Testing for COVID-19: How to best use the various tests?

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Even with promising recent news on vaccine development, testing, tracking, tracing and isolating (TTTI) quickly and on a large scale continue to be essential to public health policy responses to the COVID-19 pandemic. This note provides an update to an earlier OECD brief on such strategies in the light of recent developments in testing technologies. Molecular tests, and in particular RT-PCR, remain the reference for identifying infections because these tests are very reliable. But capacity constraints and the relatively high cost of RT-PCR limit its use on a massive scale. More recently-developed rapid antigen tests offer the advantage of producing results much more quickly. They are also cheaper, simple to use, and can be performed at point-of-care, thus allowing their use on a very large scale. However, they are less reliable than molecular tests. To achieve their objectives, testing strategies can combine different technologies and use them in complementary ways, taking into account their respective strengths and limitations.

Key findings

While the recent news on vaccine development for COVID-19 have been encouraging, **testing, tracking, tracing and isolating (TTTI) strategies will continue to be essential**. Until entire populations are immunised, only TTTI can prevent future rebounds of infections following lockdowns**. Two main types of testing technologies are widely available** to inform such strategies.

- **Molecular tests, and in particular RT-PCR**, remain the reference for identifying active infections. These tests have proven to be **very reliable** – they achieve high sensitivity and specificity. But capacity constraints and the relatively high cost of RT-PCR tests limit their use on a massive scale. It also takes long to produce test results.
- **Rapid antigen tests** have the main advantage of **producing results much more quickly.** They are also simple to use, can be performed at point-of-care, and are cheaper than molecular tests, allowing their use at very large scale. However, they are less reliable than molecular tests – they achieve good specificity but **only moderate sensitivity**.

The objectives of the testing strategy should determine the selection of the appropriate type of test, taking into account these strengths and limitations.

- **Monitoring of specific population groups** in which a new cluster of infections is suspected to occur is **the most appropriate use of point-of-care rapid antigen tests**, given that they can be used quickly and at scale. But this requires tests to be repeated. Testing passengers for air travel can be a means to provide additional screening before boarding flights and to loosen quarantine requirements upon arrival, but such strategies should be adopted with caution.
- Rapid antigen tests are **the only workable option for massive screening campaigns** in the general population. While this may appear to be an appealing strategy to guide containment measures, the related **challenges should not be underestimated and effectiveness is uncertain**.
- **Molecular testing is the preferred option in a clinical setting** to diagnose patients and inform treatment decisions, because of the reliability of these tests minimises the risk of a misdiagnosis.
- Molecular tests are **also the best option for people who show symptoms** and **people who were in contact** with a confirmed case to inform TTTI strategies. **Certain point-of-care rapid antigen tests can, however, constitute a possible alternative** to molecular tests in such situations. But repeated testing or confirmatory molecular tests might be necessary. The utility of point-of-care rapid antigen tests in TTTI strategies depends on whether increased speed and lower costs, and therefore more tests, can outweigh lower sensitivity.

Point-of-care RT-LAMP and CRISPR-based tests may ultimately overcome some of the limitations of RT-PCR and rapid antigen tests. However, their development is still ongoing and they are not yet widely available. Also, the logistical implications of using these tests are not clear yet.

Even with promising recent news on vaccine development for COVID-19, it will be some time before vaccines can be delivered to the general population. Thus, **testing, tracking, tracing and isolating (TTTI)** quickly, massively, and smartly will continue to be essential to prevent future rebounds of infections following lockdowns. Quick suppression of infections requires testing suspected cases and all their contacts to identify in a timely fashion who is infected and isolating those who are; tracking them effectively to make sure they do not spread the disease further; and tracing exhaustively with whom they have been in contact. An overview of available testing technologies has been provided in the OECD policy brief titled *Testing for COVID-19: A way to lift confinement restrictions*, published in May 2020. Since then, **progress has been made in the development of new testing methods and repurposing of existing**

technologies for COVID-19 including, among others, rapid antigen tests and other molecular diagnostic techniques (mainly CRISPR[1]-based tests and RT-LAMP[2]).

