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Cost-effective proactive testing strategies during COVID-19 mass vaccination: A modelling study

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Summary

Background As SARS-CoV-2 vaccines are administered worldwide, the COVID-19 pandemic continues to exact significant human and economic costs. Mass testing of unvaccinated individuals followed by isolation of positive cases can substantially mitigate risks and be tailored to local epidemiological conditions to ensure cost effectiveness.

Methods Using a multi-scale model that incorporates population-level SARS-CoV-2 transmission and individual-level viral load kinetics, we identify the optimal frequency of proactive SARS-CoV-2 testing, depending on the local transmission rate and proportion immunized.

Findings Assuming a willingness-to-pay of US$100,000 per averted year of life lost (YLL) and a price of $10 per test, the optimal strategy under a rapid transmission scenario ($R_e \sim 2.5$) is daily testing until one third of the population is immunized and then weekly testing until half the population is immunized, combined with a 10-day isolation period of positive cases and their households. Under a low transmission scenario ($R_e \sim 1.2$), the optimal sequence is weekly testing until the population reaches 10% partial immunity, followed by monthly testing until 20% partial immunity, and no testing thereafter.

Interpretation Mass proactive testing and case isolation is a cost effective strategy for mitigating the COVID-19 pandemic in the initial stages of the global SARS-CoV-2 vaccination campaign and in response to resurgences of vaccine-evasive variants.

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Research in context

Evidence before this study

We searched PubMed with no language restrictions on May 24, 2021, for publications since database inception focusing on the cost-effectiveness of expanding COVID-19 tests coupled with mass vaccination in the USA. We used the search terms "Economic[Title/Abstract] AND (Testing[Title/Abstract] OR Test[Title/Abstract]) AND (SARS-CoV-2[Title/Abstract] OR COVID-19[Title/Abstract]) AND (United States[Title/Abstract] OR US[Title/Abstract] OR America[Title/Abstract] OR U.S.[Title/Abstract]) AND (Vaccination[Title/Abstract] OR Vaccine[Title/Abstract])". We found only one article that estimated the impact of control strategies on the epidemiological burden of COVID-19 in the United States (e.g., viral testing, contact tracing, and household quarantine). Six articles have reviewed the public health and economic impacts of COVID-19 vaccination and testing programs. A recent paper investigates the combined impact of mass vaccination and asymptomatic testing (at different frequencies) in South Korea, Italy, Canada and the United States and finds that frequent proactive testing is sufficient to mitigate second pandemic waves in these countries [1]. However, we did not find any articles that derive cost-effective proactive testing strategies that adapt to changing risks as immunity increases through infection and vaccination.

Added value of this study

Using a data-driven model of SARS-CoV-2 transmission that incorporates daily viral load dynamics of infected individuals coupled with mass vaccination, we assessed the economic trade-offs of expanding proactive SARS-CoV-2 testing. To our knowledge, this study is the first to identify dynamic testing strategies that are expected to be cost-effective under mass vaccination, depending on the local transmission rate, vaccine coverage, and vaccine efficacy. Given the epidemiological and economic conditions in the USA as of June 2021, the optimal strategy depends on the level of the transmission in the community. Under rapid transmission scenarios (effective reproduction number R_e of 2.5), daily testing of the entire population is advised in the early stage; under lower transmission rates (R_e of 1.2), staggered weekly testing until the population reaches 10% partial immunity followed by monthly testing until 20% partial immunity is advised.

Implications of all the available evidence

Despite the intimidating upfront costs, mass testing with rapid SARS-CoV-2 antigen tests is recommended to health authorities, local governments, schools, healthcare systems, employers, and other decision makers as a cost-effective strategy for mitigating the unprecedented threat of the COVID-19 pandemic, until safe and efficacious vaccines are widely administered and have been able to reduce local transmission.

Introduction

A new coronavirus disease (COVID-19) emerged in Wuhan China at the end of 2019 and remains a threat to global health, economic activity, and political stability.[2] As of December 8, 2021, the United States (US) has reported 49 million COVID-19 confirmed cases and 790,000 deaths. Globally, there have been over 180 million reported cases and three million deaths.[3] Prior to the development and distribution of effective vaccines, authorities have relied primarily on face masking, social distancing, and testing-contact tracing-isolation programs to slow spread and avoid overwhelming hospital surges. As vaccines continue to roll out worldwide, mass expansion of proactive testing can safeguard communities and allow relaxation of strict contingency measures, even before communities attain high levels of immunity.

