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Should RT-PCR be considered a gold standard in the diagnosis of Covid-19?

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Dear Editor,

To face the new Covid-19 pandemic, the need for early and accurate diagnosis of the disease among suspected cases quickly became obvious for effective management, and for better control of the spread of the disease in the population. Since the beginning of this disease epidemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), reverse transcriptase polymerase chain reaction (RT-PCR) has routinely been used to confirm diagnosis. However, several authors have pointed out the poor performance of this technique, particularly in terms of sensitivity.[1,2] Indeed, according to some authors, sensitivity could be as low as 38%[3] (i.e. not better than chance). This made it necessary to find a more sensitive test, given the contagiousness of SARS-CoV-2. We therefore read with great interest the article published in your journal by Cassaniti et al,[4] entitled "*Performance of VivaDiag COVID-19 IgM/IgG Rapid Test is inadequate for diagnosis of COVID-19 in acute patients referring to emergency room department*". This article deals with the diagnosis of COVID-19 by serology (IgM/IgG) as a complementary approach to RT-PCR to improve its sensitivity. According to these authors,[4] as well as other authors,[5] serology is faster to implement, less expensive, easier to use, and more accessible to staff with no specific

laboratory training.[5] The article describes the metrological performances of serology, and compare it with RT-PCR as the gold standard. Using a test as the gold standard when its metrological properties are clearly perfectible raises question from a methodological point of view. Indeed, when an existing test is considered as a reference, this suggests that the test in question is always correct, and that all misclassifications (false negatives, and false positives) are due to the new test. However, the new test (in this case, serology) might be better than the old test (in this case, RT-PCR), but it would be impossible to demonstrate this. Consequently, the new test will never be able to achieve sensitivity of 100%, since it is considered responsible for all misclassifications. The same mistake has also been made by other authors regarding the use of chest computed tomography (CT) scans as a diagnostic method.[6,7] In this situation, the best strategy would be to measure the degree of agreement (using the Kappa coefficient measures[8]) between the two tests, i.e. neither of the two tests is considered to be the reference and therefore, any discrepancies could be linked to either of the tests. Thus, the serology performances presented by Xiang et al [5], are certainly better than those presented in their paper.

The difficulty of using a gold standard is an old debate [9,10], but still relevant nonetheless. In the absence of an accurate reference test, alternative strategies could be to perform the test repeatedly over time, to use the patient's clinical course, or the combination of several tests as the gold standard.

The purpose in writing this contribution is not to discuss the best diagnostic strategy for COVID-19, nor is it to question the results of the authors who used

RT-PCR as a reference. On the contrary, it purports that their results might actually be even better than those presented.

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