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Review

COVID-19 Test Frequency Versus Test Sensitivity in Disrupting SARS-CoV-2 Transmission: A Review of Statistical Modeling Simulations

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Abstract:

Objectives: This paper presents a statistical review of modelling simulations for frequency and sensitivity of COVID-19 testing paradigms.

Methods: We performed a review of preprints and published articles on PubMed from January 1, 2020 – March 1, 2021 using the search terms "COVID screening testing", "COVID testing frequency", "COVID testing frequency screening" and "SARS-CoV-2 testing frequency".

Results: Several authors' conclusions support the claim that test frequency and test sensitivity both play a role in reducing SARS-CoV-2 transmission. We highlight the interplay between frequency of testing, test sensitivity and the speed at which test results are available in our review.

***Conclusions*:** Evidence suggests that sensitivity and frequency of testing both play a part in decreasing transmission of disease. We conclude that, overall, test sensitivity plays less of a role in reducing disease transmission in a population compared to the frequency of testing and how quickly test results are available.

Keywords: COVID-19; rapid testing; test sensitivity; test frequency; testing programs; compartmental models

1. Introduction

The SARS-CoV-2 pandemic continues to impact every aspect of society, even as more vaccines are approved, manufactured and distributed. Nearly 200 million individuals have been infected, with over 4 million deaths reported worldwide[1]. Despite these growing numbers, a reluctance to vaccinate, socially distance, or adhere to masking recommendations continues to put lives at risk. Additionally, mutations, such as the Delta variant, pose a further threat with greater infectiousness than the wild-type virus[2]. The virus spreads primarily through respiratory droplets and can be transmitted from infected individuals before they begin to experience symptoms[3,4].

Identifying persons who are infected as rapidly as possible so they can be quarantined and not expose others is a key effort to slow the pandemic. PCR tests can take days to receive results, which allows for further disease transmission if individuals do not self-isolate while awaiting their results. With the development and availability of rapid tests, which offer results in hours or even minutes, mass testing has become more feasible.

This paper reviews publications that have examined rapid testing strategies as a means for reducing the spread of SARS-CoV-2, focusing on statistical simulations. The various testing strategies are discussed along with the assumptions, settings, and other factors of interest.

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This section serves as a summary of the statistical methods that were utilized in the publications under review, including the SIR/SEIR framework of epidemiological models, time-varying Poisson processes, and a brief review of less frequently used stochastic modelling approaches.

1.1. Compartmental SIR/SEIR Models

The SIR and SEIR methodologies are stochastic models which are composed of three and four compartments, respectively. The Susceptible-Infected-Recovered (SIR) model is composed of three compartments: susceptible, infected and recovered [5], with two transitions. The first transition is when a susceptible (S) individual interacts with an infectious individual and becomes infected (I). This first transition is determined based on two parameters: the number of contacts the susceptible person has had with the infected individual and the probability that each contact with an infected individual will result in transmission of the disease. The second transition is from infection (I) to recovered (R). This transition does not rely on any interaction with other individuals and is dependent only on the length of time to recover or die from the infection [6,7]

A common variant of SIR is the Susceptible-Exposed-Infected-Recovered (SEIR) model. SEIR models have an additional exposed compartment (E), which occurs between susceptible (S) and infected (I). This transition includes people who have been exposed to the disease but are not yet infectious[8]. The rate of becoming exposed and the rate of becoming infected is partially dependent on a new parameter which is the likelihood that someone who is exposed also becomes infected.

Similar model extensions were developed using the compartmental framework of SIR/SEIR models, such as SIDHRE-Q and CEACOV, to model the COVID-19 pandemic. The former model is comprised of 7 compartments, which are quarantine-uninfected, susceptible, infected-undetected, infected-detected, hospitalized, recovered, extinct (dead), and quarantine-recovered [9]. The latter model has 3 health states: susceptible, people who acquired SARS-CoV-2, and COVID-19 related deaths, and 7 possible compartments of SARS-CoV-2 transitions: latent, asymptomatic, mild/moderate illness, severe illness, critical illness, recuperation, and recovered [10].

1.2. Other Stochastic Models

A stochastic branching process simulates in terms of "timesteps". For each timestep, the disease parameters for each infected case are stochastically determined. To determine these parameters, this model evaluates the virus trajectory and viral kinetics to predict an individual's ability to transmit infection and the timing of symptom onset. The viral trajectory and kinetics are estimated by simulating for each person a 50-day titer trajectory.

See et. al used a Reed-Frost model to demonstrate the transmission of SARS-CoV-2[11]. This model is an example of a chain binomial model, meaning infection spreads in populations in discrete units of time. The primary important assumption in Reed-Frost transmission models is that all exposures are independent of each other[12].

