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RESEARCH ARTICLE

COVID-19 Testing: Impact of Omicron variants on diagnostic reliability

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ABSTRACT

Rapid antigen testing continues to be recommended across the world for the prevention of transmission of SARS-CoV-2 for anyone with COVID-19 symptoms, recent exposure, those visiting high-risk individuals or those recently in crowded spaces while traveling without wearing a mask. Evidence of decreasing diagnostic reliability of individual tests and potential benefits and harms of non-targeted testing is increasingly becoming a concern across the world. Recent research has found multiple commonly used rapid antigen tests have diagnostic sensitivities below 30%, with sensitivities at or near 0% the first 48 hours of infection, when using polymerase chain reaction (PCR) test positivity as the gold standard. Common rapid antigen test sensitivities are lower in individuals previously infected with COVID-19 or in the setting of the BA.4 and BA.5 omicron subvariants. The changes in the rapid antigen test diagnostic sensitivities is a concern with the rapidly changing Omicron variants entering the population as an effective screening tool. With the decreasing diagnostic reliability, potential detrimental effects and lack of evidence to support continued community-based testing, what is the most up to date advice for institutions and providers regarding testing? In this review, we are critically appraising the current utility of community-based rapid antigen testing for COVID-19.

Introduction

Rapid antigen testing for COVID-19 continues to be recommended by the Centers for Disease Control and Prevention (CDC) in the United States for anyone with COVID-19 symptoms, recent exposure, those visiting high-risk individuals or those recently in crowded spaces while traveling without wearing a mask.[1,2] In the US, the National Institutes of Health (NIH)'s current information on COVID-19 testing notes, that testing is critical to controlling the spread of SARS-CoV-2 and is the only way to be sure you are not passing the virus on to others.[3] In 2023, the Infectious Disease Society of America (IDSA) recommended broader testing strategies.[4] In early 2022, Scandinavian countries abandoned recommending population-based testing except in situations where a positive result can change medical management.[4,5] Protocols developed to screen individuals prior to access to medical care must be reevaluated with the emergence of the omicron variants and the decreasing sensitivities and accuracy of rapid antigen tests.[6-10] In this review, we critically appraise the current utility of community-based rapid antigen testing for COVID-19.

COVID-19 testing: Benefits and unintended consequences

In 2020-2021 hospitals, clinics and private practice offices developed screening protocols to identify patients with asymptomatic COVID-19 with the goal of minimizing infection risk for other patients, health care providers and staff.[6] It was found that the use of screening protocols can help mitigate the risk of serious COVID-19 infections, especially for unvaccinated patients, health care providers, and staff.[6]

With the emergence of the omicron variant and increasing population immunity, the infection hospitalization and infection fatality rate of COVID-19 have diminished substantially.[7] The theoretical benefit of any population-based testing program has also diminished.[7] Determining the cost-benefit ratio of such a program is incredibly complex and real-life analyses demonstrate the importance of considering unintended consequences, such as increased school and work absences, unnecessary medicalization and inaccurate test results.[8,9] The potential benefits of population-based testing programs will also depend on the likelihood a person will quarantine if the test is positive and how many deaths, hospitalizations and lost work days due to COVID-19 will be prevented or delayed (and for how long).[10] An individual with a positive test result may not be able to quarantine or only partially quarantine.[10] Some quarantines may not prevent any transmission but come with a loss of productivity and absences from major events.[10] A false negative result may cause a person to expose more individuals to SARS-CoV-2 while a true negative result may lead individuals symptomatic with a different disease to be falsely assured and expose others to a non-COVID illnesses, which could be more severe.[10]

In 2020, testing played a significant role in establishing accurate infection fatality rates and provided insight into the transmission of this novel disease.[10] Testing has been used to provide information to individuals about their own immunity and for alerting high-risk populations about periods of increased community transmission.[10] One modeling study from Italy in 2020 found a population-based rapid testing program may have been cost-effective through slowing transmission rates.[11]

However, this was based on observational data where causality between the testing and decreased disease spread, hospitalizations and deaths could not with certainty be attributed to the testing program, as many variables were changing simultaneously.[11] It was not clear to what extent COVID-19 hospitalizations and deaths, if truly diminished due to testing, may have been entirely prevented and not just delayed.[11]

In 2020 COVID-19 screening protocols, as validated by COVID-19 assay, were effective in screening out symptomatic patients infected with COVID-19 before they were seen in clinics.[6] As clinics and office practices return to pre-pandemic volumes, the use of such a screening protocol could help mitigate the risk of serious COVID-19 infection, especially for unvaccinated patients, health care providers, and staff.[6] If the accuracy of the screening testing is declining due to newer omicron variants, then the benefit of prescreening patients for medical care is potentially reduced. Now that COVID-19 has become endemic, it is important to consider the limitations and unintended consequences of ongoing testing, especially on non-high-risk groups.

Diagnostic accuracy of SARS-CoV-2 rapid antigen tests

Rapid antigen tests have had decreasing accuracy in the setting of the omicron variants.[10] There are several factors which influence the diagnostic accuracy of the COVID-19 rapid antigen tests.[10] These include the sensitivity and specificity of the individual tests, the pretest probability a person is infected with COVID-19, the circulating variant, the individual's immunity status and the stage of infection.[10]

A Cochrane review of rapid antigen tests published in 2022, based on the pre-omicron era, found an average sensitivity of 54.7% for people testing without symptoms and 49.6% for people who are not known contacts.[12] The specificity was on average 99% for all rapid tests.[12]

Studies following the emergence of the omicron variant have found lower sensitivities of rapid tests, especially early in the infection.[13] One study performed during omicron outbreaks in New York City, Los Angeles and San Francisco within the US using two popular rapid antigen tests found 0% sensitivity within the first 48 hour a person is PCR positive.[13] This study exclusively considered cases that were believed to be infectious based on a cycle threshold (ct) which is the actual number of cycles it takes for the PCR test to detect the virus.[13] Between 48- and 72-hour post PCR positivity the sensitivity improved to 29%.[13] This study suggests sensitivity may be lowest and approaching 0% with a false negative rate of nearly 100% during an outbreak and at the initial stages of infection, including periods when at least some people are already infectious.[13] This presents a potential issue for screening of individuals at medical clinics or hospitals early in the asymptomatic phase of an active infection.

