfection (Schoeman & Fielding, 2019). As such, past infection may not necessarily confer future immunity - though the mutation rate of the virus, and hence the risk of this happening, are not yet known.

1.2 Introduction to Antibodies

When a person is infected by a pathogen their body mounts an immune response. One aspect of this response is the production of antibodies. Antibodies are defensive proteins which are secreted by a particular cell type (lymphocyte B cells), and are able to specifically bind to a feature of the virus (the viral antigen). Any feature of a virus which induces the body to produce an antibody that can bind it is known as an **antigen**. One virus may therefore have multiple antigens and multiple antibodies will be produced by the body against one antigen.

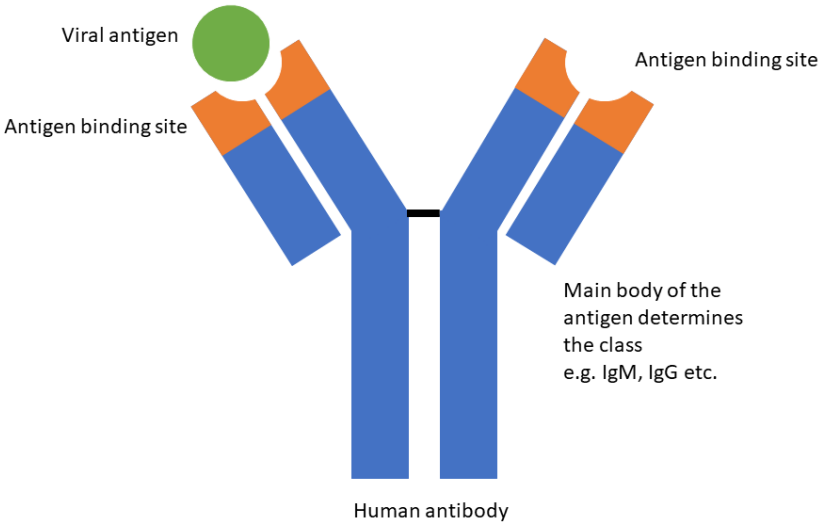

Figure 1: Antibody. Antibodies are made by the body and are specific to one type of viral antigen (a feature of the virus). The tips of the antibody (orange) are specifically shaped to bind the viral antigen (green). This is analogous to a key (binding site) fitting a lock (antigen). The main body of the antibody being produced (blue) changes as time from infection increases.

Figure 1 shows a representation of an antibody. The tips of the antibody (orange) are specifically shaped to bind the viral antigen (green). The main body of the antibody being produced (blue) changes as time from infection increases. Antibodies produced shortly after infection have one type of main body and are referred to as IgM. Over time, antibodies become more tuned to the virus and are then referred to as IgG. This distinction is sometimes taken advantage of in antibody tests to detect more and less recent infection. The specific binding of an antibody to an antigen can itself neutralise a virus or elicit further immune responses. Neutralising antibodies are ones that impede a virus' ability to infect a cell. We are most interested in detecting neutralising antibodies because they are one mechanism of providing protection (Petherick, 2020). In contrast, non-neutralising antibodies recognise parts of the virus but do not decrease infectivity, at least on their own. The time period for an antibody to develop and become detectable in the blood is known as the **seroconversion rate**. Detection is not always possible immediately after infection, as antibody levels take some time to exceed the detection thresholds of the test. Crucially for testing, antibodies remain in the bloodstream for days to months after infection (Alberts, 2002).

1.3 Introduction to available tests for SARS-CoV-2

Two main tests for diagnosing SARS-CoV-2 infections exist, one for current infections and one for past infections.

Polymerase Chain Reaction (PCR) tests determine if current infection exists using swabs taken from the back of the nose or throat, and detects genetic material from live viruses. PCR amplifies the virus' genetic material to detectable levels in a very specific way. It has the advantage that once the viral genetic sequence is known, it can be deployed rapidly (Sheridan, 2020). PCR testing is the gold standard for detecting viral infection, due to ease of development, familiarity with the test amongst molecular biologists, and accuracy. The NHS is therefore currently focussing on PCR tests to detect current infection, mainly in critical care patients and frontline healthcare workers. This is because PCR tests detect the virus early in infection, compared to antibody tests which may not detect the virus as early on in infection, since the body's immune response for IgM is lagging. Such early detection can be used to isolate individuals and enable contact tracing without exposing vulnerable hospitalised patients the pathogen.

