Letter to the Editor

Making sense of a negative COVID-19 swab test

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Submitted Jul 30, 2020. Accepted for publication Aug 24, 2020.
doi: 10.21037/qims-20-929
View this article at: http://dx.doi.org/10.21037/qims-20-929

We read with great interest the study by Li *et al.* (1). As the Coronavirus Disease 2019 (COVID-19) continues to evolve, there have been increasing reports of false-negative oropharyngeal swabs for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2,3). In response, we would like to raise two points for consideration.

First, factors that may have contributed to the false-negative results include improper or suboptimal sampling technique, transportation or storage process. Although an experimental study found that angiotensin-converting enzyme 2 (ACE2) expression was found only on the basal and not surface layer of the nasal, oral, and nasopharynx (4), SARS-CoV-2 RNA detected in nasophargyneal aspirates might be derived from the infected lower respiratory tract. In patients with COVID-19, ciliated cells in the upper airways are thought to be infected (5). As demonstrated by an earlier study of the 2003 SARS coronavirus (SARS-CoV), human ACE2 was detected in ciliated airway epithelial cells and SARS-CoV could infect the proximal airways (6). By reasonable extrapolation, this should also apply to SARS-CoV-2.

At present, we also know that there is a significant amount of SARS-CoV-2 shedding in the upper respiratory tract, even amongst asymptomatic individuals, and they can go on to infect others (7). According to data from the World Health Organisation and the Chinese Center for Disease Control and Prevention, SARS-CoV-2 can be detected in upper respiratory samples one to two days prior to symptom onset and persist for up to 12 days in moderate cases and up to two weeks in severe cases (8).

In a recent report by Wang *et al.* (9), SARS-CoV-2 was detected in specimens taken from multiple sites, with lower respiratory tract samples most often testing positive for the virus. Viral RNA was detected only in 32% (126 of 398) of oropharyngeal swabs, which was lower than that of nasopharyngeal swabs (63%, 5 of 8). The findings also suggest that testing of specimens from multiple sites or obtaining lower respiratory tract samples may improve the sensitivity and reduce false-negative test results. The alternative is retesting after 1 to 2 days, especially for patients who are epidemiologically linked or with a high index of clinical suspicion. In a study of 610 hospitalized patients, among the 384 patients with initial negative results, a retest after 1 or 2 days returned positive in 48 of them (12.5%) (2). Higher viral loads may be present after symptom onset.

More recently, clinicians have also supported the utility of chest computed tomography (CT) imaging in screening patients in whom COVID-19 is clinically suspected, especially those with negative initial RT-PCR results (10), or living in areas of high disease prevalence, e.g., Wuhan, China (11). CT imaging may facilitate early diagnosis of COVID-19 in these patients and it could also be used to monitor for complications. However, CT involves a considerable amount of radiation and cost for the patient, and like most things in medicine, these risks have to be weighed against the potential benefits.

The second point we would like to highlight pertains

to the discharge criteria for COVID-19 patients. As the number of COVID-19 cases continue to rise worldwide, many health systems have become increasingly overwhelmed. However, as the kinetics and infectivity of viral shedding in COVID-19 remain under investigation, the United States Centers for Disease Control and Prevention (CDC) and some countries (including China and Singapore) still recommend two consecutive negative respiratory specimens, collected more than 24 hours apart before discharge or discontinuation of transmission-based precautions (12,13). Naturally, collection of upper respiratory tract samples would be less invasive and cumbersome than that of lower respiratory samples. Although the viral particles detected by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) may be nonviable, the precaution of testing negative twice over a time interval provides some assurance that a productive infection is not ongoing. We recognise that this may put immense pressure on already strapped health systems and that a time-based or symptom-based strategy may be preferred but there is always the concern of discharging COVID-19 patients prematurely even though patients appear to have clinically recovered (14).

All in all, we would like to emphasize that pre-test probability matters and a negative COVID-19 swab test must be cautiously interpreted in the given clinical context.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available athttp://dx.doi.org/10.21037/qims-20-929). The authors have no conflicts of interest to declare.

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Cite this article as: Ng QX, Liew MF, Yeo WS. Making sense of a negative COVID-19 swab test. Quant Imaging Med Surg 2020;10(11):2212-2214. doi: 10.21037/qims-20-929