As opposed to RT-PCR, which has been used most widely up to now, new rapid **antigen** tests can be easily deployed at point-of-care and provide almost immediate results. These features are very useful for improving TTTI strategies but, as described below, rapid antigen tests are less sensitive than RT-PCR, and this can limit their utility in some scenarios. Point-of-care **RT-LAMP** and **CRISPR**-based tests are gaining a lot of attention and could become useful complements to the "testing tool box" in the medium term.

This note provides an update to the earlier OECD brief in the light of these recent developments in testing technologies, and discusses implications for more effective containment and mitigation strategies until vaccines become widely available. The main technologies currently available or expected in the short/medium term are described in the next section and summarised in Table 2. The subsequent section discusses testing strategies and the appropriate use of the various technologies to support these.

There are various testing technologies, with different purposes, characteristics, strengths and limitations

Molecular/Genomic tests

RT-PCR is the only well-established technique

RT-PCR is a diagnostic technique to detect viral genetic material (viral RNA) in a biological sample after having amplified it to allow for its detection. It is the current reference for detecting presence of the virus in the respiratory tract, i.e. for identifying active infections. This technique has **very good sensitivity and specificity, meaning that it is very reliable** (see Box 1). However, in some situations positive results can be difficult to interpret (see Box 2). Some more general **limitations of this method also complicate its use on a massive scale**. First, some essential testing materials (e.g. reagents, nasal swabs, transport media, etc.) are in limited supply. In addition, even if this technique can return results within hours, the logistics of sample collection, transport to a central laboratory, analysis of the sample and return of results cause a long lead time between when a sample is taken and when the results are available and communicated. This can make RT-PCR testing a bottleneck in TTTI strategies, which hinge on identifying and isolating infected people as quickly as possible. Lastly, the relatively high cost of RT-PCR is a constraint in some countries (Carter et al., 2020[1]). For the sake of simplicity, techniques that share the same general characteristics as RT-PCR, in particular transcription-mediated amplification (TMA) and standard RT-LAMP, are not discussed separately. References to RT-PCR below cover these three techniques.

Box 1. Reliability of diagnostic tests

The reliability of diagnostic tests refers to their **ability to identify positive and negative cases accurately**. This is described by two parameters:

1. **Sensitivity:** the probability that the test returns a positive result if the person tested is truly infected.
2. **Specificity:** the probability that the test returns a negative result when the person tested is truly not infected.

[1] Short for "Clustered Regularly Interspaced Short Palindromic Repeats". See below for more details.

[2] Short for "Loop-mediated Isothermal Amplification". See below for more details.

Low test sensitivity produces **a high proportion of false negative test results** among all people who are infected, while low test-specificity produces **a high proportion of false positive test results** among all people who are not infected. This implies that **the predictive value of a diagnostic test also depends on the prevalence** of the infection. That is, the proportion of "true positives" among all positive test results and the proportion of "true negatives" among all negative test results depends not only on the sensitivity and the specificity of the test but also on the share of people who really are infected in the population tested. This is further illustrated for rapid antigen tests in Box 3.

Box 2. Current RT-PCR tests may be "over-sensitive" and detect cases who are no longer contagious

In order to detect viral genetic material, RT-PCR needs to amplify the genetic material to reach a certain detection threshold. The outcome of this testing technique in the context of COVID-19 detection is binary (positive or negative) and the number of amplification cycles is one of the parameters of the technique. The higher the number of cycles performed on one sample, the higher the chances to detect (existing) viral genetic material, even if this is present in very limited quantities in the sample. In other words, if a sample has a very limited quantity of genetic material (for instance when someone is in the recovery phase of the disease), RT-PCR might give a negative result with 25 cycles, but positive with 35 (because the effect of the 10 additional cycles will enable the amplification to reach the detection threshold).

This implies that high numbers of cycles can render test results positive even where samples are taken from people who are **no longer contagious** (because they are recovering or have already recovered but still carry some remnants of virus in their nose and throat).

Molecular/genomic tests in development

Point-of-care RT-LAMP tests

RT-LAMP is a technique similar to conventional RT-PCR tests, with the exception that the nucleic acid amplification occurs at a constant temperature,[3] and thus equipment such as expensive thermal cyclers used to regulate sample temperature in RT-PCR are not required.

