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TRACE-Omicron: Policy Counterfactuals to Inform Mitigation of COVID-19 Spread in the United States

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The Omicron wave is the largest wave of COVID-19 pandemic to date, more than doubling any other in terms of cases and hospitalizations in the United States. In this paper, a large-scale agent-based model of policy interventions that could have been implemented to mitigate the Omicron wave is presented. The model takes into account the behaviors of individuals and their interactions with one another within a nationally representative population, as well as the efficacy of various interventions such as social distancing, mask wearing, testing, tracing, and vaccination. We use the model to simulate the impact of different policy scenarios and evaluate their potential effectiveness in controlling the spread of the virus. The results suggest the Omicron wave could have been substantially curtailed via a combination of interventions comparable in effectiveness to extreme and unpopular singular measures such as widespread closure of schools and workplaces, and highlight the importance of early and decisive action.

1. Introduction

The COVID-19 pandemic continues to pose a threat to the health and stability of our society. From December 29, 2021 to February 27, 2022, the Omicron variants of COVID-19 caused over 100 000 deaths and over 30 million new reported infections.[1] The negative impact of the "Omicron wave" has lasted beyond the winter of 2021-2022, including a high and growing burden of chronic disease from long-COVID,[2] as well as continued social and economic disruption.[3,4]

Disease prevention strategies have evolved since the emergence of COVID-19 in early 2020. The population now has access to a wide selection of mitigation tools: vaccines which are effective at preventing death, a larger stock of N95 masks, and multiple forms of diagnostic testing. However, the SARS-CoV-2 virus continues to evolve, both in transmissibility as well as immune evasion. New variants are already beginning to emerge, prompting predictions of a potential winter/spring wave.[5] We can prepare for the next phase—and those that are likely to follow—by using last winter's Omicron wave to help understand what might happen and how we can best respond to mitigate harm.

We have developed an agent-based model that embraces the complexity of current outbreaks and mitigation strategies, as well as the uncertainty about the future course the pandemic will take. Classic compartmental models are powerful because of their simplicity, and have been used to estimate disease dynamics and inform policy during the COVID-19 pandemic.[6–9] However, compartmental models often fail to capture strategic trade-offs that emerge in real scenarios. For example, when simulating interventions in compartmental models, both the scale of an epidemic peak (maximum number of cases at a given time) and the size of an epidemic (total number of cases over time) will decrease monotonically together. Because reality is more complex, an intervention might improve one while worsening the other. Similarly, these compartmental models also fail to capture the heterogeneity of real contact networks and therefore assume that all interventions will impact all individuals in similar ways. Again, reality is more complex, and our models should therefore account for contact patterns.

Agent-based modeling has a long history of being used to guide pandemic response strategies. In the early 2000s,

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large-scale models of influenza pandemics such as Germann et al. 2006[10] and Ferguson et al. 2006[11] simulated country-scale disease spread and contributed policy recommendations to prepare for outbreaks. Specifically, these focused on identifying effective deployment strategies of limited vaccine supplies to prevent infections and deaths. Agent-based modeling has also played a key role during the COVID-19 pandemic.[12,13] In the initial phase of the pandemic, simulations were used to forecast potential epidemic scenarios and estimate the number of deaths and hospitalizations.[14] As COVID-19 spread around the world, models were used to evaluate the effectiveness of nonpharmaceutical interventions, such as diagnostic testing and contact tracing programs at city and county,[15,16] as well as state-wide[17] scales, which informed local policy. During this period, other models provided guidance on school and community re-openings.[18,19] Additional models investigated the efficacy of vaccination campaigns[20] and considerations regarding booster shots for waning vaccine immunity.[21] More recent studies explored the performance of testing, contact tracing, and vaccination in the presence of novel variants.[22] However, few, if any, models have retrospectively analyzed the Omicron wave at a national scale to study what policy interventions may have been effective if implemented.

Our key contribution to the COVID-19 pandemic modeling literature is applying a sophisticated model to the interaction of a wide array of possible disease scenarios and potential response strategies—here, including strategies which were not used, but could have been. By looking backward at the Omicron wave, we can consider how different policy combinations might have changed the observed outcome. Because we also vary disease conditions, we can identify response strategies that might be best suited to specific future variations that are yet to be observed or are robust across disease conditions and thus useful to employ in the face of epidemiological uncertainty.

To glean actionable insights from the Omicron wave, we extend and apply TRACE, a nationally representative agent-based simulation[23] which models COVID-19 dynamics in highly realistic contact settings. Like other agent-based simulations, our model, TRACE-Omicron, allows disaggregated modeling of individual agent interactions. This allows us to incorporate large amounts of heterogeneity in disease transmissibility, contact structure, and policy interventions.

In heterogeneous, networked, populations, we want to model different policies aimed at mitigating the number of cases over time. These policies can use an array of behavioral, technological, and biomedical strategies; most importantly social distancing, masking, and vaccination. We focus on cases and not hospitalizations or deaths for a few reasons. One, we will show that it is sufficient to capture rich strategic trade-offs in policy design. Two, risk of complications could be considered as a fraction of cases and will therefore be approximately proportional to number of cases. Three, other long-term consequences of COVID-19 are not yet fully understood and focusing on certain complications could limit the applicability of the model.

Our research suggests feasible strategies that can effectively limit infection rates across a wide range of potential COVID-19 variants. Further, our results highlight potential policy substitutes, allowing decision-makers to quantitatively assess potential alternatives to disruptive or impractical options. For example, increased use of high-quality masks or combining several policies at a lower intensity, such as testing, mask efficacy, and boosting, can outperform singular high intensity interventions. The finding that infection reduction is possible without massively disruptive and unpopular strategies, such as widespread business and school closures, is broadly consistent with previous research in similar contexts.[15,17] We are also in agreement with previous research that vaccines need not confer perfect or durable immunity to remain a key tool in reducing disease spread.[21] In this paper, we provide a more extensive comparison of strategies and potential substitutions and synergies than is offered by any previous work, in the hope that policymakers will use this as part of a "response playbook" that will aid in rapid, timely, and effective action that can limit damage as COVID-19 progresses.

2. Experimental Section

2.1. Model Design and Dynamics

TRACE-Omicron built upon prior models[23] to consider what potential impact different policy interventions might have had upon the (BA.1, lineage) Omicron wave. TRACE-Omicron tracked individual agents: simulated individuals existing in realistic social structures whose actions shape, and were shaped by, their interactions with other agents. An agent's "state" includes their current disease, quarantine and testing statuses, their vaccination history, whether they are wearing a mask, and who they interact with. Opportunities for disease transmission were driven by agent states and interactions, and were shaped by policy interventions. An agent who tested positive for COVID-19, or was in contact with someone who tests positive, was expected to quarantine and not interact with other agents for 10 days, or 5 if they were asymptomatic.[24] Some amount of non-adherence was allowed, reflecting the fact that some individuals may be unable or unwilling to comply with quarantine procedures. Other interventions, such as vaccination or masking, reduced the probability of infection for a non-infected agent, and also reduced the probability of onward transmission for an agent who experienced an infection. Many combinations of these interventions were simualted to understand how these policies interacted with one another, and which ones, at which intensities, were particularly effective at reducing disease spread. In total, 88 128 000 model runs exploring 46 080 parameter combinations were conducted. The functionality of TRACE-Omicron is described in the following sections. A full description of TRACE-Omicron is given in Supporting Information.