Additionally, certain stochastic models use an agent-based approach compared to the compartmental models listed above. While compartmental models assume random mixing, agent-based models generally create a network based approach where a "person" has a probabilistic chance of interacting with people estimated from variables like geography and socioeconomic status[13].

1.3. Time Varying Poisson Process Model

A Poisson process refers to a time series model that measures the number of times an event occurs over a discrete time interval[14].For the purposes of modeling the spread of SARS-CoV-2, the model is based on two parameters: number of days since infection (also called the index) and the number of days in isolation, a random variable that estimates the effect of isolation in eliminating infections beyond time T. As the number of days

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since infection increases, the probability of infecting another follows a Poisson distribution, meaning that the infected has more chances to infect others. Isolating after T days decreases the number of chances of infecting a person as well as potentially eliminates days with the greatest likelihood of infection.

1.4. Time-Dependent Weibull Transmission Models

The time-dependent Weibull transmission model is a skewed model defined by two parameters, α (the shape parameter) and β (the scale parameter) [15]. This model is used to define the generation time, which is the time between the source (or original person) being infected, and the recipient (second person) being infected. Bootsma et. al used this model, with predefined shape (2.2826) and scale (5.665) parameters, as it was found to be the best fit for transmission of infection from Ferriti et al., who applied various functional forms to data from the early stages of the SARS-CoV-2 epidemic in China[16].

1.5. Bayesian Models

Bayesian models use Bayes' Theorem which gives the relationship between a hypothesis given evidence (H|E) and evidence given hypothesis (E|H). This relationship is broken into three components: the posterior distribution, the likelihood, and the prior distribution. The posterior distribution is the estimation of a new parameter (or H|E) and is proportional to the likelihood (observed evidence given hypothesis or E|H) and the prior distribution (historical information regarding the parameter[17]). This can be useful for estimating COVID-19 infection times. In Hellewell et al., a likelihood function was used to estimate the posterior distribution of infection time for a person based off their last asymptomatic reported date and their first symptomatic reported date. This likelihood function is estimated from the lognormal distribution for the incubation period of COVID-19[18]. Additionally, the prior for infection time is the standard uniform distribution. This is a noninformative prior, meaning that it will not bias the result towards a particular outcome[19].

2. Methods

We performed a statistical review of statistical modeling simulation studies from both preprints and published articles in PubMed from January 1, 2020 – March 1, 2021 using the search terms "COVID screening testing", "COVID testing frequency", "COVID testing frequency screening" and "SARS-CoV-2 testing frequency". The final selection of studies took place on April 1st, 2021. A variety of statistical modeling simulations were sought, as well as simulations offering differing results.

Papers were included that primarily aimed to evaluate the impact of test sensitivity and test frequency on transmission dynamics using a statistical modelling approach, and were excluded from the scope of the review if they focused on pooled testing, compared testing modalities without assessing test frequency and/or test sensitivity or focused on real world evidence.

3. Results

To evaluate the impact of various testing strategies on managing the ongoing COVID-19 pandemic, authors have considered two overarching settings: (1) cohort-level, such as college campuses, nursing homes, healthcare facilities, and businesses, which have emphasized testing as a method to quickly detect cases and reduce infection rates; and (2) population-level, which have emphasized testing as a surveillance tool and reduction of disease burden. The statistical methodologies utilized are described in further detail in the Supplement.

3.1. Cohort-Level

3.1.1. University Setting

Several authors analyzed the impact of various COVID-19 testing approaches with simulations of a college campus [20-27]. Paltiel *et al.* proposed a modified SEIR model to

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demonstrate the effect of test frequency and sensitivity on infections and isolation practices in a university environment of 5,000 students with 10 initial infections. Using a minimally sensitive (70%) but a highly specific (98%) test, their model estimated 1840 cumulative infections under weekly testing and 162 under daily testing over the course of an 80-day semester. Using a test with the same specificity but 90% sensitivity resulted in 1118 cumulative infections when testing weekly and 149 when testing daily. In this simulation, increasing frequency of testing was more important than increasing test sensitivity in reducing the number of cumulative infections. Thus, they recommend giving a highly specific test to each student weekly, regardless of symptom status [20]. In another simulation, Larremore *et al.* used a SEIR model, consisting of 20,000 individuals with a constant binomial probability of being infected from an external source [21]. As with Paltiel *et al.*, Larremore *et al.* found frequency of testing is more important than sensitivity to manage an epidemic[20,21].

