Predicting the Effects of Waning Vaccine Immunity Against COVID-19 through High-Resolution Agent-Based Modeling

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The potential waning of the vaccination immunity to COVID-19 could pose threats to public health, as it is tenable that the timing of such waning would synchronize with the near-complete restoration of normalcy. Should also testing be relaxed, we might witness a resurgent COVID-19 wave in winter 2021/2022. In response to this risk, the administration of an additional vaccine dose, the booster shot, is being implemented worldwide. Here, in a projected study with an outlook of six months, we explore the interplay between the rate at which boosters are distributed and the extent to which testing practices are implemented, using a highly granular agent-based model tuned on a medium-sized U.S. town. Theoretical projections indicate that the administration of boosters at the rate at which the vaccine is currently administered could yield a severe resurgence of the pandemic, even worse than the first wave experienced in spring and summer 2020. Our projections suggest that the peak levels of mid spring 2021 in the vaccination rate may prevent the occurrence of such a scenario. Our study highlights the importance of testing, especially to detect infection of asymptomatic individuals in the very near future, as the release of the booster reaches full speed.

1 Introduction

Winter and spring 2021 marked a long-awaited massive vaccination campaign against COVID-19, starting approximately one year after the inception of the outbreak. As of the mid-September 2021, 42.6% of the World and 63.8% of the U.S. population took at least one dose of the vaccine, while 30.8% and 54.5%, respectively, are fully vaccinated.[1] However, approaching fall 2021 brings to light a new unknown: the possibility of waning vaccination immunity and the consequent need for an additional vaccine dose —the booster shot.[2] There is evidence that the booster shot would not only restore the original protection, but would also enhance people's immunity against the most recent variants, including the widely dominant and highly transmittable Delta variant.[3, 4] Many countries, including the U.S., are starting their re-vaccination campaigns, in an attempt to prevent new outbreaks accompanied by socially and economically disastrous restrictions.[3, 5, 6]

In the original (August 2021) schedule of booster shot administration by the U.S. Centers for Disease Control and Prevention (CDC), the booster campaign was expected to start on September 20$^{\text{th}}$, 2021, with booster shots available to all the adults in the U.S. eight months after they took their second vaccine dose, with plans for expansion to people taking the one-dose Johnson&Johnson vaccine.[2] At the same time, despite a surge in new infection cases[7] and the nationwide dominance of the Delta variant,[8] non-pharmaceutical interventions (NPIs) are gradually being relaxed,[9] and preparations for a return to full-time in-person education and work are underway.[10, 11] Following mass vaccinations, COVID-19 testing is continuously reduced,[12, 13] with the enforcement of mandatory testing slowly abandoned by public health authorities[13] and contact-tracing home-isolation no longer required for fully vaccinated individuals;[9, 14] not to mention the ongoing trend in encouraging indoor gatherings (e.g., restaurants, bars, gyms) for the fully vaccinated. In this evolving scenario, scientifically backed policy-making is of paramount importance.

Mathematical modeling has played a key role in assisting public health authorities to combat the COVID-19 pandemic.[15, 16] Since COVID-19 onset, mathematical models are being routinely used to forecast the course of the pandemic and guide policymakers' decisions on several chief issues, including the enforcing of NPIs,[17, 18, 19, 20, 21] the design of testing policies,[22, 23] the implementation of contact tracing,[24, 25, 26, 27] and the implementation of vaccination campaigns in light of the concurrent uplifting of NPIs.[28, 29, 30, 31, 32, 33, 34, 35]

Mathematical modeling can also play a critical role in the present scenario, where vaccine-induced immunity seems to be waning,[36, 37, 38, 39] testing coverage is being lowered,[12, 13] and a booster shot campaign is going to be implemented.[2] The interplay of these critical issues has received only limited attention so far. Layton et al.[4] have simulated the emergence of new virus strains, including hypothetical deadlier variants in Ontario, Canada, in light of realistic vaccination and booster campaigns implemented in the region. Their results, projected until the end of 2021, point out the need of vigilance and readiness to reinstate severe NPIs, as well as the possible importance of a large-scale campaign of booster shots. Over longer time horizons, other studies have been carried out to evaluate the potential benefits of annual re-vaccination campaigns against COVID-19. In particular, Song et al.[40] have simulated different scenarios in the loss of immunity, spanning until 2029. Their findings indicate that an annual re-vaccination campaign could avoid future COVID-19 outbreaks if the vaccine is sufficiently efficacious and provides at least six months of protection. Sandmann et al.[41] have compared the economic burden of introducing a regular vaccination program in the U.K. to the cost associated with implementing social distancing measures for the next decade. Their work highlights the benefits of re-vaccination schemes, evidencing that they would allow to avoid large outbreaks and consequent restrictions. Lastly, Li et al.[42] have compared different re-vaccination strategies in 15 countries over the next 20 years in terms of long-term efficacy. Their findings identify a public health benefit in alternating re-vaccination between fragile older strata and highly active portions of the population, who habitually generate a high number of contacts.

Although conclusive evidence on the waning immunity of the vaccine and on its timing is yet to be established,[36, 37, 38, 39, 43] these studies offer an improved understanding of the potential benefits of re-vaccination campaigns for a range of possible waning profiles. Yet, this knowledge does not immediately translate into predictions on the short-term roll-out of booster shots, which could be critical in shaping the future of the pandemic. Moreover, the long-term predictions of most of these studies are limited to coarse-grained considerations, which cannot take into account granular details of the population.

