Lateral Flow Antigen Tests - not a panacea for freedom from the pandemic

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Lateral Flow Antigen Tests (LFT) rely on the detection of SARS-CoV-2 antigens in nasal or nasopharyngeal swabs or other respiratory secretions. They are increasingly used for different purposes, either self-administered or performed on-site by trained professionals. Compared with reverse-transcription polymerase chain reaction (RT-PCR) LFT have a quicker turnaround time (less than 30 minutes) and are less expensive, enabling rapid identification of infected persons and trace their contacts. When the RT-PCR test is the reference LFT is a less sensitive test. However, the measure of performance may be flawed as RT-PCR detect residual viral portions that may remain long and are not apparently associated with infectiousness (that is why people is released from isolation 7 to 10 days after diagnosis without further testing), while LFT seems to identify relevant viral loads, present for a lower period (1). However, LFT accuracy varies from test to test. In table 1 there is a comparison of different tests accuracy obtained at independent evaluations.

LFT are becoming widely available and of easy access for everyone who intends to do a test either free of charge or at the pharmacies, regardless of the clinical or epidemiological context. In England, since April 9, LFT are available to everyone who wants them twice-weekly (2) and were already available at schools (3). In Vienna LFT is being offered once a day for everyone living, working, staying temporarily, or attending school (4). France and Portugal now sell tests in pharmacies (5, 6) and from July, Portuguese may also access up to four LFT per month at the pharmacies or laboratories for free (7). They are also being used in mass testing programs (8-10).

Despite all the advantages, governments must use them wisely. Like every test, LFT do give false results, which may be false positives or false negatives. The likelihood of a false result is dependent on pre-test probability, i.e., the likelihood of infection given the setting, the clinical presentation and the history of recent contact with a case (11) and on the accuracy of the test that might be different from those acclaimed by the manufacturers (12). Therefore, this must be taken into account when planning testing strategies and interpreting the test results. The benefits and harms of testing should be balanced, and we should recognize that, despite the crucial role of testing in curbing the pandemic, at certain moments and contexts it might make sense not to test.

The most frequent intended uses of LFT are 1) testing symptomatic individuals, 2) mass testing in low prevalence context, 3) mass testing in high prevalence context, and 4) self-testing.

1) *Symptomatic individuals – clinical purposes*

Testing symptomatic individuals is the use advised by the LFT manufacturers. People with COVID-19 like symptoms have higher viral loads and are more likely not to be missed by the test. Moreover, the positive predictive values are usually high (13), i.e., most of those who test positive are true positives. This might be particularly useful in clinical practice as COVID-19 signs and symptoms are nonspecific, allowing for a more appropriate rapid sorting, alongside RT-PCR testing. In symptomatic children, the antigen test has moderate sensitivity (19). However, there is limited evidence of how it performs in asymptomatic children. Early results from English secondary schools' tests showed more false positives than true positives (20). And testing in schools may either be framed within scenarios 3 or 4, described below, and we should design the testing strategies accordingly.

Mass testing in low and high prevalence contexts – public health purpose

LFT are also used for mass testing programs, either in low (wide screening) or high prevalence settings (where, for example, an outbreak occurred). However, it is not clear the role LFT mass testing may have in curbing the epidemic (1).

2) **In a low prevalence setting**, the number needed to screen will be very high, i.e., very large numbers of tests need to be done to detect a (true) case. The positive predictive value – the balance of true positives to false positives - becomes unfavourable, even with a very specific test (14). In this context, a RT-PCR confirmatory test or second LFT can mitigate the risk of false positives. However, RT-PCR tests are expensive, and may not be a cost-effective approach to get adequate numbers of people to participate. Good backward and forward contact tracing could well be the most efficient and effective way of finding both

