Balance of Risk in COVID-19 Reveals the Extreme Cost of False Positives

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ABSTRACT

COVID-19 public health responses, including lockdowns and diagnostic testing strategies, have had consequences. Economic costs (see the CHD paper in this issue) could reach $16 trillion dollars, 90% of the US annual GDP. While harm to small businesses, unemployment, worsening poverty, death from cancer, increased suicides, social isolation, and restriction of freedom all increase the perceived need for drastic responses from the top, flawed measures are costly. A *diagnostic assay*[2] of tests for COVID-19 depends for its validity on its *sensitivity* and *specificity* assessed in terms of the true positive rate (TPR), false positive rate (FPR), true negative rate (TNR), and false negative rate (FNR) of the assays. In this pandemic, Real Time — Polymerase Chain Reaction (RT-PCR) testing has been relied on for drastic top-down responses (as in shutting down the economy of whole nations or the entire world). Here I focus on false positive results where RT-PCR testing suggests many infections by SARS-CoV-2 where there are none. I show by mathematical modeling how reporting positive results of RT-PCR testing, ones known to be false in a measurable percentage of instances, is at least 40 times more impactful (in a detrimental way) than increasing or decreasing the number of tests conducted. To balance the risks of errors in diagnosis, false positive results must be minimized by validating nucleotide sequences and estimates of *viremia* to avoid flagging individuals as contagious when they are not.

Introduction

The consideration of the outcomes of tests for use in diagnosis of COVID-19 have included concern over false positives (Kirkham and Yeadon, 2020; Yeadon, 2020), and no fully academic

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[2]**Author's Note:** A short **Glossary** is provided as an **Appendix**. Items listed there appear in the text in *italic font*.

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treatment has addressed the attendant consequences of false positive test results. The cost of the false positive depends entirely on the policies put in place to respond to positive tests, which range from a patient becoming aware, in private of their own test status (in-home, private testing) to shutting down schools, businesses, and public spaces (e.g., grocery stores and malls). Unnecessary disruptions can lead to job loss, and permanent shuttering of businesses. On an individual patient basis, false positives can lead to useless and harmful quarantining, wasteful contact tracing, and patient harm due to failure to provide an accurate diagnosis. If the patient is hospitalized due to the results of the test, hospital-acquired infections of SARS-CoV-2 and other pathogens is a real and unnecessary risk if the test result is false. For hospitals, wastage of COVID-19-related resources can result from false positives. For society, inaccurate published rates of "cases" can lead to unwarranted levels of panic, fear, anxiety, and social stress.

Whilst it is now recognized that when prevalence is low, false positive COVID-19 diagnoses may be high, the problem is not generally expressed as "when prevalence is low, the number of false positives can be vastly greater than the number of true positives"(but see Skittrall et al., 2020), as long as a test has a non-zero FPR. No consideration to any quantified cost of the false positives has been conducted; this would require the derivation of a utility function that captures consequent and indirect risks, and no system of outcomes surveillance is in place capable of capturing that information for modeling.

No generally accepted cost/benefit analysis has been applied to testing strategies in COVID-19 in the US. The initial fumbling of testing led to an urgency to get testing "up and running", with too little rational consideration regarding implementation. Little to no consideration has been given to the question of when and how symptom-based testing (i.e., testing those who have symptoms) might ethically be switched to arbitrary testing, random sampling, or screening. The haphazard program is co-occurring with the testing of contacts of confirmed cases.

With any imperfect test with non-zero false positives, false positive test results vastly outnumber true positives when prevalence is low (Skittrall et al., 2020), and, to date, prevalence of SARS-CoV-2 infections are always low. One of the few investigations into false positive rates suggested consequent validation of the RT-PCR test result using serology weeks after the initial test result (Basile et al., 2020). The current per-week average prevalence of COVID-19 "confirmed" cases is 4.5% (CDCa), a low prevalence at any given time. Basile et al. (2020) reported a false positive rate of RT-PCR testing of 11%; Lee (2020) reported 30% of reference sets mislabeled as "COVID-19 positive") and 20% mislabeled as "COVID-19 negative". The potential consequences to societal responses are immense and must be re-addressed.

