Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Testing Dilemmas: Post negative, positive SARS-CoV-2 RT-PCR – is it a reinfection?

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Facing the pandemic of the Coronavirus Disease 2019 (COVID-19) [1], caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), has presented multiple challenges for the clinician. This includes not only therapeutics, but also issues related to diagnostics and criteria to define clinical and virological recovery.

Recent studies have reported patients with positive RT-PCR days or weeks after recovery and previous negative results [2,3]. RNA detection, in any sample, does not necessarily mean the presence of the complete virus in the host nor an active infection. An RT-PCR positive does not, with certainly imply SARS-CoV-2 viability, even if the genome is sequenced [4].

Although complex, many aspects should be considered. Initially, after a positive RT-PCR, a subsequent negative RT-PCR, especially when the viral load and multiple testing is not done, may represent a false negative. Maybe the viral load is below the detection threshold? Secondly, a post-negative, positive RT-PCR may be contamination. Furthermore, also long "shedding" may reflect only the lack of elimination of the nucleic acid from the tissues [5]. Thirdly, virus infectivity depends on the presence of the whole virus, not just its RNA. Wölfel et al. [6], demonstrated that the success of virus isolation depends on the day of sampling after the onset of symptoms and the viral load [6]. Despite having a SARS-Co-2 positive by RT-PCR, the virus was not isolated after the eighth day of the day after symptom onset [6]. In many other viral diseases, such as Zika, it is well known that its RNA can be detected long after the clearance of the infectious virus [7]. RT-PCR is not able to differentiate infective virus from non-infectious RNA [5].

In patients with clinical improvement, who are asymptomatic and who have a resolution of radiological alterations, as the cases reported by Lin et al. [2], and others [3], a post-negative positive RT-PCR does not necessarily reflect reinfection or viral carriage. In addition, antibody responses, including IgM, IgG and IgA, were not measured. A thoughtful assessment should include viral load, antibody response, and detailed clinical evaluation and follow-up, complemented, if an RT-PCR again became positive, with infectivity demonstrated by inoculation on cell lines, e.g. Vero/hSLAM or Vero/E6 cells, with material from the nasopharyngeal swab of the patients to isolate SARS-CoV-2 virus in culture [6,8]. Virus isolation success also depends on viral load. Samples containing $< 10^6$ copies/mL (or copies per sample) never yielded an isolate [6]. Electron microscopy, whole-genome sequencing, and phylogenetic analysis, then, may lead to conclusions of possible reinfection, or not.

Finally, we urgently need the afore-mentioned comprehensive investigations, in addition to single or small case series to define better diagnostic and management strategies in healthcare during the pandemic, as well as for better evidence-based decisions in public health given the potential implications in SARS-CoV-2 transmission and susceptibility.

CRediT authorship contribution statement

Carlos A. Alvarez-Moreno: Conceptualization, Writing - review & editing. **Alfonso J. Rodríguez-Morales:** Writing - original draft, Writing - review & editing.

Declaration of competing interest

None.

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