Here, we fill in this gap by providing a systematic study of the effectiveness of a re-vaccination campaign in the ongoing 2021–2022 fall/winter season, considering as key factors the rate of administration of booster shots and the population coverage of testing policies imple-

mented during this phase. We perform our study by means of a high-resolution agent-based model (ABM), which faithfully provides a one-to-one digital reproduction of a real, medium-sized U.S. town. As a test case, we simulate COVID-19 spreading in the town of New Rochelle, NY, for the next six months, expanding on our previous efforts published in previous issues of this journal.[23, 34] The town of New Rochelle is chosen as a representative medium-sized US town, characterized by high levels of diversity and inequality.[44, 45] The digital town closely mirrors the geography and demographics of the actual one, including household distribution, lifestyles, and mobility patterns of its residents, thereby incorporating the diversity of its population and potential inequalities across its fabric. The progression model is expanded to include salient features of the predominant Delta variant,[8] booster shot campaign, and co-existence of three vaccines (Johnson&Johnson, Pfizer, and Moderna) providing different levels of protection over time, with a gradual waning immunity. The level of detail in the model allows us to closely study the combined effect of booster shot administration and testing practices in this stage of the pandemic. The study was designed based on information about the pandemic gathered during summer 2021; some of the original design assumptions have changed during the first part of fall 2021,[2] These changes have prompted new simulation studies, which show robustness of our findings and are included as part of Supporting Information.

2 Computational framework

Our computational framework consists of two components: a detailed database of the town of New Rochelle, NY, and a high-resolution ABM that reproduces the spread of COVID-19 at a one-to-one granularity level that includes mobility patterns among households, schools, workplaces, and non-essential locations (including leisure locations).

The database of the town contains geographical coordinates of every building, residential and public. Public buildings include governmental institutions and private companies of any kind, open to the general population —the public. The database includes any workplace and non-essential locations, identified using SafeGraph,[46] explicitly distinguishing schools, retirement homes, and hospitals. Town population is recreated using U.S. Census data on residents age, household and family structure, education, and employment char-

acteristics. Residents can work and gather in New Rochelle, and in its vicinity, including New York City. They commute to work via common means such as public transit, cars, or carpools, and visit each other in private.

Each resident of New Rochelle is mapped into an agent in the ABM, resulting in 79,205 agents. In the ABM, agents are characterized by a health state that can change according to a disease progression model detailed in the following, and they can take two types of tests — safe, contact-less car tests, and more risky ones performed in a hospital. If infected, agents may undergo three types of treatment — home isolation, routine hospitalization, and hospitalization in intensive care unit (ICU). The ABM was originally proposed in Truszkowska et al.,[23] while a later extension of the work incorporated a simplified version of the vaccination campaign.[34] Details on the generation of the synthetic population can be found in Section 2 of Truszkowska et al..[23]

For this projective study, we tailored the ABM to capture the scenario as of fall 2021, thereby introducing realistic and time-dependent vaccination effects, booster shots, increased mobility of fully vaccinated agents, and CDC-compliant contact-tracing measures.[14, 47, 48] In the following, we detail these new features. For details on the other features of the model, the reader should refer to our previous publications.[23, 34] Figure 1 schematically illustrates major components of our computational framework.

2.1 COVID-19 progression model

In our model, all the agents who are not infected, with exception of those recently recovered, are susceptible to COVID-19. Once infected, agents can undergo testing and treatment. Agents who are not symptomatic can get vaccinated, and anyone can be contact-traced and home-isolated.

The progression model is shown in Fig 2. A susceptible agent (S) can be vaccinated (S_v), may be home isolated, irrespective of their vaccination status, as a result of a home-isolation order due to a contact with an agent with a confirmed COVID-19 infection (I_{CT}). Isolation may also be triggered if a susceptible agent has COVID-19-like symptoms due to some other disease, such as seasonal influenza (I_{Hm}). Agents can be tested, via one of the two available testing types, in a car (T_c) or in a hospital (T_{Hs}). The former type is considered contact-less and safe, while the latter carries infection risks. Complete details on testing