Rogers *et al.* used SIR to model the effectiveness of a rapid testing program in a simulated university campus. They evaluated the utility of screening programs testing 0-20% of the population per day with test sensitivity ranging from 60-90%. Rogers *et al.* demonstrated test frequency was the most important factor in reducing infections compared to test sensitivity and behavioral compliance[26]. Hartvigsen also applied SIR to model networks of transmission in a university population. He found mask compliance and frequency of testing were the two most important factors in reducing disease spread, explaining 45% of the total variance in the model[25].

Muhkerjee *et al.* used an agent-based model, to evaluate the effectiveness of testing using a rapid test at a university. They found a testing program with an average of 10,000 daily tests at 92% sensitivity resulted in 8,650 less infections over a 120-day semester compared to no testing. They concluded that to implement a testing program at the university level, it is essential to consider the ratio of total daily tests to the population, which they estimated to be around 0.2 (approximately representing testing 1 time/ week) for management of infections[27].

While other compartmental models focused on testing to identify cases and prevent further infections, Martin *et al.* used a SEIR model with the focus of determining the necessary test frequency to identify an outbreak prior to having 10 cases in a hypothetical university. Assuming 85% test sensitivity, they conclude the entire campus population must undergo monthly testing to limit an outbreak [22].

In addition to SIR models, research authors have investigated other modeling strategies to consider transmission in the university setting. Brook *et al.* applied a stochastic branching process model to demonstrate the impact of asymptomatic surveillance testing and behavior modifications on COVID-19 transmission in a university modelled after UC Berkeley. They evaluated reduction in overall cases across twice a week, weekly, and every-two-week testing programs with sensitivity reflective of ranges for available tests. They found that combined with behavior modifications, the most effective testing program was a rapid test with a one-day delay, with a mean of 8,200 infections avoided over a 50-day simulation period [23].

Chang *et al.* used a time-varying Poisson process to model expected transmission in a population of 10,000 students, with testing either once every three days or weekly with a one-day delay over the course of 80 days. They use the concept of the reproductive number (R_0), denoting the expected number of infections a single infection will produce. They aimed to quantify the maximal R_0 under which infections would remain below 5% of the tested population. Under four possible distributions for test sensitivity, they found the worst-case scenario for maximal R_0 is 1.4 when testing weekly and 1.75 when testing every three days. Therefore, testing every three days allows for a higher R_0 as compared to testing weekly, while still maintaining infection control [24].

3.1.2. Healthcare Setting

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Chin *et al.* developed a stochastic simulation to model the effectiveness of routine testing in a high-risk healthcare environment. They estimated the required frequency of testing asymptomatic individuals to bring the effective reproductive number (R_e) below 1. They simulated a population of 100 individuals, with test frequency ranging from daily to once a month and test sensitivity ranging from 50-80%. Chin *et al.* found when $R_0 = 2$, twice-weekly testing would be required to manage infections and avoid an outbreak by bringing R_e below 1. Additionally, increasing test frequency was more important than increasing sensitivity in reducing infections. With daily testing and $R_0 = 1.5$, a reporting delay of 3 days reduced R_e by 56.5% compared to an 85.3% reduction with a one-day reporting delay [28]. Hellewell *et al.* used a Bayesian modeling approach to evaluate the effectiveness of routine, asymptomatic PCR testing in a population of UK healthcare workers. Assuming a one-day reporting delay, they concluded testing every other day would detect 94% of asymptomatic cases within 7 days and 57% of symptomatic cases prior to onset. They also noted a potential trade-off between test frequency and delay – *i.e.*, testing at a lower frequency can be compensated by a shorter delay in reporting results [29].

Holmdahl *et al.* applied a SEIR model in a simulated nursing home population, comparing the effectiveness of testing regimens using PCR versus antigen testing at frequencies ranging from daily to weekly. With no testing, estimated cumulative incidence is 65%. With weekly antigen testing for the entire nursing home population, estimated cumulative incidence is 42% versus 51% for weekly PCR. The most effective testing regime was daily antigen testing, with an estimated cumulative incidence of 30%. Therefore, Holmdahl *et al*. recommend antigen testing with increased frequency to reduce infections more effectively than higher sensitivity PCR testing with longer delays[30].

Obama *et al.* also used a SEIR model to evaluate testing program effectiveness in closed facilities, including long-term care facilities (LCTF) and prisons. They considered test sensitivities reflective of antigen testing (maximum 85%) and PCR (maximum 95%), and they found that in an LCTF, testing staff members daily with antigen was more effective at reducing infections than testing every 5 days with a PCR test. For example, they observed a 55% reduction in the epidemic peak during the second wave using antigen testing compared to 40% with PCR. In the prison setting, however, they noted testing alone would not be sufficient to contain infections due to high infectiousness and crowding conditions[31].