A few approaches have been devised to minimize the false positive rate but are not in widespread use. The most employed attempt is repeated RT-PCR testing. Repeated PCR with the same kit will not guarantee zero FP, especially if the patient being tested has genetic sequence that matches the primer sequences for the kit used, or if the kit used is prone to false positives. Restricting testing only to those with high prior probability of a positive result (e.g., known exposure to confirmed cases) has also been proposed as a way to prioritize patients for testing (Skittrall, 2020), and this strategy would under the scenario where cost of the false positive is much greater than cost of the false negative (CFP>>CFN) be superior to indiscriminate (random) testing and population screening. However, this does not change the intrinsic false positive rate of the tests themselves.

Among the approaches proposed, the only approach that would drive FPR to zero is the use of Sanger sequencing to validate the PCR product pool, is in fact SARS-CoV-2, and not the product of other off-target non-specific amplification (Lee, 2020).

Distortions and Misinterpretations on Testing

"Too Sensitive" – One perspective misrepresents COVID-19 false positive diagnoses as a result of RT-PCR tests being "too sensitive", with the idea that it could detect the virus if someone walked through the room with the sample within a sealed test tube. In other words, the test is too good if there is contamination. It's at best a poor choice of words to claim that the assay is "too sensitive"; the fabricated scenario itself it patently false. CLIA-certified laboratories use clean rooms and have built-in safeguards preventing among-sample contamination. While contamination can occur, the likelihood is low, and laboratories that produce false positive results due to cross-sample contamination should lose their certification. We should reserve the term "sensitive" for use in the context of performance evaluation measures.

The term "case" should not be loosely used. "Case" implies symptoms and "diagnosis". *"Test Positive = 'case'"* –, and test-only results as "cases" is commonplace and is incorrect. The medical diagnosis, COVID-19, has a set of symptoms, and is in part diagnosed with radiologic assays. COVID-19, not the presence of SARS-CoV-2, is the illness, i.e., a "case". Substitution of a positive result for the detection of the virus for a clinical diagnosis makes "COVID-19" clinically inexact. Examples of how a positive test result – a test-positive true detection of the SARS-CoV-2 virus sampled from a patient – can still be a diagnostic false positive includes (a) a person recovering from a SARS-CoV-2 infection with lingering viral remnants and (b) recent, non-transmissible infection in a person who is already immune and who will not experience sufficiently high viremia to cause transmission.

Unfortunately, and remarkably, CDC's final COVID-19 guidelines made a radical departure from the historic norm, in that COVID-19 diagnosis use the same code, "U07.1, COVID-19" for both symptomatic and asymptomatic persons with a positive COVID-19 RT-PCR test (CDCb)(5). As we will see, this will dramatically amplify not only the number of "cases" but also visit upon society a massive cost of continuous stream of false positive test results.

"Test, test, test" and *"test everyone"*. Once containment had failed, some called for mass testing under the assumption that more testing – or any testing at all – is necessary for a rational public health response to COVID-19 (e.g., Linnarsson et al., 2020)(6). In the United States, the protocols in place to contain (via early, accurate testing) and control (via testing followed by contact tracing) were both made intractable due to flaws in CDC's test kit (Hinton, 2020). FDA initially offered only emergency use authorization (EUA) to CDC, withholding the same for other RT-PCR test makers. When it became apparent that CDC's test was flawed, FDA finally allowed EUA of tests made by other providers (FDA, 2020).

FDA's EUAs only required empirical evidence of sensitivity and did not require any data in support of assertions of test specificity. In lieu of data on specificity derived using human samples, FDA allowed test manufacturers to estimate specificity based on the computational comparison of their primer sets to the host organism (*Homo sapiens*) based only on a computational comparison of the nucleotide sequences of the primer set for each test to the human genome using the Basic Local

Alignment Search Tool (BLAST) sequence matching algorithm. Due to lax standards on empirical estimation of sensitivity, FDA then requested data from PCR test suppliers on sensitivity, but not specificity, in contrast to their EUA requirements for antigen and serology testing (FDA, 2020b). Data on pathogen specificity was later supplied by some test makers proposing pooled testing.

This situation stands in stark contrast to the approach used by scientists in Germany in January 2020, who used sputum samples from healthy individuals spiked with synthetic oligonucleotides matching SARS-CoV-2 virus (Corman et al., 2020) to determine the sensitivity of their assay (100%), and matched sets of sputum samples that had not been spiked to determine the specificity of their assay (100%). They also used sputum samples of individuals with non-SARS-CoV-2 respiratory pathogen illness to estimate their test pathogen specificity (100%, Corman et al., 2020).