2.2. Disease Progression

Infection progression in the simulations used a variant of the classic "susceptible-exposed-infectious-recovered" (SEIR) epidemiological model that was intended to specifically represent COVID-19, see **Figure 1**. Agents may be in one of several disease states and progressed through each state via interactions with other agents. Agents who had never experienced a COVID-19 infection or no longer had substantial antibody protection from a prior infection were "susceptible" and moved to "exposed" after

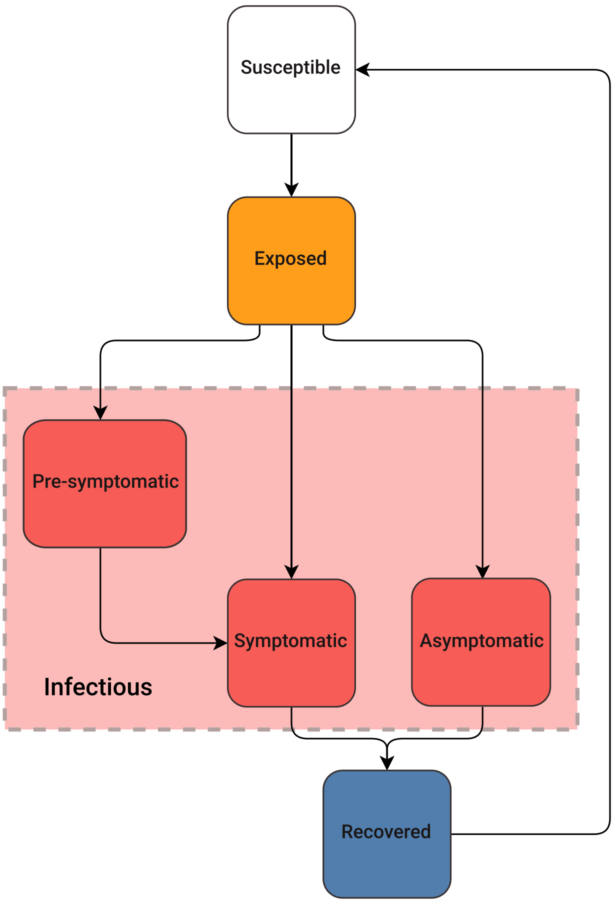

Figure 1. Flow chart of COVID-19 "states" and possible "state transitions" represented in the model.

contact with an infectious agent. After a set incubation period, they become "infectious," with some individuals having a shorter incubation and were infectious before they show symptoms (i.e., were "pre-symptomatic") and others never showed symptoms and were called asymptomatic.[14,25–31] Infectious agents progress through their disease state for a set time until they were "recovered." After a period of immunity, agents can probabilistically transition back to being susceptible based on their time since infection.[32] To capture a critical feature of COVID-19, infectivity was allowed to vary across individuals and infection type, allowing for both highly contagious "super-spreaders" as well as a lower likelihood of non-symptomatic individuals transmitting the disease. The number of agents in each disease state and their time in each state was based on CDC data from late December 2021, adjusted for undercounting.[33]

2.3. Calibration and Initialization

TRACE-Omicron was initialized to reflect the state of COVID-19 spread in the United States in late December 2021. During the Omicron wave, reinfections with SARS-CoV-2 were common. Three key features of the Omicron wave were modeled based on available literature: the amount of prior immunity in the population, the waning of antibody protection over time, and imperfect protection conferred by prior infection against reinfection by Omicron. A "burn-in" procedure was used to start a model run during a pandemic, rather than being forced to study an initial outbreak of infections. Using CDC case and vaccination data, the number of infected agents on December 29, 2021, how long each had been in their initial state, and the actions they would have taken in the days leading up to the start of the model run, were estimated. The baseline intensities of policy interventions in the United States in place in late December 2021 was also initialized.

A standard test for ABMs was whether they can achieve "generative sufficiency," that is, whether an ABM can explain empirical phenomena.[34] To calibrate TRACE-Omicron, all parameters were grounded empirically as far as possible, but allowed to vary those parameters which were difficult to measure directly, showed substantial variance in estimates across multiple studies, or require adjustment for compatibility with the model. Specifically, the false negative rate of antigen tests, daily contact tracing capacity,[35,36] the rate of mask wearing in the population (see Supporting Information), the base transmission probability of infection,[37] and the immune evasion probability were varied.[38–40]

To test the model robustness, three calibration scenarios were explored in the simulations, summarized below and in **Table 1**:

- The "best fit" calibration, which has the lowest mean-squared error when compared to the CDC data.
- The "tractable strain" calibration was chosen as an alternative that also had substantial literature and empirical support, and was representative of a class of parameterizations with lower base transmission rate and lower antigen test false negative rate. As a result, lower levels of policy intervention were required at baseline for similar calibration outcomes.
- The "high immune escape" calibration, which had the lowest mean-squared error among high immune escape scenarios. This was explored as a sensitivity test, due to ongoing uncertainty about the immune evasion of the variants in the Omicron family.

For each calibration, the mean-squared error between the number of infected agents per model step and CDC data were calculated. To establish generative sufficiency, the number of infections during the Omicron wave were tracked, as shown in **Figure 2**. In subsequent sections, the results of the Best Fit calibration was primarily presented, but the other calibrations were also explored as a robustness check throughout.

Epidemiological models were often characterized by their R_0: the measure of expected secondary cases in a completely susceptible population. In an agent-based simulation, calculating R_0 did not have a closed form solution. Following standard best practice,[10]the R_0 value was calibrated by running many repetitions of TRACE-Omicron with an initially infected "index agent." R_0 were estimated by calculating the average number of infections[51] generated by second generation infectives (as the first generation were atypical),[52] specifically, this calculating was done by the ratio of tertiary to secondary cases. The chosen base transmission probabilities of 0.2, 0.175, and 0.125 corresponded to R_0 values of about 8, 7.7, and 6.9 respectively. Despite the sizeable degree of uncertainty around the value of R_0 at the time of

Table 1. Variation in epidemiological, social, and policy conditions across 3 baseline scenarios. We also include values searched over in the calibration search space column.

Parameter	Best fit	Tractable strain	High immune escape	Calibration search space	Reference
Antigen false negative rate	0.25	0.2	0.2	0.2*, 0.25, 0.3	[41]
Daily trace capacity	250	250	250	50, 250*	[42]
Infectious duration (days)	5	5	4	4, 5*, 6	[14]
Latent duration (days)	4	4	3	3*, 4, 5	[43]
Mask wearing	0.41	0.335	0.36	0.2, 0.31, 0.335*,0.35, 0.36, 0.385, 0.41*	[44, 45]
Remote work	0.10	0.10	0.15	0.1*, 0.15, 0.2	[46]
Community distancing	0.20	0.15	0.20	0.1, 0.15, 0.2*	[47]
Quarantine adherence	0.60	0.60	0.70	0.60*, 0.70	[48]
Base transmission rate	0.20	0.175	0.125	0.1, 0.125, 0.15,0.175, 0.2	Calibrated to CDC data
Immune escape	0.40	0.40	0.80	0.4*, 0.5*, 0.6, 0.7, 0.8	[38, 39]
Antigen tests per day		20 million		10, 15, 20* million	[49]
Presymptomatic duration (days)		2		1, 2*	[25, 26]
School closure		0.0		0.0*, 0.1	[50]