Until recently, RT-LAMP tests were performed predominantly in full-fledged laboratories and provided an alternative to RT-PCR with similar characteristics, but some point-of-care and near point-of-care test kits using this method have recently been commercialised and approved for use, including several in the EU and the United States.[4] These tests report high levels of sensitivity and specificity against RT-PCR (Thompson and Lei, 2020[2]; Dao Thi et al., 2020[3]). It remains to be seen how quickly use of point-of-care RT-LAMP can be scaled up. However, depending on the cost, the technology may prove to be a more viable option for use in the context of, for example, pre-travel testing than antigen testing.

CRISPR-based tests

CRISPR-based tests work by identifying a sequence of viral COVID-19 RNA and cutting apart any nearby single-stranded RNA. These cuts release a separately introduced fluorescent particle in the test solution. When the sample is then hit with a burst of laser light, the released fluorescent particles light up, signalling

[3] In conventional RT-PCR, various cycles of heating and cooling of the sample are undertaken.

[4] MolDxDb: data on the global molecular diagnostics industry.

the presence of the viral genetic material. The current prototypes relying on this technique provide results within 30 minutes, with performance levels comparable with RT-PCR, and could also be performed at point-of-care.

In addition, this technique has another key advantage – it can quantify the amount of virus in a sample. This feature could, for example, help in estimating how contagious a patient is. Molecular tests, on the other hand, amplify the viral genetic material in order to detect it. This, by definition, changes the amount of genetic material present, thus precluding any chance of precisely quantifying how much virus was originally contained in the sample (Fozouni et al., 2020[4]; Ramachandran et al., 2020[5]).

Antigen tests

Antigen tests detect another portion of the SARS-CoV-2 virus, the protein coat that surrounds the RNA genome. Like molecular tests, antigen tests are intended to detect the viral presence in symptomatic or asymptomatic individuals and are performed on samples obtained from the respiratory tract. The main advantages of rapid antigen tests[5] over RT-PCR include their **simplicity of utilisation**: they can be performed at point-of-care; a simple swab is put in contact with the reagent. They are also **much cheaper**, from USD 15 to less than USD 50.[6] But their main advantage is the **rapidity of the result**: most produce a result in 15 to 30 minutes, while as mentioned above, RT-PCR requires several hours to be performed, and even more time until results are available because of all the pre- and post-analytical work. Therefore, rapid antigen tests could allow for an increased volume of testing and faster isolation of people who test positive, which would contribute to breaking chains of transmission sooner.

Yet, compared to RT-PCR, these tests also have drawbacks: most rapid antigen tests achieve **good specificity** compared to RT-PCR but only **moderate sensitivity** (see Box 3), although these numbers may vary depending on how performance is assessed. This lower sensitivity of rapid antigen tests needs to be qualified by the possible over-sensitivity of RT-PCR with regards to detecting people who are contagious in some scenarios (see Box 2). Indeed, some evaluations of rapid antigen tests report sensitivity close to RT-PCR at high levels of viral concentration (see, for example, Corman et al. (2020[6]) and Public Health England and University of Oxford (2020[7])). This may allow for reliable detection of the most problematic cases for transmission of the virus.

Box 3. Performance of rapid antigen tests

Using RT-PCR as a reference, systematic reviews report **reduced, and highly variable, sensitivity** and medium to **high specificity** across a number of rapid antigen tests evaluated (Cochrane COVID-19 Diagnostic Test Accuracy Group, 2020[8]; HAS, 2020[9]). The French Haute Autorité de Santé (HAS, 2020[9]) estimated that:

- **Sensitivity was around 71%** [CI 57-82] across all tests, but ranged from 17% [CI 9-27] to 97% [CI 83-100]. The lower bound is particularly problematic.
- **Specificity was around 99%** [CI 97.3-99.4] and less variable, ranging from 86% [CI 73-94] to 100% [CI 99-100].

The true performance of these tests may, however, be slightly underestimated. The estimates above are based on validations on frozen-thawed samples stored in various viral transport media and analysed retrospectively, which may have altered the performance of tests. Also, the sensitivity and specificity of rapid antigen tests in asymptomatic people has not yet been entirely validated. This may be a minor

[5] There are two types of antigen tests: rapid antigen tests that can be used at point-of-care, and enzyme immunoassays (ELISA), which are performed on automated devices in biology laboratories.
[6] By comparison, costs of RT-PCR tests vary widely but are generally more than USD 50.

problem however, because the sensitivity and specificity of RT-PCR, against which antigen tests are assessed, are not dependent on whether someone shows symptoms.

