Commentary

On the importance of early testing even when imperfect in a pandemic such as COVID-19

Neal D. Goldstein a,⁎, Igor Burstyn a,b

a Department of Epidemiology & Biostatistics, Drexel University Dornsife School of Public Health, 3215 Market St., Philadelphia, PA 19104, USA
b Department of Environmental and Occupational Health, Drexel University Dornsife School of Public Health, 3215 Market St., Philadelphia, PA 19104, USA

As the COVID-19 pandemic unfolds, health departments rely upon accurate surveillance systems to characterize local, regional, and national cases of the disease. With heterogeneous symptomology, including asymptomatic transmission, individuals may or may not receive diagnostic laboratory testing. The case definition offered by the World Health Organization, and adopted by many health departments in the U.S., only confirms a case based on a positive diagnostic test; an inconclusive test or unavailable test may be labeled a probable case [1]. A false negative test result may not be identified as a case altogether.

Early on in the pandemic when the capacity for testing was limited, the Centers for Disease Control and Prevention advised a priority-based approach to testing for the SARS-CoV-2 virus, the etiologic agent of COVID-19 disease, based on age, occupation, and morbidity [2]. Among those tested, the accuracy of the laboratory assay for SARS-CoV-2 can make the difference between a false positive based on the clinical findings that are attributable to another cause, or a false negative based on lack of clinical findings that are attributable to SARS-CoV-2. As such, testing has crucial implications on surveillance so that we can formulate a more informed response to the pandemic. Indeed, prior work has demonstrated the potential for profound bias in epidemic curves constructed from inaccurate COVID-19 surveillance data [3,4].

Despite the rapid development and deployment of various laboratory testing platforms by multiple parties, including nucleic acid/molecular and serological assays, limited data exist on the accuracy of these platforms for identifying current or prior viral infection [5]. A question naturally arises: are imperfect diagnostic tests useful to understand the true magnitude of the pandemic especially when the prevalence is low? This question is not only relevant to the current COVID-19 pandemic but is also germane to many health states in which there is potential for imperfect case ascertainment. The uncertainty surrounding the answer to this question may have contributed to a reluctance to test the virus early in the epidemic (e.g., delays in scaling up testing in the U.S. [6]), because molecular testing was known to be of imperfect accuracy for identifying SARS-CoV-2 infection. Fortunately, one can use relatively straightforward mathematical approaches to demonstrate the potential implications of imperfect laboratory testing on our surveillance programs. To this end, we conducted a simulation depicting how bias in identified cases of SARS-CoV-2 infections will vary in the face of unknown data surrounding test sensitivity and specificity.

We focused on polymerase chain reaction (PCR) testing in the U.S. as the gold-standard platform of choice to identify active infection, as opposed to serological-based antibody assays that indicate past and present infection [7]. PCR-based assays detect genetic signatures of the SARS-CoV-2 virus, however it is important to note that a positive PCR test does not necessarily mean infectiousness: one may harbor virus that is not viable [8]. Early on in the pandemic, others reported PCR sensitivity as low as 60–70% [9,10]. Reasons for this lower sensitivity included timing of the test relative to infection, anatomic site of the obtained specimen (nasopharyngeal or oropharyngeal), and early test production and quality issues; more recent reports suggest higher sensitivity values with some commercial tests reporting perfect sensitivity of 100% in their validation studies [5]. If we assume a range of test sensitivity values between 60% and 100% while holding specificity high between 90% and 100%, as would be expected in a molecular assay with specific gene targets, we can reasonably posit that the true values lie therein. The true prevalence of COVID-19 will vary in the tested population (e.g., whether a drive-thru public event, clinical referral, group home, etc.), therefore we allowed for a hypothetical range from 0% to 50%. For clarification, we are specifically modeling point prevalence at the time of testing. One could also consider period prevalence of test results since the pandemic’s inception. In this case period prevalence is numerically equivalent to cumulative incidence, as it is a new disease. Computational code is available at https://doi.org/10.5281/zenodo.3962295.

Fig. 1 depicts the result of the simulation based upon 1000 hypothetical tests. When the true prevalence of COVID-19 infection is low, as at the start of a pandemic, there will be a greater number of false positives, even under excellent specificity. For example, at 5% prevalence of disease in the tested population, we could realistically anticipate between 0 and 95 false positive results, and between 0 and 20 false negative results per 1000 tests. This can be contrasted with the expectation under ideal case ascertainment there should be 50 true positive results at 5% prevalence. In other words, when the prevalence is low, there may be more incorrect results than correct results. False negatives begin to eclipse false positives at about 20% COVID-19 prevalence among those tested. If we assume 25% prevalence of disease in the tested population, we could realistically anticipate between 0 and 75 false positive results, and between 0 and 100 false negative results per 1000 tests. Again,

⁎ Corresponding author.
E-mail address: ng338@drexel.edu (N.D. Goldstein).

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under ideal case ascertainment at 25% prevalence, there should be 250 true positive results. As prevalence increases, inaccurate testing becomes more problematic because it tends to miss an ever-increasing number of true cases.

There are two main implications of inaccurate testing as it relates to the pandemic. First, even reasonably accurate tests can lead to biased surveillance estimates early on in a pandemic. Specifically, the counts of COVID-19 in the tested population were likely inflated when the prevalence was low. This would certainly be true when the signs and symptoms of a disease are non-specific, as in the case of COVID-19 that often presents with fever and cough. Clinical disease attributable to other sources of infection such as influenza, or other respiratory viruses, is a plausible explanation. Second, as prevalence increases, we need to be concerned with underestimated the true burden of COVID-19 in the population. Given the progression of the pandemic, current epidemic curves may be underestimated because of both lack of universal testing (equivalently: imperfect ascertainment of potentially infected) and inaccurate test results among those tested [3,4]. Further, with both untested and inconclusive test results labeled as potential cases per the World Health Organization, it may not be possible to separate out those without lab testing versus those with inaccurate lab testing. To return to our original question on the utility of imperfect test data for understanding the scope of the pandemic, we maintain that imperfect testing is superior to no testing (so long as testing produces a true positive results). As prevalence increases, inaccurate testing becomes more problematic because it tends to miss an ever-increasing number of true cases.

Fig. 1. Expected variation in SARS-CoV-2 PCR-based test results as a function of true COVID-19 prevalence (Panel A: 0%–15% prevalence; Panel B: 0%–50% prevalence). Dark gray corresponds to false negative test results assuming sensitivity between 60 and 100%, light gray corresponds to false positive test results assuming specificity between 90 and 100%, and the line is the true count of cases. Results depict 1000 hypothetical PCR-based tests.

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