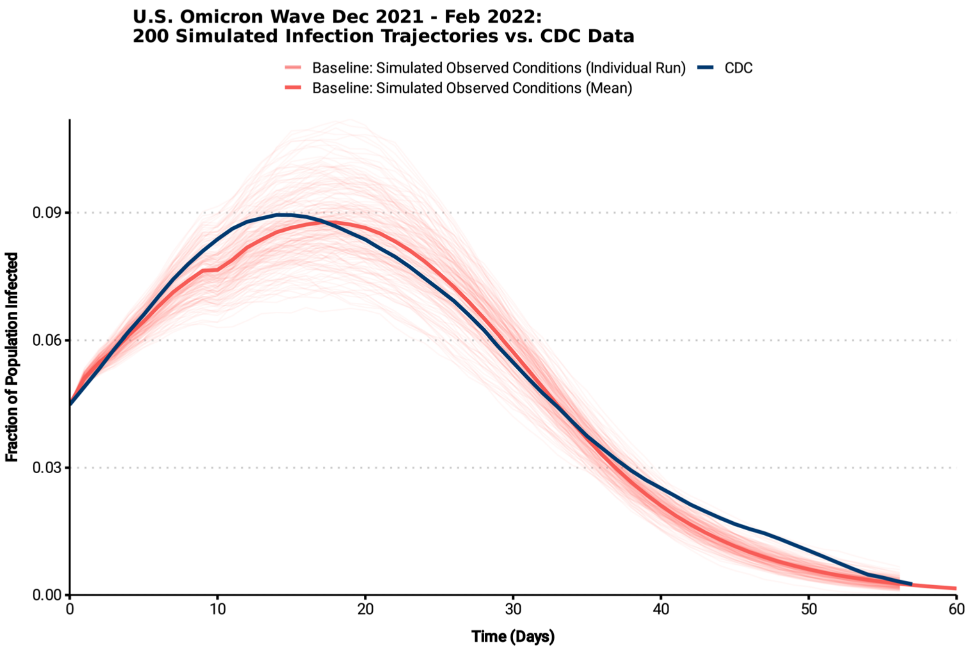

Figure 2. Estimation of baseline conditions under best fit calibration. Each curve represents the count of infected agents each simulated day, compared to estimates using CDC data. Individual trace lines represent 200 simulations, with the mean infected agents per day highlighted in bold.

experiments,[37] the calibrated values were within the range of other estimates.[53]

2.4. Population Structure

To balance computational feasibility and observational power, TRACE-Omicron used a population of 50 000 agents, with social settings (where they live, work, and attend school), demographic attributes, vaccination history, and infection states. Contacts were generated using SynthPops.[54] First widely used in ref. [15] where it was explained in detail, Synthpops is an open-source model for generating realistic synthetic contact networks of specific populations using input data from those populations. After inputting data on nationally representative population age distributions,[55] employment rates stratified by age,[56] school enrollment rates by age,[57] household head age distributions by family size,[58] and household, school, and workplace size distributions[46,58,59] from federal surveys, Synthpops generated contact structures which were realistically transitive by generating synthetic locations for school, work, and home and assigning contacts based on these locales. Community contacts were generated at random with quantity drawn from a negative binomial distribution, similar to previous work that also used Synthpops.[15] Twenty random population contact structures were created and simulations were dispersed uniformly between them. For a given agent in a given population, the list of potential contacts was fixed throughout, but interactions were stochastic and dependent on agents' quarantine statuses and active interaction settings based on social distancing policies (see Section 2.6).

2.5. Infector–Infectee Dynamics

Besides disease state, agents had a number of other statuses attributed to them which can affect their contact structure and the probability of infection given an interaction. Some agent variables can affect contact structures in ways that impeded infection opportunities. These included quarantine, and social distancing measures of working from home, school closure, and not engaging with social community contacts. Other agent variables affected probability of an infection given an interaction between an infectious agent and a susceptible agent. These included masking status (of both the infectious and susceptible agents) as well as vaccine-related attributes (vaccination status, type of vaccine administered, time since vaccine, and number of vaccinations).

2.6. Modeling Interventions

To study ways to mitigate COVID-19 spread, TRACE-Omicron modeled an array of policy interventions across a high-dimensional parameter space. Policies were simulated at baseline, representing the policy context in the United States in late 2021, as well as levels of increasing policy strength to model policy counterfactuals: preventative actions that might have been taken before or during the Omicron wave, but were not. Specifically, vaccination and boosting, masking, testing and contact tracing, and social distancing measures were modeled.

Vaccines and boosters were one of the most critical tools for managing COVID-19.[60] The protective impact of vaccination and boosting, as interventions, were driven by several key implementation details: who gets vaccinated, when they get vaccinated, what vaccine they receive, how effective that vaccine is at preventing infection, its efficacy against transmission, and how long this protection lasts. Further, vaccine effectiveness and duration of protection was specific to each individual vaccine formulation (e.g., Moderna) and each variant of COVID-19, and much effort had been made to estimate these quantities across variants and vaccine products.[61] Using the CDC's time-series data of vaccination in the United States, vaccines were distributed proportionally by age group among the agents in the simulation.[62] When agents were vaccinated, they receive two multipliers, one which reduced the probability of transmission, should they experience a breakthrough infection, as well as one reducing the probability of infection relative to an unvaccinated agent. This protection against infection wanes over time, and was updated weekly for each agent, based on real-world vaccine-effectiveness studies.[63]

Agents can also be boosted 180 days after they have been vaccinated, if their age group was eligible.[64] Boosting restored an agent's vaccine efficacy multipliers to their original values. TRACE-Omicron investigated policy questions regarding how many agents needed to be vaccinated and boosted before the Omicron wave, as well as the estimated efficacy of a faster distribution of available doses. Boosting policies were implemented identically to vaccination policies, but boosting and vaccination were separate interventions in TRACE-Omicron.

A proportion of agents wear masks, which decreased (as separate parameters) both the infectiousness of masked infectious agents and susceptibility of masked susceptible agents. There were two masking-focused policy levers: the rate of mask wearing in the population, and the type of masks agents wear. For computational feasibility, agents who wear masks were assumed to wear them at all times. To more closely match mask-wearing in TRACE-Omicron to observational data, the estimates of baseline mask-wearing downward were adjusted by the population's average number of non-home contacts.[44,45,54] Two types of masks were implemented in TRACE-Omicron, one which represented standard cloth masks, and one which more closely represents N-95 masks, which have higher protection against both infection and transmission.[65,66]

Each day, a sample of non-quarantined agents, subject to test availability, were tested. Agents who test positive were asked to quarantine and report their contacts.[24] Testing included polymerase chain reaction (PCR) and antigen (rapid) testing, each with their own false positive and false negative rates.[41,67–70] PCR tests were first distributed to a sample of symptomatic agents, and any excess capacity was allocated randomly. Antigen tests were distributed to a random sample of contacts of agents who had tested positive recently, and excess capacity was allocated randomly. A similar procedure was used to simulate contact-tracing, where subject to contact tracing capacity, random contacts of symptomatic agents were asked to quarantine. As policy interventions, the amount of PCR and antigen tests and contact tracing capacity in the model were varied, and specific policies were represented as multipliers above baseline testing and tracing levels observed during the Omicron wave.[1]

Social distancing measures encompassed individual quarantine or reducing the number of contacts agents had in a given setting. Agents who believe they were infected, receive a positive COVID-19 test, or were contact-traced and asked to self-isolate for a period of time based on whether they were symptomatic. Agents adhered to quarantine directives probabilistically, representing their willingness and ability to do so.[48,71,72] TRACE-Omicron implemented business and school closures, and community distancing via removing contacts agents had through the corresponding setting (work, school, or community/other) during the period that closure/distancing was in effect.[47,50,73] A visualization of TRACE-Omicron's contact structure is shown in **Figure 3**.