As we will see, the absence of a requirement of empirical estimates of false positive rates for EUA may prove to have cost society far more than the benefit of the resulting ad-hoc, irrational indiscriminate testing program.

"Flatten the Curve"

The overall strategy to "Flatten the Curve" was a derivation on the initial effort to "protect the medical community" while they prepared for a "surge" in cases of COVID-19. While the number of test-positive "cases" certainly did increase, few hospitals reported ICU demand beyond capacity. This is in part due to the shut-down of non-essential medical care visits. Emergency care resulting from medical errors and hospital-acquired infections dropped. In-person care for those struggling with mental conditions plummeted.

Weeks after the medical community came to be aware that they could handle the number of confirmed cases of COVID-19 requiring hospitalization, the social contract to protect the medical community morphed into "Flatten the Curve" – including extensions of policies of social distancing, closure of businesses, and masking. In Pennsylvania, Governor Tom Wolf classified businesses as
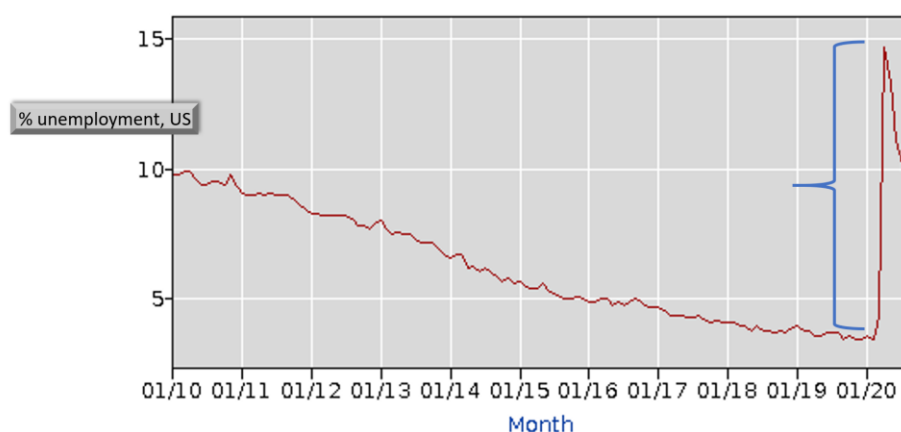
Figure 2. US Unemployment 1/10-present. The massive rise is usually attributed to "COVID-19" but is actually due to the unnecessary and damaging effects of societal responses mediated through mass false positive rates of diagnoses of "cases" of COVID-19. Source: US Bureau of Labor Statistics, 10/20

"essential" and "non-essential". After clamor from some, certain businesses were re-categorized as "essential", demonstrating that the Governor's decisions and actions have been arbitrary.

In the meantime, messages from voices like Bill Gates and Anthony Fauci warned that there may not be a return to normalcy, i.e., re-opening businesses, return to work, etc. until a vaccine was approved by the US FDA. Importantly with no definitive timeframe available, these reactive policies had a devastating effect on the unemployment rate in the US, which had declined steadily for ten years prior to 2020 only to shoot up from 2.5% to just under 15% (US Bureau of Labor Statistics) between 2019 and 2020 (Fig 1).

"All COVID-19 Cases Must Be Detected"

The sentiment that deaths from COVID-19 are somehow more tragic than other deaths seems to have taken hold to the point where the presumption of concern over other deaths – including deaths of despair due to unbalanced public health policy responses – was only able to take hold nine months following the beginning of the outbreak in the US – and then only by part of the medical and scientific community (Signees, 2020). Comparisons of death rates between COVID-19 and influenza are made impossible due to loose accounting and exchanges of default diagnoses for people dying from respiratory viruses of any kind without a molecular test, a practice started by CDC in 2014.

Deaths due to cancers undiagnosed due to the suspension of non-essential medical care, deaths due to delayed "elective", but life-saving surgeries, can be combined with deaths of despair due to unemployment and social isolation. The consideration of deaths from COVID-19 as more important than deaths from suicides due to economic despair has no rational basis.