While PCR tests are highly accurate, they generally require a laboratory setting and, with the logistics of sample delivery factored in, take around 24hr to process. A low-cost and simpler alternative PCR-based technique called LAMP (Loop-mediated isothermal amplification) is more field-proof and takes under an hour to generate results. It is harder to develop, but is now being validated for SARS-CoV-2, and so could be available for use as a point of care test in the near future (Park et al, 2020).

Antibody tests determine if someone has previously been infected by checking for the presence of antibodies specific to SARS-CoV-2 in small blood samples, and thus are necessary for surveilling exposure and development of immunity in the population. However, antibody tests are harder to develop as they require more detailed knowledge of the proteins on the viral coat that might trigger production of antibodies to flag or neutralise the virus. Although antibody tests can also be carried out in a laboratory, a key focus is on **developing point of care tests,** i.e. tests which can be performed next to the patient. These are less sensitive and specific (see below) than PCR tests and the uncontrolled environment outside a laboratory could lead to lower reliability, but they are easier to use and deliver results in 20-60 minutes (Sheridan, 2020).

1.4 Quality of tests

Note that there are three key parameters which need to be evaluated to ensure that the results of any test are useful:

Sensitivity**:** how good a test is at detecting its target, here antibodies associated with an immune response to SARS-CoV-2. In this case, antibody tests should detect the **IgM**, the class of antibody generally produced earliest in response to infection, and/or **IgG**, the longer-lived class of antibody generally produced later in response to infection. The higher the sensitivity, the more likely a test will correctly identify the relevant antibodies and give fewer **false negatives**.

Specificity**:** how focused the test is on the target it is designed to detect, without being triggered by other similar ones. Low specificity means tests could wrongly identify antibodies that do not recognise SARS-CoV-2, and give a **false positive**. The higher the specificity, the more likely it will only identify past COVID-19 infection and give fewer false positives.

Positive Predictive Value: proportion of positive results that are true positives. Given the sensitivity and specificity of the test, **and the proportion of the population being tested expected to be positive**, how valuable is a positive result in telling you anything about the individual's status. For instance, a test that is 90% sensitive and 90% specific may sound good, but if only 5% of the population is positive, then only 90% of them will be correctly diagnosed as positive due to low sensitivity (90% of 5% = 4.5% of the population), whereas 10% of the 95% who are actually negative will test positive due to low specificity (10% of 95% = 9.5%), so a positive test result is more than twice as likely to be an error than correct. This is also known as the precision:

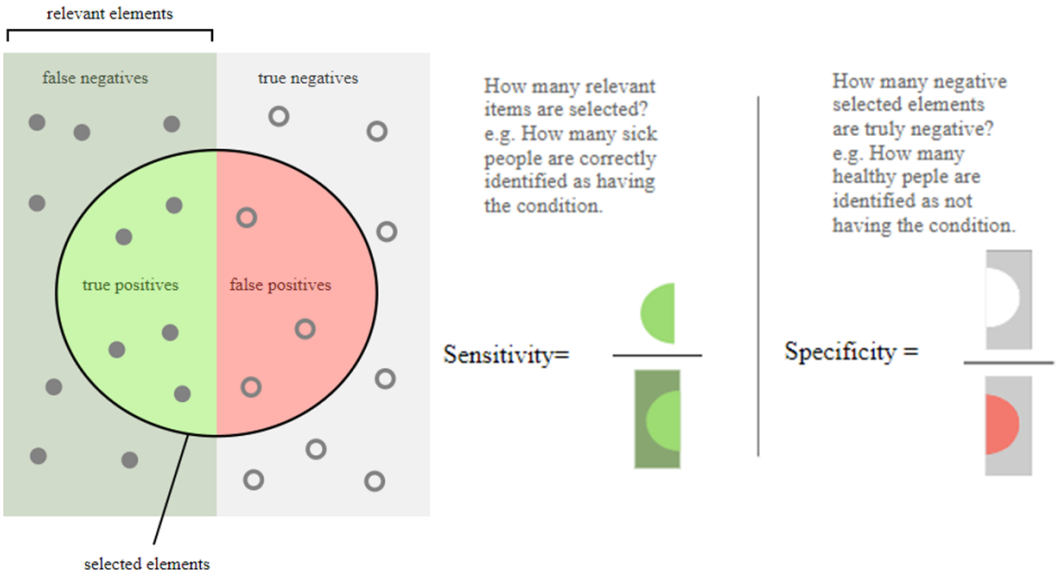

Figure 2: Important statistical concepts for evaluating antibody tests (Fean Doe, 2020).