2.7. Policy Intervention Intensities

Combinations of the selected policies were generated at multiple levels of intervention. These policy combinations were synthesized into a subset of available policies, and considered singular interventions (i.e., substantial increases in one policy dimension such as testing or social distancing) as well as policy mixtures (i.e., moderate increases in several policy dimensions). Somewhat large increases were denoted in policy interventions with a "+" and even more intense increases with "++." The considered policies were summaried, with detailed descriptions, in **Table 2**.

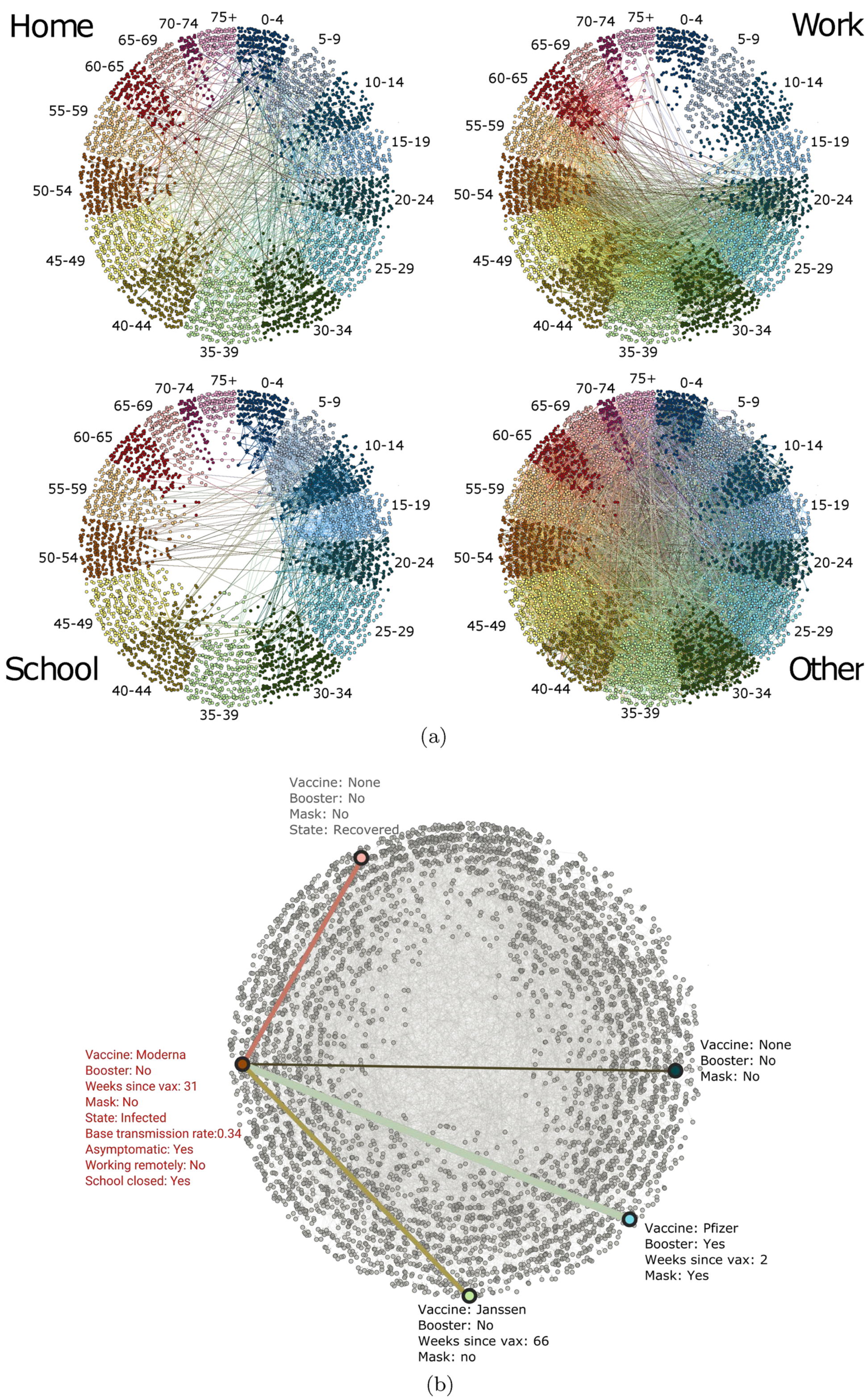

Figure 3. a) A visual representation of the contact network for the populations used in simulations. Each subfigure shows the contacts in a given setting for the same sample of 10% of nodes. Node layout is according to a novel algorithm which bins nodes angularly according to categorical variable (age group in this case) and distance from the center is inversely proportional to total number of contacts across all settings. b) Contacts of an example infectious agent from (a), detailing its variable and the variables of its contacts which affect the probability of an infection. Edge width denotes infection probability if susceptible, text color denotes infection state.

Table 2. Summary of policy interventions and intensities. The "+" column represents a somewhat large increase in the strength of the policy relative to baseline, and "++" represents a much larger increase. Vaccination, boosting, and mask wearing represent the proportion of the population receiving that policy. Testing represents the amount of tests available per day, by test type. Mask efficacy represents the percentage reduction in infection probability in an interaction. Social distancing represents the percentage reduction in contacts for each social setting. Across our three calibration scenarios, we estimate slightly different baseline values for mMask wearing and social distancing, which are displayed here. The parameters displayed here may be combined with Table S2, Supporting Information for a full characterization of the model parameters.

Policy	Baseline	+	++
Vaccination			
Ages 18+	0.73	0.73	0.73
Ages 12–17	0.54	0.73	0.73
Ages 5–11	0.15	0.15	0.73
Ages 0–5	-	-	0.15
Boosting	0.2	2×	4×
Testing			
PCR	1.9 million	2×	5×
Antigen	20 million	2×	4×
Mask efficacy			
Against infection	40	-	57
Against transmission	60		76
Mask wearing			
	Best fit: 41	-	70
	Tractable strain: 33.5		
	High immune escape: 36		
Social distancing (Work, school, community)			
	Best fit: 0.10, 0, 0.20	0.35, 0.30, 0.30	0.60, 0.60, 0.50
	Tractable strain: 0.10, 0, 0.15		
	High immune escape: 0.15, 0, 0.20		

2.8. Epidemiological Counterfactuals

Finally, the results of policy interventions were explored to study the Omicron wave if a different variant of SARS-CoV-2 had become dominant, for example, one that could evade immunity more effectively than Omicron or was even more contagious. In this way, insight can be gained into whether or how policy impacts might differ against a future variant of the virus.