"Diagnostic Substitution of Respiratory Viruses is 'Erring on the Side of Caution' "

In 2014, CDC changed the manner with which it counted – and reported – deaths due to influenza. Prior to 2014, CDC reported deaths from confirmed cases of influenza viral infection (i.e., "influenza") separately from pneumonia. Following 2014, they began combining influenza and pneumonia deaths into "influenza & pneumonia", and then also combined "influenza & pneumonia" (aka "P&I") with deaths from RSV, SV, and coronaviruses into a catch-all category they referred to as "Influenza Disease". Prior to 2014, about 11% of cases of P&I were deaths that involved confirmed influenza viral infections (Lyons-Weiler, 2020).

At the tail end of 2019/2020 flu season, the reporting of "Influenza Disease" in 2020 clearly had to exclude COVID-19 – and any reports of COVID-19-like respiratory illnesses not confirmed by RT-PCR. Coming into the 2020/2021 flu season, influenza-related infections and deaths have decreased dramatically – a shift sometimes attributed to widespread masking and social distancing – and yet COVID-19 "cases" continued simultaneously to increase. It is reasonable to suspect diagnostic substitution of "influenza disease" for "COVID-19" 'cases' as the northern hemisphere enters the influenza season. The default that all respiratory cases without molecular testing defaults to COVID-19 is harmful to society's ability to mount a rational and appropriate response.

Social Pressure

In the US, enforcement of public health policies, however well- or ill-founded, falls largely to the Governors of each state as empowered by their state constitution and amendments thereto from legislation. The policy makers seem to suppose that "the tools of social pressure are appropriate in response to an outbreak/epidemic/pandemic". The media plays a large role in the public's perception of their rights and responsibilities in matters of public health. Appeals to self-sacrifice for the "greater good" do not work for all individuals, especially to members of the public who are suspicious of clustered profit incentives, and of government/industry collaborations which are seen as serving interests other than the public "good".

Top-down control, one-sided public health strategists made weakly supported assumptions. When combined with a clear — and in some cases overtly stated — bias against antiviral treatments (CNBC, 2020)(10), and with the use of disparaging name-calling (e.g., "Anti-maskers" and "Anti-vaxxers"), the polarizing effects of the politicization of deeply intimate personal and private matters of choice become worse than ineffectual — they can damage public health by ignoring or externalizing unintended consequences. The positions held by public health servants can become juxtaposed as antithetical to an informed public's positions on matters of medical and public health. Industry profits priorities lead to what many in the public and professional sphere now see as a cycle of abuse and betrayal of trust.

Tests for SARS-CoV-2 have a bad track record in the US, beginning with CDC's failure to adopt a validated test available from Germany (Corman et al., 2020)(11), available in mid-January. By January 16, a total of 141 other countries had adopted that test. While computational predictions provided to FDA led to the expectation of zero false positives, field experience has shown that SARS-CoV-2 RT-PCR testing indeed has a significant false positive rate that can no longer be ignored. Formal empirical field estimates range from 30% (Lee, 2020) to 11% (Basile et al., 2020). Use of test cycle counts that bias the result toward positive in a manner that does not quantify the viral load can be expected to lead to positive test results in people who do not necessarily pose a risk of contagion. They, too, count as false positive "diagnoses". The real-world performance evaluation characteristics of diagnostics (SN, SP, Accuracy, PPV, NPV) will be a function of the design of the test. The benefits and costs of their use depend also on our strategies, rational or not, and the attendant costs of both false positive and false negative diagnoses of COVID-19.

Balance of Risk

I assert that the most productive representation of COVID-19 testing risks is a Balance of Risks between cost of false positives (CFP) and cost of false negatives (CFN). This reality has counterintuitive and important consequences for national testing strategies. As medical care improves for COVID-19 and shifts primarily to outpatient protocols, the cost of the false negatives has been dramatically reduced. As issues around COVID-19 public health policy become increasingly politicized, the perceived need to control the public's perception that the greatest risk to them is COVID-19, leads to public health strategies that maximize the cost of the false positives. I introduce this analysis under various scenarios reflecting the relative size of CFN and CFP. These various application-of-testing scenarios all have distinct outcomes of the attendant costs of false positives to society. In this analysis, I review each scenario from the perspective of a public health

official seeking information on when, and how, to incorporate testing into a public health response to an outbreak similar to COVID-19.

