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ARCHIVES OF
Community Medicine and Public Health

ISSN: 2455-5479 DOI: https://dx.doi.org/10.17352/acmph

Mini Review

Rapid antigenic tests to detect asymptomatic covid-19 infections

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Received: 24 December, 2020
Accepted: 22 January, 2021
Published: 23 January, 2021

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Keywords: COVID-19; SARS-CoV-2; Asymptomatic infections; Epidemiological characteristic

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Coronavirus disease 2019 (COVID-19) is a new disease, and obviously many things about it are not yet known for sure. But, the evolution of knowledge about it is being very fast. From not knowing anything about the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in early 2020, the scientific community has already managed to isolate it, sequence it, identify it, develop diagnostic tests and vaccines. However, as with any new epidemic, there are still many unknowns that will be resolved as it evolves and as scientists understand more about the behavior of the virus.

While more information becomes available every day, many questions about transmission remain. Infected people can transmit the virus both when they have symptoms and when they don't have symptoms. Current evidence suggests that COVID-19 spreads between people through direct, indirect (through contaminated objects or surfaces), or close contact with infected people via mouth and nose secretions. These include saliva, respiratory secretions or secretion droplets. These are released from the mouth or nose when an infected person coughs, sneezes, speaks or sings, for example. People who are in close contact (within 1 metre) with an infected person can catch COVID-19 when those infectious droplets get into their mouth, nose or eyes. There have been reported outbreaks of COVID-19 in some closed settings, such as restaurants, nightclubs, places of worship or places of work where people may be shouting, talking, or singing. In these outbreaks, aerosol transmission, particularly in these indoor locations where there are crowded and inadequately ventilated spaces where infected persons spend long periods of time with others, cannot be ruled out [1].

In this scenario, how to manage "silent" (asymptomatic) cases? Identify the points where asymptomatic cases are occurring by approaching the situation from a comprehensive perspective. This inevitably includes (in addition to other approaches such as: test system, trace and public health measures; the strict follow-up of negative cases as well as positive ones; and backward follow-up of the contacts of positive cases, looking for the source of a new case together with the contacts of that person), massive and opportunistic tests for the detection of general and specific populations: rapid response tests for COVID-19 available to everyone, specifically for those without symptoms, performed as mass population screening, to certain groups such as health workers and students, such as opportunistic detection in the general practitioner's office, and even in concerts, in the cinema, in large commercial surfaces, or at home self-administered by anyone (maintaining the rest of public health measures: masks, distancing, capacity limitation, hand washing, mobility limitation). In this approach, even with the possible errors, most of the possible vectors of the disease would be detected.

Moreover, it is said that "rapid antigen tests are effective, inexpensive and could end the pandemic in a few weeks (in theory)" [2]. It is the frequency that really matters. It has been pointed out that the frequency of SARS-CoV-2 tests at the population level is more important than the sensitivity of the test in controlling the pandemic. Effective detection is highly dependent on test frequency and reporting speed, and only marginally improves with high test sensitivity. Therefore, screening must prioritize accessibility, frequency, and time between sample and response; the analytical limits of detection must be secondary [3].

What has been seen is that where there is frequent testing, outbreaks simply do not occur. The accuracy of a test depends entirely on what its objective is. If the target of rapid antigen tests is infectious people (focus on infectiousness), which is really the most important public health goal -not for medical

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diagnostic purposes; rapid antigen tests are less accurate if you apply a standard reverse transcription Polymerase Chain Reaction (PCR)-, these tests become extremely accurate, and can help us control the spread of the disease. But on the other hand, under no circumstances can you start implementing antigen tests without providing confirmatory tests along with them to avoid false positives: once someone tests positive, they are not called positive; at that time a confirmation test is performed [2].

Thus, antigen testing is predicted to change the fight against the pandemic. Rapid antigen testing has been reported to be highly sensitive in detecting the presence of SARS-CoV-2 in nasal or nasopharyngeal swabs from symptomatic and asymptomatic individuals. Diagnostic performance of the test is particularly good in samples with viral loads associated with a high risk of viral transmission (Cycle threshold <25), which show high positive and negative predictive values even when a prevalence as low as 5% is assumed [4].

In a community transmission scenario, what we want to know is whether a patient is contagious. The antigen test is the most powerful tool we have to find out. It seems that most of PCR test for SARS-CoV-2 positives, that the antigen tests do not detect, are people who have passed the infection although there are remains of the virus in their body and the PCR may find them. Detecting these positives is relevant in a diagnosis -knowing if the patient passed the infection-, but not to cut chains of infections. "We can give up that sensitivity to win where we had a huge problem, which was the time it took to communicate positives and isolate." Rapid antigen tests would perform particularly well in those cases, "associated with a high risk of transmission." "SARS-CoV-2 can be transmitted before symptoms appear, so by the time a symptomatic case is detected, it may have infected others - which means that conventional testing and tracing is always playing catch" [5].

The indications of numerous international organizations have meant that antigen tests are being used in symptomatic cases, where they were better studied by the manufacturers [6]. But some studies suggest that they could also be used for close contacts without symptoms [4]. Thus, the current official recommendation is that the use of rapid antigen tests can be recommended to test individuals, regardless of symptoms, in settings where the proportion of test positivity is expected to be ≥10%, e.g. in the context of contact tracing and outbreak investigations. If a rapid antigen test is used in a population with high infection prevalence, negative results should be confirmed either by PCR or by a repeated rapid antigen test. If a rapid antigen test is used in a population with low infection prevalence, positive results should be confirmed either by PCR or by a repeated rapid antigen test. In both situations, the use and choice of the confirmatory test depends on the tolerability of the risk associated with missing positive cases or with detecting falsely positive cases [6].