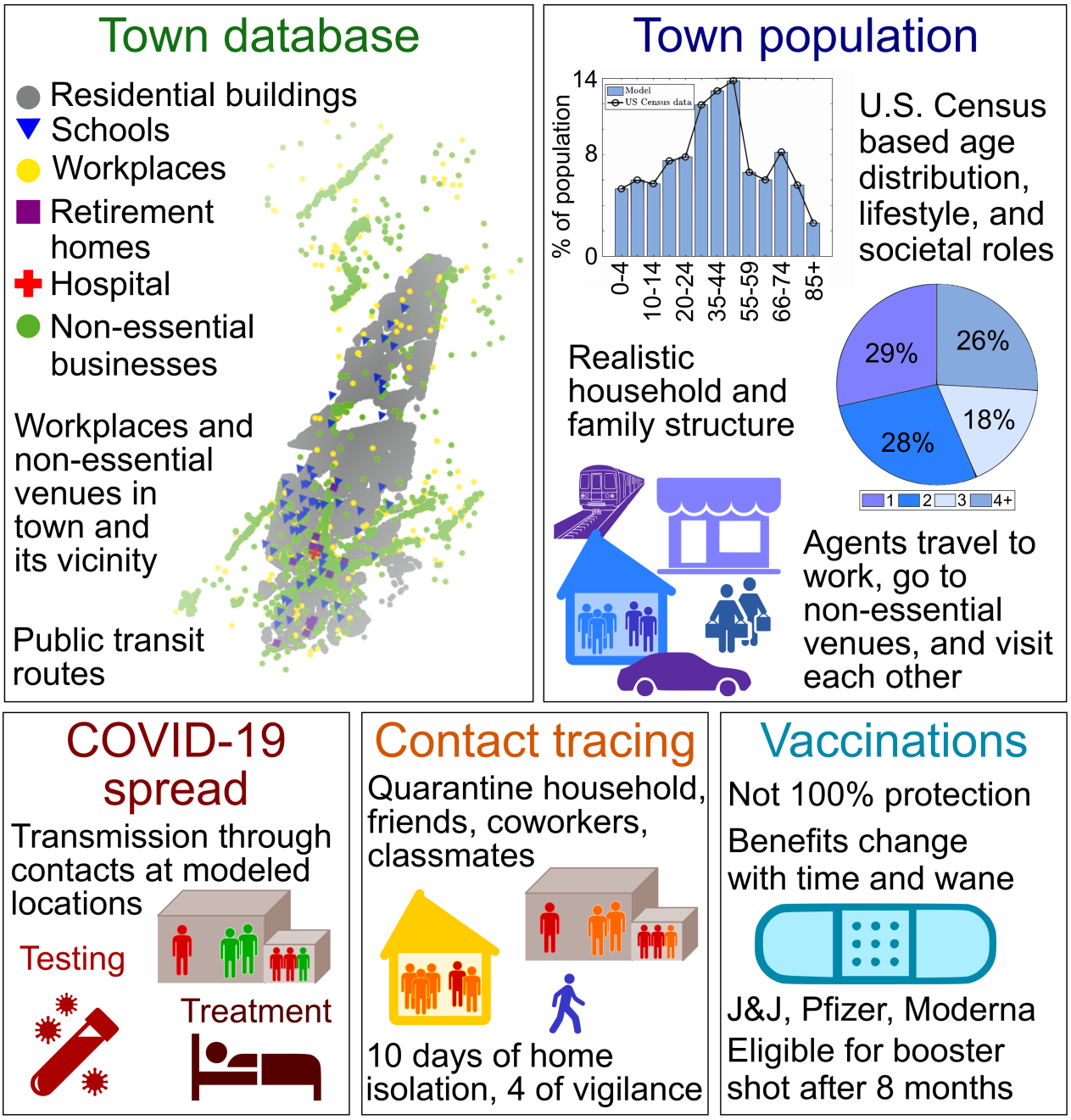

Figure 1: **Schematic outline of the ABM computational framework.** The database of New Rochelle, NY, includes geographical information of every residential and public building in the town. It also incorporates workplaces and non-essential venues in the area as many town residents work outside of town and some frequent non-essential locations locations in its vicinity. Each resident is represented as an agent. The population faithfully mirrors the sociodemographic profile of the actual one. The top-right panel shows the age distribution of agents, as registered in the U.S. Census data. The pie chart represents the percentage of households with the indicated size, also in close agreement with the Census (values omitted for clarity). COVID-19 spreads through contacts at different locations associated with the agents, and infected agents can be tested and treated. Positive test result triggers contact tracing, resulting in CDC-compliant home-isolation of potentially exposed individuals. Finally, the platform models imperfect, realistic vaccines, which grant a number of benefits, and wane with time. After eight months, vaccinated agents become eligible for an additional vaccine dose, the booster shot.

procedures and the corresponding parameters are outlined in our two previous works.[23, 34]. Specifically, we refer to Section 3.3 of Truszkowska et al.[23] for more details on the testing procedures and to Table S4 in the Supporting information of Truszkowska et al.[34] for updated parameters.

Susceptible individuals may become infected upon interactions with infectious individuals who are in the same building. The same building may have a role in multiple spreading pathways; for instance, a school provides pathways of infection between students, and students and teachers, but it is also the workplace for its teachers. Infections occur according to a probabilistic mechanism that accounts for differences in infection probability with respect to the characteristics of the location and the number, role, and symptomatic state of infectious individuals in the location, as detailed in Truszkowska et al.[23, 34] (see the Supporting Information for more details and precise references). Specifically, following Ferguson et al.,[49] we assumed that symptomatic individuals are twice as much likely to transmit the disease than asymptomatic and pre-symptomatic individuals. For non-essential locations, like leisure ones, we neglect spreading between employees and visitors, while retaining spreading within the two groups. This choice was motivated by the enforced use of personal protective equipment and social distancing toward minimizing contagions between employees and customers.

Upon infection, a susceptible agent becomes exposed (E), not showing symptoms of the disease. The exposed agent can also get vaccinated (E_v) as long as their infection status is not known. Even without any symptom, exposed agents can be tested and home isolated. Agents can either recover after being asymptomatic (R), or develop symptoms after the latency period and transition to the symptomatic state (Sy). Symptomatic agents cannot get vaccinated, which is also the case for agents with symptoms similar to COVID-19 due to another disease. However, vaccinated agents can become symptomatic as a result of an infection (Sy_v), potentially leading to milder symptoms.

Agents with symptoms can test and subsequently receive treatment through home isolation (I_{Hm}), normal hospitalization (H_N), or hospitalization in an intensive care unit, ICU (H_{ICU}). Agents can either recover or die (D). Symptomatic and exposed agents can also get contact traced, and home isolated on that account. A contact-traced symptomatic agent will undergo treatment regardless of their testing status. Recovered agents are temporar-

ily immune to COVID-19 and, after a certain period of time, they can also be vaccinated. Once their natural immunity is lost, these agents transition to the vaccinated susceptible category (S_v). Recovered agents who do not receive the vaccine spontaneously lose natural immunity after a fixed period of time. Based on some (possibly conservative) estimations,[50, 51, 52, 53] in our simulations we fixed such a period to six months. Additional simulations to assess the robustness of our findings with respect to different duration of natural immunity (loss of natural immunity after four or eight months) are reported in the Supporting Information (Figs. S5–S6).

Contact-traced agents cannot be vaccinated, and even if susceptible; they become vaccine-eligible only after some period of time. These restrictions hold for the booster shots as well. All the parameters that characterize the transitions in the COVID-19 progression model are listed in Table S4 in the Supporting Information. An explicit expression of the contagion probability for each agent i, $p_i(t)$, depending on the agent's characteristics (including lifestyle, workplace or school, household in which they live) can be found in our previous publications (see Section 4.4 of Truszkowska et al.[34]). The main elements of novelty of the present modeling extension include realistic treatments of the effect of vaccination and contact tracing and are detailed in the following.

