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DIAGNOSTICS: POINT-OF-CARE

Optimizing Covid-19 isolation: the role of virus testing and the technology requirements

By Nick Collier, Chief Technology Officer at Sagentia

As work, education and recreation resume following Covid-19 restrictions, further isolation regimes must be proportionate, effective and properly supported by technology. Molecular tests for SARS-CoV-2, the virus that causes Covid-19, will play a central role. But it's not all about the testing methods: the development and implementation of an effective long-term testing strategy is critical as the comparative graphs demonstrate.

Businesses, schools and other establishments across the UK and around the world are bringing people back together as lockdown measures ease. Much has been done to ensure this is done as safely as possible, but there is still uncertainty surrounding the effect it will have on Covid-19 infection rates. In the UK, there are fears that a second wave of cases could result in another national lockdown, causing immense harm to economic, educational and social recovery.

To mitigate this risk, the UK's National Health Service (NHS) is rolling out its test and trace service to 'trace the spread of the virus and isolate new infections and

play a vital role in giving us early warning if the virus is increasing again, locally or nationally'[1].

The principle is simple. If an individual is infected with SARS-CoV-2, their recent contacts are notified. The risk of onward infection is assessed based on type and duration of contact. If the risk is high (e.g. >15mins of face to face interaction) contacts will be asked to self-isolate for 14 days. If symptoms develop during this time, they need to request a home testing kit. Then, depending on the result, they either complete the 14 day isolation or begin a seven day isolation from the date symptoms started.

Clearly test and trace has an important role to play supporting and managing the UK's recovery from the pandemic. Yet flaws in the current testing strategy mean that it risks becoming an anti-pattern, ultimately doing more harm than good.

Current testing logistics hinder test and trace

The primary limiting factor of test and trace is the turnaround time of test results.

Currently, molecular testing of throat and nasal swabs via RT-PCR is the principal method to ascertain whether someone is infected with the virus. These tests typically take between two and four hours to run on central lab equipment. However, the logistics of sample collection, transportation to the lab and scheduling the test means the overall process takes much longer.

According to the NHS website, it can take up to 72 hours for a patient to receive results after a sample is submitted. When you factor in the postage time for a home testing kit, this is likely to extend to four or five days. Some NHS workers have reported waiting as long as seven days for their test results[2].

This has become a contentious issue, with the Royal College of Pathologists saying limitations with the current testing regime need to be 'urgently addressed'[3].

The Royal College of Pathologists has published Covid-19 testing: a national strategy to look beyond the peak of the pandemic and help build robust processes and structures for both viral and antibody testing. According to the organization's President, Professor Jo Martin:

"Testing is not something that is just done and counted. It is a process with clinical purposes for individual patients, for those who care for them and for the population at large. It is a conscious and targeted use of valuable materials and highly skilled professionals within the context of a pathway and purpose."[4]

The testing bottleneck extends the time lag between display of symptoms and diagnosis, which compromises the effectiveness of test and trace. If large numbers of people and their contacts isolate unnecessarily, it creates a ripple effect of needless inefficiency hindering the UK's return to normality. Conversely, if asymptomatic people spend several days mixing with others before they are advised that a contact has tested positive and they need to self-isolate, the number of cases could quickly rise. Ultimately, this could trigger extensive regional lockdowns, or even a second national lockdown.

An alternative, localized testing regime

Virus shedding during the asymptomatic period means contact tracing needs to commence rapidly when someone starts to show symptoms. Unless RT-PCR results can be made available within 24 hours, the current approach introduces delays which frustrate efforts to control the virus spread. It would be better if high risk contacts of someone displaying symptoms isolated immediately, without testing. Then, if the original patient's test result is negative, the isolation can end early.

Contrary to popular expectation, tracing and isolation is not enabled by testing. Rather testing becomes a means of avoiding unnecessary isolation and loss of productivity.

Current issues with test and trace are largely rooted in the limited number of central laboratories that can conduct RT-PCR. A more localized approach could turn this situation around, enabling the service to play a more effective and constructive role in reducing the likelihood of a second spike in cases, while protecting economic and social recovery.