If assuming the same performance as in symptomatic patients, population-wide screening with rapid antigen tests alone would result in a high proportion of false positives despite their high specificity. This is because disease prevalence in the general population is low, meaning that most people tested are in reality negative. Combined with lower sensitivity, resulting in a high proportion of false negatives, the ability of such tests to identify true positive cases is limited. As illustrated in Panel A of Table 1, in a hypothetical population of 1 000 000, in which 10 000 people (1%) are infected, a test with 71% sensitivity and 99% specificity results in 17 000 positive tests, of which 9 900 (58%) are false positives. Thus, a positive test would only correspond to an infected person in 42% of cases (positive predictive value). The positive predictive value of a test with 50% sensitivity and 99% specificity is as low as 34%. This implies that, in such circumstances, positive test results would need to be confirmed by RT-PCR. The only other option to compensate for inaccuracy would be to use rapid antigen tests repeatedly to monitor the infectious status of a given population group (see next section).

In a scenario of higher prevalence (Table 1, Panel B), the positive predictive value of a test with moderate sensitivity is much more favourable. Therefore, the test achieves its highest potential when confirming infection in scenarios where the probability of a person being infected is high – for instance, when testing a symptomatic patient and RT-PCR is not feasible. Here, a positive rapid antigen test almost certainly identifies an active infection. There is no need to confirm with RT-PCR. This of course comes at the cost of a lower negative predictive value, i.e. a higher proportion of false negatives. So, conversely, it is not possible to conclude with certainty that a symptomatic patient with a negative result is not infected. This is even more of a problem if the test is not taken at an early stage of the infection: the more time passes, the higher is the chance of testing negative in an antigen test even if someone is infected. This is why in some clinical scenarios (like an at-risk patient), RT-PCR should be performed to confirm a negative antigen test result.

Table 1. Predictive values of tests depend on sensitivity and specificity of the test and on prevalence of the disease

Panel A: Assuming low disease prevalence (1% of the population is infected)

Population = 1 000 000 Prevalence = 1%		**Test A** Sensitivity = 71% Specificity = 99%		**Test B** Sensitivity = 50% Specificity = 99%	
		Positive	Negative	Positive	Negative
Infected	10 000	7 100	2 900	5 000	5 000
Not infected	990 000	**9 900**	980 100	**9 900**	980 100
Total	1 000 000	**17 000**	983 000	**14 900**	985 100
Predictive value		***41.76%***	*99.70%*	***33.56%***	*99.49%*

Panel B: Assuming high disease prevalence (20% of the population is infected)

Population = 1 000 000 Prevalence = 20%		**Test A** Sensitivity = 71% Specificity = 99%		**Test B** Sensitivity = 50% Specificity = 99%	
		Positive	Negative	Positive	Negative
Infected	200 000	142 000	**58 000**	100 000	**100 000**
Not infected	800 000	8 000	792 000	8 000	792 000
Total	1 000 000	150 000	**850 000**	108 000	**892 000**
Predictive value		***94.67%***	***93.18%***	***92.59%***	***88.79%***

Serologic tests

Serologic tests look for the presence of disease-specific antibodies in someone's biological fluids (usually blood). Such tests determine whether a person has developed antibodies against a given pathogen as a result of exposure or infection. These tests come in many forms: some require complex machines installed in laboratories (e.g. ELISA tests), others use less complex hardware and can be used at point-of-care (rapid tests). Serologic tests play an important role in epidemiology and vaccine development. **However, they are not suited for diagnosis of new infections in exposed or symptomatic patients, and as a result, have no role in the implementation of TTTI strategies**.