To combat the catastrophic health and economic threat of COVID-19, scientists, governments, and pharmaceutical companies sprinted to develop safe and effective vaccines against the SARS-CoV-2 virus.[4] As of June 24, 2021, 94 vaccine candidates have been tested in humans and 31 have made it to final phases of clinical trials.[4] Three COVID-19 vaccines have received emergency-use authorization in the US after completion of Phase III trials.[4] Specifically, trial data for vaccines developed by Moderna, Pfizer-BioNTech, and Johnson & Johnson suggest 94%, 95% and 66% efficacy at preventing symptomatic COVID-19, respectively.[5,6] The US began administering vaccines to priority groups, including healthcare personnel and residents of long-term care facilities, on December 24, 2020.[7] As of June 24, 2021, 66% (169 million) adults over age 18 have received at least one dose, and 56% are fully vaccinated.[8] The pace of the rollout peaked around March 29, 2021, with 18 million administered nationwide that week, and slowed to 3 million the week of May 3, 2021.[8] Vaccines are not yet approved for children under 12 years and, according to a survey conducted in May 2021, 31% of all adults in the US remain vaccine hesitant, ranging from 19% of adults over age 65 to 48% of 18-29 year olds.[9]

Mass diagnostic testing of asymptomatic individuals is a viable, cost effective, yet underutilized strategy for mitigating the COVID-19 pandemic.[10–13] Reverse transcription polymerase chain reaction (PCR) to detect SARS-CoV-2 particles swabbed from noses or throats were the first and most commonly used diagnostic.[14] However, PCR testing during the first year of the pandemic was hindered by slow turnaround times throughout the US, and interpretation was complicated by the fact that cases remain PCR positive for weeks after the active infection has resolved.[15–17] Cheaper and faster technologies are now widely available.[15] In August 2020, the U.S. Food and Drug Administration (FDA) approved both a 48-hour saliva-based PCR test[18] and a 15-minute COVID-19 antigen test.[19] The new PCR test,

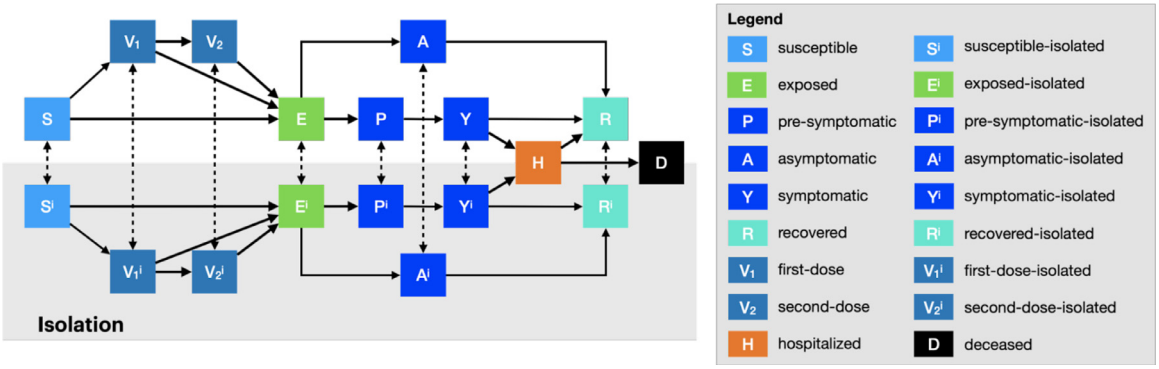

Figure 1. Schematic of the individual-based mathematical model of COVID-19 transmission, vaccination, and testing. Following infection, susceptible individuals (S) enter an exposed state (E), where they are not yet infectious or symptomatic. A fraction of cases then progress to a moderately-infectious asymptomatic state (A). The remaining progress first to a moderately-infectious pre-symptomatic state (P) before becoming highly infectious and symptomatic (Y). A fraction of symptomatic cases will be hospitalized (H), and a subset of those will die (D). Eventually, asymptomatic and symptomatic individuals recover (R) and remain protected from future infection for the duration of the simulation. To model proactive testing, we assume that individuals are tested at a specified frequency, ranging from daily to monthly, according to an evenly staggered testing schedule, regardless of their disease state. Upon receiving a positive test result, cases are isolated and their household contacts are quarantined for a specified period of time (indicated by the superscript *i*). Vaccinated individuals progress to a one dose (V_1) followed by a two dose state (V_2), where the assumed level of protection is based on recent estimates for vaccine efficacy.

which only requires a small sample of saliva, has an estimated 94% sensitivity and 100% specificity at a price point of $1.21-$4.39 per test.[20] Antigen tests detect viral surface proteins, offering a rapid and precise indication of active infection. For example, BinaxNOW diagnostics cost roughly $10 per test,[21] with an estimated sensitivity of 97.1% and specificity of 98.5%.[15,19] Since April 2021, antigen tests are available for over-the-counter purchase at major US pharmacy chains.[22]

