
September 11, 2020

The Independent Scientific Advisory Group for Emergencies (SAGE)

The Independent SAGE Report 13

Independent SAGE: The complexities of testing for COVID-19: the why, the who and the how

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Submitted to The UK Government and the People of Great Britain & Northern Ireland by Sir David King, former Chief Scientific Adviser, UK Government, Chair of Independent SAGE

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INTRODUCTION

COVID-19 will likely remain in circulation for many years. Nevertheless, in the absence of widespread and sustainable herd immunity (generated through vaccination), we advocate a strategy which aims to minimise new transmissions as much as possible, aiming for Zero COVID. If we want to avoid further damaging lockdowns, we need a wider testing strategy than at present, in combination with fast and effective isolation with support for those affected, and other public health interventions. Given that about 50% of people infected remain asymptomatic—with younger people and children even more likely to be so—it is self-evident that identification of [asymptomatic individuals](#) may contribute to such a strategy, although any such approach should focus on those at highest risk, on top of capturing all symptomatic individuals.

Of crucial importance is to view testing as a pathway, starting with the individual, community, or population being tested, through to an intervention based on a result. The “NHS T&T” system [is flawed](#), with an illogical focus on numbers tested, inadequate contact tracing, and increasing evidence that only a low proportion of those asked to isolate for 14 days are able to do so.

Further, existing UK laboratory expertise and capacity (particularly in England) has been bypassed, rather than being asked to lead the required expansion of testing to support the pandemic response, contributing to a disconnect between outsourced testing and the local public health infrastructure required to support contact tracing and isolation. Despite current inadequacies of basic issues such as the logistics of swab and test supply, and the difficulties of isolation, leaked details have emerged now of a government “[moonshot](#)” initiative- an hugely ambitious plan for 2021 involving testing of the whole population at regular intervals to allow “normal” life to re-appear. While we welcome plans to improve the current NHS Test and Trace programme, and explore new, easy to access testing technologies, we worry about the enormous projected cost of £100 billion – close to the entire annual NHS budget, with poor rationale, and its reliance on private sector contracts, given their poor performance in the testing and tracing systems so far. A lot more detail about the approach and proper scrutiny is required.

Although not the focus of this brief report, we also recognize the critical importance of human behavior in ensuring that any expanded testing programme does indeed deliver the desired outcome- namely, that individuals wish to be tested, can easily access a test, are willing to provide their contacts and that they are supported to isolate if required. It is essential to have clear communication of the government pandemic mitigation strategy in a way that is understandable by all our communities, that there is no stigma attached to being infected, and that there is no disincentive to participating in this plan. Lastly, we must row back from portraying any initiative as “world beating”, “moonshot”, “a magic bullet” and the like. Regardless of the success or not of current vaccine trials, in the end testing will need to be one component of a series of measures, including behavior change, social distancing and public health contact tracing, in moving us towards zero COVID.

This document focuses on how best to optimize and develop the current testing environment.

In essence, there are three core purposes to testing, which are not mutually exclusive:

1. **Diagnose COVID disease** in symptomatic individuals - for clinical management (providing treatment if required) and infection control (self-isolation of newly infected people).
2. **Identify infection in close contacts of cases** - for infection control (ensuring that contacts of cases self-isolate whether symptomatic or not, while allowing non-infected contacts to be released from isolation) and possible clinical management (providing treatment if symptoms worsen). This process particularly protects those vulnerable to severe infection.
3. **Identify infection within communities** - to instigate public health measures at community level (e.g., impose restrictions to increase social distancing and other hygiene measures if levels of infection are

rising). This will also be an important way of identifying levels of infection in people without symptoms.

These purposes are described in more detail later. In all cases, data capture, linkage, and accessibility (including rapid access to data by primary care physicians) are critical to effectiveness of the testing pathway. Further, all testing pathways have limitations, for instance, test performance, and these should be considered prior to implementation.

TYPES OF TESTS

The term 'antigen test' has been used to describe detection of the virus, or rather chemical components of the virus. This requires a sample from the nose or throat, which is where the virus replicates. Saliva may be a particularly useful alternate to a swab, although requiring further validation against a range of test types. Swabs or saliva are required to detect the virus - almost always meaning detection of the viral genome, although there are some emerging approaches to detecting virus proteins (correctly termed antigens). The typical (but not the only) genome detection test is based on the polymerase chain reaction (PCR), a well-established approach to laboratory testing for all human viruses, including other respiratory pathogens such as influenza, as well as blood borne viruses such as HIV, hepatitis B and C. These assays define someone infected with COVID, who may be pre-symptomatic, symptomatic or recently symptomatic, or indeed may not experience any symptoms at all.