Table 2. Different types of testing technologies available in the context of COVID-19

	Molecular/genomic tests			Antigen tests	Serologic tests (not relevant for TTTI strategies)	
Objective of the test	***Detection of the virus presence in the organism***				***Detection of the immune response to the virus***	
Technique	**RT-PCR**	**Point–of-care RT-LAMP tests**	**CRISPR-based tests**	**Rapid antigen tests**	**ELISA tests**	**Immunochromato -graphic assays (rapid tests)**
What does it look for?	Looks for the presence of viral genetic material (RNA) in a sample taken from the patient (usually a nasopharyngeal swab)	Looks for the presence of viral genetic material (RNA) in a sample taken from the patient (usually a nasopharyngeal swab)	Looks for the presence of viral genetic material (RNA) in a sample taken from the patient (usually a nasopharyngeal swab)	Looks for the presence of viral antigens in a sample taken from the patient (usually a nasopharyngeal swab)	Looks for the presence of an immune response (antibodies) against the virus in the patients' fluids (usually blood)	
What does a positive test mean?	The virus is present in the patient				The patient has been exposed to the virus and is either recovering or has already recovered	
What is the test used for?	To know whether an individual is currently infected with SARS-CoV-2 To know whether SARS-CoV-2 circulates in a given group or population				To know whether a patient has been exposed to SARS-CoV-2 and could therefore be protected against new infections (and potentially not spread the disease anymore)[1]	
Pros	- High sensitivity and specificity	- Performance close to RT-PCR - Can be used at point–of-care - Give result in less than one hour usually	- Reported performance close to RT-PCR - Can be used at point-of-care - Can quantify viral load - Give result in 15 to 30 minutes	- Simple to process - Cheap - Give result in 15 to 30 minutes - Can be used at point-of-care - Good specificity	- More reliable than immunochromato -graphic assays - Provides a quantitative information (concentration in antibodies)	- Less resource intensive than ELISA tests - Can be performed at point–of-care - Rapid (15 to 30 minutes)
Cons	- Labour-intensive; - Majority of tests still need to be processed in a lab - Takes time to give results (several hours at least) - Testing materials in short supply	- Not yet widely available at point-of-care. - Price still uncertain	- Not yet available at point-of-care - Price still uncertain	- Lower sensitivity compared to RT-PCR	- Possible errors of interpretation if performed too early in the infection process as antibodies have not yet been produced - Possible false positives (interaction with other diseases) - Needs to be performed in a lab - Resource Intensive (1 to 5 hours)	- Provides only a qualitative information (presence or not of antibodies)

1. Under the assumption that COVID-19 infection induces a satisfactory immune response.

Source: Updated by the authors based on OECD (2020[10]) "Testing for COVID-19: A way to lift confinement restrictions", https://www.oecd.org/coronavirus/policy-responses/testing-for-COVID-19-a-way-to-lift-confinement-restrictions-89756248/.

Which tests should be used in what circumstances?

In general, the strengths and limitations of the various testing technologies discussed above mean that **the selection of the most appropriate technology** should depend on the **objectives of the testing strategy**, and not the other way around. In practice, there are three main objectives of testing:

1. The accurate diagnosis of patients to inform **decisions in clinical care**;
2. Confirming or disconfirming suspected cases, e.g. because a person shows symptoms or was in contact with a confirmed case, to **inform TTTI** strategies; and,
3. **Monitoring specific population groups**, in which infections are suspected to occur (e.g. nursing homes, companies, schools and universities, geographic areas with suspected clusters, etc.).

None of the testing technologies currently available is suitable in all three scenarios and the different implications in terms of costs and logistical requirements need to be taken into account when deciding which tests to use for what and on whom. Table 3 summarises which tests should be used primarily in each of the three scenarios. **Testing technologies can also be combined** to achieve the objectives of testing strategies and tests can be repeated to compensate for lower testing accuracy. As explained below, for example, RT-PCR can be used to confirm uncertain results of rapid antigen tests, and repeated rapid antigen tests increase the probability that their results are accurate.

While point-of-care RT-LAMP and CRISPR-based tests may ultimately overcome some of the limitations of RT-PCR and rapid antigen tests, their development is still ongoing and they are not yet widely available. Also, the logistical implications of using these tests are not clear yet.