The US may face future SARS-CoV-2 resurgences, given incomplete vaccine coverage and the emergence and spread of SARS-CoV-2 variants worldwide. As of December 8, 2021, two SARS-CoV-2 variants of concern have been reported in the US: Delta (B.1.617.2 and AY lineages) and Omicron (B.1.1.529).[23] Several of these variants are reported to be more transmissible and cause more severe illness than the wildtype virus.[23] With affordable rapid SARS-CoV-2 tests widely available in the US,[19] mass proactive testing may be an effective strategy for mitigating SARS-CoV-2 variants in communities with high levels of susceptibility, either overall or in vulnerable demographic or geographic subgroups. Here, we identify cost-effective strategies for proactive testing of unvaccinated individuals, including adaptive testing in which the frequency of testing decreases as population-wide immunity rises. We assess the costs and benefits of testing schedules using an individual-based mathematical model that incorporates household-specific and age-stratified SARS-COV-2 transmission rates, diagnostic sensitivities that vary with viral load, and vaccination rollout. We consider the costs associated with antigen testing, COVID-19 illness, hospitalization, and lost wages during isolation, and the economic benefit of preventing COVID-19 deaths. We derive optimal adaptive testing strategies for a range of SARS-CoV-2 transmission scenarios reflecting the heterogeneous implementation of non-pharmaceutical interventions across the US.

Methods

Epidemic model

We simulate the transmission of COVID-19 in a typical US community for 150 days using a stochastic agent-based model, with the parameters given in ***Supplementary Table S1***. At every time point, each individual is in one of 18 possible epidemiological states, which reflects the individual's infection, vaccination, and testing status (**Figure 1**). When an individual is infected, they progress through several stages of infection. Initially, they experience a non-infectious incubation period. We assume that a fraction of cases will eventually develop symptoms and the remaining cases remain asymptomatic. Asymptomatic cases progress from the incubation period to an infectious asymptomatic period, where they remain before recovering. In contrast, symptomatic cases progress first through a pre-symptomatic infectious period and then through a symptomatic infectious period before recovering. A fraction of symptomatic cases will be admitted to the hospital before either recovering or dying from infection. Recovered cases remain protected against reinfection for the duration of the simulation. The model does not capture births or deaths from other causes.

When an individual becomes infected, we assume that their infectiousness to another individual depends

on their state of their infection and whether the other individual is a member of their household. Asymptomatic and pre-symptomatic cases are less infectious than symptomatic cases, by factors of $\hat{\omega}$ and ω, respectively. We use a within-household transmission rate that results in a secondary attack rate within households of 35%, according to recent estimates in the US.[24]

We consider a range of scenarios for the non-household transmission rate to model different levels of community transmission. For a specified effective reproduction number (R_e), we solve for the corresponding non-household transmission rate using an interior point algorithm (***Supplementary material***).

For each simulated epidemic, we begin by assuming the population is fully susceptible and infect 10 randomly selected individuals. Once 100 infections have occurred, we initiate the rollout of vaccines and a *status quo* testing strategy in which 29.4% of symptomatic cases are tested and then immediately begin a 10-day isolation period while all members of their household begin a 10-day quarantine period, starting an average of two days following symptom onset.

We track the proportion of people with some degree of immunity, acquired through past infection or receiving at least one vaccine, and refer to the quantity as the *partial immunity* of the population (***Supplementary material***). Partial immunity can be estimated from a combination of serological and vaccination data and thus used to tailor intervention strategies. Although we can also track the *effective immunity* of the population, accounting for imperfect and waning immunity, it is more difficult to estimate in reality.

SARS-CoV-2 vaccination

Vaccines made by Pfizer-BioNTech, Moderna, and Johnson & Johnson have been authorized and recommended for mass vaccination to prevent COVID-19 in the US.[4] Given the relatively low uptake of the Johnson & Johnson vaccine[8] and epidemiological similarities between the other two (mRNA) vaccines, we model the two-dose Pfizer-BioNTech mRNA vaccine with 21 days between doses. We assume that, 14 days after receiving a first dose, individual susceptibility to infection is reduced by 47.6%; 14 days after the second dose, it is further reduced to 33% of baseline susceptibility. If infected, a single dose does not lower the likelihood of developing symptoms, but a second dose reduces the risk by 82%. In the ***Supplementary material***, we consider two alternative scenarios for vaccine efficacy. In one, the first dose also protects against symptoms (**Table S3**); in the other, neither dose provides such protection (**Table S2**). We assume that 20 million doses are administered nationwide per week[25] in a US population of 328.2 million people,[26] corresponding to a daily proportion receiving a single dose (first or second) of 0.4% (v) over a period of 20 weeks (w_v) (**Table S1**). Our model rolls out vaccines according to public health priorities. First, they are administered to healthcare workers, followed by high-risk adults over age 17, and finally low-risk adults aged 18-64 and individuals under age 17. We assume 100% uptake among healthcare workers and 70% for all other groups.[27]