1.5 Antibody tests for SARS-CoV-2

Some SARS-CoV-2 antibody tests are commercially available. The US Food and Drug Association (FDA) has relaxed the rules governing such tests, giving emergency authorisation for some antibody tests to be carried out in a laboratory setting or by healthcare workers with the disclaimer that they have not been reviewed by the FDA and should not be used as the sole method of diagnosis. Australia has introduced similar emergency authorisations (Mallapaty, 2020b).

The UK's Medicines and Healthcare products Regulatory Agency (MHRA), on the other hand, has published their minimum specifications for antibody tests that are delivered by healthcare professionals or self-administered. These minimal acceptable requirements for clinical sensitivity, clinical specificity and analytical specificity are included in the table below (MHRA, 2020).

Measure	Requirements
Clinical Sensitivity (measure of the proportion of false negatives – those who do not test positive despite having been infected previously)	Greater than 98%
Clinical Specificity (measure of the proportion of false positives – those who do test positive despite having not been infected previously)	Greater than 98% for IgG between 14 and 20 days from appearance of first symptoms
Analytical Specificity (interferents and cross reactivity)	No cross reactivity with other coronaviruses

Table 1: UK's Medicines and Healthcare products Regulatory Agency minimal acceptable requirements for clinical sensitivity, clinical specificity and analytical specificity

These requirements should result in a high positive predictive value for the test given current expectations of numbers of individuals who have recovered from COVID-19 in the UK. However, the need to develop these tests quickly has meant most tests have only been validated in tens of people, which is not enough to reach these thresholds. **As a result, to our current knowledge, no antibody test submitted so far to PHE has been approved for use in the UK.** The Foundation for Innovative New Diagnostics (FIND), based in Geneva is independently evaluating 220 submissions of antibody tests under development and hopes to release results to manufacturers by the end of this month.

Conventional validation would usually involve hundreds of people with COVID-19 and thousands without, highlighting the need to critically evaluate manufacturer's reports of sensitivity and specificity independently (Mallapaty, 2020a). Different tests have a wide range of sensitivities due to the differences between methods and time they are administered from the onset of symptoms. Sensitivities are lower closer to time of infection. For example one test in a study of nine commercially available tests had a sensitivity as low as 40% within one week from onset of symptoms, which is why Table 1 specifies the number of days since symptoms (Lassaunière, 2020).

Care should also be taken to differentiate between random and systematic uncertainties in testing. The former consist of 'uncorrelated failures': e.g. one particular test being faulty due to being left in a hot car. The latter might consist of failures in the underlying reaction mechanism in a particular batch of the tests. These would be correlated failures. If a particular method returns a true positive 99% of the time, and the 1% is associated with random uncertainties, then two separate tests both returning a positive result combine to make the overall chances of a false positive being recorded 1% times 1%, or 0.01%. On the other hand, if the 1% uncertainty is due to purely systematic issues, then repeated testing will not necessarily increase the confidence level of any result. Of course, in practice most uncertainties are a mixture of systematic and random. As a result, repeated tests being performed on a single individual can reduce the uncertainty, but will likely never reduce it to zero.

1.6 Overview of groups developing antibody tests

There are currently no antibody tests approved for use in the UK. This is despite the fact that several have passed **equivalent regulatory systems** such as the US Food and Drug Administration (FDA). It would appear that higher standards are being applied in the UK than in other countries (Institute for Global Change, 2020). Although unsuitable for point-of-care individual testing, tests with lower but known accuracies may have a role in epidemiological surveillance at the population level.

Below (Table 2) is a **selection** of some of the many COVID-19 antibody testing kits currently in development or on the market.

The selected testing kits are all point-of-contact rapid antibody testing kits, selected based on one or more of the following criteria: demonstrated high sensitivity and specificity in small-scale clinical trials, widespread current use in other countries, or having already met the criteria for and received the EU's CE Mark, US Food and Drug Administration's (FDA) Emergency Use Authorisation (EUA), Chinese National Medical Products Administration's (NMPA) Emergency Approval Procedure (EAP) or equivalent.

Only two producers (Table 2), Pharmact AG & Zhejiang Orient Gene Biotech China, make tests with response rates that would meet or come close to the UK MHRA guidelines (MHRA, 2020).

