Do not blindly trust negative diagnostic test results!

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The shift to a colder season is generally accompanied by an annual increase in respiratory infections. In early September, 2023, European epidemiological surveillance systems reported the first annual signs of increased COVID-19 infections.[1] Efforts to increase testing activity have started,[2] and the expected rise in testing frequency calls for a precautionary reminder of the limitations of diagnostic testing and screening for infectious pathogens. Every diagnostic test system has unique performance characteristics, including its overall sensitivity and specificity, which reflect the assay design. Clinical samples with infectious pathogen loads lower than the detection limit of the assay generate negative test results.

The overall sensitivities of the two most common methods for detecting SARS-CoV-2 clearly differ, with nucleic acid amplification tests generally having higher sensitivity than antigen detection tests. External quality assessments of SARS-CoV-2 genome detection tests revealed substantial performance differences with a range of representative assays, and no improvement was observed over the course of the COVID-19 pandemic.[3] Clear differences in sensitivity, notable deficiencies in detecting low virus loads, and subjective difficulties in visually recognising weakly positive reactions were reported for rapid antigen detection tests.[4] Rapid antigen detection tests continue to show reduced sensitivities with newer SARS-CoV-2 variants, and the sustained heterogeneity in the performance among available tests is noteworthy.[5,6] Negative effects of sampling and pre-analytical procedures on pathogen detectability reduce the accuracy of a diagnostic test, which is based on its analytical sensitivity.[3,7] Ultimately, a wide variety of factors can lead to false-negative test results.

False-negative results can induce an inappropriate sense of safety for the people concerned and their environment, delay and misdirect therapy for people with higher health risks, and encourage the further spread of infection. However, false-negative results are well recognised as outcomes that cannot be completely prevented; only their frequency can be reduced. National and regional testing strategies should aim to maximise the detection rates for individuals with suspected infections and those with symptom-free infections and to minimise the proportion of false-negative results by using high-quality diagnostic tests. The medical community should not support or promote the use of test methods that do not conform to the highest quality standards. Using suitable quantified control materials, the minimum detection limits of the assays should be evaluated, and appropriate testing procedures should be monitored to reduce error rates and associated harm. Appropriate procedures for monitoring the performance of different test systems and entities have been previously described.[8]

An essential task is to raise awareness among health-care professionals and the public that test systems are capable only of detecting infection but not ruling out infections; negative test results do not resolve whether a pathogen was absent or the test system could not detect it. In the context of diagnostic testing, the alternative to positive can be conveyed more explicitly by reporting negative results as not detected instead of negative, thereby reducing the risk that affected individuals misinterpret a negative test result as meaning that they are not infected because they tested negative. In addition, reporting the detection limit of the assay can enable readers to cautiously estimate the reliability of negative results.

Diagnostic tests for pathogens other than SARS-CoV-2 have not been discussed as extensively, and no other pathogen has been tested recently. However, the findings discussed here apply not only to SARS-CoV-2 tests but

***Panel.* Recommendations for pathogen detection and pathogen testing strategies**

- National and regional testing strategies should aim to maximise the detection rate of infected individuals and minimise the proportion of false-negative results.
- The medical community should not support or promote the use of test methods that do not conform to the highest quality standards.
- Health-care professionals and the general public should be aware that testing is capable of detecting infections but not of ruling out infections.
- Negative test results should be reported as (pathogen) not detected for a more factual representation of the data obtained.
- The detection limit of the test system used should be included when reporting negative results to guide readers in interpreting the results.

also to all diagnostic tests for infectious pathogens. We summarise our recommendations for pathogen detection and pathogen testing strategies for future outbreaks of SARS-COV-2 and other infectious causes of epidemics in the panel.

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