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PREVALENCE AND COVID-19 TESTING

Mitch Kunce
DouglasMitchell Econometric Consulting, Laramie, WY 82070 USA.
dmitchel428@gmail.com.

ABSTRACT: *An outbreak of pneumonia of unknown etiology in Wuhan City, Hubei Province, China was initially reported to the World Health Organization in December 2019. Global health authorities purportedly identified a novel coronavirus (SARS-CoV-2) which continues to effect most of the world. Diagnostic testing for SARS-CoV-2 continues to advance and interpreting test results is paramount. The most commonly used diagnostic test has been the reverse transcriptase polymerase chain reaction amplification. Determining test precision not only depends on operating characteristics, sensitivity and specificity, but more importantly on prevalence of the infectious in the population tested. This paper develops a numerical optimizer (model) to explore the effect of prevalence on surveillance testing accuracy. Findings herein suggest that large scale COVID-19 surveillance testing should be curbed or eliminated. Results advocate a more flexible and narrowly targeted approach to testing strategies.*

KEY WORDS: Prevalence, SARS-CoV-2 testing, COVID-19

INTRODUCTION

In December 2019, an outbreak of a respiratory disease associated with a purported novel coronavirus (SARS-CoV-2) was reported in the city of Wuhan in the Hubei province of the People's Republic of China. On March 11, 2020, the World Health Organization declared Coronavirus Disease 2019 (COVID–19) a pandemic.[1] The first alleged case of COVID–19 in the United States was reported in January 2020 and the first alleged death in February 2020, both in Washington State.[2] As of November 28, 2020, the number of known cases in the United States has increased to over 13 million and assigned deaths 265 thousand.[3]

Diagnostic testing for SARS-CoV-2 continues to advance and interpreting test regime findings appears paramount. In most settings, reverse transcriptase polymerase chain reaction (RT-PCR) tests are used.[4] Due to the lack of an ideal gold standard [5], multiple

[1] World Health Organization (WHO) Timeline COVID-19, April 2020. www.who.int.
[2] Vital Statistics Reporting Guidance: NVSS, Report Number 3, April 2020. p. 1.
[3] Tracking COVID-19 Cases in the U.S. John Hopkins University Center for Systems Science and Engineering. November 28, 2020. www.cnn.com.
[4] Antigen tests also detect the presence of SARS-CoV-2 but are less sensitive (more likely to produce a false-negative result) than RT-PCR tests. Negative antigen tests should be confirmed with a RT-PCR test before considering a person negative for COVID-19. Serology blood tests detecting IgG and IgM antibodies of active and past infections are also available. Problems with both of these testing regimes are also numerous and not the main focus of this analysis.
[5] To date, no research available has isolated and purified SARS-CoV-2 following Koch's postulates.

RNA gene targets have been developed.[6] A positive RT-PCR test reflects only the detection of the targeted RNA genome sequence and not the presence of viable virus.[7] As a result, determining test precision is challenging and perhaps unattainable.[8] Two operating characteristics are used to evaluate the credibility of a diagnostic test. Sensitivity (percent positive agreement, PPA) is the share of a population with the targeted genome sequence and test positive for its presence. The other measure is specificity (PNA), those who are target free and test negative. A review of the literature attempting to quantify SARS-CoV-2 test accuracy find sensitivity rates ranging from 71% to 98% and specificity rates between 90% and 99%.[9] A myriad of factors can effect accuracy rates including sample quality, infection[10] stage, gene sequence load, RNA gene targets, reverse primers, cycle threshold (Ct)[11], in vitro verification versus clinical settings, prevalence during test development, and numerous others.[12]

Evaluation of broad surveillance testing depends not only on PPA and PNA but also on prevalence of the infectious in the population tested.[13] Some would argue prevalence of what you are testing for is the most important factor.[14] Infectious prevalence obviously is unknown and may vary considerably across communities. Estimating prevalence is governed by the spread of SARS-CoV-2 and is thwarted by the existence of false test results. Broad regional surveillance based estimates range from 0.1% to 11% but appear to be drawn from simple conjecture.[15]

This paper develops a mathematical framework to explore the effect of prevalence on surveillance testing accuracy. Precision metrics PPA and PNA are embedded in a numerical model that demonstrates the relationship between prevalence, true and false test results. The model combines a simple interface, algebraic expressions, and an