Proactive testing strategies

We model rapid antigen testing of the entire unvaccinated population at different frequencies, ranging from dailly to once per month, with testing staggered so that the same number of individuals are tested each day. We assume imperfect SARS-CoV-2 test specificity (**Table S1**) and sensitivity that changes over the course of an infection (**Table S4**). We assume that infected and newly recovered individuals can test positive for up to 41 days, with the sensitivity of the test depending on days since infection (**Table S4**). Susceptible individuals and recovered individuals at least 42 days post infection test positive based on the false positive rate of the test.[19] Following a positive test, an individual is permanently released from future testing.

Individuals that test positive and all members of their household move into their corresponding isolation or quarantine states for a ten-day period, where they are unable to infect others outside of their household. We assume that household transmission can still occur and that, when the isolation period ends, individuals progress to the non-isolated state corresponding to their current infectious/non-infectious state.

During isolation, all household members that have not already tested positive continue testing according to the current regimen. If any member tests positive during isolation, the isolation clock restarts for the entire household. At the end of the isolation period, all vaccinated or unvaccinated members of the household who did not test positive during isolation are tested again. If any are positive, the clock restarts; if none are positive, the entire household is released.

We explore dynamic policies in which a community adopts one of four testing frequencies (daily, weekly, monthly or no testing) and can change the frequency at most twice over the 20 weeks of the simulation. We assume that policy decisions are based on cumulative partial immunity (i.e., the percent of the population previously infected or vaccinated), and that the testing protocol can change at immunity deciles. For example, a community might begin with weekly testing, shift to monthly testing once 20% of people have gained partial immunity, and terminate the program after 40% are immune. In total, we consider 6561 (9^4) candidate testing strategies. To determine the public health benefits of each strategy, we also model a *status quo* strategy that assumes a baseline level of symptomatic testing without additional proactive testing.

Individual-based network

The SARS-CoV-2 infection dynamic model assumes that the virus spreads through a fixed contact network consisting of 2019 individuals and 25,428 contacts between those individuals. We populate the network by first constructing 1000 households. The size and age composition of each household is based on a randomly sampled household from among the 129,697 households included in 2017 National Household Travel Survey.[28] We assume that individual members of each household are fully connected (i.e., all nodes in the same household are linked by edges). We assume that our model represents the household structure, contact patterns, and SARS-CoV-2 transmission dynamics of a typical US community, and directly scale our results from the 2019 individuals in the model to the 328 million residents of the US.[26,29] Following Ref.,[13] we randomly connect individuals from different households, according to the US data about age-specific contact rates[29] in which all people are divided into four age groups: 5-17, 18-49, 50-64, and > 65. Specifically, to determine the number of contacts a node in age group a_i has with nodes in age group a_j we draw a random deviates from Poisson distributions centered at the mean number of contacts between a_i and a_j. The resulting network includes 1000 households, 2019 nodes (people), and degrees (numbers of contacts per person) that roughly follow a gamma distribution with a mean of 12.6 contacts and standard deviation of 6.6 contacts.

Estimating the years of life lost (YLL) averted and monetary costs for each strategy

For a given simulation of a strategy (τ), we estimate the years of life loss (*YLL*) averted by the strategy in comparison to a simulation of the status quo (no testing), as follows:

1. Calculate the difference in incidence by age group as $\Delta_{a,\tau} = I_{a,\circ} - I_{a,\tau}$, where $I_{a,\circ}$ and $I_{a,\tau}$ are the total incidence of infection in age group a produced by the status quo and strategy τ simulations, respectively.
2. Estimate the YLL averted by the testing strategy τ as

$$B_\tau = \sum_a (\lambda_a - a)\delta_a \Delta_{a,\tau}$$

where λ_a denotes the future-discounted life expectancy for individuals of age a and δ_a denotes the age-specific case fatality rate for COVID-19.[30]

Similarly, we determine the incremental monetary costs for each strategy τ as given by

$$C_\tau = (T_\tau - T_\circ)c_T + \sum_a \left(Q_{\tau,a} - Q_{\circ,a}\right)s_a + \sum_a c_{H,a}\left(H_{\tau,a} - H_{\circ,a}\right)$$

where T_τ and $T_\circ$ are the total number of tests administered in the strategy (τ) and status quo simulations, respectively, c_T is the price of administering a single test, $Q_{\tau,a}$ and $Q_{\circ,a}$ are the total people-weeks of isolation and quarantine in age group a in each simulation, s_a is the average weekly salary for age group a, $H_{\tau,a}$ and $H_{\circ,a}$ are the total number of hospitalizations in age group a in each simulation, and $c_{H,a}$ is the median COVID-19 hospitalization cost for age group a. The cost parameter values are given in **Table S5**.