However, it is worth noting that Hangzhou AllTest Biotech, one of the two companies from which the government recently purchased £16 million of tests which were insufficiently accurate, has, **on paper**, one of the most effective tests on the market, with a *reported* 100% sensitivity and 98% specificity for IgG antibodies (though only 85% sensitivity for IgM antibodies), but still failed PHE testing. (Sheridan, 2020; Kirkpatrick & Bradly, 2020). This underscores the fact that these tests have not been **rigorously** tested prior to release, given the urgent need for tests, and so their advertised specifications have wide confidence bounds (Mallapaty, 2020a; Mallapaty, 2020b). Their performance in more robust trials by public health officials may therefore **vary** quite significantly from their advertised specifications.]

Lab/Supplier	Availability Status
BioMedomics/Jiangsu Medomics Medical Technology, *USA/China*	- Commercially available, half a million sold in China - Received CE Mark for in vitro diagnostics - Already sold in Italy - Submitted to FDA for EUA approval
Innovita Biological Technology, *China*	- Available - Approved by NMPA (China)
Pharmact AG *Germany*	- Available. - Received CE Mark - Shipping
Zhejiang Orient Gene Biotech *China*	- Available. - Received CE Mark. - Currently one of only a few tests used for coronavirus screening in China (but not approved by NMPA)
Cellex, *USA*	- Commercially available. (Limited to labs certified to perform moderate and high complexity tests) - Obtained EUA approval from US FDA 1 Apr 2020. - Approved for inclusion in Australia's ARTG 31 Mar 2020
Biolidics, *Singapore*	- Provisional authorisation from Health Science Authority, Singapore
Predictive Laboratories, *USA*	- One of tests authorised without FDA approval - Associated myID app can transmit results to public health authorities
Sugentech, *South Korea*	- Received CE Mark
ChemBio Diagnostic Systems, *USA*	- Commercially available - Handheld analyser received CE Mark in 2019 - Obtained EUA approval from US FDA on 15 April 2020

Table 2: Selection of COVID-19 antibody testing kits currently in development or on the market (Institute for Global Change, 2020; Sheridan, 2020; NUS Saw See Hock School of Public Health, 2020; Beroni Group, 2020; 360dx, 2020; Azad & Griffin, 2020; GlobeNewsWire, 2020; China Daily, 2020)

It is important to note that this is a small selection of **currently available** antibody tests - there are hundreds of tests in development and testing as of the time of writing. New tests may prove more accurate than those currently available; but comparative evaluation is likely to remain challenging.

A number of companies are involved in developments of antibody tests in the UK:

- **Mologic (Bedfordshire)** - Recipient of a £1m grant from the UK government to develop an antigen test (for viral genetic material) and an antibody test (for viral proteins). Mologic has African partners, and manufacturing will take place in Senegal (Institute for Global Change, 2020).

- **Biopanda (Belfast)** - Has developed a rapid antibody test that is sold **privately** (without PHE approval) within the UK and has previously despatched orders “throughout Europe and across the world” (Institute for Global Change, 2020).
- **SureScreen (Derby)** - Claim to have developed a test with a 98% accuracy rate at detecting past COVID-19 infection with a 10-minute diagnostic time. Sells to private buyers in the UK, Ireland, Germany, Spain, Switzerland, the Netherlands, Turkey, UAE, Kuwait and Oman. It is believed that around 175,000 tests have been conducted with the SureScreen kit, and the company claims it has had more than two million orders for next month (Institute for Global Change, 2020).
- **YorkTest Laboratories (York)** - Diagnostic test developers with a focus on point-of-care antibody-based allergy and health tests. Currently developing a COVID-19 IgG antibody test, and crowdsourcing COVID-19 positive blood samples to test the feasibility of their prototype antibody test (WiganToday, 2020; Yorktest, 2020)
- **UK Rapid Test Consortium (UK-RTC)** - Consortium made up of the University of Oxford, Abingdon Health (York), Omega Diagnostics (Clackmannanshire), BBI Solutions (Co. Antrim) and CIGA Healthcare (Co. Antrim) to develop a rapid antibody test (Abingdon Health, 2020; MedTech News, 2020)
- **Roche Diagnostics** - The UK division of this pharmaceutical giant has announced it is developing a new antibody test, which it is planning to launch in the UK in early May. Roche is a reputable diagnostics firm with a large testing capacity, but it is unclear how useful this test will be until details of the test are released (Siddique, 2020; Roche, 2020; Science Media Centre, 2020)

UK antibody testing development is currently being held up by a **shortage of blood samples** to work on. As part of a mechanism put in place together with NHS Blood and Transplant, people tested for COVID-19 are being contacted and asked to donate blood. Some of this blood can be used for antibody test development and validation (Sample, 2020).