However, the strategy of mass testing has been criticized [7]. On the one hand, due to its high rate of false negatives; that is, it does not have a high enough sensitivity to rule out COVID-19. Thus, it can give people the mistaken assurance that, "at least for a limited time, they are unlikely to have the virus and that they are at low risk of transmitting it to others" [8]. But, the asymptomatic patient with a false negative that assumes false security and puts others at risk, would also incur the same role of not being infected and would also put others at risk, without proof; thus we would be in Pascal's wager, an argument in philosophy presented by the seventeenth-century French philosopher, Blaise Pascal (1623–1662): a rational person should choose to believe in God, because, if it exists, the reward -eternal glory- would be infinite. And if it did not exist, it does not matter much if one chose one or the other belief) [9].

It is also said that many asymptomatic people who test positive for COVID-19 on the rapid test are probably relatively non-infectious. Although avoiding risk, even a small risk, is possibly a wise decision. Likewise, it is said that half of asymptomatic cases can develop symptoms later and be detected at that time, without the need for a rapid test [10]. But, the presymptomatic stage seems to be the most contagious [11] and in the end that patient would also require a PCR test for diagnosis. In any case, users of these tests should certainly be explained the erroneous belief that they "accurately detect infectivity" and that their negative result does not imply that they are released from the restrictions.

The criticisms of mass testing perhaps are summarized in cost problems or in the results of a cost-benefit evaluation to calculate the relative cost of mass testing versus other testing protocols or different interventions [12]. But, these reviews do not contemplate all the necessary approaches to manage asymptomatic (silent) cases of COVID-19. From this comprehensive perspective, it seems that the advantages outweigh the problems as an approach to asymptomatic patients, and the initial acceptability of these tests is high. Rapid, cheap and frequent mass testing, will likely be a vital tool to help control COVID-19 and make life more normal by cutting the chains of transmission [13].

Anyway, mass testing is still one piece to fit the puzzle. In several countries, from Spain to India to the United Kingdom, massive screening has been done to find positives in places such as a university campus or a neighborhood. If thousands of people are tested, some will be found infected. But it is still a challenging strategy. Firstly, for the false positives; some of the people who test positive are not actually infected -between 10 and 150 people for every 10,000 tested, depending on the specificity of the antigen test and the prevalence of the disease [14]. For example, in Slovakia [15] they have tested two thirds of its population and quarantined the 57,000 people who tested positive, although a part will not have the virus. It is not clear whether the screenings performed so far have worked well, but it is possible that in the coming months the efficacy of the use of antigens for mass testing will improve.

For example, compared to PCR tests for SARS-CoV-2, the Abbott BinaxNOW Rapid Antigen Test has a sensitivity of 64% among symptomatic individuals and 36% among asymptomatic individuals, based on analysis of paired respiratory samples of about 3,400 patients in Arizona. Meanwhile, the specificity

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was almost 100%. Consequently, symptomatic individuals or individuals with or known exposure who have negative SARS-CoV-2 antigen test results should consider obtaining confirmation with a PCR test, as should asymptomatic individuals who have an antigen test positive [16,17]. A negative antigen test does not necessarily need to be confirmed by PCR if the pretest probability is low, such as in cases where the individual is asymptomatic or has no known exposures [18].

Thus, rapid COVID-19 tests that trade a certain degree of reliability for speed could prove to be a valuable public health tool in the most affected communities. Researchers in San Francisco, California, tested about 3,300 people for SARS-CoV-2 with a rapid test and the standard PCR test. The rapid test, BinaxNOW, detected 89% of the 237 people who tested positive with PCR, and detected all those who had high levels of the virus. The rapid results, which returned in about an hour, meant that infected people were able to quickly self-isolate themselves, reducing the chance that they would spread the infection [19].

PCR tests are capable of detecting minute amounts of viral RNA; although powerful, these molecular tools cannot be scaled to meet the demands of more extensive public health testing. To combat COVID-19, the "one size fits all" approach that has dominated and confused decision-making regarding testing and evaluation of tests is not adequate: diagnoses, screening and surveillance have different purposes, require different strategies and require separate approval mechanisms. By supporting the innovation, approval, manufacture and distribution of simpler and cheaper detection and surveillance tools, it will be possible to more effectively limit the spread of COVID-19 and respond to future pandemics [20]. It is known that there are 20% of PCR positives that are negative for antigen: they are "false negatives". But they are usually patients with low viral load and who will hardly transmit the disease; they are probably not contagious [21].

On December 15, 2020, the Food and Drug Administration (FDA) granted an Emergency Use Authorization (EUA) for the first over-the-counter COVID-19 test that can be performed entirely at home. A rapid lateral flow antigen test, the Ellume COVID-19 Home Test produces results in as little as 20 minutes. In symptomatic individuals, the test was found to correctly identify 96% of positive samples and 100% of negative samples, while in asymptomatic individuals, the rates were 91% and 96%, respectively. It has been authorized for people 2 years and older, whether or not they are symptomatic. Another home antigen test, the BinaxNOW COVID-19 Ag Card home test, available by prescription, received a EUA from the FDA on December 16, 2020. It is licensed for use in individuals 4 years of age and older in whom COVID- 19 is suspected, and the test must be done within 7 days of the onset of symptoms [20].

Therefore, one can even speak of an individual use; almost a home use. Having cheap, fast and self-executing antigens, they may become mandatory for risky activities: travelling by plane, dining in a restaurant or hanging out with a group of friends for a few days. Even if the vaccine arrives, the virus will not disappear completely and it will continue to be important to protect ourselves in the best possible way [22].

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