Lighthouse Labs controversy

The UK Lighthouse Labs network, established at speed to offer industrial testing capacity during the height of Covid-19, has been the source of much debate. An investigative report by The Independent suggests a failure to mobilize existing NHS and university lab facilities has resulted in lengthier turnaround times for test results. Several senior epidemiologists and microbiologists have indicated that using local labs in conjunction with the three central Lighthouse Labs would have been a better approach. This could represent a workable solution for long-term, largescale testing going forward.

According to Dr Lewis, an NHS microbiologist and national lead for pathology in NHS England's Getting It Right First Time Programme:

"[Testing] results have been too slow to be useful clinically, and they have not helped us direct our efforts. If we believe that testing is important in reducing the impact and ultimately saving lives, the fact this testing has been sub-optimal means we have to learn lessons. So now is our chance to take stock, and we've probably got three months to get this right before a second wave."[2]

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How test and trace timing impacts infection rates

It's clear that accelerating the turnaround time of Covid-19 test results needs to be a high priority. Pinpointing individual infections at the earliest possible stage can play a pivotal role in strategies to prevent an escalation of cases.

The following graphs compare various reinfection pathways resulting from a single infection, based on length of delays impacting test and trace for each subsequent symptomatic case.

The graphs included in this paper are simple illustrations showing how Covid-19 infections can grow. They assume each person can infect 2 others on average before self-isolating on getting symptoms. The goal is to illustrate the impact of obtaining test results and triggering contact tracing at an earlier stage.

Three or four day delay

Figures 1 to 3 demonstrate the rate of reinfection when test and trace is hindered by a three or four day delay in test results. We've illustrated the potential impact over a 35 day period beginning with one infected individual, although infections will continue beyond this point.

As Figure 1 shows, after 15 days, a four-day delay causes an exponential surge in cumulative cases. Figure 2 indicates how this stems from the first infected individual, resulting in more than 1,000 cases in 35 days. Compare this with Figure 3 where reducing the delay by just one day results in a total of 47 people being infected in the same timeframe.

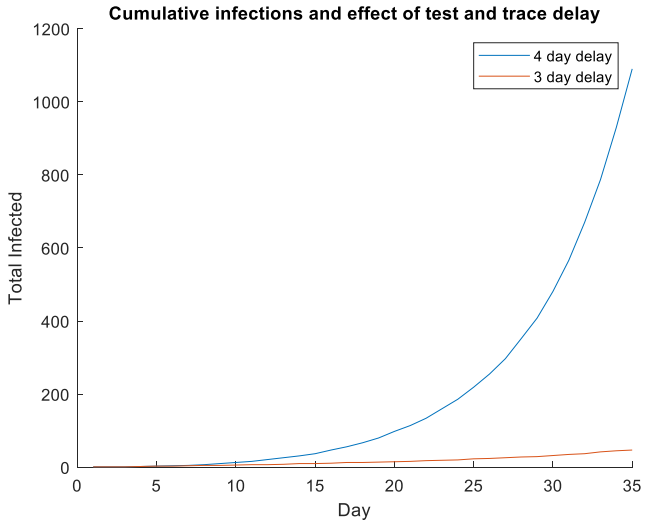


Fig 1: cumulative infections based on a three or four day delay to test and trace

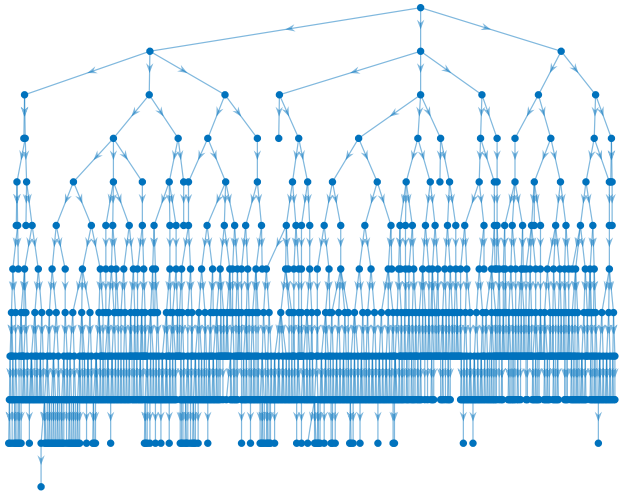


Fig 2: onward infections from the first case with a four-day test and trace delay