Another study from the Netherlands found a low sensitivity of 27.5% among asymptomatic individuals using a rapid antigen test.[14] The sensitivities of multiple test brands were found to be consistently lower among previously infected individuals.[14] This may explain some of the decreasing sensitivity of rapid antigen testing we are seeing over time.[14] Overall sensitivity increased to 48.3 % when a viral load cutoff was used, above which at least 95% had a positive viral culture.[15]

A study of ten commonly used rapid antigen tests in the setting of the BA.4 and BA.5 omicron subvariants reported low sensitivities.[15] This included tests that had previously had sensitivities nearing 90 % prior to the emergence of the omicron variant.[15] The impact of the omicron variants is an evolving situation that is impacting the sensitivities of many rapid antigen tests.[15]

Nucleic acid amplification tests, including polymerase chain reaction (PCR) assays, are more sensitive for the detection of COVID-19 than rapid antigen tests, and are the gold standard for diagnosis of acute COVID-19.[16] Rapid antigen tests remain the mainstay of COVID-19 diagnosis due to their convenience, speed and high specificity.[16] In late 2021 when the rapid antigen tests became available in Australia their wide availability, convenience and speed of providing results has led to them becoming the dominant testing method for testing.[16] The development, refinement and implementation of diagnostic tests for COVID-19 have been a major achievement and critical to the well-managed pandemic in Australia.[16] The involvement of patients in their own diagnostic testing, public health notification and management (primarily isolation) has represented a paradigm shift.[16] This will form the basis of future development in the management of infectious diseases and outbreaks.[16]

Potential benefits and harms

Individuals who are temporarily immune-compromised may benefit during a specified period of time from avoiding exposure to COVID-19.[17] Screening of contacts with rapid tests may be misleading, particularly early in the infection, and the introduction of various omicron variants.[10] There are concerns with sensitivities under 30% in the setting of the omicron subvariants, and as low as 0% during the initial days of infection.[10] The use of rapid antigen tests is likely to provide a false sense of security for situations that may include high-risk individuals such as the immune-compromised.[10] Symptomatic individuals who test negative may also expose high-risk individuals to non-COVID-19 illness at higher rates.[10]

Testing for COVID-19 of high-risk individuals can help provide appropriate, disease-specific treatment.[10] Testing of non-high-risk individuals that will not result in behavior changes, which may decrease community transmission rates, is of questionable value in the identification and prevention of COVID-19.[10] This has not been demonstrated with high-quality data that allows for causal inference.[10]

Behavior changes related to repeat quarantines that were common in the early phases of the COVID-19 pandemic may increase the risks of other health problems including mental health related issues.[18] The cost of testing, missed work and school days for quarantines, particularly for asymptomatic positive test results, should all be considered in any risk-benefit analysis.[18] A requirements of rapid antigen testing of non-high-risk asymptomatic individuals prior to gaining access for medical care would be of questionable value.

A current lack of evidence of net benefit

Determining whether encouraging rapid testing can improve overall community health, increase the safety of health care workers and vulnerable patients and decrease the likelihood of spread of COVID-19 will require either randomized trials or high-quality observational data which

permit causal inference.[10,19] Testing is only useful as far as its results can leverage behavioral changes that improve outcomes.[10]

It has been recommended by numerous studies that the performance of rapid antigen tests was optimized when asymptomatic participants tested three times at 48-hour intervals and when symptomatic participants tested two times separated by 48 hours.[16,20] Is this practical in most healthcare settings where patients are seeking medical care for acute and chronic problems? There are costs and rapid access to health care issues that would have to be addressed to implement the screening strategy. Policies of testing multiple times over a defined period of time would in most cases delay care for most individuals. Patients may be able to test multiple times over a defined period or time in a home situation if they have access to rapid antigen tests available to them and are able to successfully complete the testing as instructed.

Conclusion

The current review describes decreasing accuracy of rapid antigen testing due to various omicron variants and previously infected individuals with COVID-19. Coupled with decreasing COVID-19 disease severity, we argue that better evidence of benefit should be required before additional or continued broad recommendations on community-based rapid testing are implemented. Utilization of specific protocols in clinic and hospital settings must weigh the costs of implementation and delayed access to health care for the individuals.

It has been shown that point of care testing utilizing rapid antigen testing for early diagnosis of COVID-19 in the healthcare setting has been beneficial. As the omicron variants are changing, it is important to estimate the scale and variation in antibody prevalence over time. Community self-testing and reporting produce rapid insights into the changing course of the pandemic and the impact of vaccine rollout, with implications for future surveillance. This would be directly applicable to screening of individuals with or without symptoms prior to gaining access to health care.

Of greatest concern are the low sensitivities of many of the rapid antigen tests, with many brands showing lower sensitivities amongst previously infected individuals, in the initial stages of the asymptomatic disease state and with the newer omicron variants. This consideration must be part of the discussion in the implementation of policies regarding the screening of symptomatic and asymptomatic individuals.

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