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International Journal of Infectious Diseases 103 (2021) 23–24

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

# SARS-CoV-2 sensitivity limbo – How low can we go?

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ARTICLE INFO

*Article history:*
Received 3 November 2020
Received in revised form 6 November 2020
Accepted 8 November 2020

*To the Editor,*

Since the beginning of the pandemic, molecular methods such as real-time RT-PCR have been used as references for severe acute respiratory syndrome (SARS-CoV-2) detection. With unprecedented demands for SARS-CoV-2 testing, and difficulties acquiring NAAT supplies, clinical laboratories are challenged with providing timely results. Rapid diagnostic tests (RDTs) are simple, rapid, and portable technologies that offer a potential solution to increase the diagnostic testing capacity. Recently, some RDTs have become licensed under emergency use authorization for SARS-CoV-2 detection in the laboratory or point-of-care settings (Food and Drug Administration (FDA), 2020), but despite their high specificity, the applicability of RDTs has been hampered by poor clinical sensitivity, which often falls below the ideal target product profiles recommended by the World Health Organization (Dinnes et al., 2020; World Health Organization (WHO), 2020a; World Health Organization (WHO), 2020b). In a recent systematic review and meta-analysis (Dinnes et al., 2020), the average pooled sensitivity of antigen-based RDTs was 56%, and values as low as 11.7% have been reported (Nagura-Ikeda et al., 2020). In contrast, a recent study in this journal by Porte et al. (2020) described high clinical sensitivity of an antigen-based RDT at 93.9%. Given the wide variability in RDT sensitivity, careful consideration is needed on the generalizability and applicability of these findings.

Traditionally, SARS-CoV-2 detection methods strive to achieve the highest sensitivity possible (LeBlanc et al., 2020). From an individual diagnostic perspective, the decreased analytical sensitivity of RDTs ($\sim 10^5$ copies/mL vs. $\sim 10^3$ copies/mL for NAATs) would likely only be relevant during a short period in the acute stage of illness, or late in disease (LeBlanc et al., 2020; Wölfel et al., 2020; Mina et al., 2020; Larremore et al., 2020). As individuals with resolving viral loads are less likely to be infective [i.e., high cycle thresholds (Ct values) in real-time RT-PCR], this situation may adequately be served by an RDT (Wölfel et al., 2020; Mina et al., 2020; Larremore et al., 2020). However, on a population level, the identification of individuals with early or late disease would allow for more complete contact tracing and potentially lead to more case finding and interventions.

In recent publications, an alternative strategy has been proposed that might overcome the poor sensitivity of RDTs by repeat testing of target populations over time, thereby increasing the probability of capturing individuals who fall into a period of high viral shedding (Mina et al., 2020; Larremore et al., 2020). To date, the feasibility of repeat testing using RDTs has been hampered by limitations such as scalability (with low throughput devices), human and material resource requirements, and acceptability of repeat collections with the authorized specimen types (e.g., nasopharyngeal swabs). Regardless of the challenges of RDT implementation, thorough validation is required with consideration for factors that are method-, virus-, host-, and context-dependent.

With the above considerations in mind, key parameters that remain to be defined for repeat testing using RDTs is the minimal acceptable value for sensitivity, the optimal testing frequency in target populations, and for which population or setting RDTs would be of best benefit. If the goal is case-finding and containment, the sensitivity of an assay would logically influence the testing frequency, and ideally, should be targeted to ensure the maximal and accurate detection of SARS-CoV-2 in the target population. However, if capacity or resource limitations defines a certain testing frequency, high sensitivity becomes increasingly relevant. As these parameters have yet to be defined for RDTs, we find ourselves in a “sensitivity limbo,” asking not only “how low

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https://doi.org/10.1016/j.ijid.2020.11.138

can we go?" for accurate SARS-CoV-2 detection, but also "how low *should* we go?"

## Conflict of interest

The authors declare that they have no conflicts of interest related to this manuscript.

## Funding source

There was no funding for this manuscript.

## Ethical approval

Institutional research ethics board approval was not required for this work.

## References

Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database Syst Rev 2020;8:CD013705, doi:http://dx.doi.org/10.1002/14651858.CD013705 Aug 26. PMID: 32845525.

Food and Drug Administration (FDA). In vitro diagnostic EUAs. 2020. . (last accessed Nov 3, 2020) https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas.

Larremore DB, Wilder B, Lester E, Shehata S, Burke JM, Hay JA, Tambe M, Mina MJ, Parker R. Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. medRxiv [Preprint] 2020;, doi:http://dx.doi.org/10.1101/2020.06.22.20136309 PMID: 32607516; PMCID: PMC7325181. Jun 27:2020.06.22.20136309.

LeBlanc JJ, Gubbay JB, Li Y, Needle R, Arneson SR, Marcino D, et al. COVID-19 Pandemic Diagnostics Investigation Team of the Canadian Public Health Laboratory Network (CPHLN) Respiratory Virus Working Group. Real-time PCR-based SARS-CoV-2 detection in Canadian laboratories. J Clin Virol 2020;128:104433, doi:http://dx.doi.org/10.1016/j.jcv.2020.104433 Jul Epub 2020 May 13. PMID: 32405254; PMCID: PMC7219382.

Mina MJ, Parker R, Larremore DB. Rethinking Covid-19 Test Sensitivity - A Strategy for Containment. N Engl J Med 2020;, doi:http://dx.doi.org/10.1056/NEJMp2025631 Sep 30, Epub ahead of print. PMID: 32997903.

Nagura-Ikeda M, Imai K, Tabata S, Miyoshi K, Murahara N, Mizuno T, et al. Clinical Evaluation of Self-Collected Saliva by Quantitative Reverse Transcription-PCR (RT-qPCR), Direct RT-qPCR, Reverse Transcription-Loop-Mediated Isothermal Amplification, and a Rapid Antigen Test To Diagnose COVID-19. J Clin Microbiol 2020;58(9)e01438–20, doi:http://dx.doi.org/10.1128/JCM.01438-20 Aug 24PMID: 32636214; PMCID: PMC7448663.

Porte L, Legarraga P, Vollrath V, Aguilera X, Munita JM, Araos R, et al. Evaluation of a novel antigen-based rapid detection test for the diagnosis of SARS-CoV-2 in respiratory samples. Int J Infect Dis 2020;99:328–33, doi:http://dx.doi.org/10.1016/j.ijid.2020.05.098 Oct Epub 2020 Jun 1. PMID: 32497809; PMCID: PMC7263236.

Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581(7809)465–9, doi:http://dx.doi.org/10.1038/s41586-020-2196-x May Epub 2020 Apr 1. PMID: 32235945.

World Health Organization (WHO). Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. Interim guidance. 11 September. 2020. https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays.

World Health Organization (WHO). COVID-19 Target product profiles for priority diagnostics to support response to the COVID-19 pandemic v.1.0. 29 September. 2020 Geneva, Switzerland. https://www.who.int/publications/m/item/covid-19-target-product-profiles-for-priority-diagnostics-to-support-response-to-the-covid-19-pandemic-v.0.1 (last accessed Nov 3, 2020).