Estimating the cost-effectiveness acceptability curve

The willingness to pay per YLL averted is the maximum price a society is willing to pay to prevent the loss of one year of life. Based on healthcare expenditure data, health economists have estimated that the US is willing to pay US$100,000-$200,000 per life-year.[31] For a given willingness to pay for a YLL averted (θ), we calculated the net monetary benefit (NMB) of a strategy as

$$\mathrm{NMB}_\tau = \theta \cdot B_\tau - C_\tau.$$

Assuming a price of US$10 per test and a US $100,000 willingness-to-pay per YLL averted, we determined the optimal strategy across a range of scenarios, where each scenario is defined by the effective reproduction number (R_e) and .willingness to pay for YLL. For a given scenario, we run 1000 rounds of stochastic simulations, where a round includes one stochastic simulation of each of the 6562 candidate testing strategies (including the status quo). All parameters are held constant across strategies, except for those governing testing. At the end of a round, we estimate the NMB of each strategy in comparison to the status quo simulation, rounded to the nearest ten million USD. Finally, we estimate the probability that a strategy has the greatest net benefit among all strategies by the proportion of rounds in which it gives the highest NMB. The strategy with the highest probability of having the greatest NMB is considered optimal.

Ethics committee approval

Not applicable.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Using an individual-based model of within-host and between-host SARS-CoV-2 infection dynamics, we compare 6561 testing strategies during the mass distribution of a vaccine that lowers both susceptibility to infection and severity once infected. For each strategy,

all individuals are tested at a specified frequency, either daily, weekly, monthly, or not at all, and this strategy can change depending on the proportion of the population immunized by prior infection or vaccination. Upon receiving a positive test result, individuals immediately enter a 10-day isolation period and their household contacts enter a 10-day quarantine period (**Table S1**). Outcomes are quantified in terms of Years of Life Lost (YLL) from infection, costs of diagnostic testing and hospitalization, and salary lost during isolation.

We analyze thirteen different transmission scenarios, with initial reproduction numbers ranging from 1.1 to 3.0. For each, we performed stochastic optimization to identify the optimal adaptive testing strategy (Figure 2) assuming a test cost of US$10 and WTP per YLL averted of US$100,000[31] the optimal strategy is to begin with daily testing of all unvaccinated individuals daily and transition to weekly testing once the population has accumulated sufficient immunity. For reproduction numbers of 2.0 or 2.5, this transition is recommended when 10% or 30% of the population has been immunized via either infection or vaccination, respectively. At reproduction numbers below 2.0, weekly followed by monthly testing is expected to be cost effective, but only at relatively low levels of population immunity. As the transmission rate increases, testing becomes more economical and the