In these runs base transmission rates 0.09, 0.2 (the calibrated baseline value from the Best Fit calibration), and 0.55 were chosen, which corresponded to R_0 values of 6, 8, and 10.

2.9. Computational Implementation

TRACE-Omicron was programmed in Python 3.9. 88 128 000 model runs were conducted exploring 46 080 parameter combinations. Computations were performed, in part, on the Vermont Advanced Computing Core and the Washington University Scientific Compute platform. Source code of TRACE-Omicron is available on a public repository.

3. Results

3.1. Retrospective Analysis

Given that TRACE-Omicron achieves generative sufficiency in recreating the number of infections during the Omicron wave, we analyze what policies may have mitigated the spread of COVID-19 if implemented prior to or during the Omicron wave of late 2021 and early 2022. A sample of policy interventions are summarized in **Figure 4**. Our analysis shows multiple policy options allowing for significantly lower rates of cumulative infection and peak surge levels during the Omicron wave than baseline. In particular, policies such as social distancing ++, mask wearing ++ and mask efficacy ++, mask efficacy ++ and social distancing +, and mask wearing ++ and boosting ++, all reduced simulated cumulative infections by 40% or more. We also observe combinations of less disruptive policies that project similar reductions in infection to mass social isolation policies, which are effective but socially disruptive.

Selecting optimal policies depends not only on acceptable cost but on the choice of metric to evaluate the impact of these policies. The total size of the wave as a number of cases and the height of the epidemic peak are not fully correlated. While the ultimate goal may be to reduce the total number of cases, doing so without exceeding a threshold of concurrent cases that overwhelms the healthcare system is often a priority for policymakers. Notably, the combination of mask wearing ++ and mask efficacy ++ policies are a close second to strong social distancing in terms of limiting the total number of cases, yet the combinations of these strong masking procedures better reduce the peak of the wave compared to social distancing alone. They might therefore be preferred to lighten the load on the healthcare system. Conversely, a combination of mask wearing ++ and boosting ++ achieves a similar epidemic peak as strong social distancing alone, but leads to a longer wave with more total cases (**Figure 5**).

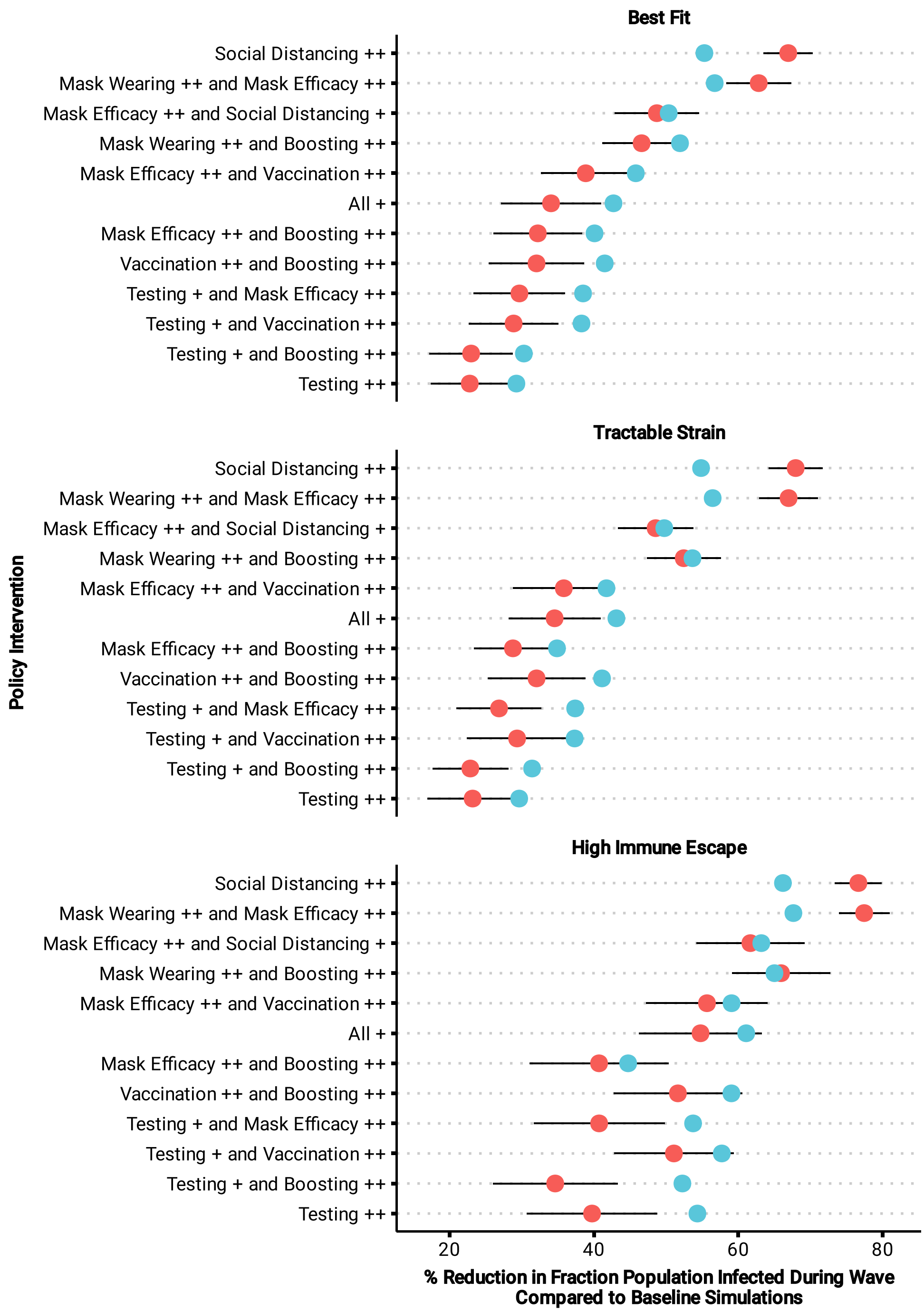

Figure 4. Summary of selected policy interventions across baseline scenarios. Red dots represent the average percentage reduction from baseline in cumulative infections (with 95% confidence intervals), and blue dots represent the maximum number of infected agents at one time across model repetitions.

3.2. Synergistic Effects

Our results also show the potential for synergistic policy effects: combinations of increased use of high-quality (e.g., N95) masks and increased testing were estimated to be about as effective and increased vaccination and booster uptake. Vaccinating children under 18 at the rate of adults would have also been estimated to largely decrease disease spread. Both boosting and vaccination policies were even more effective when combined with other policies, such as masking or testing.