2.2 Vaccinations

An agent can get vaccinated with one of the three vaccine types distributed in the area according to their availability. We considered one vaccine mirroring the one-dose Johnson&Johnson (abbreviated as J), and two vaccines with the characteristics of the two-dose Pfizer and Moderna vaccines (abbreviated as P and M, respectively). The probability of being administered a given vaccine type was computed based on data collected manually on actual vaccine offer in the town, as of late July 2021, see Table S5 in the Supporting Information.[54]

Once agent i is vaccinated, five of the model parameters related to the individual are modified accordingly. Specifically, four quantities decrease upon vaccination: (1) the probability of being infected by SARS-CoV-2, (2) the transmission rate if infected, (3) the probability of requiring hospitalization, and (4) of dying if infected. Conversely, (5) the probability of being asymptomatic when infected increases upon vaccination.

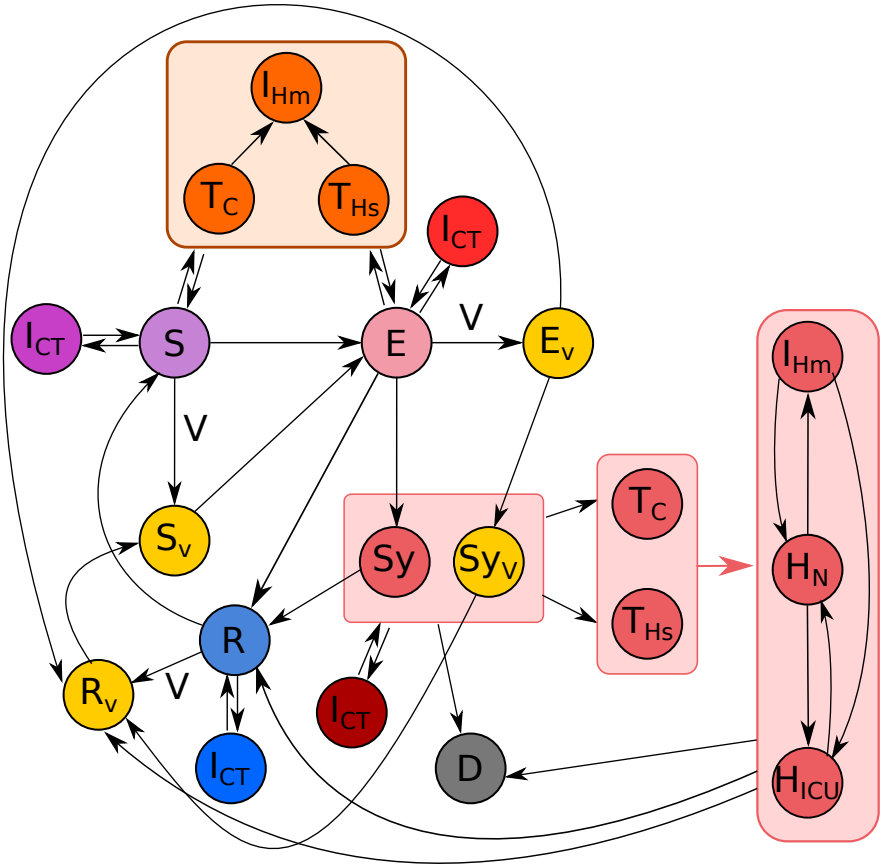

Figure 2: **Diagram of the COVID-19 epidemic progression.** Agents' health states are susceptible (S), exposed (E), and symptomatic (Sy). Since a vaccination does not grant 100% immunity, and exposed agents can be vaccinated, the progression distinguishes those three health states in their vaccination version, S_v, E_v, and Sy_v. Susceptible and exposed agents can be tested and home isolated (I_{Hm}). Testing can take place in a contact-less form in a car (T_c) or in a hospital (T_{Hs}). All the agents can be subject to contact tracing and subsequent home-isolation (I_{CT}). Exposed agent may recover without ever developing symptoms (R), or become symptomatic after a latency period. Symptomatic agents can undergo testing and subsequent treatment through home isolation (I_{Hm}), normal hospitalization (H_N), or hospitalization in an intensive care unit, ICU (H_{ICU}). They can either recover or die (D). A recovered agent, if not already vaccinated, can vaccinate as well (R_v). Recovered agents are temporarily immune to the disease and after some period of time they become susceptible again, regardless of their vaccination status.

To model such a temporal effect, for each vaccine $\alpha = J, P, M$ and for each model parameter $k = 1, \ldots, 5$, we introduce a function $\gamma_{\alpha,k}(s)$, which models the effect of vaccine α on parameter k as a multiplicative coefficient, s days after vaccine administration. As an example, the probability of COVID-19 infection $p_i^v(t)$ for agent i vaccinated with vaccine α at time t_i is reduced compared to the original probability in the absence of vaccination $p_i(t)$ to

$$p_i^v(t) := \gamma_{\alpha,1}(t - t_i)\, p_i(t)\,. \tag{1}$$

Similar expressions can be written for the other four properties (see the Supporting Information for more details).

The shape of these functions is estimated from efficacy data on vaccines. Specifically, they are all defined as piece-wise linear functions. For the one-dose vaccine, they increase up to their most favorable values two weeks after the shot (smaller than one for property $k = 1, \ldots, 4$ and greater than 1 for property 5). In case of two-dose vaccines, the functions linearly interpolate efficacy values collected at the time of the first shot, of the second one, and at the attainment of full immunity. The second dose is always contemplated in the model, following local vaccination campaign that sets the appointment for the second shot at the time the first shot is administered, one month later.[55] The peak benefits for all three vaccine types last for an eight-month period following recent studies on the humoral and cellular immune responses.[37, 36] In this period, the functions have a constant value.

The scientific community has not yet reached consensus on the duration of such period. Studies by Barouch et al.[36] and Colliet et al.[37] provide only a lower-bound on it, whereas some preliminary analyses based on epidemic data collected over summer 2021 in countries with fast vaccination campaigns (for instance, Israel and Qatar) suggest shorter duration of peak-level immunity.[38, 39] To strengthen the robustness of our claims, some parametric studies encompassing different timings of the waning vaccine immunity (six and 10 months) and a delay in the effect of the vaccine are considered and discussed in the Supporting Information (Figs. S3–S4 and S9).