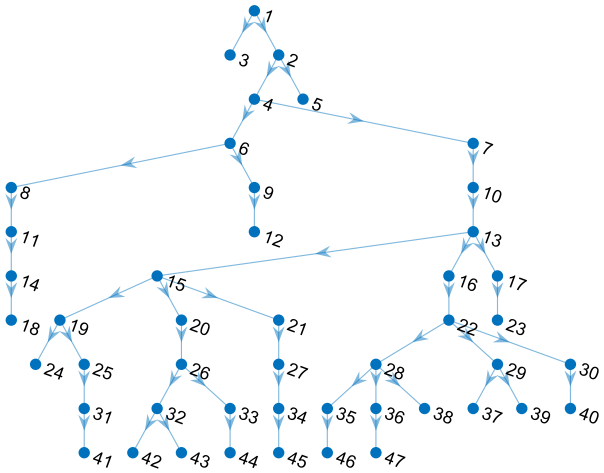


Fig 3: onward infections from the first case with a three-day test and trace delay

One or two day delay

As Figures 4 and 5 indicate, reducing the delay in test results to one or two days can make a significant difference to onward spread. The number of cases resulting from the initial infection is kept between five and eight, and spread is halted between days five and ten.

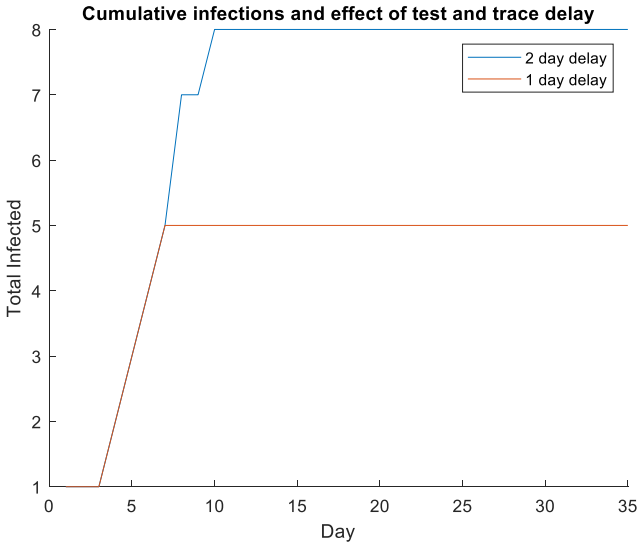


Fig 4: cumulative infections based on a one or two day delay to test and trace

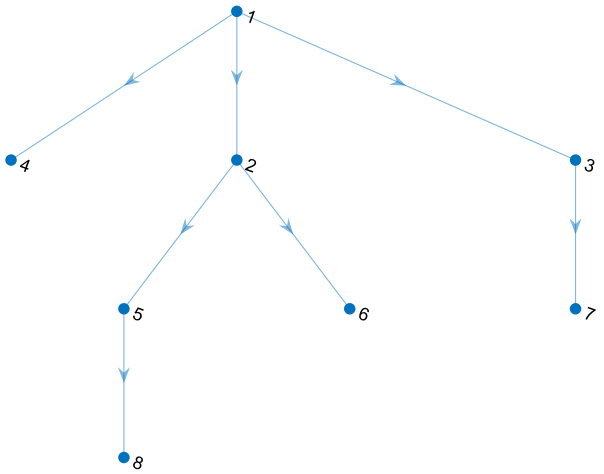


Fig 5: onward infections from the first case with a two-day test and trace delay

Four day delay versus no test and trace

This is not to imply that test and trace does not have any benefit with a four-day delay. As Figure 6 shows, many infections would be avoided over a 35 day period, compared to a situation with no test and trace mechanism. Nevertheless, a shorter delay is clearly preferable, and significant improvements are possible.