[6] Numerous gene targets are used by different manufacturers. See Vogels, C.B.F. et al., (2020) Analytical sensitivity and efficiency comparisons of SARS-CoV-2 qRT-PCR assays. medRxiv 20048108.
[7] Wölfel, R., et al., (2020) Virological assessment of hospitalized patients with COVID-19. *Nature* April 1, 2020.
[8] It is remarkable that Kary Mullis himself, the inventor of the Polymerase Chain Reaction (PCR) technology, did not think it was useful in a clinical diagnostic setting. His invention earned the Nobel prize in chemistry in 1993. Unfortunately, Mullis passed away last year (2019) at the age of 74, but there is no doubt that he regarded PCR as inappropriate to detect a viral infection. The reason is that the intended use of the PCR was, and still is, to apply it as a manufacturing technique, being able to amplify DNA sequences millions and billions of times, and not as a diagnostic tool to detect viruses.
[9] Watson J, Whiting PF, Brush JE. (2020) Interpreting a covid-19 test result. *British Medical Journal* 2020 May 12; 369: m1808. See also Brooks CZ and Das S. (2020) COVID-19 Testing Impact of Prevalence, Sensitivity and Specificity on Patient Risk and Cost. *American Journal of Clinical Pathology* November 154:575-584. A meta-analysis can be found here. FIND Foundation for Innovative New Diagnostic. Test performance dashboard. https://finddx.shinyapps.io/COVID19DxData/. Meta-analysis of 35 manufactures and 35 different tests.
[10] Used throughout for the lack of a better term.
[11] Ct is the number of replication (amplification) cycles required to produce a fluorescent signal.
[12] Schlenger, RL., (2020) PCR tests for SARS-CoV-2, Interpreting results correctly. *Dtsch Arztebl* June 12; 117 (24).
[13] For an individual this would be pre-test risk probability (anchor). How likely is it that you have the infection.
[14] Brooks ZC and Das S. (2020) COVID-19 Testing Impact of Prevalence, Sensitivity and Specificity on Patient Risk and Cost. *American Journal of Clinical Pathology* November 154:575-584.
[15] Centers for Disease Control and Prevention. Interim guidelines for COVID-19 antibody testing. See also footnote 14.

optimizer for nonlinear problems.[16] The optimizer uses generalized reduced gradient (GRG) and branch and bound (BB) methods to find the optimal solution. The remainder of this analysis is divided into three sections. The Model Section details the numerical model and relevant equations. Section 3 presents simulation results including graphs that transition understanding. Implications and conclusions of the analysis are drawn out in Section 4.

MODEL

Equations (1) - (4) represent the fundamental algebraic system linked to the evaluation of diagnostic testing.

$$(TP) = (PPA)(p(PT)) \tag{1}$$

$$(FP) = (1-p)(PT) - (TN) \tag{2}$$

$$(TN) = (PNA)((PT)(1-p)) \tag{3}$$

$$(FN) = p(PT) - (TP) \tag{4}$$

Table 1 gives a detailed description of each variable in equations (1) - (4).

Table 1. Variable Definitions

(PT)	Population tested.
p	Percent of the population tested with the infection. Infectious Prevalence. Pre-test risk probability.
(TP)	Those actually infected that test positive.
(PPA)	Sensitivity.
(PNA)	Specificity.

[16] Nonlinearity lends itself to a broad general approach useful in most applications. Restricting linearity to an optimizer can lead to model scaling issues.

(TN) Those actually infection free and test negative.

(FP) Those who test positive and are not infected.

(FN) Those who test negative and actually have the infection.

Equations (1) - (4) form the basis of the model suitable for a generalized optimizer. For a nonlinear programming construct, the focus centers on the Jacobian matrix of partial derivatives of the problem equations with respect to the choice variables. In this nonlinear setting, the Jacobian matrix elements are variable and must be recomputed at each new trial point. The optimizer only focuses on equations related to the objective and constraints to the choice variables. All other equations and variables are treated as constants. The optimizer relies on GRG methods which are arguably superior to other nonlinear constructs.[17]

The inclusion of integer variables requires a branch and bound (BB) algorithm combined with GRG methods. The BB algorithm begins by solving the unconstrained problem using GRG yielding a best bound starting point. The algorithm then begins branching and solving sub-problems now satisfying all constraints. Each incumbent solution is saved with the algorithm continuing to iterate until the following relative difference is minimized or equals some defined tolerance.

$$\frac{Incumbent - BestBound}{BestBound} \tag{5}$$

Generally, the BB algorithm finds an optimal solution quickly. To illustrate, consider the following simple problem. A small community within a US State has decided to initiate a surveillance COVID-19 testing program. The population of the community is 65,000 and 50,000 tests have been administered in the past month. The local public health official asserts a positive test rate of 6 percent or 3,000 positive results. Additionally, health officials would like to have an estimate of the infectious prevalence (p) in the community.