Once the peak-benefit period is over, benefits start to gradually wane, yielding a gradual loss of immunity. Here, we assume that such an immunity is totally lost over the course of the following six months. This is modeled by letting the functions $\gamma_{\alpha,k}$ linearly approach 1, over a period of six months.

Following the original CDC guidelines, we assume that people are eligible for booster shots starting from eight months after their second vaccine dose.[2] We hypothesize that the booster shot restores peak vaccination benefits in one day after its administration and beneficial effects remain constant for a period that is longer than the simulation horizon (that is, six months). The exact expressions of all the mathematical functions modeling such a phenomenon and details on their estimations are reported in the Supporting Information.
Agents 12 years and older can vaccinate. We model local vaccine hesitancy using an upper bound on the vaccination coverage in the town. Specifically, no more than 64,364 people are considered as eligible for vaccination (approximately the 81% of the population), computed as a projection based on the temporal evolution of the number of new vaccinations in New York State,[1, 56] re-scaled to the population of New Rochelle. An agent is considered fully vaccinated two weeks after their shot of a one-dose vaccine, or two weeks after the second shot of a two-dose vaccine. A fully vaccinated agent is more socially active, and is more likely to visit other agents or non-essential venues, as detailed in Table S4 in the Supporting Information.

2.3 Contact tracing

Contact tracing is implemented in the model by complying with local guidelines,[14, 47, 48] in accordance to their stricter version issued in winter 2021. When an agent is tested positive to COVID-19 (we contemplated a realistic quota of false positives corresponding to 5% of the tests[57]), their household members and all the agents with whom they carpool, in case this is their transit mode to work, are immediately home-isolated.
Moreover, a predetermined number of coworkers is home-isolated. To account for realistic implementation of contact tracing, we bound the maximum number of home-isolated coworkers to a given value of 10 and the same upper bound is used throughout for schools and residents. In particular, contact tracing of a retirement home employee results in home-isolating 10 residents in addition to coworkers. Conversely, a confirmed positive resident leads to home-isolating 10 other residents and employees. With respect to schools, the granularity of our model was set to the single school. Hence, contact tracing of a student who tested positive is modeled by home-isolating 10 students of the same age from that agent's school, plus one teacher. The same logic applies also upon tracing a teacher, with a ran-

dom choice of 10 same-aged students to be home-isolated.

Finally, since agents visit each other in private, we model contact tracing imposing home-isolation to the entire households visited by a COVID-19 positive agent during the course of 14 days preceding the time the agent was determined positive, according to local policies. Due to the limited supervision on restrictions to private visits, we accounted for reduced compliance, estimating such a parameter from the literature, see Table S4 in the Supporting Information.

In the model, home-isolation is implemented by placing the agent in home isolation for a period of 10 days. Afterwards, the agent continues to monitor themselves for COVID-19 symptoms for a duration of 4 days, reflecting the guidelines. If during this two-week period the agent develops COVID-19 symptoms, they are assigned to an adequate treatment, regardless their testing status. Finally, following the guidelines, fully vaccinated agents still have to home-isolate, and negative test results do not shorten the home-isolation duration.

2.4 Simulation setup

Simulations are initialized with a predetermined number of COVID-19 infected agents in the two phases of the disease, that is, exposed or symptomatic, to mimic real conditions in the town. These initial cases can be in different testing stages and undergo treatment. An initial number of vaccinated agents is also contemplated, based on the data collected from the vaccination campaign put in place between January 2021 and the start of the simulation. We assume that each of the 51,342 individuals already vaccinated at the beginning of the simulations has received their first shot in a randomly chosen day between the beginning of the vaccination campaign in January 2021 and September 7$^{\text{th}}$ 2021 (see the Supporting Information for the temporal distribution of first shots), resulting in different level of immunity at the beginning of the simulations for these vaccinated agents. In the Supporting Information, we also provide some additional simulations to show robustness of our findings with respect to different approximations of the temporal distribution of first shots (see Fig. S10).

Model parameters related to vaccinations and contact tracing are based on the literature and official releases from the CDC,[58] as detailed in the above. The characteristics of different vaccine types are based on official CDC and Food and Drug Administration (FDA)

releases[59, 60, 61, 62, 63, 64] and are outlined in detail in the Supporting Information. As indicated therein, in the absence of confirmed values, we either interpolated between the known benefit levels, or we used them for scaling. The parameters used in our contact tracing practices are also listed in Table S4 in the Supporting Information, where our assumptions on the number of contacts each agent has in their workplaces, schools, and other visited locations, are detailed. The complete parameter set and all the modeling assumptions are detailed in Table S4 in the Supporting Information.

3 Results

Our simulations projected COVID-19 spreading over a time span of six months starting from September 7th 2021. At this time, most of the town residents eligible for a vaccine had received their vaccination earlier in the year. Specifically, 51,342 residents were vaccinated with at least one dose as of September 7th 2021.[56] As the first dose was administered in January 2021, during the six-month simulation window many of the vaccinated residents would lose their immunity (see Fig. S2b in the Supporting Information). The types of the vaccines and their effects mirrored those that were distributed in the area and included the two double-dose vaccines (Moderna and Pfizer) and one single-dose vaccine (Johnson&Johnson), see Table S5 in the Supporting Information. Per the original, August 2021 CDC guidelines, an agent was set to start losing their immunity at approximately eight months after they become fully vaccinated.[2] At this time, they become eligible for a booster shot, which would restore their peak resistance to the virus, thereby immunizing again the population at the rate set by the administration. Booster shots in the model are distributed alongside regular vaccination doses. In every simulation, only a fixed number of shots can be administered each day, in the form of booster or first shots, with no particular prioritization. For example, a rate of twenty vaccines per day implies that twenty randomly chosen, eligible agents will receive their vaccine dose that day, either their first or their booster shot, according to their vaccination status.