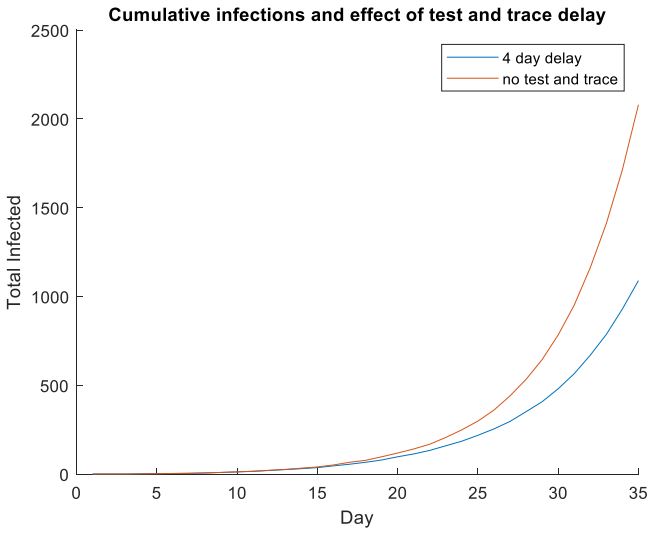


Fig 6: cumulative infections based on no test and trace vs test and trace with a four-day delay

Recursive tracing

The above illustrations are based on the tracing of direct contacts of a person suspected to have a Covid-19 infection. However, it's also worth considering the impact of tracing the contacts of contacts. This becomes particularly relevant if there is a significant delay between the first person displaying signs of infection and contact tracing being completed.

Figure 7 illustrates how this would impact cumulative infection rates, assuming everyone who is infected is traced and then self-isolates. With test and trace as it stands, the first infection has a four-day delay between initial display of symptoms and isolation of contacts. However, recursive tracing isolates contacts of contacts with a one-day delay because there is no need to wait for test results. Figures 8 and 9 show how infection cases escalate from the initial infected individual in each of these scenarios.

The cumulative infection rates are much reduced, but a downside is that this could result in large numbers of people self-isolating and needing tests to exit isolation. For example, if the first case has ten close contacts and each contact has a further ten close contacts, then 101 people will need to enter isolation.

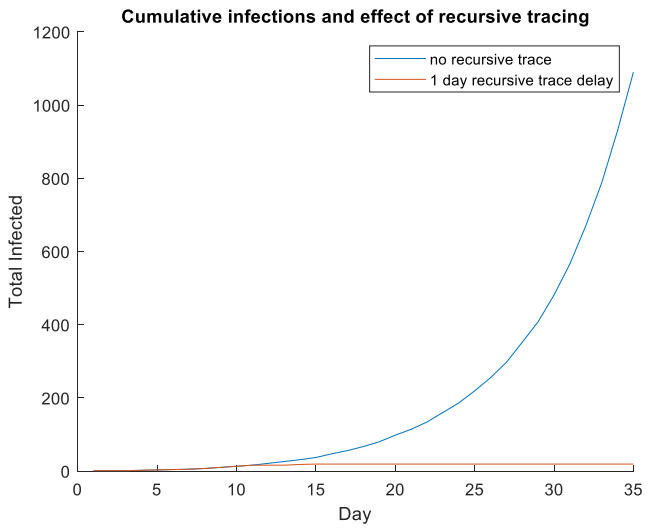


Fig 7: cumulative infections based on a four-day test and trace delay with no recursive tracing vs a one-day recursive trace delay

