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## BRIEFING

## Covid-19: How the UK is using lateral flow tests in the pandemic

Lateral flow tests are pivotal to the UK government's strategy to reduce the spread of the coronavirus by identifying asymptomatic patients. But with questions over their accuracy, **Ingrid Torjesen** asks whether they are being used appropriately

Ingrid Torjesen *freelance journalist*

As many as 384 million kits have been ordered by the UK government at a cost of over £1.3bn (€1.5bn; \$1.8bn), with most being spent on a test made by the US firm Innova Group. And an additional £0.9bn worth of contracts have just closed. Lateral flow tests have become a lucrative business in the covid-19 pandemic.

Laboratory based polymerase chain reaction (PCR) tests are often seen as the "gold standard" test for identifying clinical cases of infection. But they take time, are relatively expensive per sample, and are not very portable, because of the need for laboratory processing. They are also not perfect, detecting viral shedding long after the infectious period, with people continuing to test positive for a mean of 17 days. This means that people who are not infectious are unnecessarily quarantined.<sup>1</sup>

This is where lateral flow devices can have a role. They can detect people with higher viral loads, are relatively inexpensive, do not require laboratories, and provide results rapidly.

As the pandemic continues, countries around the world are looking at rapid diagnostic tests such as lateral flow tests as a way to test themselves out of the cycle of lockdowns and restrictions and reopen their economies.

### How accurate are lateral flow tests?

Lack of a central registration process and of comparative data means that Public Health England's Porton Down laboratory and the University of Oxford have been tasked with evaluating the sensitivity, specificity, and kit failure rate of lateral flow tests. Only three of 40 test kits evaluated made it through the first assessments.<sup>2</sup> And only one of these has been evaluated in field studies; it is still unknown how the others work in the real world.

The World Health Organization points out that the accuracy of lateral flow tests depends on several factors, including the time from onset of infection, the concentration of virus in the specimen, the quality and processing of the specimen collected from a person, and the precise formulation of the reagents in the test kits.<sup>3</sup>

The quality and processing of the specimen are determined to a large extent by who carries out the tests. Public Health England's evaluation of the Innova test showed that its sensitivity was 79.2% when used by trained laboratory scientists, 73% when used by trained healthcare staff, but only 57.5% when

used by track and trace centre staff employed by the pharmacy chain Boots.<sup>4</sup> But performance should improve with experience, especially among regular users such as people testing themselves several times a week before going to work, says Iain Buchan, professor of public health and clinical informatics at the University of Liverpool.

WHO says that lateral flow tests are more likely to detect positive cases when viral loads are highest and patients are most infectious—typically, one to three days before the onset of symptoms and during the first five to seven days after the onset of symptoms. WHO's Essential Diagnostics Test states that negative results should never be used as a basis of decision making.

A recent evaluation of data from a quarter of million people who had participated in the NHS Test and Trace programme, available as a preprint, supports this.<sup>5</sup> The evaluation, by the University of Oxford and Public Health England, used NHS Test and Trace data to ascertain whether lateral flow tests were sufficient to detect the most infectious cases. It found that only six in 100 contacts of people with cases of infection went on to get infected themselves, and its modelling predicted that lateral flow tests would detect most of the people who would otherwise go on to infect someone else. This modelling indicated that the tests would detect up to 90% of the infections that individuals passed on.

### What about asymptomatic people?

All the studies from Public Health England and Oxford University have focused on patients with symptoms.

"Asymptomatic people have a viral load peak that looks to be, on average, lower than the viral load peak of people with symptoms, and it stays at that peak for less long," says Mike Gill, former regional director of public health for the South East of England.

In other words, if you don't show symptoms, you shed virus or clear virus more quickly, he says, which means that any test with a relatively low level of sensitivity (such as lateral flow tests, in comparison with PCR tests) could struggle to pick up asymptomatic infections on an "intolerable" number of occasions.

Where the tests have been used among asymptomatic people in real world settings, the reported performance has indeed been lower. In a pilot study conducted in Liverpool 60% of infected asymptomatic

people went undetected, including 33% of those with high viral loads.<sup>6</sup> Up to 21 January nearly 560 000 lateral flow tests had been done on more than 200 000 Liverpool residents, identifying 4421 people who may not have otherwise known they were likely to be infectious. Among students undergoing lateral flow tests at the University of Birmingham in December, only 3% of those who would have tested positive on PCR were detected.<sup>7</sup>

This is why WHO recommends repeat testing using lateral flow devices or preferably confirmatory testing with a PCR test after a negative lateral flow test.<sup>3</sup>

“We already knew that lateral flow tests do appear more accurate with patients who have more virus present,” says Alexander Edwards, associate professor in biomedical technology at the Reading School of Pharmacy. “It follows that they may be better suited to spotting ‘spreaders’ than identifying everyone infected.”<sup>8</sup>

The question is how to manage false negative results, he says. Are people who receive a negative test result “safe” or “safer” than they were before they were tested?

That’s a worry, particularly as lateral flow tests bought over the counter become more common, and with tests easily bought on the internet and members of the public willing to purchase them for peace of mind.

In other countries the tests are available to buy over the counter whether or not customers have symptoms. For example, in the US the Food and Drug Administration authorised its first home test in December. Germany plans to make self-testing kits available from pharmacies from this month (February) at a cost of €10-15.

In the UK the Medicines and Healthcare Products Regulatory Agency (MHRA) has granted an “exceptional use authorisation” so that the Innova test can be deployed as a self-testing device as part of the NHS’s national testing programme (the authorisation was granted on the basis of data from the Liverpool pilot). Innova cautions that, as the test has been evaluated only in symptomatic patients, its performance may differ in asymptomatic patients.

