Interpretation of Antigen-Detection Rapid Diagnostic Tests (Ag-RDTs) should take into Account the Pre-test Probability of COVID-19 Infection

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Dear Editor,

Antigen-detection rapid diagnostic tests (Ag-RDTs) are single use, lateral flow tests that can be performed outside healthcare settings for diagnosis of COVID-19 infections. These tests offer direct visual results on small portable devices within 15 minutes. Thus, Ag-RDTs offer significant promise in rapidly identifying COVID-19 infections, facilitating isolation and treatment.

When Al-Alawi et al.[1] evaluated four rapid antigen tests, they found moderate sensitivity (64.0% to 69.8%) and high specificity (94.1% to 100%) compared to real-time reverse transcription PCR (RT-PCR). They recommended that negative results may need repeat testing or RT-PCR to reduce the possibility of false negatives. A similar study by Bruzzone et al.[2] comparing the performance of 7 Ag-RDTs against RT-PCR also found a wide range of sensitivity (66.0 to 93.8%), which was maximal at a cycle threshold (Ct) cut-off value of 29. Although the sensitivity appeared dependent on viral load, there was still significant variability in the diagnostic performance of Ag-RDTs. Subsequently, a systematic review and meta-analysis which included 17,171 suspected COVID-19 patients found a pooled sensitivity and specificity of 68.4% and 99.4% respectively.[3] When

subgroup analyses were performed, sensitivity was better with nasopharyngeal specimens, symptomatic patients, low Ct values and in European or American settings.

In addition to considering RT-PCR to identify false negatives, what else can be done to improve sensitivity of Ag-RDTs? A novel study by Nikolai et al.[4] showed that there were no differences in yield between anterior nasal or nasal mid-turbinate sampling using Ag-RDTs. When mid-turbinate self-testing was compared with nasopharyngeal sampling by a healthcare professional, the sensitivity and specificity of Ag-RDTs compared to RT-PCR were also similar. This implies that nasal self-testing is simple enough that users can reliably carry out sampling themselves.

Thus, if technical sampling is already optimised, clinicians have to decide how to interpret these tests. This goes back to the basic principle of pre-test probability. After the acute phase (more than 5 days), a low viral load may lead to false negative Ag-RDTs, thus molecular or antibody tests are more appropriate. When there is a low probability of COVID-19 cases, (for example, asymptomatic people in low prevalence settings such as workplaces or schools), Ag-RDTs with a high negative predictive value is useful to rule out infections. In this situation, as there is a high false positive rate, RT-PCR may be required to confirm positive results. For healthcare workers or close contacts of confirmed cases, there is an intermediate risk compared to the general population. A two-step testing algorithm should be considered using a high sensitivity Ag-RDT for initial screening for asymptomatic COVID-19 infections; followed by confirmatory tests for positive results. The World Health Organisation (WHO) recommends a 97% minimum specificity, which offers a 63-83% positive predictive value. Provided the likelihood of positive tests is 5-10%, this is more likely to lead to false positives rather than false negative results.[5]

In conclusion, Ag-RDT is a useful tool for diagnosis of COVID-19 infections. However, clinicians need to consider the pre-test probability to determine how to appropriately interpret results.

References

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