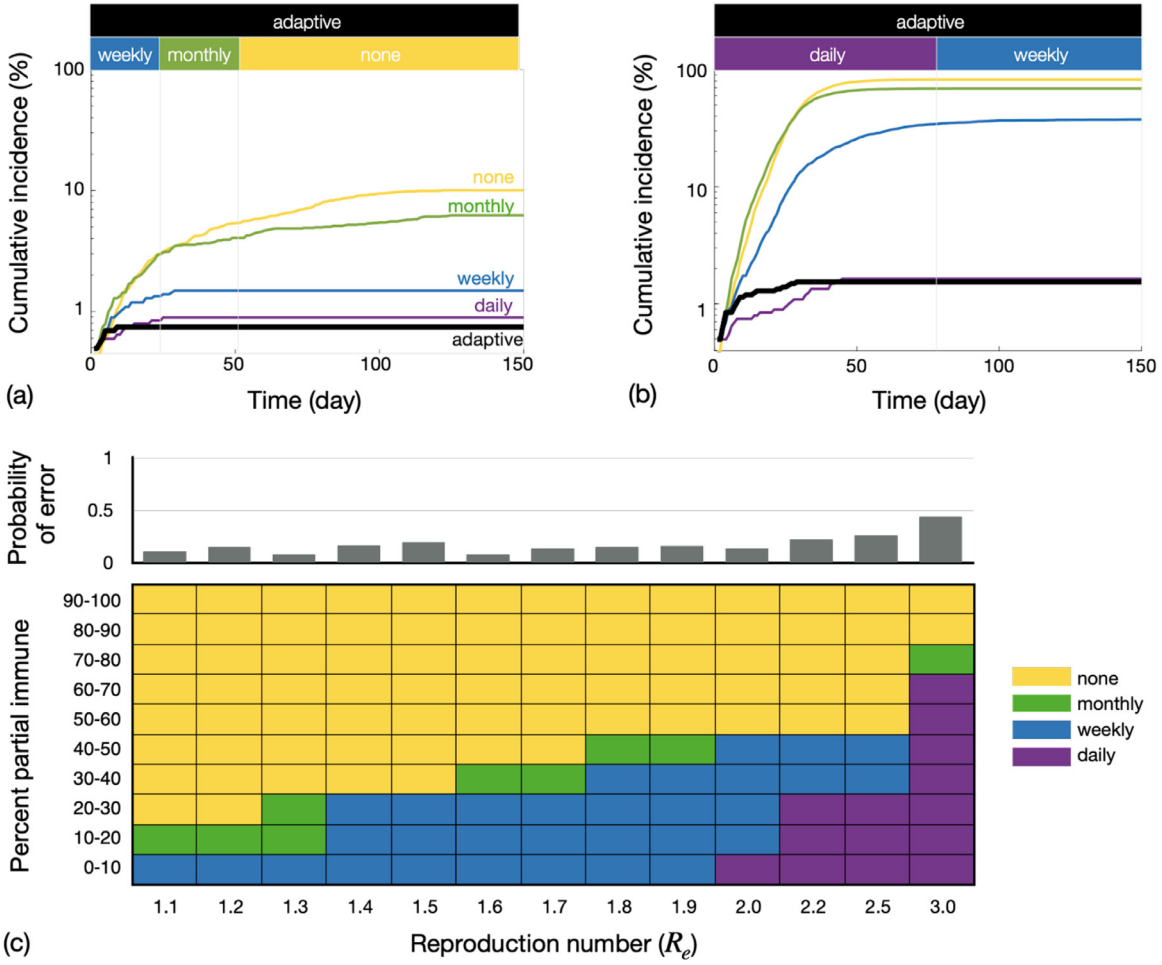

Figure 2. Adaptive strategies for proactive testing under a range of COVID-19 transmission scenarios during a mass vaccination campaign, assuming a willingness to pay per YLL averted of $100,000 and cost per test of $10. Estimated cumulative incidence of COVID-19 across testing strategies assuming effective reproduction numbers of (a) 1.2 and (b) 2.5. Colored lines indicate a consistent frequency of testing, with yellow, green, blue and purple corresponding to no testing, monthly testing, weekly testing and daily testing, respectively. The black curve corresponds to an adaptive strategy, with the changing frequency of testing indicated at the top of each graph. (c) Optimal testing strategies for initial reproduction numbers (R_e) ranging from 1.1 to 3.0 (columns in lower table) and probability that the given strategies are optimal (upper graph). For each reproduction number (column) and partial immunity decile (row), the cell color indicates the testing frequency that is expected to maximize the net monetary benefit (NMB). All vaccinated and previously infected individuals count towards the percent partial immune. Additional statistics are provided in Table S6 and Table S9.