symptomatic and asymptomatic cases. It is important to recognize that no test will work well in a very low prevalence setting and it is important to consider that in some contexts it makes any sense to do any test, despite social and political pressures. The European Centre for Disease Control and Surveillance (ECDC) does not recommend the use of LFT in low prevalence settings (15). The BMJ's tool for interpreting COVID-19 test results is useful to illustrate the limitations of testing according to the pre-test probability (11). For example, in a setting with a prevalence of 1%, even if the test sensitivity is 90% - much higher than it has been described (16) – and the specificity is 99%, half of those who test positive are false positives. As the prevalence of the disease goes down – or those who are getting the test have a lower pre-test probability, most of the positive results will be false positives and the individual and their contacts are unnecessarily isolated (14) – this may lead to distrust of future testing strategies and public health measures, such as vaccination. As the proportion of vaccinated people increases, false positives are expected to appear among those who are already vaccinated, and this may lead to distrust of vaccination.

3) **In a high prevalence setting**, the number needed to screen will be lower, and positive predictive value will be higher, i.e., a lower number of tests are needed to find a (true) case and we will more true positives among the positives when comparing with a low prevalence setting (14). The higher concern then moves to individuals who get false-negative results. These people may be capable of spreading the virus further. In high prevalence settings with high laboratory demand, LFT might be useful to identify cases with a quick turnaround time and likely to detect cases otherwise not detected. However, to get on top of local outbreaks backward and forwards contact tracing must be in place simultaneously with other preventive measures. The message is to be clear: a negative LFT result does not rule out a SARS-CoV-2 infection. A negative test in a person with high pre-test probability must be confirmed with sequential RT-PCR testing.

   Moreover, the prevalence in a local or subgroup of a population is used as an indicator of pre-test probability; however, this is only valuable when we are

performing testing on a random sample of the population or testing the whole population. As mass testing are frequently voluntary and tests are being offered to anyone, the question is: who is getting the tests? In the Liverpool population-wide asymptomatic testing program, it was observed that testing uptake was lower among populations with higher positivity rates (17). If those who are getting tested have a lower pre-test probability, the chance of the number of false-positive results overlaps the number of true positives increases (PPV below 50%) and we get closer to mass testing in a low prevalence context. This also applies to tests available for anyone free of charge or at the pharmacy.

4) *Self-testing*

Little is known on who, why, and when is accessing these tests. Data on self-testing LFT available either free of charge or at the pharmacies are and will be scarce. People may be acquiring tests to feel safer when meeting friends or familiars; people may be symptomatic and use a test to avoid contact with health authorities and/or to be quarantined when having contact with a confirmed. We do not know the motivations for testing, how people interpret the test result and how they change their behaviour. Thus, governments must state a preventive and clear message to be spread along with the LFT acquisition to self-testing to be an additional tool to test-trace-isolate instead of a disruptor of it.

Experiences from mass testing in Slovakia, Austria, and UK

A population-wide LFT programme in Slovakia appears to have reduced the prevalence of the infection, although it is impossible to disaggregate the results produced by the mass testing and other non-pharmacological measures simultaneously in place (10). Moreover, individuals who did not do the test were recommended to be isolated for 10 days or risked paying a 1650€ fine (18). Importantly, the mass testing did not alter the positivity rate for polymerase chain reaction (PCR) tests, and it did not reduce hospitalisations (18). Contrary to the England situation, the test was performed by thousands of health professionals and was unsustainable over time, in an already

overstretched period for health care workers. Public confidence in adherence to future public health measures was challenged: “The first mass testing was advertised by the PM as a tool to avoid lockdown. If one is imposed, there is a risk people will lose trust in any government measures and so by the time a vaccine comes around they won’t trust what the government says and won’t take it” (18). Subsequently, a further explosion of COVID-19 cases ensued in January 2021 and a government collapsed, over its Sputnik vaccination deal (19). The LFT mass testing programmes in Liverpool and Birmingham found a sensitivity of 66% - even in high viral loads (cycle threshold ≤25) - and 3%, respectively (8, 9). However, it has been acclaimed that the “city’s pilot events did not cause any detectable spread of COVID-19 in the area” (20). A review of point-of-care tests found a sensitivity of 58.1% among asymptomatic individuals and 72.0% among symptomatic (21). Additionally, as the authors state “At 5% prevalence using data for the most sensitive assays in symptomatic people (SD Biosensor STANDARD Q and Abbott Panbio), positive predictive values (PPVs) of 84% to 90% mean that between 1 in 10 and 1 in 6 positive results will be a false positive, and between 1 in 4 and 1 in 8 cases will be missed. At 0.5% prevalence applying the same tests in asymptomatic people would result in PPVs of 11% to 28% meaning that between 7 in 10 and 9 in 10 positive results will be false positives, and between 1 in 2 and 1 in 3 cases will be missed” (21). In asymptomatic individuals, 66.7% of those who had a positive LFT were false positives (13).