2. ANTIBODY TESTS

2.1 How does an antibody test work?

The most common type of antibody test uses a similar design and method to a home pregnancy test although it requires two drops of blood, rather than urine.

The SARS-CoV-2 antigens are printed on the testing device in a known region (e.g. along a line). Other antibodies in the blood sample which are not specific to the SARS-CoV-2 antigen are washed away. These non-specific antibodies may have been produced by the patient in response to other infectious agents or other parts of the SARS-CoV-2 virus. A second antibody labelled with a colour or light can then bind the SARS-CoV-2 antibody:antigen combination. If the test is positive we only see colour in this region e.g. the pink line in Figure 3.

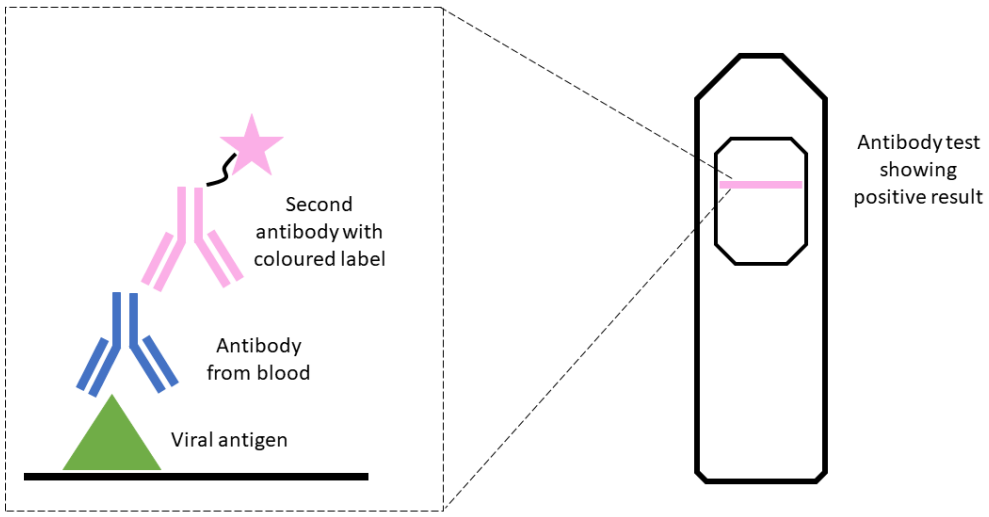

Figure 3: Basic principles underlying antibody tests. The antigen (green) is immobilised in an area of the test. Antibodies from the patient's blood (blue) can bind specifically to the antigen or else be washed away. The binding of the specific antibody (blue) allows the binding of a second "detection" antibody (pink), which produces a detectable reaction. In this case a pink line on the test in the area the antigen is immobilised.

2.2 Potential Benefits of Antibody Testing

Antibody testing is able to identify if a person has previously been infected with SARS-CoV-2. It is important to note that just the detection of SARS-CoV-2 specific antibodies **does not guarantee immunity** and the timing of testing is extremely important. We discuss in more detail the limitations of antibody testing such as **seroconversion** (the time taken for antibodies to become detectable in the bloodstream), the distinction between **neutralising and non-neutralising antibodies** and the limitations of antibody testing with regards to **immunity** in section 2.4.

Regardless of how much immunity is conferred after past infection, antibody testing is still a useful tool, especially if combined with epidemiological surveillance such as contact tracing (Petherick, 2020). This is especially true as widespread antibody testing can yield an estimate of the fraction of cases which are asymptomatic, an important metric for understanding how the virus spreads through the population and making informed policy decisions (Heneghan, 2020; Sayburn, 2020). Such asymptomatic patients may well be less likely to receive a labour-intensive PCR test, and hence such information is difficult to come by otherwise.

Herd immunity, the resistance to the spread of a virus within a population that results if a sufficiently high proportion of individuals are immune to the disease has been raised in the media and antibody tests could act as a tool for monitoring this. In the case of SARS-CoV-2, this proportion is estimated to be around 60% of the population, or about 40 million people in the UK (Osman, 2020). Using antibody testing as a tool to investigate herd immunity assumes that 1) antibodies are present and accurately detectable in the bloodstream at the time of testing 2) detection of antibodies correlates with immunity 3) previously infected individuals do not continue to transmit the disease (Mallapaty, 2020b).

