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August 12, 2020

Dear editor,

We are writing to submit an original research article entitled *"Declining SARS-CoV-2 PCR sensitivity with time and dependence on clinical features: consequences for control"* for consideration by Nature Medicine.

Seven months into the COVID-19 pandemic, an accurate determination of the clinical sensitivity of SARS-CoV-2 molecular detection in routine respiratory samples is still a lacking, a pivotal pillar of an adequate clinical and public health response that urgently needs to be addressed. Here, we determined the sensitivity of SARS-CoV-2 RT-PCR in upper respiratory tract (URT) samples based on Bayesian modeling of diagnostic outcomes of a large heterogeneous cohort of COVID-19 patients. Control of the SARS-CoV-2 pandemic aims at reduction of the basic reproduction number (R_0) through physical distancing and early case-finding followed by case isolation and quarantining of close contacts, the so-called track and trace strategy. Especially when countries have succeeded in flattening of the epidemic curve through (partial) societal lockdown, the track and trace policy is essential to keep the R_0 below 1 and the extent of virus circulation under control. Worldwide, track and trace policies are based on molecular detection (RT-PCR) of SARS-CoV-2 RNA in URT samples. A thorough understanding of the (lack of) sensitivity of the SARS-CoV-2 RT-PCR on URT is a crucial aspect of an adequate track and trace policy.

To date, the precise sensitivity of RT-PCR on URT samples remains uncertain, because the very few studies addressing this issue have important limitations, such as insufficiently described methods thereby casting doubt on the validity of study outcomes, the use of cohorts of limited size and without a proper representation of the clinical variety in COVID-19, or the use of a doubtful gold standard. Our methodology considers several tests (PCR and antibody tests) applied to the individuals, inferring the sensitivities by analysing patterns of positive and negative results, and fully quantifying uncertainty in the estimates by means of Bayesian statistics. We further determined the clinical sensitivity in relation to the number of days post symptom onset and different patient characteristics and observed a decline in sensitivity with time, particularly in mildly symptomatic persons. These results have important implications for both hospital-based care and public health, and provide a solid foundation for SARS-CoV-2 testing, tracing and isolation guidelines.

Given the diversity of disciplines that Nature-published papers represent, and the focus on SARS-CoV-2 mathematical modeling, we believe our research will appeal to subscribers of Nature. Our findings will interest statisticians as well as clinicians and policymakers, since an accurate clinical RT-PCR

sensitivity has not been reliably determined to date and it is a major point of discussion in both clinical and public health practice.

We confirm this is original work and that none of the material has been published elsewhere, nor is it under consideration for publication elsewhere. All authors confirm having no conflicts of interest to disclose. The nature of the study and potential consequences have been explained to, and informed consent was thereafter obtained from, those patients who had blood drawn for this study. All data are available upon request.

The auxiliary files contain an article on the SARS-CoV-2 protein microarray validation, which is currently under consideration at Emerging Microbes and Infections.

Thank you for your consideration,

Sincerely,

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