None of the considerations above have represented evidence-based attempts to derive a public health policy founded on a Balance of Risk scenario. In a Balance of Risk scenario, all information, regardless of whether it supports a specific conclusion or not, is seen as highly valuable, and it is imperative to use all information to derive optimized decisions on policies. Balance of risk is used by US Federal Reserve banking theorists to balance the opposing risks of inflation and risks of recession. Since costs to economic health exist on both sides of the equation, due consideration of costs by changing interest rates in favor of inflation or recession is seen as counterbalancing.

In public health no rational approach described as a Balance of Risk has been formulated in which costs associated with specific public health and medical options are seen as counter-balancing forces, leading to an optimization by which harm from both sides of the equation can be simultaneously minimized. Just like the Federal Reserve can adjust inflation rates to attempt to balance the opposing dangers of both inflation and recession to maximize overall economic health, a similar approach could be envisaged in which the costs of false positives might be weighed against the costs of the false negatives, if not in a manner designed to impact public health policy, certainly in a manner by which such policies might be more realistically interpreted by health care professionals and the public.

Parameters

The modeling of scenarios requires input parameters of N, population size, CFN (always 1.0, a stabilizing parameter), CFP (relative to CFN, so CFP = 1.1 is 10% higher CFP relative to CFN), prevalence, test sensitivity (SN=0.99), test specificity (SP=0.89), and %T, the percentage of the population tested over the time period of interest. In the US, the average weekly number of tests has been 581,631. Testing "rates" (per capita) therefore depend on the timeframe and should be expressed as such (581,631/328M or 0.177% of the population tested per week, 4*581,631/328M or 0.709% of the population tested per month, 52*581,631/328M, or 9.22% of the population tested per year). The percentage of the population tested, %T, is thus varied from low (5%) to high (95%). The output terms of CFP and CFN can be thought of (inexactly) as the sum of individuals impacted negatively by all possible negative impacts represented as the input levels of CFN and CFP. The scenarios below therefore reflect the costs over any period, given a specific prevalence of active transmissible infections, chosen from over the entire range of possible prevalence. The analyses below assume the population size of the US (328M); across the entire outbreak, the prevalence across all states has averaged 4.5% (source: Our World in Data). I used the FPR estimate of 11% for SP = 0.89 (Basile et al., 2020); the spreadsheet for these analyses will be made available as supplementary material for parameter value exploration.

Outcomes

Cost of the False Positive = CFP, Cost of False Negative = CFN, Total Cost = CFP+CFN; Cross-Over Prevalence = COP = incidence (% infected) during an outbreak when CFN > CFP. MaxTotalCost% is the Total Cost at the prevalence where the Total Cost is maximized; when

MaxTotalCost% = 100%, more testing is warranted once the population achieves the COP (before then, the CFP may be prohibitive). When MaxTotalCost% = 1%, no testing is warranted because the cost of the false positive vastly exceeds the cost of the false negatives and every test endangers society more than an additional false negative. In the Scenarios below, a is the constant of proportionality of the CFP relative to the CFN; i.e., when a = 0.1, CFP = 0.1(CFN).

Scenarios

The goal of the analysis is to characterize the responses of costs of each type, and total costs, to variation in input parameters that we can control, such as %T, and, via our responses to positive test results, CFP. In each of the following scenarios, testing of a given percentage of population is modeled over a range of prevalence. In practice, the spatiotemporal clustering (or lack thereof) of testing in juxtaposition to risk of being infected or being infectious varies with testing strategy, which therefore might have different exact relative and total values, such as symptom-based testing, random limited testing (sampling), and screening. Thus, relative input values of CFN and CFP are assumed to be independent. Importantly, the modeling is not dynamic, i.e., it does not include consideration of spread of the virus throughout the population, nor the effects of transmissions from FNs or the untested to those not infected. It is a demonstration of principle of a decision-making tool that could be used on daily basis for best-available Balance of Risk. Other models can be used to provide inputs on exact types of costs via utility function.

Scenario 1 – CFP << CFN

When CFP << CFN (e.g., CFP = 0.1CFN), the maximum cost exists at highest prevalence until near-universal testing is achieved (Fig 2A). Under these conditions, CFN makes up most of the of the total cost (Fig 2B), with a cross-over prevalence (COP), depending on testing level, ranging from COP=0.01 (5% testing) to 0.36 (99% testing; (Fig 2C). The Max Cost Prevalence (location on the curve) when the total cost (CFN+CFP) is highest is at 100%. The Total Cost Prevalence when CFP << CFN varies with testing (arbitrary units of cost) and is minimized at 99% testing.