Table 3. Most appropriate uses of current testing technologies

	RT-PCR (and similar molecular tests)	Rapid antigen tests	CRISPR-based tests[4]	Point-of-care RT-LAMP[4]
Accurate diagnosis of patients to inform decisions in clinical care	√		(√)	(√)
TTTI (i.e. confirming or disconfirming suspected, including symptomatic, cases and contact persons)	√	√[2]	(√)	(√)
Monitoring specific population groups (nursing homes, schools and universities, etc.)	(√)[1]	√[3]	(√)	(√)

1. Limited by cost and capacity constraints.
2. In RT-PCR-confirmed outbreaks, rapid antigen tests can be used for testing symptomatic and asymptomatic contacts to facilitate early detection of further cases as part of contact tracing and outbreak investigation, in case RT-PCR is not an option. For symptomatic patients suspected of COVID-19 or at-risk populations, negative results should be confirmed by RT-PCR.
3. In such circumstances, tests need to be repeated regularly to increase precision (see Box 4). Positive results may need to be confirmed by RT-PCR.
4. Tests are still in development and, although some point-of-care RT-LAMP kits are being marketed already, they are not yet widely available.

Diagnosing patients to inform clinical decisions

RT-PCR tests (and similar molecular tests) remain the reference in this scenario because of their higher sensitivity and specificity. In the medium term, point-of-care RT-LAMP tests and CRISPR-based tests could complement RT-PCR because their performance is very close. In the clinical setting, the objective is to minimise the risk of misdiagnosis and an incorrect management decision, which could have serious adverse consequences for patients. This is particularly important in winter when other respiratory pathogens are circulating. The most reliable test will therefore always be favoured.

Use in Testing, Tracking, Tracing and Isolating by confirming suspected and contact cases

This scenario includes confirming or disconfirming infection in people who show symptoms in the outpatient setting (as a first diagnosis step) and people who were in contact with a confirmed case to inform TTTI strategies. **RT-PCR tests (and similar molecular tests) are also appropriate for this purpose and, for now, remain the reference in such scenarios.** Yet, cost and capacity constraints may limit their suitability for confirming suspected cases, especially when their number is very large. **Point-of-care rapid antigen tests constitute a possible alternative here if RT-PCR cannot be used** (European Centre for Disease Prevention and Control, 2020[11]).

The utility of point-of-care rapid antigen tests in TTTI strategies derives from **increased speed and lower costs, which can outweigh lower sensitivity**. Models that have tried to estimate the possible impact of rapid antigen tests (HAS, 2020[9]) suggest that:

- Lower sensitivity can be compensated by performing a higher number of tests. But **assuming a sensitivity of 70%** (see Box 3), **the number of tests needs to increase by at least 50%**.
- Lower sensitivity can be compensated by getting results faster. The effect of this gain in time will of course depend on the point in time at which the person is being tested after the onset of symptoms (the closer to it, the higher the impact will be), but **receiving a result instantly (as opposed to 2 days after taking the test) may reduce the possibility of transmissions by roughly 30%**. This means that the main utility of these tests could be for symptomatic patients, shortly after symptom onset, to provide results more quickly and lead to quicker isolation.

In sum, **if RT-PCR results cannot be accessed in less than 24 to 48 hours or the number of people to be tested exceeds RT-PCR capacities, point-of-care rapid antigen tests can be used for rapid diagnosis of symptomatic and asymptomatic patients in outpatient settings as a second best option.** Given that sensitivity of currently available rapid antigen tests varies widely (see Box 3), it is important to use the best-performing antigen tests.[7]

Monitoring specific population groups

Early detection of clusters in some specific population groups will be key when current containment and mitigation measures, including a second round of general population lockdowns in some countries, will start being lifted. This can contribute to preventing yet another round of costly containment measures while a vaccine becomes available in the needed quantities.

For monitoring of specific population groups such as nursing homes, universities, schools, companies, or any population group in which a new cluster of infections is suspected to occur, **point-of-care rapid antigen tests constitute the most appropriate tool but may require repeated testing**. First, this is because new infections can occur at any time, leading to the random emergence of new clusters, so that tests have to be performed regularly in order to increase chances of detecting them. Second, repeating tests on a regular basis improves testing precision (see Box 4).

[7] In its interim guidance on the use of antigen tests, WHO recommends a minimum ≥80% sensitivity and ≥97% specificity compared to RT-PCR. See WHO (2020[17]).

Box 4. The benefits of repeated testing

When using an imperfect test, i.e. one with specificity or sensitivity <100%, repeated testing can increase the reliability of test results. This is true at both, the individual and population levels.

Repeated testing in selected population groups

It is impossible to predict when an event of interest, i.e. a new infection or emergence of a new cluster, will occur in a given population group. Therefore, from a purely probabilistic standpoint, repeated testing increases the chances of detecting the virus at a moment when new infections are occurring or have just occurred.