To further explore policy synergies, combinations of vaccination, boosting, testing, and masking policy strategies for our best fit are displayed in **Figure 6**. Additional heatmaps are available in Supporting Information. In each heatmap, every 3×3 matrix

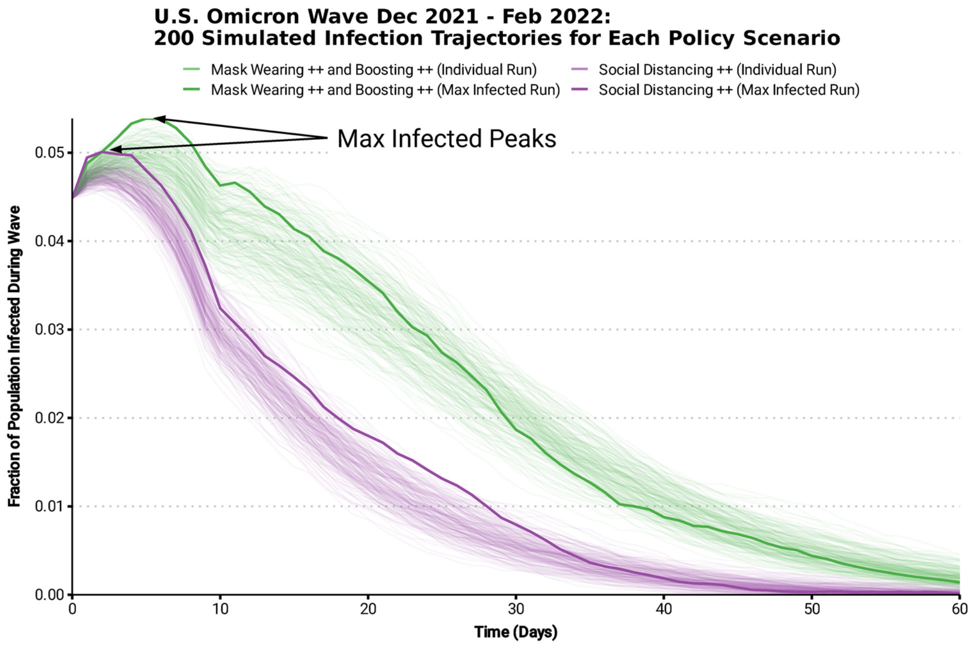

Figure 5. Comparison of boosting ++ and mask efficacy ++ versus social distancing ++ under best fit calibration. The highlighted curves represent the model runs resulting in the maximum number of infected agents at one time.

(sub block) represents a specific combination of social distancing policy (top) and masking policy (right hand side). In each of these sub blocks, cells represent a given combination of vaccination policy (bottom) and boosting policy (left hand side).

Overall, the best fit results shown in the heatmap suggest that it is possible to achieve large-scale reductions in COVID-19 infections through multiple means. This includes policies with no increases in social distancing or quarantine adherence, even without increasing policies to the highest levels we simulated in TRACE-Omicron. More specifically, 49 of 108 available policy interventions would have decreased cumulative infections by 50% of infections observed at baseline.

Mixtures of several policies can substitute, or even outperform large increases in individual policies. Individually, boosting ++, vaccination ++, and testing ++ on their own lead to cumulative infection reductions from baseline of 16% (cell J1), 22% (cell L3), and 23% (cell L7), respectively. A mixture of all 3 policies at lower intensities (boosting +, vaccination +, tests +) resulted in a simulated cumulative infection reduction of 23% (cell K5), as good or better than any of the larger intervention scenarios alone. Supplementing this policy mixture with mask wearing ++ or mask efficacy ++ resulted in simulated cumulative infection rates of 51% (cell E5) and 37% (cell H5), respectively. Overall, notice how in each 3×3 matrix, the middle cell representing a mixture of policy interventions is better than the top left corner representing doing more of one policy and not increasing others. Mixtures of policies outperform policies focused on one intervention specifically.

3.3. Specific Effects: Masking and Timing

Digging into specific policies, we find that masks, especially high-quality ones, remain powerful tools in mitigating disease spread. Simulated cumulative infection rates under all mask wearing ++ and mask efficacy ++ scenarios were reduced on average by 63% (cell C1) representing a substantial reduction from baseline. We also present the results of a time-series comparison of a mask-focused policy versus baseline in **Figure 7**. We see that the number of simulated infections, the rate at which agents are infected, and the variance of model simulation outcomes, are all much lower under a policy intervention with high proportions of effective masking.

The timing of policies is also crucial for pandemic response. In **Figure 8**, we investigate the impact having a higher boosted population prior to the start of the omicron wave (boosting ++), along with an additional comparison line which adds, in addition to this preventative measure of a higher boosted population, the marginal effect from the reactive policy measure of increasing vaccine and booster distribution rates after the start of the Omicron wave (boosting ++ and rollout ++). We find that pandemic preparedness (i.e., the proportion boosted before an outbreak) to be the more important factor in reducing simulated cumulative infections compared to ramping up boosting and vaccination efforts after disease spread has already begun.

3.4. Robustness under Alternate Baselines and Epidemiological Counterfactuals

The results highlighted above are generally robust under a suite of different calibration baselines, but there are key differences worth highlighting in the high immune escape scenario. Mainly, with high immune escape, we find that most policies are much more effective, especially social distancing ++ as well as the combination of mask wearing ++ and mask efficacy ++. This result can be explained by the fact that if the Omicron wave

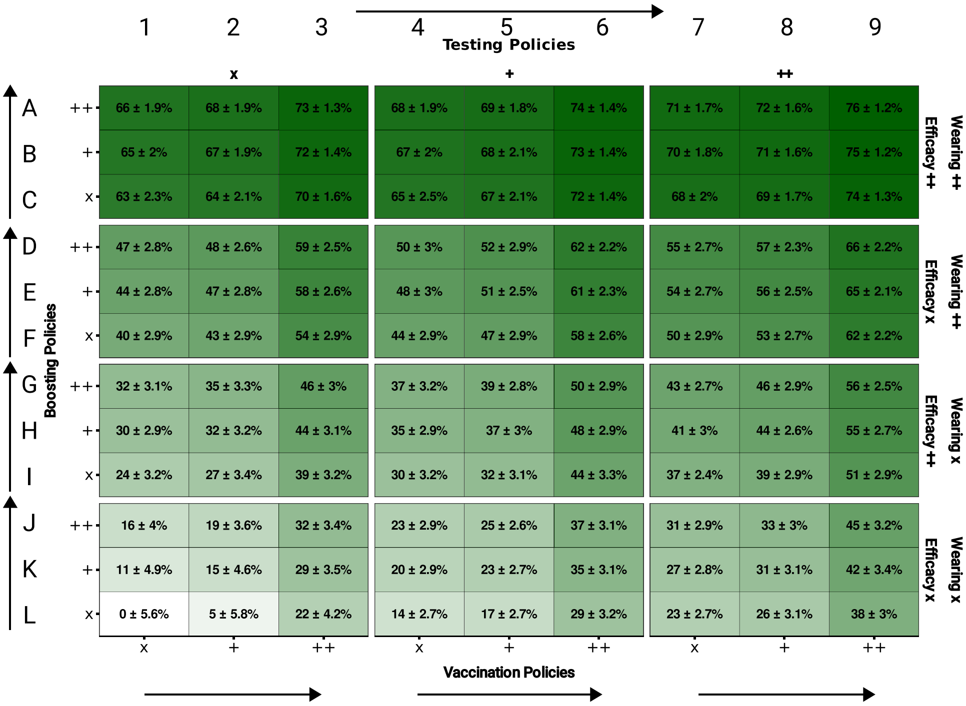

Figure 6. Summary of policy intervention landscape under the best fit baseline. Cells represent the average percentage reduction from baseline in cumulative infections (with 95% confidence intervals). All simulations shown hold social distancing policies (remote work, school closure, and community distancing) to their baseline levels. Magnitudes of policy interventions are described in Table 2.