In this setting, testing is warranted until somewhere between 95-100% testing, at which point the optimization function flips and less testing becomes less costly. It is important to note that this analysis considers real costs, not perceived costs, including indirect costs and costs externalized to the medical testing industry. Thus, for relevance to current events, the CFP must be much lower than the CFN in reality, not via argumentation or rationalization.

Scenario 2 – CFP < CFN

When CFP << CFN (e.g., CFP = 0.9CFN), the maximum total cost is found at highest prevalence until between 75% and 90% testing, at which point the optimization function flips and less testing becomes the optimal decision.

Scenario 3 – CFP = CFN

When CFP = CFN (e.g., CFP = 1.0CFN), the maximum total cost is found at highest prevalence until between 75% and 90% testing, at which point the optimization function flips and less testing becomes the optimal decision, a repeat of Scenario 2.

Scenario 4 – CFP > CFN

When CFP > CFN (e.g., CFP = 1.1CFN), the maximum total cost is found at highest prevalence until between 75% and 90% testing, at which point the optimization function flips and less testing becomes the optimal decision, a repeat of Scenarios 2 and 3.

Scenario 5 – CFP >> CFN

When CFP >> CFN (e.g., CFP = 1.9CFN), the maximum total cost is found at highest prevalence until between 75% and 90% testing, at which point the optimization function flips and less testing becomes the optimal decision, a repeat of Scenarios 2-4.

Scenario 6 – CFP >>> CFN

When CFP >> CFN (e.g., CFP = 3CFN), the maximum total cost is found at highest prevalence until between 50% and 75%, at which point the optimization function flips and less testing becomes the optimal decision.

Table 1. Output of Modeled Scenarios Among Various Testing Levels

5% Testing Scenario		a	Max Cost prevalence	Crossover prevalence*	Total Cost Prevalence 0.045	RelMaxTotalCost**
1	CFP << CFN	0.1	100%	0.01	15934240	0.135728
2	CFP < CFN	0.9	100%	0.1	43643680	0.371756
3	CFP = CFN	1	100%	0.11	47107360	0.40126
4	CFP > CFN	1.1	100%	0.12	50571040	0.430764
5	CFP >> CFN	1.9	100%	0.12	77631040	0.66126
6	CFP >>> CFN	3	100%	0.26	117398580	1
10% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	100%	0.01	15284800	0.131011
2	CFP < CFN	0.9	100%	0.1	44309520	0.379792
3	CFP = CFN	1	100%	0.11	46457920	0.398206
4	CFP > CFN	1.1	100%	0.12	49921600	0.427895
5	CFP >> CFN	1.9	100%	0.19	77631040	0.665402
6	CFP >>> CFN	3	100%	0.27	116667960	1
50% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	100%	0.05	10899440	0.092841
2	CFP < CFN	0.9	100%	0.17	38464560	0.327641
3	CFP = CFN	1	100%	0.18	41910200	0.356991
4	CFP > CFN	1.1	100%	0.2	45355840	0.386341

5	CFP >> CFN	1.9	100%	0.3	72920960	0.62114
6	CFP >>> CFN	3	100%	0.4	110823000	1
75% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	100%	0.05	7246340	0.067615
2	CFP < CFN	0.9	100%	0.17	34811460	0.324825
3	CFP = CFN	1	100%	0.28	41910200	0.391063
4	CFP > CFN	1.1	100%	0.32	41702740	0.389127
5	CFP >> CFN	1.9	100%	0.45	69267860	0.646337
6	CFP >>> CFN	3	1%	0.57	107169900	1
95% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	100%	0.16	4323860	0.041477
2	CFP < CFN	0.9	1%	0.63	31888980	0.305897
3	CFP = CFN	1	1%	0.65	35334620	0.33895
4	CFP > CFN	1.1	1%	0.68	38780260	0.372002
5	CFP >> CFN	1.9	1%	0.78	66345380	0.636422
6	CFP >>> CFN	3	1%	0.85	104247420	1
99% Testing			Max	Crossover	Total Cost	
Scenario		a	Cost prevalence	prevalence	Prevalence 0.045	RelMaxTotalCost
1	CFP << CFN	0.1	1%	0.36	3739364	0.036072
2	CFP < CFN	0.9	1%	0.84	31304484	0.301983
3	CFP = CFN	1	1%	0.85	34750124	0.335222
4	CFP > CFN	1.1	1%	0.86	38195764	0.368461
5	CFP >> CFN	1.9	1%	0.86	65760884	0.634372
6	CFP >>> CFN	3	1%	0.95	103662924	1

