Throat Wash Testing and COVID-19 Disease: Should We Put Our Money Where Our Mouth Is?

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Accurate and efficient identification of infected persons is necessary if the COVID-19 pandemic is to be optimally managed and contained. Unfortunately, patient reported symptoms and physician examinations, especially early in the clinical course, have not been consistently helpful in diagnosing COVID-19 disease. Moreover, asymptomatic or pre-symptomatic transmission of COVID-19 disease has been described [1]. The tragedy that is the US aircraft carrier *Theodore Roosevelt*, in which 60 percent of the 600 sailors who tested positive for SARS-CoV-2 infection were asymptomatic, further highlights the need for accurate laboratory diagnostics for COVID-19 disease [2].

The US Centers for Disease Control and Prevention (CDC) currently recommends that initial diagnostic testing for COVID-19 disease be performed using a nasopharyngeal (NP) swab [3]. SARS-CoV-2 has been detected in a variety of clinical samples including sputum and bronchoalveolar lavage fluid. And when compared directly to oropharyngeal (OP) samples, nasopharyngeal testing for SARS-CoV-2 was not consistently shown to be superior [4-6]. There are other obvious drawbacks to using a nasopharyngeal swab-based test compared to a throat wash-based test both to the individual patient and the healthcare system. To begin with, the swab sample collection method is an unpleasant experience for the patient. Moreover, personal protective equipment (PPE) is required for clinicians collecting NP swabs, resulting in increased utilization of PPE and supply shortages. Similarly, there have also been shortages of nasopharyngeal swabs, leading to delays in COVID-19 testing [7].

In this issue of *Clinical Infectious Diseases*, Guo and colleagues compared SARS-CoV-2 testing of NP swabs versus self-collected throat washing samples [XXX]. The trial is remarkable for its focused question and simple design. Eleven laboratory-

confirmed participants (presumably by either NP or OP swab RT-PCR testing) underwent further paired RT-PCR testing for COVID-19 disease using a proprietary assay kit. All paired samples were collected at a median of 53 days (range 48-57 days) after symptom onset. For 18 of the 24 paired samples, the results were in agreement (17 paired samples both tested negative, and one sample pair was positive for SARS-CoV-2). However, 6 of the paired tests were incongruent, with the throat wash samples being positive and the NP swabs being negative for SARS-CoV-2. The authors assumed that these throat washing results were not falsely positive and concluded that RT-PCR testing of throat washes resulted in a higher rate of detection of SARS-CoV-2 infection compared with NP sampling.

The limitations of this study are worth noting. This is a single center investigation with a relatively small number of participants (n=11) enrolled. The technique by which samples were collected ("asking the patient to oscillate over posterior pharyngeal wall with 20 ml of sterile saline") may have differed among study participants. And whether the test results are due to pharyngeal sampling or oral rinsing at the time of expectoration cannot be determined. In terms of the actual laboratory testing, the details of the assay kits used, including which primers were employed, were not disclosed. Finally, the authors also assume that RT-PCR testing did not yield any false positive results. Although rare, false positive results with RT-PCR testing can occur secondary to sample contamination.

These shortcomings aside, Guo et al. make the case that testing of throat wash samples may be more sensitive than testing of NP swabs for COVID-19 disease. NP testing compared to throat wash testing failed to detect SARS-CoV-2 nucleic acid in 86%

(6/7) of paired samples. Interestingly, there is biologic plausibility that a sample collected via the oral cavity (such as a throat wash) may yield higher results than a NP swab test based on a study by Xu et al. which demonstrated high ACE2 receptor expression on the epithelial cells of oral mucosa and the base of the tongue which is a part of the oropharynx [8]. Whether two consecutive RT-PCR tests using NP swab specimens (currently recommended by the CDC as part of a test-based strategy for discontinuing isolation precautions) results in a sensitivity comparable to one throat wash is not known [9]. Admittedly, the sensitivity of throat wash testing almost seems "too good to be true;" nonetheless, the ramifications of failing to identify COVID-19 positive patients would have dire consequences amid a pandemic.

Regardless of testing method employed, this study is further remarkable for the fact that SARS-CoV-2 nucleic acid was detected in persons late in their clinical course and had presumably recovered. Of the paired samples, 29% (7/24) were notably positive in individual 48 days after the onset of symptoms. These findings are consistent with another study showing that the median duration of viral shedding in a cohort of 41 patients with severe COVID-19 disease was 31 days from onset of illness [10]. Other investigators have also described the clinical course of 191 patients with COVID-19 disease and reported the median duration of viral shedding was 20 days in survivors and shedding continued to the time of death in non-survivors [11]. While the presence of detectable viral RNA does not necessarily mean that replicating virus is present or that a patient is infectious, it does raise the question of whether current isolation guidelines are adequate to contain the spread of disease. For example, the duration for transmission-based precautions can be as brief as seven days based on current CDC recommendations

[9]. Ultimately, the period of SARS-CoV-2 infectivity can only be determined with serial viral culture testing (unlikely to be performed except at centers where laboratory containment standards are in place) or possibly estimated using longitudinal serology testing.

Improved laboratory detection of SARS-CoV-2 infection is critical if the medical community is going to effectively contain and curtail the COVID-19 pandemic. The use of an NP swab sample has its drawbacks. Putting their money where their mouth is, Guo and colleagues suggest that RT-PCR testing of a throat wash sample--which represents a non-invasive, painless, self-administered (without the need for PPE), swab-free method--may be a more sensitive test for COVID-19 disease. Finally, the authors' detection of virus late in the patients' clinical course emphasizes the uncertainty faced by policy makers as they try to determine the optimal length of isolation for an individual recovering from COVID-19 disease.

Neither author has any potential conflicts of interest.

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