2.3 Combined testing-technology approaches

Groups around the world, including teams in China, Australia, Iceland, Italy, Germany, and several in the United States are running **sero-epidemiological surveys** (antibody tests combined with epidemiological monitoring). The World Health Organization is also coordinating a global seroprevalence study, known as Solidarity II. Combined with epidemiological data (such as age, gender, symptoms, co-morbidities and socio-economic status), antibody tests are an inexpensive way to gather large amounts of information to inform policy decisions (Mallapaty, 2020a).

One example given as a beneficial outcome of sero-epidemiological studies that could inform policy is establishing the role of children in spreading infection and thus deciding how much SARS-CoV-2 might spread through schools and daycare centers. These studies could resolve whether confirmed cases in children and teens are scarce because they typically have mild disease, and are thus less likely to get tested, or because they are less likely to be infected in the first place (Vogel, 2020).

2.4 Limitations and uncertainties in antibody testing development

There are still significant uncertainties in the understanding of antibody production and the conferral of immunity in response to SARS-CoV-2 infection. The science is fast-evolving, but the fundamentals must be well-understood to ensure that sensible mitigation and exit strategies are developed. Multiple lines of research are still being pursued, and these include questions such as:

- Which antibodies are the best to aim for in detection tests?
- How much correlation, if any, between the levels of neutralising antibodies and the degree of immunity conferred can be shown?
- Do all infected individuals produce neutralising antibodies to levels detectable in the bloodstream (Lovelace & Feuer, 2020)?

- What trade-offs should be considered when choosing which antibodies to target in antibody testing?
- How long after infection will the presence of particular antibodies in the blood become detectable?
- How much variation across population demographics will there be in all of these parameters?
- How much cross-reactivity (to other coronaviruses) is a specific antibody test likely to generate?
- Are there trade-offs to be made between choosing antibodies generated in response to highly conserved parts of the viral genome (those which are not expected to evolve rapidly, such as the spike protein), and those which generate the best sensitivity and specificity?
- How sensitive to future mutation in the virus' genome are antibody tests, and is there a risk of such tests ceasing to work against novel variants of the virus?

3. DISCUSSION

3.1 Mass testing in other countries

The WHO advice throughout this crisis has been for widespread testing - initially to try and prevent a pandemic from occurring, and now to enable uninfected individuals to continue in frontline jobs. Initial efforts focussed almost exclusively on PCR tests, and recent work has used a mixture of PCR and antibody tests - though the WHO has cautioned against over-reliance on potentially inaccurate forms of the latter. As countries around the world move toward easing of restrictions, different approaches are being taken to ensure that this is done in a safe manner.

Widespread use of reliable testing measures is clearly one part of the solution, but it is also clear that high rates of testing alone are not sufficient. For example, the United States is now carrying out more tests per capita than South Korea was at a similar stage of the pandemic, but sees a far larger fraction of its population contracting the disease (Our World in Data, 2020).

Whilst disentangling the many complex factors in such comparisons is not, at this stage, likely to prove useful (in part due to the temporal lag between an increase in tests and a decrease in infections); the data do suggest that other factors are at play.

One pertinent example is the combining of technologically-enabled contact tracing to prevent spread with widespread testing, as has been done for example in Singapore and South Korea. Here, the use of contact-tracing apps has enabled a prioritisation list for testing to be devised, ensuring that the still-limited testing capacity is used as optimally as possible.

Directly copying across some of the testing-technology combinations used in these nations is unlikely to be feasible in the UK - both due to differing population demographics and rates of smartphone usage, and varying standards of data privacy (Deloitte, 2017). Both Apple and Google are working to try and address these privacy issues (Greenberg, 2020). . However, there are clearly lessons to be learnt in terms of how contact tracing is combined with widespread testing to optimise the mitigation against resurgent infections. It may be that such

solutions need not be high-tech in and of themselves, but simply need to be rigorously pursued.

3.2 What could widespread testing tell us? And could immunity passports work?

The exact definition of what would constitute 'widespread testing' is debatable, but the UK's current strategy of only administering tests to those admitted to hospital is clearly not enough. Ideally, regular exhaustive testing would be carried out throughout the entire population.