Assume the local health authority sourced the COVID-19 tests from Abbott. Results from a clinical study released on October 7, 2020 shows Abbott's ID NOW™ with Sensitivity of 95% and Specificity of 97.9%.[18] Employing the optimizer described above, we seek to achieve a target value $((TP)+(FP))/(PT)$ equal to 0.06 by iterating (changing)

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[17] See Lasdon, L.S. and Smith, S. (1992) Solving large sparse nonlinear programs using GRG, *ORSA Journal on Computing* (4) pp 2-15.

[18] See Abbott press release dated October 7, 2020 announcing results of a Clinical Study involving 1,003 subjects. Abbott.com. Reported accuracies are much higher for in vitro studies which are performed in carefully controlled conditions. www.abbott.com

the value of (p) subject to the constraint equations (1) - (4). Results are depicted in Table 2.

Table 2. Simple Problem Optimum (Optimizer run time 1.4 seconds)

Infectious Prevalence (p)	4.198%
Sensitivity (PPA)	0.950
Specificity (PNA)	0.979
Population Tested (PT)	50,000
Infectious in the Population $p(PT)$	2,099
Correctly Test Negative (TN)	46,895
Infected and Test Positive (TP)	1,994
False Positive (FP)	1,006
Has the Infection and Test Missed (FN)	105
Share of Positive Tests	6.0%
Share False Positives	33.5%
Share of False Negatives	0.22%

The optimal solution for infectious prevalence is 4.198% in this community. Interestingly, more than one third of the 3,000 reported positive tests are potentially false positives. The conventional positive predictive value (PPV) is simply 1 - $\%(FP)$ which equals 66.5%. Moreover, potentially 105 have the gene target and the test came back negative. In order to understand the differences in proportions of false test results, equations (1) - (4) can be rearranged yielding equations (6) and (7). The term θ represents the variables PPA and PNA where PPA = PNA = θ. Meta-analysis cited above shows that these terms generally take the value of 0.70 or higher. Holding θ constant in this manner assists in understanding equations (6) and (7) as they pertain to prevalence.

$$\%(FP) = \frac{(1-p)(1-\theta)}{\theta p + (1-p)(1-\theta)} \tag{6}$$

$$\%(FN) = \frac{p(1-\theta)}{(1-p)\theta + p(1-\theta)} \tag{7}$$

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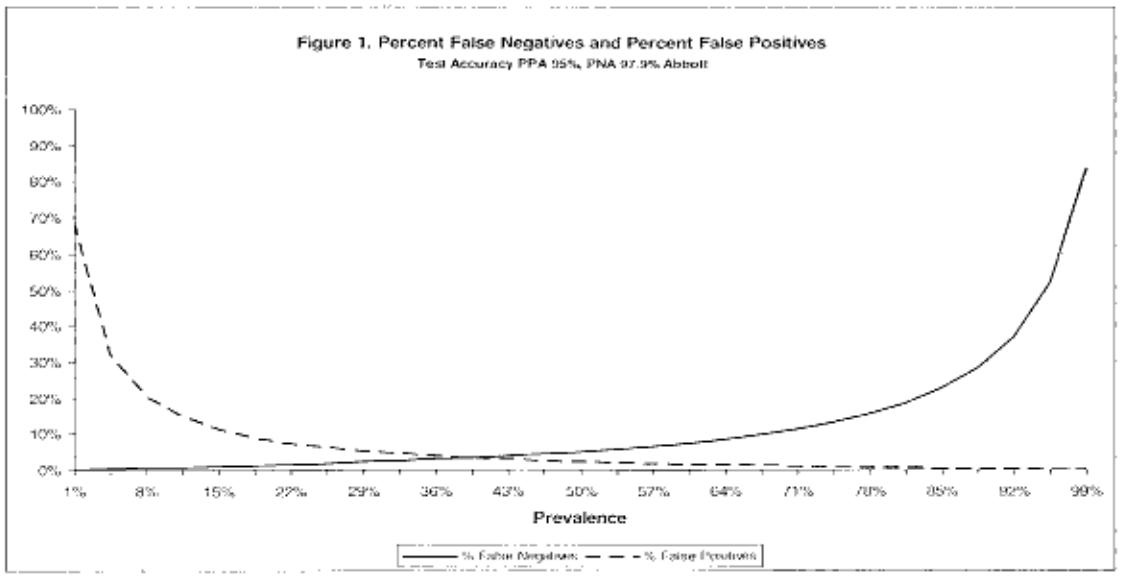
Focusing first on the numerators, low infectious prevalence (p) results in the numerator of (6) being greater than the numerator in (7). When (p) is greater than 0.50 the numerator in (7) will be greater than the numerator in (6). Understanding the denominators is more complex due to the summation of two terms. At levels of low prevalence, the denominator in (6) will be less than the denominator in (7). As prevalence rises to over 0.50 the denominator in (6) exceeds the denominator in (7). In summary, within the relevant range of broad community prevalence, proportions of false positives will dominate false negatives.[19]