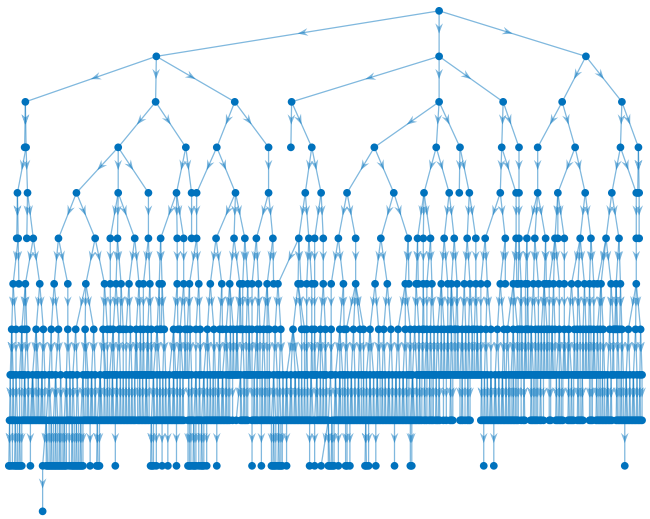


Fig 8: network diagram of onward infections with no recursive tracing

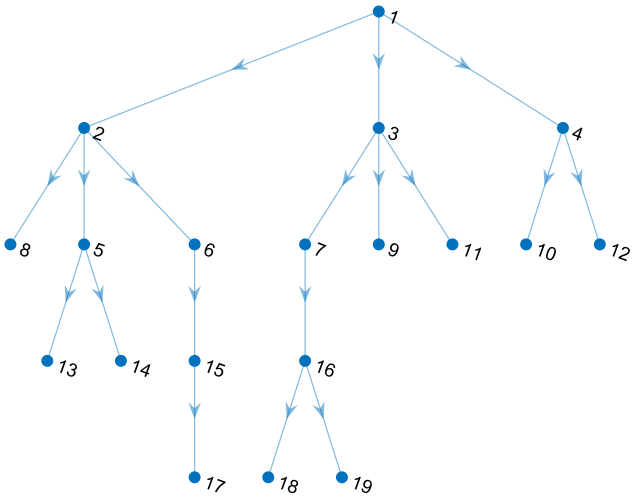


Fig 9: network diagram of onward infections with recursive tracing and 1 day delay

When to test contacts of confirmed infections

We have seen that unless testing is quick, it is better for those with Covid-19 like symptoms to self-isolate and then exit isolation based on a test result or recovery.

But what about the contacts of confirmed infections? For the traced contacts deemed at high risk of developing the infection the current UK advice would be to isolate for 14 days. This is based on the average virus incubation period of five days, with 97% of cases developing within 11.5 days and 99% within 14 days (see Fig 10). This is a long time, especially if you need to isolate several times, as may be the case for someone in frequent contact with many people.

Testing these contacts could offer a way to avoid unnecessary self-isolation. However, if testing is conducted too soon before symptoms develop it is unlikely to be sensitive enough.

So, when is the optimum time to test?

Let's assume a laboratory PCR test can detect infection two days prior to symptoms being displayed. From here, we can estimate the percentage of infections that would be detectable on each day of isolation (detectable by PCR or development of symptoms prior to testing).

Testing at day three could identify up to 50% of cases, whilst at day five it could identify 80%. Testing under these assumptions only shaves an average of two days off the isolation period if a patient develops symptoms. This is a relatively small gain, and no gain at all if the turnaround time is several days or more. However this could prove beneficial in identifying asymptomatic cases.

Day	%
3	50
5	80
7	90
9	97

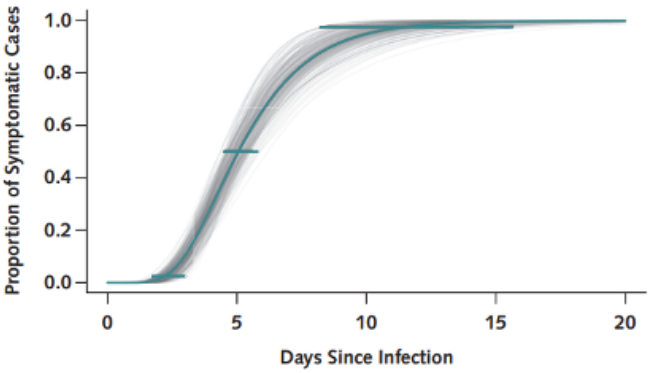


Fig 10: Covid-19 incubation period[5]

To offer greater benefits, tests of asymptomatic contacts need to detect infection >2 days before symptom presentation. Whether this is possible will require more research.