Given the strain on resources at present, exhaustive testing will take time. However, testing only a subset of the population will still be informative if representative of the whole population (i.e. randomised testing). Such a program should consider the following points:

- **If past infection does confer immunity, which is currently unknown,** then it could be used to 'clear' those who have recovered to return to frontline work.
- **Again, if immunity is conferred,** then this information could also be used to redistribute limited supplies of PPE amongst other frontline workers who are most at risk.
- Irrespective of immunity, it would help establish the ratio of symptomatic to asymptomatic cases in the population and better understand the spread of the disease.
- Irrespective of immunity, to better predict where the next local outbreaks are likely to occur
- Irrespective of immunity, to try to understand how different demographics are differentially affected by the disease, for example evaluating whether those who are from a BAME background are more likely to have severe immune responses
- To feed into development of an exit strategy, for example in determining the order in which businesses are allowed to re-open
- To reassure the public that steps are being taken to evaluate the actual impact of the disease (and any future recurrence), and reduce the uncertainty in predictions associated with poor knowledge of spreading rates

The caveats to this are of course that such a program is likely to require significant resources, both financial and in terms of manpower, and hence may risk distracting from frontline care if not properly implemented. Furthermore, there are clear unknowns associated with the nature of the antibody response to SARS-CoV-2, and hence there will be inherent uncertainty in conclusions drawn from any testing regime. This will translate into the need to consider the associated risks when designing and implementing public health policy based on, or informed by, such tests.

If these risks are not clearly communicated to the public, the behavioural changes that will likely be introduced by 'false positive' results could be significant - if a positive result is seen as a guarantor of safety from re-infection, risky behaviours which contravene social distancing are may ensue, undermining gains associated with a thorough testing program.

If testing is not always being carried out by medical professionals, but can be undertaken at home, there is also likely to be a fraction of the population who claim to have already tested positive without there being any guarantee of this result being accurate.