MODEL SIMULATIONS

The strength of the numerical model developed for this analysis is the ability to simulate optimal solutions by perturbing key choice variables and/or projecting over time or space. As described above, the goal of this paper is to explore the relationship between prevalence and testing accuracy. Two cohorts of PPA and PNA are modeled; 1) The Abbott Clinical Study described above, 95%, 97.9%, and 2) The Foundation for Innovative New Diagnostics (FIND) meta-analysis results also described above, 86%, 96%.[20] Figure (1) shows the relationship of percent of false negatives and false positives over the unit interval of infectious prevalence for the Abbott cohort.



[19] See footnotes 14 and 15.

[20] This meta-analysis PPA baseline is similar to results found in Jarrom, D., et al (2020) Effectiveness of tests to detect the presence of SARS-CoV-2 virus, and antibodies to SARS-CoV-2, to inform COVID-19 diagnosis: a rapid systematic review. *British Medical Journal Evidence-Based Medicine*. 10.1136/111511. This study failed to calculate an estimate of specificity.

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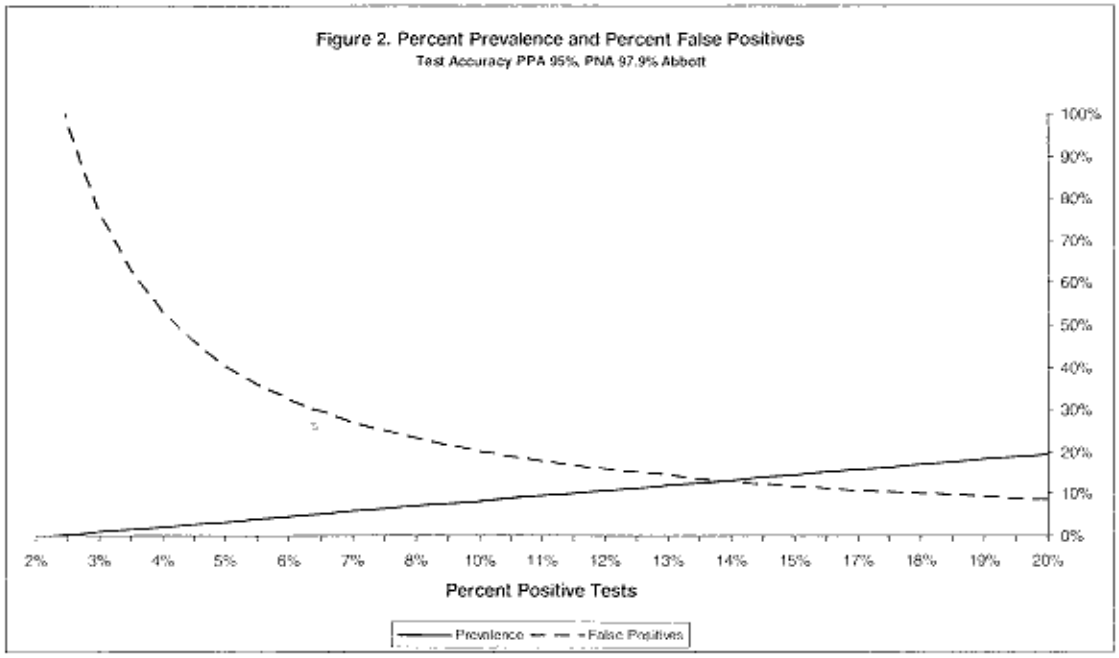
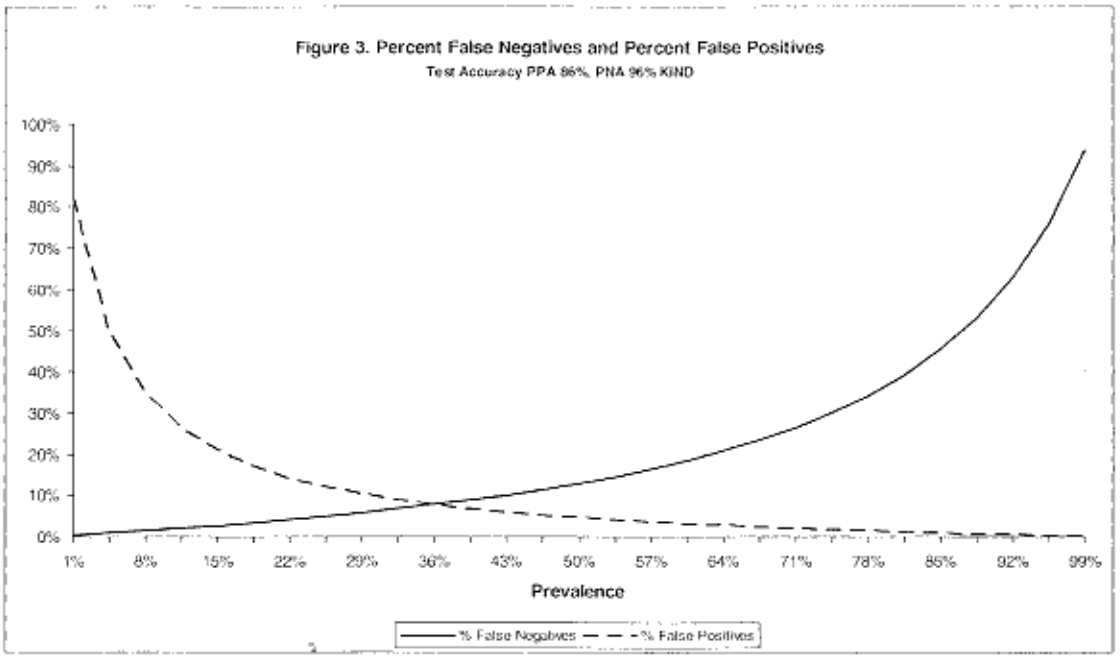
The prevalence U reinforces that false positives are more likely when the contagious are fewer in a population while false negatives are likely abundant when risk prevalence is high. Because true infectious prevalence is unknown, shares of positive test results ascend to become a deficient substitute. Figure (2) depicts the relationship of false positives and prevalence over the relevant range of percent of positive tests. The targeted choice variable, percent of positive tests, is iterated until terminal at 20%.[21]