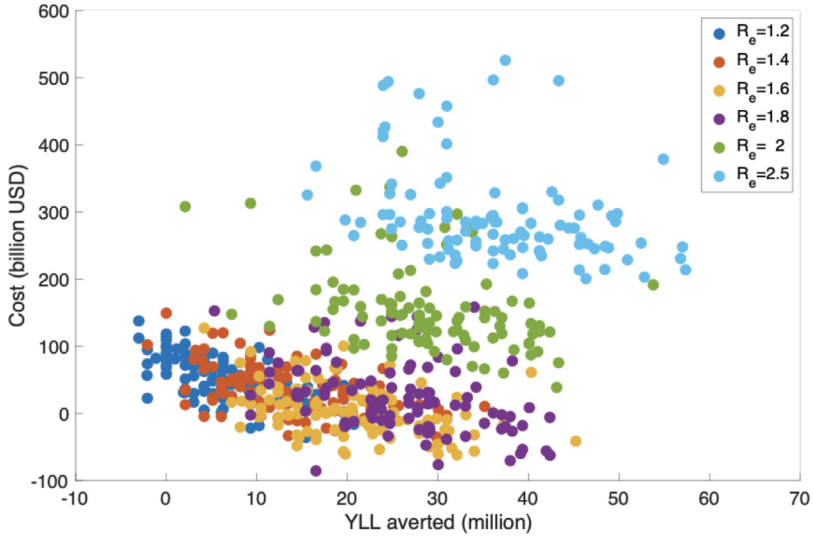

Figure 3. Estimated costs of optimal testing strategies during rollout of a vaccine and YLL averted, under five transmission scenarios with effective reproduction numbers ranging from 1.2 to 2.5. Each point corresponds to one of 100 stochastic simulations for the optimal testing strategy for each R_e, under parameters given in **Table S1**. Costs include the incremental monetary costs of administering tests, salary lost during isolation following a positive test result, and costs associated with COVID-19 hospitalizations; YLL averted considers morbidity and mortality due to COVID-19 disease. The costs and YLL averted are all scaled assuming a US population of 328.2 million, as estimated in 2019.[26]

thresholds for transitioning from weekly to monthly testing and for disbanding mass testing increase. We obtain similar estimates assuming that vaccines offer either more or less protection against symptomatic illness if infected (**Table S2**, **Table S3**, **Table S7**, and **Table S8**).

For each scenario, we estimate the health and economic outcomes of the optimal adaptive strategy (Figure 3). Intuitively, expected costs increase both with the transmission rate, because of the costs associated with COVID-19 hospitalizations and mortality, and with the frequency of proactive testing, because of the direct costs of administering tests and wages lost during isolation of confirmed cases and their households (Figure 2). Under a high transmission scenario (R_e=2.5), the optimal adaptive strategy, which entails daily testing until 30%of the population is immunized and then weekly testing until half the population is immunized, is expected to avert 36 (95% CrI: 20, 57) million YLL, corresponding to a cost of 279 (95% CrI: 208, 496) billion USD.[31] Under a low transmission scenario (R_e=1.2), the optimal strategy is to conduct weekly testing until 10% of the population has been partly immunized and then relax to monthly testing until immunity reaches 20%. This strategy would be expected to avert 5 (95% CrI: -2, 21) million YLL and exact a cost of 50 (95% CrI:-22, 118) billion USD (**Table S9**).

Discussion

Proactive SARS-CoV-2 testing with inexpensive and widely available antigen-based diagnostics, when coupled with voluntary isolation of positive cases and quarantine of their household contacts, can substantially reduce transmission, morbidity, mortality, and strain on our healthcare systems. However, as population-wide immunity increases from a combination of prior infection and vaccination, the need for proactive testing and other mitigation efforts will decrease. Cost effectiveness analysis allows us to tailor the frequency of testing to address changing epidemiological risks within a community. Across a range of SARS-CoV-2 transmission scenarios, we have derived optimal staged strategies in which the frequency of testing decreases as the population surpasses threshold levels of partial immunity. These strategies assume that cases and their households isolate for 10 days following receipt of a positive test result. If the virus initially spreads rapidly, with an effective reproduction number around 2.5, then the optimal staged strategy starts with daily testing, reduces to weekly testing once 30% of the population has acquired partial immunity through either infection or vaccination, and halts completely once half the population is immunized. For communities in which non-pharmaceutical measures reduce the reproduction number below 1.6, weekly or monthly testing is only recommended while population-wide partial immunity remains below 30%.

The basic reproduction number for SARS-CoV-2 has been estimated to range from 1.90 to 6.49[32] many cities managed to keep the effective reproduction number well below two for over a year through a variety of non-pharmaceutical interventions.[33,34] Public use of face

masks and adoption of other precautionary behaviors continue to vary across communities and through time.[35,36] By July 1, 2021, many US states had relaxed social distancing and face mask restriction.[37] In addition, approximately 45% of the population had been fully vaccinated and over 35% have been previously infected by SARS-CoV-2.[8,38] At these intermediate levels of transmission and immunity, weekly testing is expected to be cost effective until at least half of the population is immunized, followed by monthly testing. However, testing strategies should be tuned to local conditions, given the considerable variation in COVID-19 policies, transmission rates, cumulative incidence, and the pace of vaccination across the US.[39,40]

Multiple SARS-CoV-2 variants of concern have emerged worldwide and begun to spread in the US.[23] Several, including the Alpha, Gamma and Delta variants, are thought to spread faster, cause more severe disease, and evade immunity conferred by vaccines more effectively than the wildtype virus.[23,41] With 41.4% of the global population fully vaccinated by November 19, 2021 and logistic, resource, and behavioral barriers slowing progress,[42] the virus will continue to evolve. The US may face future waves of SARS-CoV-2 transmission caused by vaccine evasive variants. As such threats arise, proactive testing will remain a cost effective strategy for reducing risks and avoiding more socioeconomically burdensome restrictions. The testing effort can be adapted to balance the costs associated with test administration and lost productivity and education during isolation with the benefits of averting COVID-19 related morbidity and mortality. Such analyses can take a static approach, based on real-time estimates of the reproduction number and viral severity,[13] or a dynamic approach similar to this study, anticipating future changes in testing requirements as the epidemiological situation evolves.