Delaunay *et al.* used a stochastic, agent-based model for a hypothetical LTCF consisting of 280 residents and healthcare workers. This simulation introduces one infection at baseline with all individuals susceptible. The simulated LTCF follows a specified testing strategy until a first positive case is identified, at which point the number of people already infected is estimated. At 90% sensitivity, the authors compared test frequencies ranging from 100% of the population twice a week to every 2 weeks using a base $R_0 = 3$. Testing 100% of the population weekly resulted in a mean of 3.8 cumulative cases at first positive case identification; increasing this frequency to twice weekly reduced the mean to 1.8 cases. Delaunay *et al.* recommend testing 100% of the population weekly when $R_0 = 3$, with increased frequency required in higher infectiousness scenarios[32].

See *et al.* used a Reed-Frost stochastic model of transmission to examine the effect of testing in a simulated nursing home population including 86 residents and 129 healthcare providers. They found testing asymptomatic people when there are known infections using a rapid test every 3 days with 85% sensitivity reduced infections by 89.7%, whereas using a test with a 2-day delay every 3 days reduced infections by 79.3%. For the 2-day delay test, sensitivity is modeled after RT-PCR testing, with a peak sensitivity of 95% that varies over the course of illness. When testing asymptomatic people with no known infections, using the same parameters, the point-of-care test reduced infections by 94.8% and the 2-day delay test by 85.9%. Therefore, the authors suggest implementing tests with rapid reporting times at a high frequency of testing, prioritizing symptomatic residents/healthcare providers but also testing asymptomatic individuals if possible[11].

3.1.3. Workplace Setting

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In the business environment, research authors considered whether implementing routine testing can permit return-to-work programs by managing disease spread. Meier *et al.* investigated the value of an employee screening program in a hypothetical workplace, varying test sensitivity/specificity, delay, frequency, and disease transmission dynamics such as prevalence and group size in the employee population. They conclude test frequency and sensitivity are the primary factors impacting the effectiveness of a screening program, with repeat testing able to compensate for lower sensitivity. For example, a test with 80% sensitivity would have a 96% probability to detect an infected person after 2 test cycles[33].

Lying *et al.* simulated transmission in a workplace setting by including a time-dependent term to represent "the rate in (people/time) of infections from outside interactions continuously in time." They considered a test sensitivity of 98% with a two-day delay in results, 98% test sensitivity with no delay, and 60% test sensitivity with no delay. They found a 98% sensitive test implemented weekly with a two-day delay resulted in 58 cases in the low infectiousness scenario and 249 in the high infectiousness scenario. For the 60% sensitive test with no delay, testing every 3 days resulted in 11 cases in the low infectiousness scenario and 71 in the high infectiousness scenario. Thus, implementing a less sensitive test more frequently can more effectively reduce the burden of disease in a workplace compared to a more sensitive test with a longer delay[7].

In specific workplace settings, VanderWaal *et al.* evaluated the utility of a PCR-based screening program in pork processing plants. Across possible parameters such as test delay, frequency, proportion of the population tested, they found frequency had the most substantial impact on reducing transmission, with testing every 3 days reducing cases by 25-40% and testing every 14 days reducing cases by 7-13%[34]. Chowell *et al.* also assessed the value of a PCR testing program, but in the environment of a cruise ship in which outbreaks could lead to high infection rates. They considered two strategies for testing passengers: 1) at embark, and 2) at embark combined with daily testing. Chowell *et al.* found embarkation testing resulted in a mean of 14.9 cases, whereas embarkation combined with daily testing resulted in a mean of 2.9 cases. Therefore, they concluded embarkation testing in addition to regular testing on a cruise ship would reduce the possibility of an outbreak[35].

3.2. Population-Level

3.2.1. Testing as a Surveillance Tool

Research authors have considered the utility of testing as a surveillance tool for large populations. Bergstrom *et al.* used a stochastic modeling approach to compare testing programs with sensitivity ranging from 50% to 90% at frequencies ranging from 1 to 7 days. They found less sensitive tests administered at higher frequencies can be effective at the population level compared to less frequent tests with higher sensitivity. For instance, assuming immediate turnaround in test results, administering a 50% sensitive test daily yielded a reduction of 80% in contagious exposure time for an infected individual, compared to a 60% reduction when testing twice weekly with a 90% sensitive test. Thus, Bergstrom *et al.* suggest implementing a proactive testing regime employing frequent use of rapid tests with minimal turnaround times[36].