3.1 Curbing an upcoming wave requires a vaccination rate at least equal to the rate in spring 2021

To quantify the impact of the vaccination rate on the spread of COVID-19, we performed simulations with two different rates: 0.58% and 0.11% of the total population per day. These two values correspond to the maximum first-dose vaccination rate attained at the beginning of April 2021 and the rate registered in early September 2021, respectively.[56] The former represents an optimal scenario, which can be achieved only if local authorities implement large, temporary vaccination centers or other viable alternatives; the latter could be considered as a worst case scenario of low vaccination rate.

In our simulations, whose outcome is illustrated in Fig. 3, we assumed that highly effective testing practices were enacted during the entire period. In particular, we hypothesized that each symptomatic agent was tested with probability equal to 80%, while such a probability was reduced to 40% for asymptomatic agents. These parameters are representative of optimal testing practices,[65] and they are used to illustrate that, even under optimistic assumptions on the efficacy of testing practices, low vaccination rates may lead to tremendous increases in infections and death toll.

We compared the number of infections and death toll for the two vaccination rates for six months starting from September 7^{th}, 2021. Results from Fig. 3 show that, for the higher vaccination rate (green curves), the number of active cases should start decreasing from mid-October. The average peak of active cases should exceed 400 active cases per day, and then it should quickly drop in few weeks, potentially reaching the end of the outbreak at the beginning of 2022. On the contrary, the current vaccination rate (red curves) would lead to a 50% increase in number of cases per day during fall 2021. Even more alarming is the projection that it would not be sufficient to eradicate the disease, leading to a possible slow rise in number of cases during winter 2022, and potentially a resurgent wave in spring 2022. These results indicate the need to maintain a fast pace during the booster campaign toward curbing potential upcoming waves and quickly eradicating the disease.

In all the simulations, we observed an initial phase in which the number of cases steadily increases. We believe that such an increase could be caused by an underestimation of the initial number of infected individuals, due to under-detection in the officially reported data used to initialize the simulations. However, such an initial increase does not impact our in-

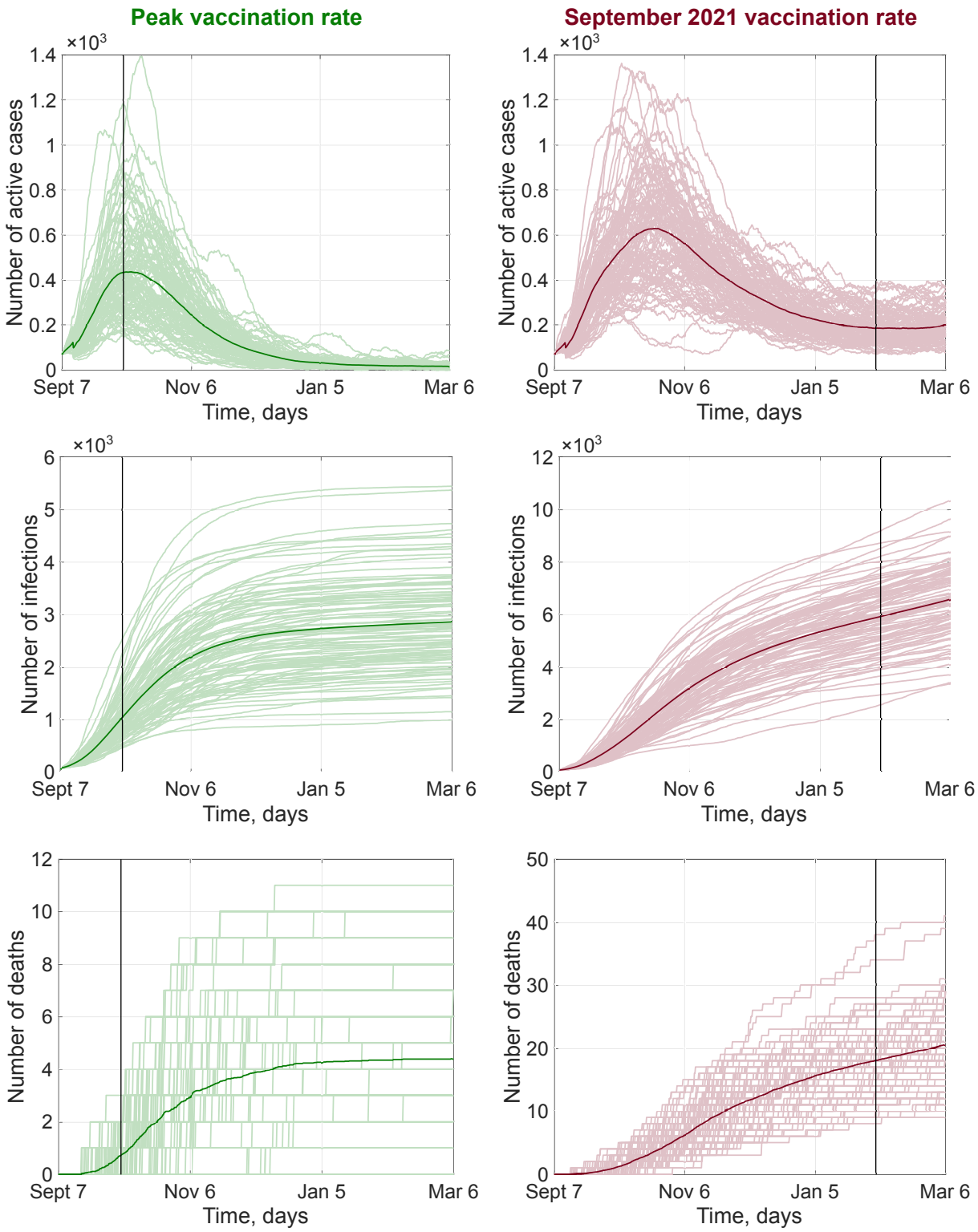

Figure 3: **COVID-19 spreading over six months from September 7th 2021, amid two different vaccination campaigns.** Active cases, total number of infections, and total deaths for the next six months at either peak vaccination rate of 0.58% population/day (green) or present vaccination rate of 0.11% population/day (red). For each scenario, 100 independent realizations are shown and their average is highlighted. The vertical lines denote the date at which the entire non-hesitant eligible population is expected to be vaccinated with at least one shot.

sights into the effects of waning immunity, as more than 88% of the individuals vaccinated during spring and summer 2021 has still full immunity at the end of October 2021 (see Fig. S2b in the Supporting Information). To support the insights of our numerical analysis, we performed a set of additional simulations to show robustness of our findings with respect to different assumptions on the underestimation of the initial number of infected individuals. These simulations are reported in Figs. S7 and S8 in the Supporting Information.