1. PCR test performance

Although such tests are very sensitive for detecting viral genome, any **reduced sensitivity (i.e. a negative test in someone who has virus genome)** seen in practice is overwhelmingly due to an 'inadequate' swab which has not captured an optimal amount of virus containing cells. In contrast, a range of laboratory procedures are usually in place to make false positive PCR results (i.e. **a positive test in someone who does not have virus genome**) highly unlikely. Such false positive results can be further minimised by a process of repeating initial positive tests from the same sample or raising the test output signal threshold for defining a positive. These are all well-established laboratory procedures used for other virus tests.

Having said this, the impact of any suboptimal test performance will be determined by the way in which it is used. For instance, mass molecular testing without such confirmatory processes, as described within the proposed Moonshot programme, brings a risk of false positive results at a low population prevalence of infection.

2. Infectivity

The performance characteristics of the test itself (which asks whether the viral genome is present or not) are not to be confused with whether or not a positive test indicates that that individual is infectious to others. The concentration of virus in the throat/respiratory secretions of an infected individual will increase during the course of disease and then decline. This reflects the degree of viral replication at the time (the more virus, the more viral genome will be detectable by tests). In general, the higher the concentration of virus, the more potentially infectious that individual is to others - put another way, contact with respiratory droplets from such an individual is more likely to give rise to a new infection in a close contact. Of course, infectivity to others is a function not only of the concentration of virus, but also of **behavioural, social and clinical factors**. Typically, the highest concentration of virus appears 24-48 hours prior to symptoms, and may persist for 7 or more days after onset of symptoms. Infected individuals without any symptoms can also be infectious to others. Virus genome detected after disease recovery will be at a low level, and therefore will present less of an infectious risk compared to earlier on in the disease process when the concentration of virus being shed will be higher. This broad generalisation skirts over many more detailed aspects of viral replication, such as the balance between upper and lower ([lung](#)) respiratory tract, and other anatomical sites. There is interest in developing a standard reporting method which allows results to be defined as a **concentration** of virus in the throat/nose, rather than as a binary positive or negative, as a way of teasing out these subtleties.

3. Antibody tests

Antibodies are produced in the blood by B cells, and antibody tests are useful to identify those who have had infection in the recent past, since they develop in the blood 7-10 days after onset of infection. There is concern that such antibodies may decline over weeks or months, such that using such a test to assess 'previous exposure' may be unreliable. The degree to which antibodies may also represent potential protection from subsequent infections has been questioned by emerging reports of 'reinfection' - although this appears a very rare event. Another arm of immunity is conferred by T cells, which may play an important role in prevention of subsequent infection. Unfortunately, measurement of blood T cells targeting COVID is more technically challenging, and outside the realm of routine diagnostic laboratories for the near future.

Testing for virus or antibody is usually undertaken in laboratories where the required equipment for preparation of the sample, actual testing, and recording of the result can occur. However, a number of tests are being developed which can be undertaken outside of laboratories. These are variably termed 'point-of-care' or 'near patient' tests and are currently used for some other infections. There is considerable hype around some of the new tests; however, like any other technologies, they should go through a formal evaluation process before being approved for use. Evaluation criteria include sensitivity and specificity for detecting the target virus.

We remain very concerned about the use of such tests to provide "immune passports" and the like. Not only may interpretation of test results be flawed, but the social, political and administrative implications of such a stratification of the population will be highly problematic.

4. UK Testing Pillars

The UK government has defined different [Pillars](#) to describe COVID testing. These relate to issues such as where testing is done (NHS vs Lighthouse labs) and whether testing is for individual feedback or for wider surveillance. It neither refers to the type of test done, nor its diagnostic or public health function, which has caused some confusion. Currently, the reported total number of new cases are calculated by adding together Pillar 1 and 2 test results.

PURPOSE OF TESTING

The main functions of testing are as follows:

1. Diagnosis of COVID Disease (symptomatic infection)

Purpose: To support a diagnosis of symptoms in order to subsequently initiate infection control procedures (e.g. isolation of new case and their close contacts)

Scenarios: Healthcare or community setting. Mild to severe symptoms. Low threshold for testing, i.e. within 24 hours of symptoms consistent with COVID19.