In Austria, LFT are part of a bigger testing system and are used primarily for screening. A lot of workplaces where people are not fully in homeworking also have regular weekly workplace testing and a fully covering school testing system, most importantly, in case of a positive Ag test, the person right away gets a free RT-PCR test done within 24h.

The UK government states “that for every 1,000 LFT carried out, there is less than 1 false-positive result” (2). The Public Health England assessment of the Innova test gave a higher false-positive rate than the government’s quoted figure at 3 per 1000 persons (22). Positive tests in the UK are now running at only around 3 positives per 1000 persons – calling into question whether they are finding any real positives.

Conclusions

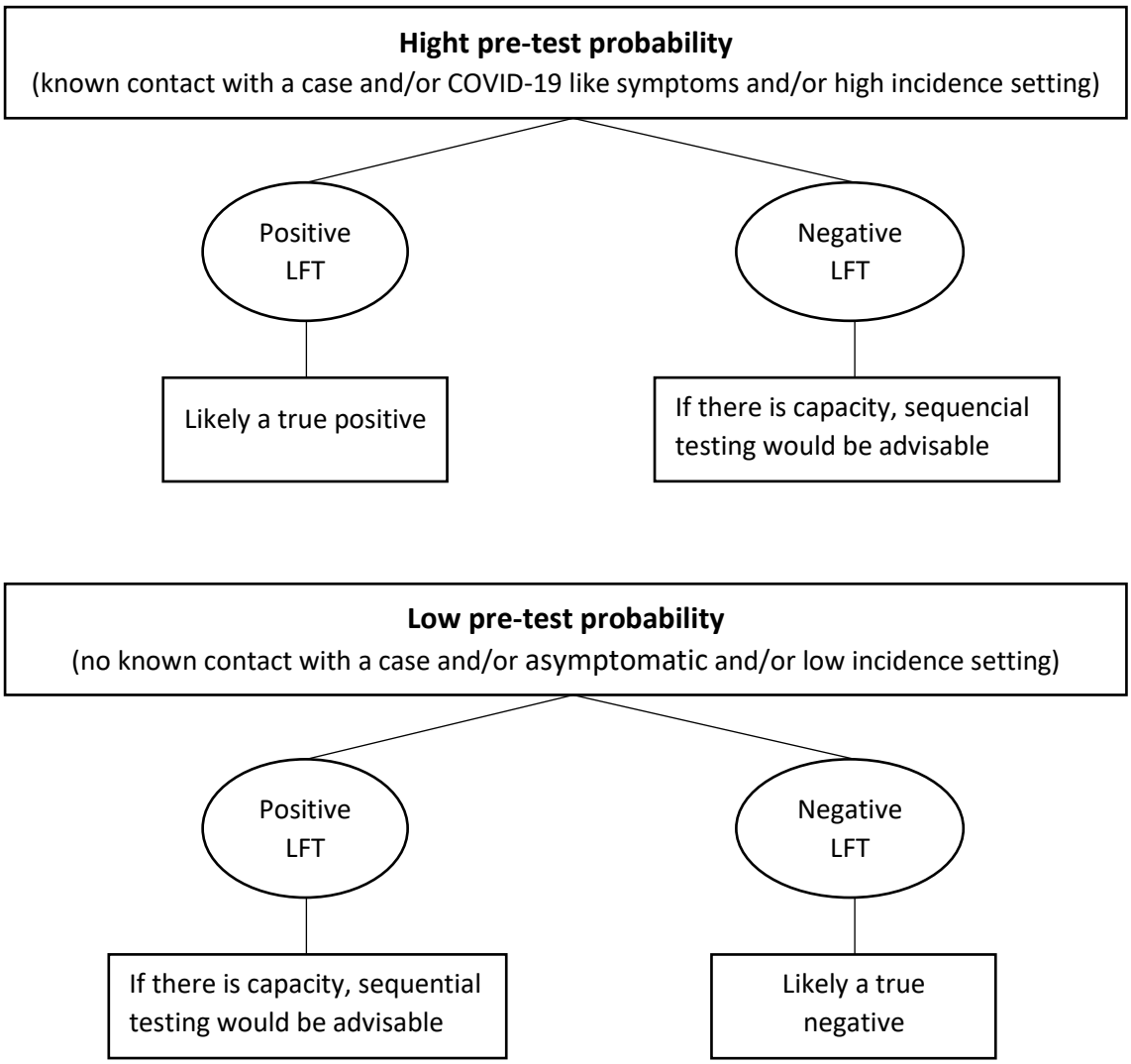
The place of LFT in curbing the epidemic is still in doubt (1). The role of mass LFT testing in reducing the transmission and the harms they may cause are not clear (23). Supporters take the view that LFT is designed to pick up infectious people. They argue that every new case uncovered would only be so through this testing. In effect, they claim that there are no false negatives because they would not have been tested anyway. However, human behaviours do change, and people use a negative test as reassurance. LFT were not effective in reducing outbreaks in care homes in Liverpool (24). However a different study found that antigen tests could be useful to identify infectious people during an outbreak in nursing homes (25). Governments must be clear that they have a full range of effective interventions alongside the testing; that means effective test-trace-isolate-support policies (26). Contact tracing practice in the UK is weak lacking clinical input and public health coherence (27). Adherence to self-isolation is low and financial support for self-isolating individuals is grossly inadequate (28). Public understanding of what test results mean is also grossly inadequate (29). Since the Liverpool pilot study, some of the public could be forming the notion that they can get a test, then go about their life and business with less caution (30). Any careless messaging risks the further spread of infection. Clear public health messages should be in place to help people to understand the result of a LFT so people with a negative result keep on the other preventive measures and do understand that it was likely to be negative at the moment of testing. As new tests become available, there may be a case for sequential testing regimes, applying tests that are fit for purpose (31). All of these require thorough and rapid evaluation if we are not to risk outbreaks of cases arising from false-negative superspreaders (32)

LFT are not a panacea and must be used wisely as part of an armoury of other effective interventions.