Effect of repeated testing in individuals

To the extent that there are random errors in test results, repeating a test for the same person can help reduce the error rate statistically. Errors related to the technical ability of the test to accurately detect the virus in a sample will remain, but the "precision", linked to random errors, will be increased. For example, when testing a person who is infected using a test with 71% sensitivity (see Box 3), there is a 29% probability that the test returns a false negative result. Given that the first result is negative, the chance that the same test will return a false negative result when done a second time is only 8.4% (= 0.29 x 0.29), if this error is random. A third consecutive test would reduce the probability to 2.4% (= 0.29 x 0.29 x 0.29). "Random" in this context means that the 29% probability of a false negative is independent across consecutive tests, i.e. there is no underlying characteristic of the test or the sample tested that would cause the result to be true or false every time.

Yet, it is important to bear in mind that positive results obtained in such circumstances might still need to be confirmed by RT-PCR. Whenever prevalence is low, a high number of false positives can be a significant problem (see Box 3).

For some purposes, **wastewater surveillance** can be used for location-specific surveillance of large population groups. It is now convincingly demonstrated that COVID-19 infected persons shed virus in stool, even before symptoms manifest. Wastewater-based surveillance of nursing homes, companies, campuses, certain neighbourhoods, etc. would detect COVID-19 appearance and fluctuations over time, possibly offering actionable evidence to guide "reopening" or to initiate more intensive testing.

Testing for safe air travel

Rapid antigen tests are increasingly being used in association with **air transport, to ensure that only people who have tested negative can travel and as a means of removing or relaxing quarantine requirements on arrival**. It should be noted however, that air travel can increase exposure to the virus because physical distancing measures may be difficult to achieve. Taking a flight requires spending time in busy areas of airports, such as security and boarding lines, and in the enclosed space of an airplane close to other passengers for several hours, especially during long-haul flights. It may also involve traveling to and from airports using public transport. While testing can help reduce risk, it cannot eliminate it. Testing must therefore be combined with other precautionary measures before, during and after travel, in order to reduce the likelihood that travellers will spread the virus. This also means that **the logistics of a reliable testing strategy for air travel can be complex**.

So far, most airlines have been asking passengers to present a negative RT-PCR test taken less than 48 hours prior to flying. Countries have also set testing and isolation requirements for passengers entering their territory, including self-isolation or enforced quarantine for a specified period of time upon arrival. **Regardless of the type of testing arrangements that could be designed to improve travel safety, a**

period of strict isolation on arrival in destination countries could remain necessary to limit the spread of the virus, particularly in countries or regions that have managed to reach very low levels of transmission, as illustrated by the experience of Iceland. When the country reopened its borders on 15 June 2020, the authorities exempted travellers from a two-week quarantine if they tested negative on arrival. However, cases started rising less than a month later. Three months later the authorities revised their policy and now require two tests – one on arrival, and another five days later, with mandatory quarantine in between.

While the switch to rapid antigen tests looks appealing, in particular because the time between taking the test and the results being available is shortened, **testing strategies need to remain cautious**. As mentioned, increased speed might not remove the importance of some days of self-isolation when reaching the destination country. In addition, a reliable testing strategy contributing to improved travel safety would **require repeated tests some days before travel**, with confirmatory RT-PCR for positive results. It would also require that all passengers accept getting tested, that they wait for their results before traveling and do not to travel if results turned out to be positive, going into isolation instead. For those people who do travel, **another test is necessary some days after arrival** to ensure that they did not contract the virus while in transit. The US Centers for Disease Control and Prevention (CDC) published detailed guidance for testing in the context of air travel in November 2020 (CDC, 2020[12]). The European CDC considers that rapid antigen tests are not suited for screening incoming travellers to prevent virus introduction or reintroduction in regions/countries that have achieved zero or very low levels of transmission. In these situations, only RT-PCR should be used to reduce the risk of false negative results (European Centre for Disease Prevention and Control, 2020[11]).

Is there a role for population-wide testing?