Not all authors agreed on the feasibility of a widespread testing program as a surveillance tool. Bootsma *et al.* developed a time-dependent Weibull transmission model in which they modelled sensitivity as a function of time since infection. Under a base R_0 of 2.5, they found 100% of the population would need to be tested every 3 days to bring R_e below 1. If additional protective measures were implemented to bring R_0 to 1.3, 80% of the population would need to be tested weekly to bring R_e below 1. They conclude regular testing of the population is not a viable strategy to reopen society due to the magnitude of R_0 and the delay of any test to detect infections after exposure. Despite this, Bootsma *et al.* emphasize increased test frequency is more impactful on controlling transmission than

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increased sensitivity – accordingly, targeted rapid screening could be a feasible strategy for population-level surveillance[15].

3.2.2. Testing to Reduce Disease Burden

Reduction of disease burden has also been considered at the population level. Nash *et al.* evaluated the impact of a rapid testing program on infections, hospitalizations, and total deaths in three regions in the United States as well as São José do Rio Preto, Brazil. They concluded increasing test frequency rather than increasing test sensitivity more substantially reduced the proportion of individuals with infections, hospitalizations, and deaths. For example, in Los Angeles where an outbreak already affected the population, administering a 90% sensitive test every 10 days resulted in 2.5% of the population being infected, while a 30% sensitive test would require testing every 5 days to achieve the same infection rate[9]. Bosetti *et al.* considered the implementation of mass testing in metropolitan France to reduce infection rates. They found using a 90% sensitive test, one round of mass testing 75% of the population reduced infections by 21% in the 10 days following the campaign[37]. More frequent testing could further reduce the impact of disease burden if implemented at the population level.

Authors, such as Neilan *et al.*, have also considered the potential economic impact of testing programs. They considered the economic utility of testing in Massachusetts under four possible testing scenarios: hospitalized only, symptomatic only, symptomatic + one-time asymptomatic, and symptomatic + monthly asymptomatic. They found compared to hospitalized only, all repeated testing scenarios reduced infection rates. Considering hospitalization and testing costs, symptomatic and monthly asymptomatic testing became cost-effective at a $R_e \geq 1.6$. Additionally, Neilan *et al.* note that less expensive, rapid testing could improve economic utility – "if low-cost testing were available at $5/test, it would be cost-effective or cost-saving to offer repeat testing in all epidemic scenarios"[10].

Atkeson *et al.* evaluated the economic benefits of a testing program in the US using a behavioral SIR model consisting of five age groups and 66 private economic sectors. Using a screening test with 97% sensitivity assumed to cost $5, their model predicted avoiding 66,000 deaths when testing weekly. They found net economic benefits range from $75-120 billion for bi-weekly testing and $150-200 billion for weekly testing, depending on screening test sensitivity. Overall, they emphasize the economic and health benefits of testing programs outweigh their costs, especially when rapid tests are accompanied by highly specific confirmatory testing[6].

Paltiel *et al.* examined the clinical and economic outcomes of a nationwide, home-based, antigen testing program. For their base-case scenario, they used a sensitivity of 80% in addition to pessimistic assumptions for behavioral responses to testing, with 50% of individuals participating in at-home testing, 50% of individuals isolating after receiving a positive result, and 20% of isolated individuals abandoning their isolation each day. They found compared to no testing, weekly home testing under the base case scenario reduced infections from 15 to 11 million and deaths from 125,000 to 106,000. This intervention also averted a cost of $5,400 per infection and $1.1 million per death. Paltiel *et al.* conclude a nationally implemented, home-based testing program would be beneficial both clinically and economically, even given potential variations in adherence[38].

4. Discussion

The numerous studies above conclude that disrupting the transmission of SARS-CoV-2 is attainable under testing strategies that optimize the test frequency of the test given its sensitivity. Using a variety of statistical models and varying the different parameters of SARS-CoV-2 transmission, the majority of authors conclude that testing frequently is more impactful in reducing transmission than testing with a highly sensitive test. Thus, using a less sensitive test, such as a rapid test, can provide huge benefit if utilized frequently. Additionally, some studies showed that the speed of test results plays an important role in reduction of transmission of disease. As both asymptomatic

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and pre-symptomatic patients, and perhaps even fully vaccinated persons, will continue to spread SARS-CoV-2, cost-effective and scalable screening methods are essential to identify these patients for quarantine and to stop transmission. Rapid tests that can be used frequently compensate for their lower sensitivity and would serve to make re-openings more feasible and safer. With these key findings in mind, frequent screening with a rapid test could identify silent spreaders of SARS-CoV-2 to disrupt and control the COVID-19 pandemic.

Conflicts of Interest: All authors are employed at Abbott Laboratories.

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