All in all, self-testing using lateral flow tests leaves a lot of possibility for misinterpretation of results.

### What should the tests be used for?

In a nutshell, lateral flow devices must be used within strictly defined parameters.

The Innova test is being used as a self-test in asymptomatic individuals as a part of the UK’s Test to Find strategy. A positive result is a “red light,” says the Department of Health and Social Care for England, requiring the most infectious individuals and their contacts to rapidly isolate themselves to protect other people from infection.

The tests are for people who cannot work from home, including NHS staff, care home staff, teaching staff, students allowed to attend higher education institutions, and employees of companies that have signed up to the government testing scheme.<sup>9</sup> Self-tests are generally conducted twice weekly before users leave home.

The tests are also being rolled out to local boroughs to enable them to offer community testing to asymptomatic people.<sup>10</sup> This has been very well received in Liverpool, says Buchan, one of the senior clinicians involved in analysing the pilot data. It enabled people to get tested before doing something that would put them in contact with others, such as going shopping. Buchan says it engages communities and engenders hope by enabling people to do

something for themselves, while allowing the public health team to reinforce key hygiene messages such as “hands, face, space.”

The MHRA continues to pilot the test for uses outside its exceptional use authorisation, and, after successful a pilot, the tests are now being used in hospital emergency departments to quickly identify patients arriving with the infection so they can be separated from other patients.<sup>11</sup> Patients currently receive a PCR test, where the longer turnaround time raises the risk of spread.

Lateral flow tests are also being piloted for use by visitors to care homes to potentially allow them to meet residents without an intervening screen.<sup>12</sup>

### What should they not be used for?

At present, lateral flow tests are not authorised for “serial testing” of school pupils who have been exposed to a confirmed positive case of covid-19 to enable them to attend school (pupils who are exposed to infected cases have to isolate).

The government had hoped that serial testing would enable it to reopen schools but soon abandoned such plans. (It blamed the U turn on concerns over rising cases of the Kent variant, but it seems it still plans to test the strategy in a small number of trials<sup>13</sup>). The MHRA has pointed out that lateral flow tests are still not authorised for use in this way.<sup>14</sup>

The tests also cannot be used to shorten quarantine of travellers arriving in the UK, under the government’s Test to Release scheme. That can be done only with a PCR test result.<sup>15</sup>

Jon Deeks, who leads the Biostatistics, Evidence Synthesis and Test Evaluation Research Group at the University of Birmingham’s Institute of Applied Health Research, says the health department’s “red light” interpretation of a positive result is a good use of the tests. But a “green light” negative result should not be taken as a sign that all is well, he says, and particularly not to do anything you would not have done otherwise.

That’s hard to control, particularly in a population that has spent over a year enduring lockdowns and social distancing. There is a concern that people who test negative will gain a false sense of security and adopt more risky behaviour. Deeks says studies have shown that people who have recently had a negative result from cancer screening are less likely to have potential symptoms checked out.

Gill agrees. “More and more negative tests are being thrown out there with absolutely no understanding at a serious or psychological scientific level of how to minimise the false reassurance that that generates,” he says.

A lack of consistent messaging across the UK is exacerbating the situation.<sup>16</sup> People who receive a negative result in Lewisham are told it’s “great news,” while in Blackpool they are told that “you were not infectious when the test was done.” They are encouraged to keep getting tested “regularly” in Lewisham, which translates to “once a week” in Bradford and “twice a week” in Havering.

### How can lateral flow and PCR tests work together?

As well as being asked to isolate, anyone with a positive result from lateral flow testing should have their result confirmed with a PCR test.

Buchan says everyone in the Liverpool pilot who tests positive is invited for a confirmatory PCR test. This is important for surveillance purposes: the data help with planning, and samples can be sequenced to look for new variants in the community. And it will

become even more important if, as is likely, covid-19 becomes endemic rather than pandemic.

However, because of the high prevalence of infections, from 27 January the government temporarily removed confirmatory PCR tests.

### Regulation grey zone

Lateral flow tests occupy a strange, deregulated grey zone. Most such “in vitro diagnostic tests” can be declared by their manufacturers as conforming to the UK Medical Device Regulations 2002. A UK approved body approves tests for higher risk infections, such as HIV, or if it is a self-testing kit. The list of high risk infections is outdated and doesn't include SARS-CoV-2. So, manufacturers can self-declare covid-19 tests for professional use. The only stipulation is that they must be carried out by trained staff: they cannot be simply rolled out as part of a self-testing programme.

That said, they can be used for research purposes. Innova's test was piloted for community testing in Liverpool last year. And the MHRA has issued an exemption for the Innova test so that, even though it is approved only for use by professionals, it can be sent out for self-testing under the NHS testing programme. This has highlighted the need to reform the regulations, at least in the UK.

The claims of diagnostics companies have been “without any serious scrutiny” for years, says Jon Deeks, of University of Birmingham's Institute of Applied Health Research. “They tend to be based on selected results, published with minimal detail, and their performance claims are rarely ever replicated. It is possible for the government to use tests for purposes for which there is absolutely no evidence or approval,” he says.

### What's the difference between lateral flow tests and PCR tests?

#### Lateral flow tests

These simple test kits detect viral proteins (antigens) from the SARS-CoV-2 virus in respiratory samples, such as from a nose or throat swab. If the target antigen is present in enough quantity it will bind to specific antibodies fixed to a paper strip enclosed in a plastic casing and generate a visual signal, usually within 30 minutes. These tests are not to be confused with rapid antibody tests, which use blood to detect antibodies generated in response to infection.

#### PCR tests

Polymerase chain reaction tests detect the virus's RNA in a sample. The test amplifies small bits of genetic material to enable detection. So a test can give a positive result long after a person stops being infectious.

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