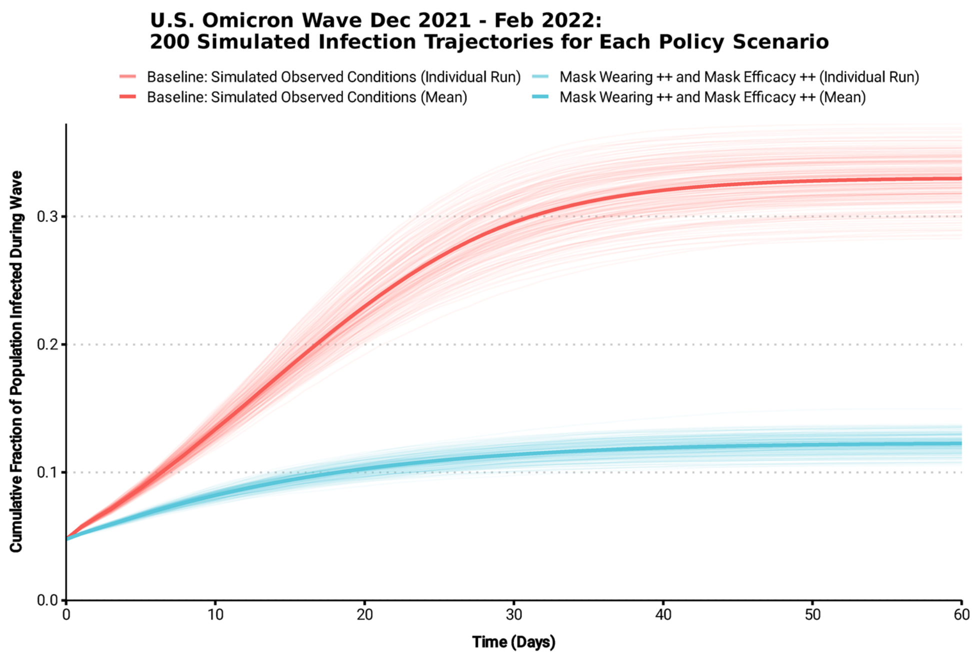

Figure 7. Comparison of a mask-focused intervention (mask-wearing ++ and mask efficacy ++) to baseline under best fit calibration.

featured a high immune escape rate, then its susceptible pool would have been effectively much larger than expected and its effective transmission rate lower and easier to control. Following the same logic, we actually see an increase in the importance of vaccination under a high immune escape rate. This might appear paradoxical but it is again due to the reduction in natural learned immunity in the population. As a caveat, it is also worth noting that all scenarios under the high immune escape scenario produce larger confidence intervals, further confounding our ability to produce a simple ranking of policy combinations.

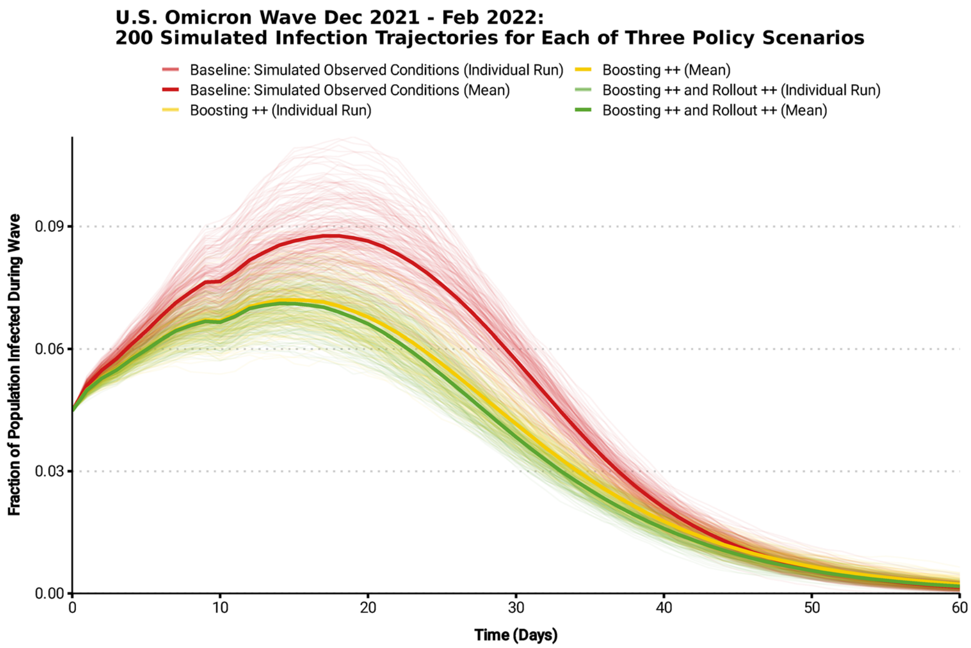

Figure 8. Comparison of baseline, vaccination ++ and boosting ++, vaccination ++ and boosting ++ and rollout ++ under best fit calibration.

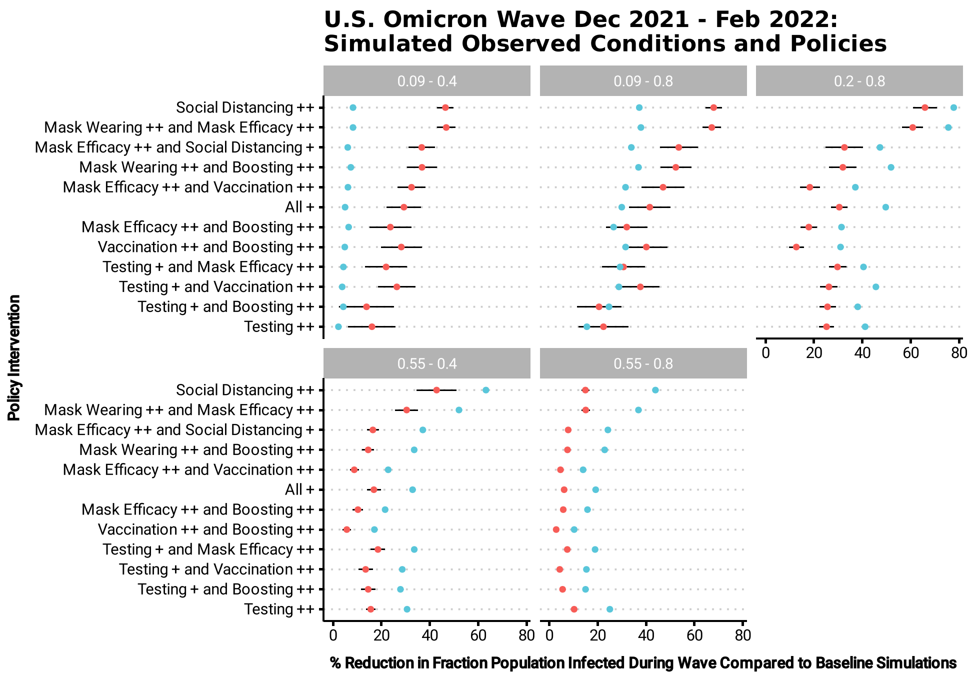

Figure 9. Summary of selected policy interventions by epidemiological scenario (base transmission and immune escape rates) using best fit as baseline. Red dots represent the average percentage reduction from baseline in cumulative infections (with 95% confidence intervals), and blue dots represent the maximum number of infected agents at one time across model repetitions.