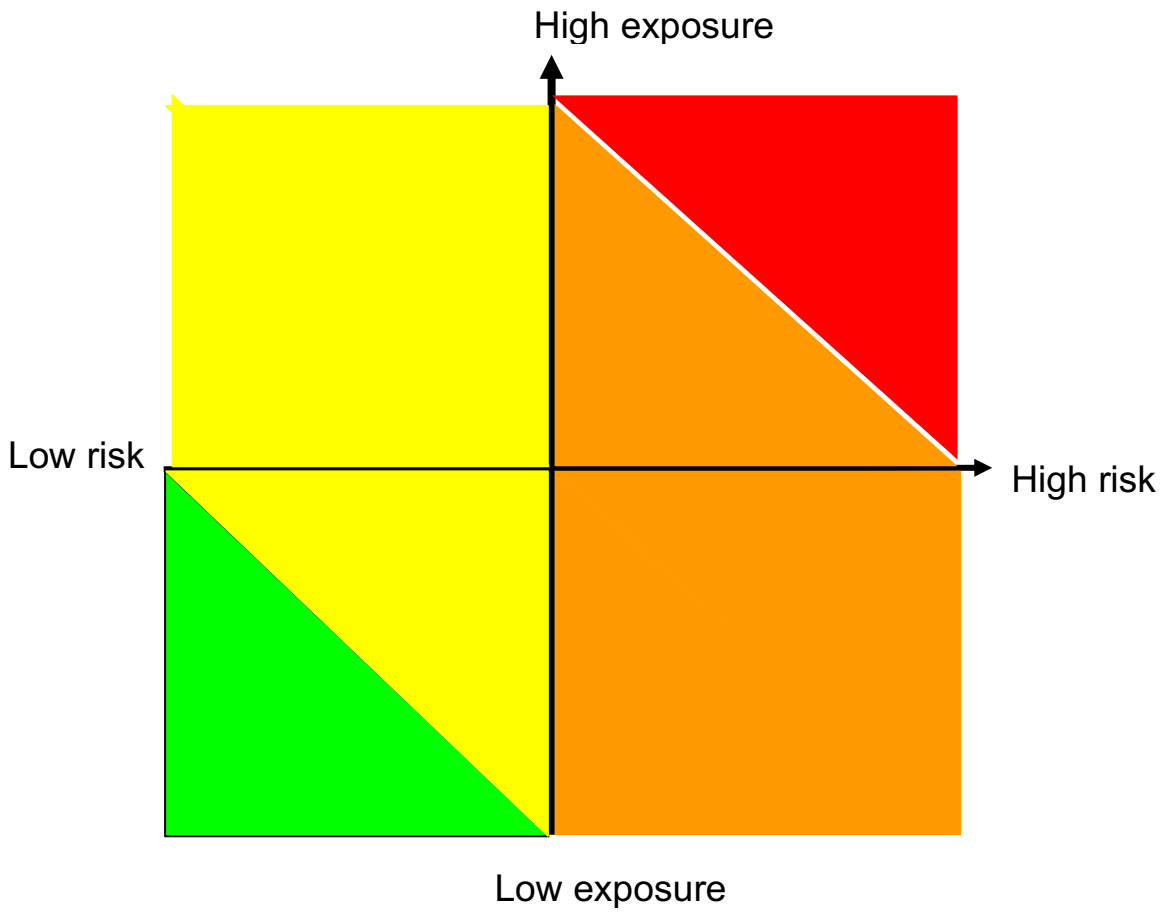

Figure 4: Individuals in red would be of very high priority to be tested, in orange of high priority to be tested, yellow would of medium priority to be tested and green to be of the lowest priority to be tested. Note: this diagram is entirely schematic and is not intended to suggest demarcations between different testing groups with regard to any particular characteristic.

Fig 4. displays an *exemplar* testing strategy which could be used in the case where widespread reliable antibody testing does become available. Such prioritisation is likely to be essential due to the strain on resources needed for testing.

In light of the concerns discussed above, relating to the quantity and quality of available tests, concerns about the social implications of false negatives, and associated concerns regarding compliance and data privacy if information is held centrally, relying on 'immunity passports' appears, at this point, to be a risky strategy. This is of course compounded by significant uncertainties in the degree of immunity actually conferred by past infection.

Furthermore, public concerns are likely to ensue if it becomes perceived that particular sectors of the population are preferentially issued with such passports. This will almost certainly *appear* to be the case, as exposure and recovery rates are not uniform across the population, and hence rates of true positives are unlikely to be either. Already disadvantaged groups, such as the immunocompromised (who may require lower risks of re-infection post recovery to feel safe), may feel further sidelined if such a scheme is implemented.

4. Important policy questions

In light of the issues raised above, numerous questions remain to be answered about the government's testing strategy. Some of these questions should be considered in light of both possible outcomes with regard to test development: that reliable antibody tests are developed in a useful timeframe, or that they are not.

Similarly to the questions posed concerning future vaccines in our previous report, the risks of over-reliance on as yet unavailable technologies (here tests, there vaccines) in the development of an exit strategy should be minimised where possible.

Supporting test development:

1. Can the government expand upon what efforts it is taking to support research into new antibody tests, and how many such projects are currently underway?
2. Should new antibody tests be successfully developed in the UK, what steps will the government take to ensure that the intellectual property concerns do not inhibit their sharing around the world?
3. What steps are the government taking to support research laboratories and companies in developing new and better antibody tests?

Testing capacity:

1. If most testing (both PCR and antibody types) is to be carried out by healthcare workers, do we have the capacity in terms of people, and do the benefits of testing outweigh the risks to those workers?
2. There have already been shortages in critical reagents for testing, what is the government doing to sure up supply and prepare for widespread antibody testing?
3. Who will bear the brunt of the administrative cost associated with selecting those for testing, recording those tested, and retaining data on test results? Does the NHS have capacity for this currently?
4. What steps will the government take to regulate the supply of private or unverified tests; given that such devices are already being sold online, with limited evidence that they work?
5. Can the government confirm the situation with regard to the supply of reagents needed for PCR tests within the UK?

Using tests:

1. What is the government's current prioritisation strategy for the administration of antibody tests?
2. What steps have been taken in designing this strategy to ensure that it is both fair and equitable?
3. How is antibody testing being considered as part of a lock down exit strategy?
4. How does the government intend to combine contact-tracing technology with widespread testing, and will it work with Apple and Google to make the contact tracing privacy-preserving?

5. How will the government address the risks associated with lower-than-optimal specificity and sensitivity of antibody tests?
6. Who will bear the risks of poor specificity and sensitivity of antibody tests if they are distributed by the NHS and are later found to be significantly sub-optimal?
7. What steps are the government taking to mitigate against the unknown degree of immunity from future re-infection implied by a positive antibody test?
8. What is the maximum per-unit cost of an antibody test that the government would be willing to support?

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