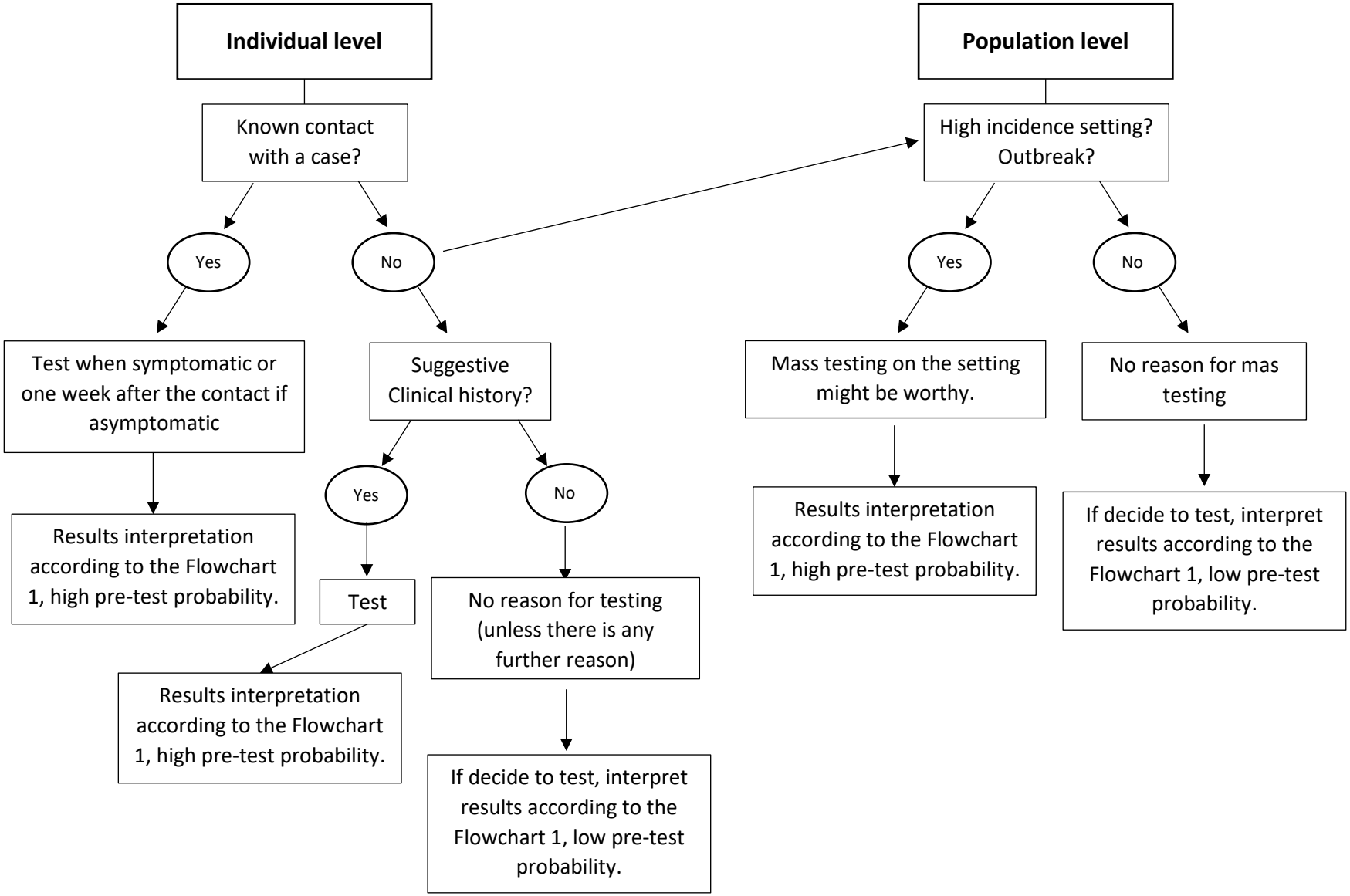
Table 1. Antigen detection LFT (CE-IVD) – comparison of independents evaluations.

Company	Assay	Clinical Sensitivity	Clinical Specificity	Reference
Abbott Rapid Diagnostics	Panbio COVID-19 Ag Test – Nasopharyngeal	85.5%-86.8%	99.9%-100%	(33, 34)
Abbott Rapid Diagnostics	Panbio COVID-19 Ag Test – Nasal	86.4%-90.9%	99.2%	(34, 35)
SD Biosensor, Inc.	STANDARD Q COVID-19 Ag Test – Nasopharyngeal	73.2%-89.0%	87.6%-99.7%	(34, 36, 37)
SD Biosensor, Inc.	STANDARD Q COVID-19 Ag Test – Nasal	80.5%-84.6%	99.3%	(34, 37)
Innova Medical Group	Innova Lateral Flow	48.9%	99.9%	(38)
Roche	Roche SD Biosensor	72.5%-84.9%	99.4%-99.5%	(39, 40)

Flowchart 1. How to interpret test results according to pre-test probability: high test probability vs. low test probability.



Flowchart 2. When to use LFT: individual vs. population level.



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