*Cross-over prevalence is the switch point at which more testing become the rational decision. At lower prevalence, testing, especially indiscriminate testing, becomes more costly than less testing. RelMaxCost is the relative scale of the cost of a given level of testing compared to the worst-case scenario modeled in this study.
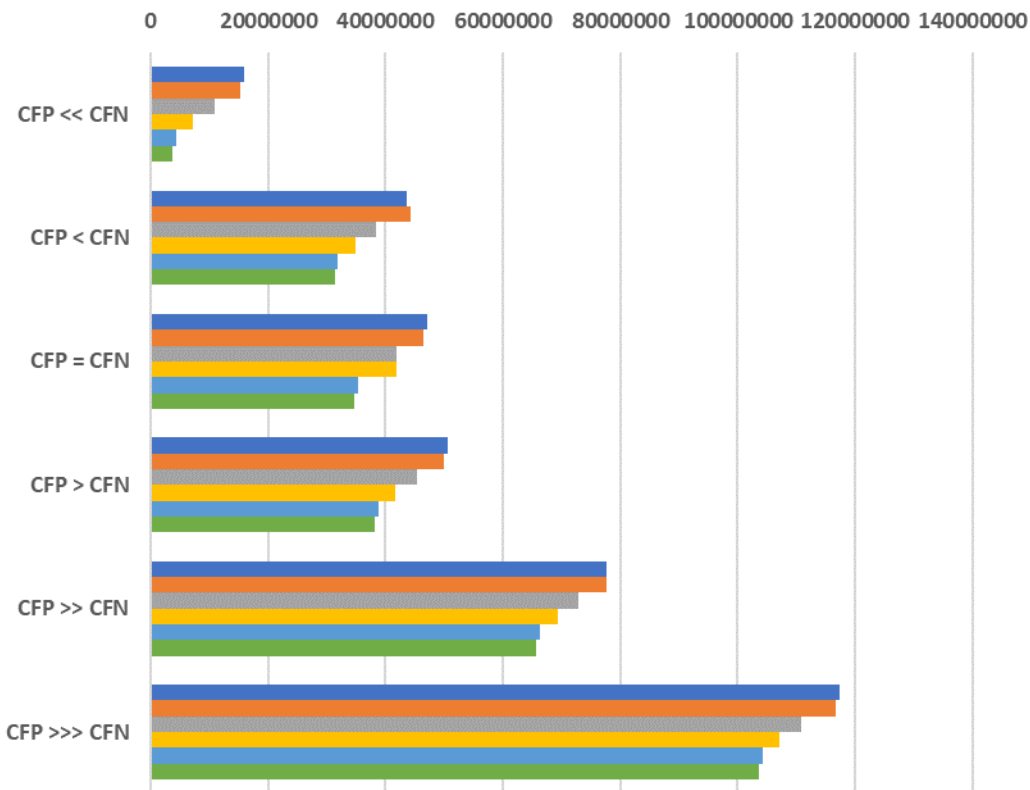
Figure 2. Total Costs Under Six Scenarios Across Testing Levels. Cost units are arbitrary and represent in "real" terms the number of people affected by costs considering both CFP and CFN.