3.2 Testing is still needed, even with high vaccination rates

We also investigated the role of testing and contact tracing implemented during the booster shot campaign, toward elucidating the impact of these practices, their interplay with the vaccination rate, and, ultimately, to understand whether massive testing campaigns are still needed in this phase.

We conducted a parametric study by varying the vaccination rate and the overall efficacy of testing practices over a two-dimensional grid. Specifically, we considered re-vaccination rates ranging between 0.01–5% of the population per day. These two extreme values represent scenarios in which the entire re-vaccination campaign would last more than 20 years or just 20 days. For context, the first-dose peak vaccination rate was 0.58% during April 2021 and the lowest rate was 0.027% in mid-summer 2021.[56] The efficacy of the testing practices was encapsulated by a global parameter, termed "testing efficacy," which measures the probability that a symptomatic agent is tested. In the simulations, we varied such a parameter from 10% to 100%, representing scattered to ideal testing.

We performed these parametric studies within three different detection scenarios, according to the ability of detecting pre-symptomatic and asymptomatic agents (hereby, referred to as exposed): high detection (in which exposed agents are tested with the same probability of symptomatic ones), medium detection (in which the probability for an exposed individual to be tested is reduced by 50% with respect to the one of a symptomatic agent), and low detection (in which exposed agents reduce the probability of being tested to 10% of the one of symptomatic agents). While high detection of exposed is ideal —but likely unrealistic, since asymptomatic infections are more difficult to be detected without a massive implementation of testing practices and contact tracing— medium detection could be

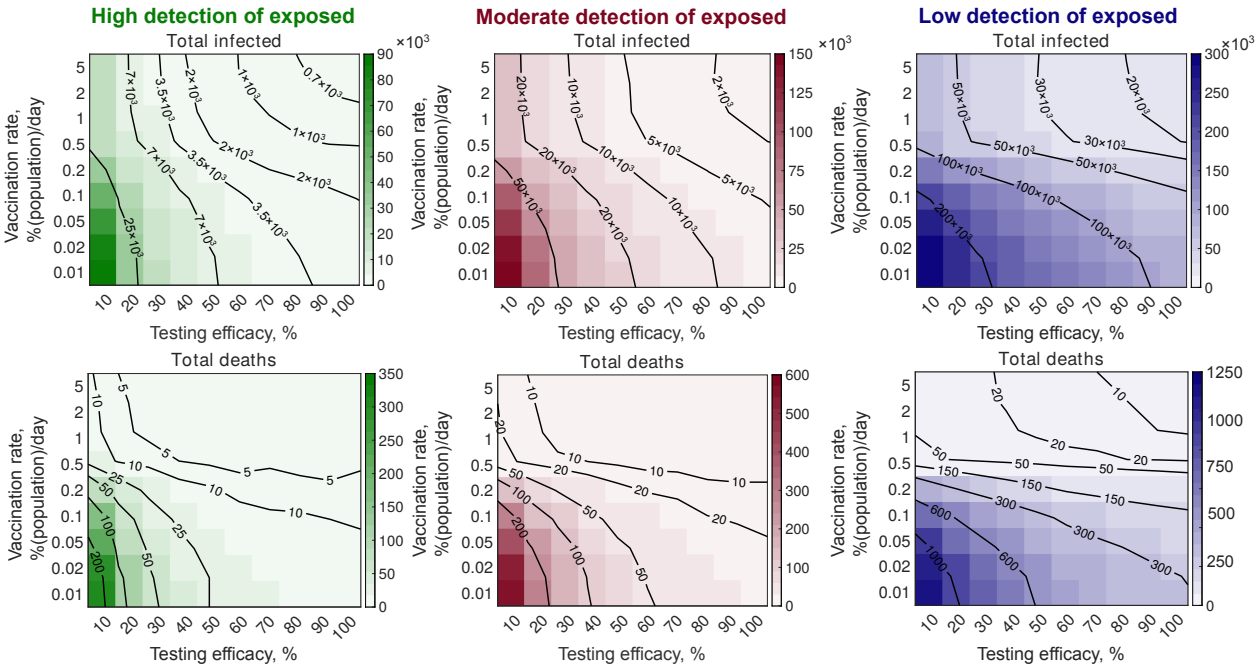

Figure 4: **Interplay between re-vaccination rates and testing efficacy.** Two-dimensional heat-maps showing the combined effect of vaccination rate and testing efficacy on the total number of infected and deaths over a period of six months starting from September 7$^{\text{th}}$ 2021. Three different detection levels of exposed agents capture a range of contact tracing efforts.

a realistic proxy of testing practices seen since the onset of the pandemic,[65] and low detection could potentially represent a scenario in which most routine testing practices are disbanded.

Our results, shown in Fig 4, highlight the need to continue testing during the upcoming booster shot campaign. In particular, for all the examined detection scenarios, testing less than 20–30% of symptomatic agents always resulted in a dramatic increase of infections and deaths. To overcome the ensuing surge it would necessary to apply unprecedentedly high vaccination rates of 1–5% of the total population per day, likely beyond the capacity of the healthcare system that we have seen in spring 2021.