Proactive SARS-CoV-2 testing at daily, weekly or monthly frequency may not yet be logistically feasible everywhere, as it requires considerable resources, including large quantities of low-cost rapid tests and trained staff, as well as high levels of community participation. For example, monthly testing across the US would require 12 million tests a day. Despite these hurdles, recent efforts demonstrate that rapid implementation can be feasible. For example, as of November 12 2021, Abbott Labs is manufacturing 50 millions of BinaxNow antigens tests per month, which are available over the counter at CVS, Walgreens and Walmart pharmacies in the US,[43,44] and the Biden administration has budgeted over $12 billion to ramp up mass COVID-19 testing across the US.[45]

While we believe our qualitative findings are robust and provide actionable insights, we highlight several simplifying assumptions. Our individual-based model does not explicitly include subgroups with anomalously high contact rates, such as nursing home residents, populations experiencing homelessness, essential workforces; nor does it consider subgroups that have persistently low vaccination rates, driven by hesitancy or lack of access.[46] Such populations can amplify transmission or serve as viral reservoirs, if even average risks are low. We also assume that communities will comply with voluntary isolation of cases and their households and adapt easily to changes in testing frequency. In fact, there may be substantial resistance and delays in responding to policy changes. Our economic analyses consider only the direct costs of testing, salary loss during case isolation and household quarantine, and the benefits of hospitalizations and deaths averted. We do not consider the indirect socioeconomic benefits of slowing transmission via proactive testing, including the relaxation of taxing social distancing measures.

Since we focus on immediate and adaptive policy guidance as vaccines roll out, we consider only a five-month time horizon and make the plausible assumption that recovered individuals cannot be reinfected. However, the duration of immunity following SARS-CoV-2 infection or vaccination remains uncertain. There is increasing evidence that immunity wanes over several months following recovery.[47,48] The durability of immunity against reinfection has been estimated to be 16 months.[49] A study in Italy reported that only 0.31% (95% CI, 0.03%-0.58%) of infections that occurred between February 2020 and February 2021 were reinfections[50] 2.34-fold.[51] If immunity is more transient than we assumed, leading to frequent breakthrough infections shortly after vaccination or infection, then the optimal testing frequencies would likely be even higher. Finally, our assumptions regarding vaccine efficacy are based on clinical trial data for the SARS-CoV-2 vaccine manufactured by Pfizer-BioNTech[52] and may not apply to other vaccines or the spread of immune evasive variants.

Policymakers will likely face new and uncertain challenges, as COVID-19 continues to spread and evolve, population immunity increases through infection and vaccination while waning through time, and individual and community behaviors change. Proactive testing coupled with case isolation and contact quarantine is a powerful yet underutilized weapon in our arsenal for combating the pandemic. This study suggests that testing strategies can be rapidly tuned to mitigate changing levels of COVID-19 risk to ensure that they are cost effective. Translating this work into national policy may be hampered by chronic conflicts among local, state, and national authorities that have plagued the US response to the pandemic.[53] However, the qualitative finding——that testing can be life saving and cost saving if tailored to local risks——is relevant at all scales, from neighborhoods to the country as a whole. The quantitative recommendations are relevant to US communities, roughly the size of census tracts or larger, and the modeling approach can be readily adapted to model the costs and benefits of testing in smaller communities,

including individual schools, universities, workplaces, and healthcare settings.

In closing, mass asymptomatic testing for SARS-CoV-2 across the US is expected to provide a cost effective strategy for mitigating the lingering threat of the COVID-19 pandemic as vaccine coverage increases. As we look ahead to the 2021-2022 influenza season and the possibility of emergence of vaccine evasive SARS-CoV-2 variants, we hypothesize that combined SARS-CoV-2 and influenza proactive testing may provide substantial health and economic benefits on a societal scale.[54]

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Data sharing

The computer code and simulated data will be made available to anyone for any purpose upon request to the corresponding author.

Declaration of interests

We declare no competing interests. Dr Chinazzi, Dr Pastore y Piontti and Prof. Alessandro Vespignani report grants from Metabiota Inc, outside the submitted work. Prof. Benjamin J. Cowling reports honoraria from AstraZeneca, GSK, Moderna, Pfizer, Roche and Sanofi Pasteur. The authors report no other potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2021.100182.

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