Tracing the results from Table 2, at 6% positive tests, move up to the solid line - 4.2% prevalence, move up to the dashed line - 33.5% false positives. The percent of positive tests tends to overestimate true infectious prevalence.

Figure (3) shows the relationship of percent of false negatives and false positives over the unit interval of infectious prevalence for the KIND cohort. Markedly lower sensitivity (PPA) tends to upward flatten the curves of the prevalence U and increases the proportions of false results. Notably, the percent false negative curve is flattened upward in greater proportion.

[21] As of November 28, 2020, the Centers for Disease Control (CDC) reports overall 7.7% positive test results in the US. covid.cdc.gov. Overall estimates such as the CDC's are deficient because they include results of individuals that are tested more than once.



To illustrate, at 50% prevalence the Abbott cohort simulates the percent of false negatives at 4.9% and the percent false positives at 2.2%. Conversely, the KIND cohort simulates the percent of false negatives at 12.7% and the percent false positives at 4.4%. Lower sensitivity impacts false negative results in greater magnitude.

IMPLICATIONS AND CONCLUSIONS

This analysis emphasizes the importance of infectious prevalence in the tested population as it relates to COVID-19 test accuracy. Likely prevalence should be a key consideration for public health officials when interpreting test results and conceiving surveillance testing strategies. The numerical optimizer developed provides an improved method to estimate community infectious prevalence. In addition, the optimizer can simulate a myriad of scenarios highlighting the levels of false test results. False results have significant costs, both tangible and latent. Research on quantifying simple accounting costs of a false test result (e.g. test cost, treatment cost, etc.) are abundant, while estimates of latent costs (e.g. true economic costs of quarantines and lockdowns) are scant and simply inadequate. [22]

[22] See for example, Brooks ZC and Das S. (2020) COVID-19 Testing Impact of Prevalence, Sensitivity and Specificity on Patient Risk and Cost. *American Journal of Clinical Pathology* November 154:575-584.

The relevant range of broad infectious prevalence is contained within the lower portion of the unit interval. Low levels of prevalence produce proportionally more false positive results. Findings herein suggest that large scale COVID-19 surveillance testing should be curbed or eliminated. The potential for large numbers of false positives and associated costs outweigh purported benefits of broad surveillance. Testing strategies need to be more flexible and narrowly targeted in order to respond to changes in prevalence. Moreover, this paper illustrates that a test's sensitivity and specificity, while important, do not independently drive probabilities of false test outcomes.