Is there a role for Point of Care testing?

A number of Point-of-Care (PoC) molecular tests for SARS-Cov-2 exist, with turnaround times of 15 minutes to 1 hour. These include the Abbott ID Now, Cepheid Xpert Xpress SARS-CoV-2 and Mesa BioTech Accula SARS-CoV-2 as well as DRW's SAMBA II.

The tests vary in sample preparation and amplification method and have different sensitivities, although comprehensive data is not available due to the speed at which these have been brought to market.

PoC clearly offers a potential route for Covid-19 testing with a quicker turnaround. However, there are issues linked to achieving PoC testing at scale. The challenge of shipping samples to one of three large facilities is replaced with the challenge of distributing many instruments to disparate locations. Consideration also needs to be given to the skill level required to conduct tests. While CLIA-waived PoC devices can be used without the need for specialist training, others may need to be handled by skilled staff.

Frequent testing as a possible alternative to isolation

Another consideration is whether it might be possible for those in close contact with a suspected infection to continue as normal if they were symptom free and regularly tested.

Imagine a situation where a colleague develops Covid-19 symptoms and self isolates on day four post-infection. You were exposed to them on days two and three, so there is concern that you may have been infected. If your employer conducted high sensitivity testing on the morning of day four, and the result was negative, might you continue to work?

The answer will very much depend on the level of virus required for transmission and whether this is above or below the limit of detection of the test technique used. Certainly, it would seem sensible to test every day for a period of time such as seven to nine days. For this to be useful, a PoC test that gives immediate results (<20mins) will be required. It will need to use an easily acquired sample, such as saliva, and be sensitive enough (10^3 copies/mL) to detect early stages of infection.

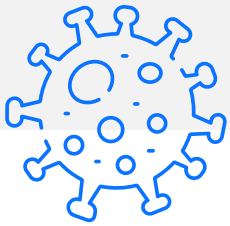
Final thoughts

Arguably, for test and trace to be effective, testing needs a rapid turnaround time to prevent onward spread of Covid-19 while samples are being processed. If turnaround and contact trace times cannot be maintained below 48 hours, people with symptoms AND their close contacts need to proactively isolate.

In the absence of fast results and tracing, recursive tracing may be needed to bring a local outbreak to an end. However, this is hugely inefficient and would result in many people isolating.

An alternative to isolation for close contacts of confirmed cases could be rapid and daily testing with a PoC device, possibly conducted by employers or schools. Such a test would need to provide almost immediate results, use a sample type that is easy to acquire and be sufficiently sensitive to detect infections two days before onset of symptoms.

It's our belief that innovation in PoC testing technologies and strategies will play a vital part in the ongoing, long-term efforts to protect global populations from Covid-19. This goes for the avoidance of infection and the wider recovery of economic, educational and social systems alike.



[1] NHS test and trace: how it works https://www.gov.uk/guidance/nhs-test-and-trace-how-it-works
[2] Failing the test, The Independent, June 28 2020 https://www.independent.co.uk/news/health/coronavirus-testing-lighthouse-labs-nhs-deaths-delay-a9589381.html?amp
[3] Pathologists warn UK coronavirus testing needs 'urgent' improvement, Financial Times, June 10 2020 https://www.ft.com/content/11b7cd42-0170-47da-995f-bee8ba36a3fd
[4] Covid-19 testing: a national strategy, The Royal College of Pathologists https://www.rcpath.org/profession/on-the-agenda/covid-19-testing-a-national-strategy.html
[5] The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7081172/pdf/aim-olf-M200504.pdf

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