Testing: Requires the most sensitive tests, since even a low level of RNA (possibly non-infectious) likely reflects either previous COVID infection or early pre-symptomatic infection depending on the clinical scenario.

Requires laboratory processing with minimal delay. Consider a judicious use of [antibody testing alongside PCR testing](#) to optimise diagnostic performance.

As winter approaches there is an advantage of testing for multiple infections (including influenza) from a single sample. However, this will require new pathways of care, since testing for non-COVID respiratory infections is not currently widespread. Advantages of very early detection of influenza, for instance, can lead to timely oseltamivir treatment.

2. Identify infection in contacts of cases (asymptomatic and symptomatic)

Purpose: To limit isolation to those requiring it, with the objective of motivating and supporting those actually needing isolation, whilst minimising stress for those not requiring isolation and supporting the economy.

Scenarios: These are, in essence, individuals who have been at **risk of infection**, and asked to isolate for 14 days. This includes those arriving from high risk countries, as well as contacts of known cases within the UK.

PHE have presented a modelling study to [SAGE](#) in relation to port of entry that suggests a test on entry and then 5-8 days later could reduce the period of quarantine.

Such an approach could also be applied to contacts of cases, with several advantages:

- engagement with the individual asked to isolate
- incentive to maintain isolation until test
- ability to reduce period of isolation
- opportunity to seek clinical advice following a positive test, and stimulate further contact tracing if need be

This will require more than the current SERCO/SITEL call centre approach, since it requires a more active level of engagement with those asked to isolate.

Testing: If symptomatic, then as described above. If asymptomatic, then tests with lower level of sensitivity may be appropriate since these will better predict infectivity to others (higher viral load). This allows consideration of near person, point of care (POC) testing approaches.

It is important to get a very rapid result – ideally POC test obtained at home or near to home so as to enhance infection control. If home tests, then they can be provided to an individual at beginning of isolation. Ideally there would be immediate data linkage for transmission of the result, including to primary care.

3. Identify Infection within communities (asymptomatic and symptomatic)

Purpose: As lockdown is eased, to identify the potential for specific settings to become a focus for new infection spread, thus allowing a rapid public health intervention and its evaluation.

Scenarios: Where infections are rising, such as defined geographical areas, or more focused high-risk settings such as schools, universities, workplaces, health and social care settings. Such routine testing is already offered in some in hospitals and care homes, and pilots are underway for other settings. We urge rapid sharing of pilot data to inform policy.

Testing: This requires most imagination for maximizing effectiveness, but with sensitivity to detect early indications of infectious virus. Options and issues include:

- Frequency of testing- for instance twice weekly, given a latent period of 3-6 days
- Rapid turnaround to facilitate isolation and intervention when needed. This could mean an onsite lab for closed system PCR or other molecular systems (e.g., schools, universities)
- Pooled testing
- Consideration of saliva as alternative to throat/nasal swab, with advantages of acceptability as well as being more appropriate for children
- Consider population approaches such as [sewage testing](#), which may provide an early indication of asymptomatic or unreported infections within the community

RECOMMENDATIONS

1. **Establish at the outset the primary testing function and pathway**, from initial sampling through to public health or clinical intervention and data management. Whilst we support development of novel testing technologies for detecting the virus and for immune responses, we recognise that testing is more than just the technical process.
2. **Increase overall testing effectiveness**, through a focus on cases and their contacts as a prerequisite for reducing the current high levels of new cases and supporting our goal of reaching Zero COVID. The current NHS Test and Trace programme needs urgent strengthening, including support and incentives for those asked to isolate. The Moonshot aspiration appears as a distraction.
3. **Put in place mechanisms to assess the effectiveness** of each testing modality.

4. **Assimilate testing pathways into existing structures**, including NHS laboratories and local public health functions, to ensure optimal delivery.
5. **Provide clear messaging and engagement** with the general population and local communities for new testing pathways, particularly with regard to the purpose of testing, and caveats around test results. Plans for any future additional testing strategies must be extensively road tested with the communities to be involved and with co-development of protocols, to ensure acceptability.
6. **Ensure public trust in new technologies**, by avoiding exaggerating the performance of tests in development prior to full validation, nor with consideration of how they will be assimilated into a diagnostic pathway. Scientists as well as government have this responsibility.

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Following the science