Despite the remaining uncertainty in the epidemiological conditions of the early Omicron variants, our comparison across the alternate baselines suggests a consistent encouraging message that given proper preparation, variants like Omicron can be mitigated. However, our concerns extend beyond Omicron-like variants. In addition to our policy counterfactuals, we also analyzed epidemiological counterfactuals, simulating the same policy interventions under scenarios alternate to the observed Omicron wave in immune evasion and transmissibility.

Our key findings (**Figure 9**) are that while the overall effectiveness of policy interventions changes under different epidemiological scenarios, the rank-ordering of these policies is largely unchanged. In particular, increased levels of effective mask-wearing are nearly as effective at reducing cumulative infection as large increases in social distancing. These interventions are also much more effective at reducing the maximum number of infected agents at one time, especially for more pessimistic epidemiological scenarios (with high virus transmission and immune escape). Under the two most pessimistic scenarios, we observe that vaccination and boosting focused strategies alone are the least effective among the selected policy interventions at lowering cumulative infections. This is due in part to lower baseline levels of vaccination and boosting in the United States, as well as the waning effectiveness of vaccines against infection.

However, small increases in all policies (All +) can still outperform large interventions focused on one of two policies. This is especially apparent in the scenario with a more transmissible variant with the same estimated levels of immune escape, where the All + scenario is the fourth most effective policy, in contrast to being the sixth most effective at baseline.

Further analyses of the epidemiological counterfactuals are available in Supporting Information.

3.5. Summary

Altogether, we find that ranking of potential policies is a complex task. First, the expected effectiveness of a policy will depend on our current knowledge on the incoming wave, as shown by our epidemiological counterfactuals, especially in those parameterizations with high immune escape. Second, we found that the effectiveness of a policy depends on the synergies between the numerous possible pairings of interventions. Third, the rankings also depend on the preferred metrics of intervention outcomes, or combinations thereof. We here analyzed our results based on multiple combinations of interventions and two key metrics, total cases and epidemic peaks. Despite these complexities, TRACE-Omicron proved a useful tool for generating actionable insights, and we identified several consistent themes across all of the scenarios explored. We find that testing-based strategies alone will likely not be sufficient to contain disease spread, vaccination-based policies are most effective when implemented ahead of time rather than in response to disease spread, and mask-based policies, which can be deployed quickly, tend to be highly effective. Underlying all these analyses, we also see the effectiveness of mixtures of policy interventions, which often outperform aggressive individual policy increases. We make our complete database of simulation runs available in the hope of encouraging further analysis of the complex interplay between policy combinations and epidemic dynamics.

4. Discussion

TRACE-Omicron was designed and analyzed to estimate the effects of policies had they been implemented in late 2021 or early 2022. Given that the emergence of the Omicron variant produced a severe wave of cases in a vaccinated population, studying the impact of putative response strategies that might have been deployed can provide useful insights in advance of future waves. As of early Fall 2022, less than 15% of Americans have received the newest booster.[62] Mask wearing is less common than it was before the Omicron wave.[74] On the positive side, the Omicron wave resulted in a large increase in the frequency of use of at-home tests.[75]

Our results provide an important path forward in considering the implications of these behavior shifts and policy possibilities for protecting against future waves. We outline, promisingly, how a number of different mixtures of policies can be quite effective—even outperforming large interventions focused on one policy. One such policy that particularly underperforms when used alone is vaccination. Even a massive speedup to the (already historically fast) vaccination pipeline that would have been necessary prior to Omicron to be able to vaccinate young children, and to vaccinate older children and teens at the rate of young adults, still only reduced outbreaks in our model by less than a quarter in the “best fit” and “tractable strain” scenario and while better, perform near the worst of any solo extreme strategy in the “high immune escape” scenario. However, in combination with or in place of vaccines, there are several combinations of alternate strategy suites which yield lower outbreak sizes. This is fortunate in the wake of recent concerns over rapidly evolving variants[76] outpacing vaccine advancements as well as vaccine uptake.[77]

That is not to say however, that vaccination is not critical for controlling this disease, as studies show that vaccinations significantly reduce serious complications and deaths.[78] Current discussions in this work were focused on the number of cases during the Omicron wave, both in total and at its peak. It is thus an important limitation that we do not directly model severe disease and mortality which are increasingly becoming the key indicator of policies. Even then, the number of cases remains the key output as other metrics like mortality could be extracted by using an appropriate stratified risk of complications. However, some important outcomes such as long COVID or severe post-COVID conditions are still too poorly understood to be modeled directly in this fashion. And current science shows that risks of such complications increase with repeated infections.[79] Without accurate models for individual risk of complications, we will continue to report cases as the main output of TRACE-Omicron.

Like all epidemiological models, TRACE-Omicron utilizes necessary simplifications, and cannot fully express all aspects of human behavior and interaction. Specifically, TRACE-Omicron does not model social influence on policy adoption. For example, it is well-known that mask-wearing in the United States has been a divisive issue, and differs across social and demographic groups.[80] We also do not model treatment of COVID-19, specifically therapeutics under Emergency Use Authorization in the United States such as Paxlovid, since these were not widely available during the Omicron wave and were only recommended for a subset of the population.[81] Finally, we do not model competing variants or viral evolution in TRACE-Omicron.

The range of potentially equally effective mixed strategies which avoid socially disruptive lockdowns is promising from an economic and policymaking standpoint. We identify sets of direct substitutes with quantitative equivalency in epidemiological containment; these could be analyzed further from the perspective of economic or social cost, equity concerns, or policy constraints. To further this goal, we provide, as open data, the complete set of 88 128 000 model runs with daily agent state counts, including

46 080 policy combinations (a subset of which are covered here) that can be used for systematic analyses of economic or social cost (see Data Availability). Additionally, the computational laboratory our open-source code provides can be used for analyses of more specific or more extreme parameterizations not included in our dataset.

TRACE-Omicron also offers substantial scope as an extensible framework for future research, due to the agent-based, object-oriented, modular nature of the contagion dynamics, population, and policy representation. Additional dynamics can be added to study multiple contagion systems like the current epidemics of COVID-19, influenza and respiratory syncytial virus (RSV),[82] or multiple competing variant systems. Given accurate data, any number of demographics can be included in our representation of the population, as well as correlations between demographics and behavior (e.g., compliance) or risk (e.g., RSV in young children). Additional policies can be simulated. This includes policies which could take advantage of the site-based framework of the population (e.g., ventilation system infrastructure),[83] as well as policies which take advantage of the network aspect of the contact structure such as network-informed targeted immunization strategies.[84,85]

The individual-level granularity of our ABM design, coupled with additional demographic input data, presents an opportunity to take health equity into consideration when weighing future response strategies. The negative impact of COVID-19 in the United States has been greatest for those from racial and ethnic minority groups.[86] We provide a powerful tool for policymakers who wish to prevent those inequitable patterns being repeated during future pandemic waves. For example, although social distancing might be protective overall for the population, future model application can be used to determine whether and to what extent exposure risks borne by "frontline" workers who cannot work remotely[87] might nonetheless drive disturbing racial disparities in harm.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.7857351, https://doi.org/10.5281/zenodo.7857483, https://doi.org/10.5281/zenodo.7857519, https://doi.org/10.5281/zenodo.7857553 reference numbers 7857351, 7857483, 7857519, 7857553.

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