Massive screening campaigns in the general population may appear to be an appealing strategy to guide containment measures, but the related **challenges should not be underestimated and effectiveness remains uncertain.**

First, testing millions of people every week, with all the pre- and post-analytical work required, is a complex and labour-intensive task. Second, in terms of capacity and cost, **rapid antigen tests are the only workable option** at this point for testing at a massive scale of millions of people. Their currently poorer performance discussed above, however, **raises challenges**. Even if the performance of rapid antigen tests improves over time, the issue of low prevalence in the general population and therefore the high number of false positives will remain a problem (see Box 3). In other words, a considerable proportion (quite plausibly more than half) of all “positive” tests will actually be false positives. This risks undermining the acceptance of the test – especially if, as would be necessary for the strategy to be effective, people with a positive test result are expected to isolate themselves. At scale, this is difficult to handle. This means that many people would face restrictions in their daily lives, including on their ability to work, even if they do not carry the virus. Policymakers need to consider whether public support for such a scenario would be sufficient to make the strategy viable. Mass screening is only effective if people are willing to be tested and if those who are identified as positive isolate quickly, and they may resist doing so especially if they doubt the validity of test results.

Some countries are already piloting population-wide screening (see Box 5) but these initiatives have so far delivered uncertain results, and are proving complex and costly to set up. From a technological standpoint, next-generation sequencing (NGS) might potentially constitute a suitable solution in the future. But this technology is still in development. NGS offers a highly sensitive and specific test modality with the possibility of providing extremely high throughput rates. Some companies and laboratories are developing COVID-19 testing capacity using NGS that can test up to 10 000 samples at a time with a turnaround time to obtain results in 24 to 48 hours (National Academies of Sciences, Engineering and Medicine, 2020[13]).

Box 5. Population-wide testing in Liverpool (United Kingdom) and the Slovak Republic

The city government of Liverpool in the United Kingdom and the national government of the Slovak Republic recently introduced population-wide testing campaigns.

Liverpool

Following an increase in COVID-19 incidence, the Liverpool city government initiated a pilot testing initiative on 6 November 2020 to test the city's entire population of approximately 500 000 people. The objective is to evaluate whether population-wide asymptomatic testing can help identify more cases and break chains of transmission better than opportunistic case finding. Participation is voluntary and every participant receives two tests, a RT-PCR and a "lateral flow" antigen test that can provide results within 1 hour. RT-LAMP tests are used to test hospital staff. When evaluated against RT-PCR, the lateral flow test used was estimated to have 76.8% sensitivity and 99.68% specificity (Public Health England and University of Oxford, 2020[7]). However, it was also found to accurately detect 95% of people with high viral loads, who may be more infectious than others, and have a comparable ability to detect viral antigens in symptomatic and asymptomatic people (ibid.). People can be tested twice within two weeks. All people with a positive result from either one of the two test are asked to self-isolate and are registered for contact tracing.

As of 17 November, the pilot had not been completed yet and about 20% of the population had been tested within the first 10 days. The pilot is proving to be a formidable logistical challenge, involving 2 000 personnel of the armed forces in addition to local health and social care staff. It has also been criticised for being too costly for an unproven strategy and concerns have been raised that its voluntary nature may result in those at highest risk being least likely to present for screening (Gill and Gray, 2020[14]). Compliance with self-isolation has previously been reported to be low in the United Kingdom, raising concerns about whether asymptomatic people tested positive in the pilot would comply to make the initiative effective in reducing transmissions.

Slovak Republic

The Government of the Slovak Republic launched an initiative in October 2020 to conduct rapid antigen tests for the country's entire population between the ages of 10 and 65 years, approximately 4 million people. Participation *per se* was not mandatory. However, those who did not participate had to self-isolate for 10 days at home and people unable to produce a negative test certificate if stopped by police could be fined. People who tested positive were also required to self-isolate in their homes or go into a public quarantine facility for 10 days.

On the first weekend of testing, on 31 October and 1 November, some 3.6 million people were tested, of whom approximately 1.06% were found positive. Some 2 million people were tested again on the weekend of 7 and 8 November, of whom 0.6% were found positive.

Reported incidence of new COVID-19 cases has decreased substantially between early and mid-November 2020. However, while this is promising, restrictive physical distancing measures have been in place since early October, so it is not possible to attribute the decrease in incidence to the testing programme. The initiative has mainly been criticised for exposing people to infection at crowded testing sites and for being too resource-intensive, while having uncertain benefits (Holt, 2020[15]).

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