A Bayesian Analysis of Strategies to Rule Out Coronavirus Disease 2019 (COVID-19) Using Reverse Transcriptase–Polymerase Chain Reaction

To the Editor.—The coronavirus disease 2019 (COVID-19) pandemic may overwhelm health care capacity in parts of the United States and United Kingdom in the coming months.1 Erroneously ruling out COVID-19 based on a false-negative diagnostic test poses a public health hazard. The probability of such an error is quantified by the false omission rate (FOR). The $\text{FOR} = \frac{\text{false negatives}}{(\text{true negatives} + \text{false negatives})}$, and this value depends on the prevalence of disease and operating characteristics of the diagnostic test. Preliminary data suggest the sensitivity of the COVID-19 reverse transcriptase–polymerase chain reaction (RT-PCR) may be 70% for nasopharyngeal (NP) and sputum samples, and 90% for bronchoalveolar lavage (BAL).2–4 We examined strategies to rule out COVID-19 by RT-PCR with an acceptably low FOR in hospitalized patients suspected of having COVID-19.

MATERIALS AND METHODS

We calculated the FORs of 4 strategies to rule out COVID-19 using RT-PCR across the range of prevalence rates in hospitalized patients. Strategy 1 was a single negative test result with a sensitivity of 70%, such as a single NP swab or sputum sample. Strategy 2 was a series of 2 negative tests, each with a sensitivity of 70%. Strategy 3 was a series of 2 negative tests in which the first had a sensitivity of 70% and the second a sensitivity of 90%, such as an NP swab followed by BAL. Strategy 4 was a series of 3 negative tests, each with a sensitivity of 70%. Specificity was assumed to be 99% in all calculations. We recalculated strategy 4 using a sensitivity of 50% to explore the effect lower sensitivity would have on FORs.

UNACCEPTABLE AT PREVALENCE RATES ≥20% FOR STRATEGY 1 AND AT PREVALENCE RATES ≥50% FOR STRATEGY 2. THE FORS WERE ACCEPTABLE AT PREVALENCE RATES UP TO 90% FOR STRATEGIES 3 AND 4, BUT REDUCING SENSITIVITY TO 50% IN STRATEGY 4 INCREASED FORS 3-FOLD.

DISCUSSION

The prevalence of COVID-19 among patients admitted with pneumonia exceeds 50% in some areas of the United States and United Kingdom, as was previously reported from Wuhan, China.3 The FORs of all diagnostic strategies rise with prevalence, and they have reached unacceptable levels for strategies 1 and 2 in many localities. Strategies 3 and 4 may retain acceptable FORs at prevalence rates <90% if we have not overestimated sensitivity. Strategy 3 incorpo-
rates BAL, which has the highest reported sensitivity (3) but may aerosolize infectious particles. The sensitivity of sputum obtained from intubated patients by deep tracheal suctioning through a closed ventilator circuit has not been reported, but it may present a practical alternative to BAL. Sensitivity and FOR can be optimized by employing proper techniques for collecting, handling, and testing of clinical specimens, but clinicians who feel an individual patient has very high pretest probability might reasonably decide not to completely rule out COVID-19, even after negative results using the best diagnostic strategies we modeled.

Our analysis relates to patients admitted with a clinical–radiographic syndrome consistent with pneumonia and is not generalizable to outpatients. Significant variation between patients in day-to-day viral shedding has been observed, and our model does not account for the possibility that COVID-19 patients with initial false-negative results may be more likely to have repeated false-negative results. Despite limitations, our modeling should help clinicians recognize that FOR increases with disease prevalence and make more objective decisions about how to interpret COVID RT-PCR test results when considering the discontinuation of infection control precautions in patients suspected of having COVID-19.

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