Discussion

These results demonstrate the feasibility of modeling cost functions in Balance of Risk scenarios to optimize decisions of public health responses to outbreaks and epidemics. The ratio of the variance among scenarios relative to the variance among testing levels is >44. These results, summarized as a total cost figure in Fig 2, show that society's response to handling positive test results, via the cost of the false positive, has > 44-fold greater impact on variation of total cost of outbreaks and epidemics relative to increasing or decreasing testing overall, without exceptions among scenarios. The Cost of the False Positive reflects the sum impact of our decision on whether we demand 100% Specificity, or whether we spend the energy and resources to perfect our understanding of the impact of cycle number thresholds on the resulting transmission dynamics of those diagnosed via a given cycle number. Most importantly, we must derive — immediately — a reason-based approach to minimize CFP, reducing as much as possible CFP/CFN, while also working to reduce CFN. The problem, therefore, is indeed and inherently a Balance of Risk problem. Modeling the process of bringing testing online may have some utility in informing whether specific test kits and approaches are acceptable, as well as allowing the consideration of strategic layouts of testing to minimize total costs. Lockdowns are an unhelpful extreme in which CFP becomes far greater than CFN without any rational justification.

As medical care improves toward primarily outpatient care for COVID-19, and policies fail to relax – or become more stringent (i.e., unwarranted lockdowns based on high reported "cases") the nightmare scenario for CFP >>> CFN becomes a more likely reality. The media should report statistics on COVID-19 confirmed and presumed cases, and treat the data stream more like those related to economics, focused on measures such as the number deaths per cases, the change in the percent of tests that are positive over time. Reporting total number of "cases" and "largest number of cases to date" can be misleading and harmful due to public acquiescence to massively costly responses such as lockdowns. All possible efforts are necessary to reduce the FPR of every PCR kit in use to zero, even if that includes the more expensive "complex" sequencing of PCR products, so be it. Society can no longer afford a half-hearted or half-baked attempt at diagnostics in COVID-19.

Limitations

This demonstration of principle does not map to any specific real-world situation or country; instead, it provides a proof of principle and reveals features of the cost functions in a Balance of Risk setting which could, in principle, be conducted with ever-increasing granularity. The most important feature is the finding that the amount of overall testing has lower impact than how we configure our approach to responding to positive test results.

Conclusions

To date, public health responses have included oversimplification of public messages, and bleed-over from misguided attempts using inhumane and immoral tactics to control perception and social behavior, all designed to reduce "vaccination hesitancy," — and all without consideration of the attendant negative consequences of such programs to some families and to society as a whole. Any cost to society stemming from errant policy is blamed on "the pandemic", not on the malformed policy or politicization of public health policy positions. Social pressures, once in place, are difficult to reverse. The unquestioned idea that more testing is always better must come under new review unless FPR = 0, CFP = 0, or CFP <<< CFN. Given the massive impact of top-down control of public health perception on society, serious consideration must be given to the question of whether the powerful tools of social pressure are in any way appropriate in the arena of public health at the expense of allowing society to attend to and address, overtly, consequential costs of one-sided policies.

In the "Fog of Outbreak", the fear factor has driven people and policies to the naïve position that (1) any death due to COVID-19 is more important than any deaths due to other factors, (2) therefore, all COVID-19 cases must be detected. This is a clearly suboptimal strategy — and it is worth giving due consideration to scenarios in which an adaptively flexible strategy might be adopted. One thing is clear: false positives are non-zero, and their cost cannot be externalized: they impact everyone. Harvard economists Cutler and Summers project economic losses attributable to COVID-19 to be $16 Trillion dollars, or 90% of the US GDP. Change must be made to public health perception so we can minimize the cost of the false positives as well as the cost of the false negatives. COVID-19 has provided an extremely valuable but expensive lesson that perception-control based public health is a failed paradigm — it is ours to learn from if we have the tenacity. We must decentralize public health, reduce its "authority", and restructure it to be as non-political

and non-corporatized as possible. A follow-up essay will describe a far superior arrangement of public health infrastructure for the United States and for any country concerned with the impact of centralized authoritarian-based public health and medical care.

The importance and value of educating public health officials, the medical community and the public of these issues and factors should not be understated.

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Appendix - Glossary of Terms

cross-over prevalence - incidence (% infected) during an outbreak where the cost of the false negative becomes greater than the cost of the false positive (CFN > CFP)

diagnostic assay – a medical procedure used to aid in the diagnoses of disease or medical injury.

sensitivity (of an assay) – the probability that a diagnostic assay will lead to an accurate diagnosis of "disease" when a person does, indeed, have the disease state or condition for which the assay is designed to detect.

specificity (of an assay) – the probability that a diagnostic assay will accurate not lead to a diagnosis of "disease" when a person does, in fact, not have the disease state or condition for which the assay is designed to detect.

viremia – viral count or concentration in a person.

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