Our results also emphasize that detecting pre-symptomatic and asymptomatic agents is a critical issue. In fact, for all combinations of re-vaccination rate and testing efficacy, reduced detection of such agents results in a many-fold increase of total number of infections and deaths. For example, with low detection of exposed agents (third scenario, in blue in Fig. 4), the number of deaths may exceed over 600 (that is, approximately 0.8% of

the population of the town), reaching peaks of more than 1,000 deaths in the worst case scenarios of both low testing efficacy and low re-vaccination rates. Further evidence on the key role of contact tracing comes from an additional set of simulations (reported in Fig. S11 in the Supporting Information), in which no contact tracing practices are enacted. The results of these simulations suggest that, in the absence of any form of contact tracing, the COVID-10 death toll can dramatically increase, even in the scenario of fast re- vaccination rates.

4 Discussion and conclusion

The chief goal of this work was to systematically analyze the spread of COVID-19 in the upcoming 2021 fall/winter season, as immunity gained due to vaccination wanes over the year and testing practices change. Toward this aim, we extended a mathematical model designed in our previous efforts,[23, 34] a high-resolution ABM of a medium-sized U.S. town faithfully reproducing spatial layout, demographics, and lifestyles of urban areas, to quantify the effects of a range of vaccination and testing efforts. As in our previous studies, we focused on the town of New Rochelle, NY, which was the location of one of the first COVID-19 outbreaks in the U.S.. New Rochelle is representative of many towns in the country and is characterized by high levels of diversity and potential inequalities.[44, 45]

Complementing our earlier efforts, we enhanced the capabilities of the computational framework along three main directions. First, we considered realistic types and administration of vaccines, as well as time-varying vaccination benefits, including waning immunity after a tunable period[36, 37, 38, 39] and administration of a booster shot.[2] Second, natural immunity achieved through recovery was also considered to be no longer permanent.[50, 51] Third, we modeled contact tracing, consistent with the CDC and local health department guidelines.[14, 47, 48] Overall, the current model is a highly realistic and detailed digital representation of the town and its residents, with the resolution of a single individual, thus allowing for reliable "what-if" analyses of the epidemic during the upcoming fall/winter season. Equipped with a new parameter set tuned on the now-dominant Delta variant, we studied the local outcome of the interplay between the rate of vaccination and efficacy of testing practices.

Predictably, we found that low testing efficacy may lead to a disastrous increase in both infections and deaths, irrespective of vaccination efforts of any intensity. In fact, low testing efficacy seems to hamper any benefits that would be offered by realistic re-vaccination campaigns. The final count of cases and casualties would be substantially independent of vaccination rates, unless booster shots were administered to more than 1% population per day (an unrealistic scenario, since it exceeds the peak vaccination rate during spring 2021). For low-to-moderate testing efficacy, vaccination rates below 0.5% consistently lead to a case and death toll comparable with those experienced during the first wave.[23]

These results, in agreement with other studies on testing practices during previous phases of the COVID-19 pandemic,[66, 27] highlight the central role of testing, contact tracing, and home-isolation in the fight against COVID-19 and echo the "Path out of the Pandemic," presented by the U.S. Government on September 10$^{\text{th}}$, 2021, as part of "President Biden's COVID-19 Plan."[67]

To contain COVID-19 mortality below the level of the first wave, we predict that at least 0.5% of population per day should be immunized/re-immunized, as testing and contact tracing are carried out with moderate efficacy. Such a 0.5% vaccination rate is not unreasonable, as it is comparable to the average vaccination rate during the peak of the spring 2021 vaccination campaign.[56] However, such a peak vaccination rate was accompanied by large, temporary vaccination centers that no longer exist. Hence, local authorities might need to restore these temporary vaccination centers or provide viable alternatives, to keep the administration of boosters at the desired rate. On the contrary, vaccination rates below 0.5% might lead to scenarios that are worse than those recorded in spring 2020.[68] In particular, using a vaccination rate equal to that adopted in September 2021 would lead to a potentially disastrous rise in the number of infections around the beginning of 2022. While the number of deaths projected in this scenario are still lower than those occurred in the first wave, likely due to reduced mortality rates of vaccinated individuals, the steep increase portends that this number would ultimately overcome first wave figures.

These projections emphasize the importance for a booster shot, in line with the "President Biden's COVID-19 Plan"[67] that highlights the need of "further protecting the vaccinated" (with the booster shot). To efficiently combat the spread, the booster shot campaign should be conducted on a scale close to the one implemented during the peak im-

munization efforts in spring 2021. Similar conclusions have been drawn by other authors. For example, Layton et al.[4] report doubling of deaths by late December 2021 in Ontario, Canada, as a consequence of reducing the baseline vaccination rate by 20%. Sandmann et al.[41] predict the occurrence of up to two annual COVID-19 waves in the UK, whose magnitudes are strictly tied to vaccine efficacy and active NPIs. In the worst case scenario, it is expected that there will be a new wave this fall, with a magnitude comparable, or even higher, than the one observed during 2020. Similarly, Song et al.[40] indicate reoccurring new surges in the worst cases of vaccination efficacy and immunity duration, and a constant, but non-zero COVID-19 incidence in the best scenarios, starting from mid-2021. Testing of symptomatic individuals plays a key role in controlling the spread, especially when it is accompanied by moderate contact tracing efforts. Seen from another perspective, testing a mere 40% of the symptomatic individuals with moderate contact tracing efforts should avoid exceeding mortality rates of the first wave. Beyond a 60% testing efficacy, the effect of increased testing is diluted and higher vaccination rates are needed to bring‘ down mortality rates. While testing levels of 40% or above are achievable,[69] as they are comparable with the estimates for the late summer 2020 in France[65] they are still challenging to attain. Reducing delays in testing and contact tracing could offer a pathway to mitigate difficulties in reaching high testing levels.[26, 27]

Likewise, the detection of asymptomatic individuals is of paramount importance to combat the spreading. In particular, going from high- to low-detection of such individuals more than doubles the number of cases and deaths. This finding is consistent with the literature, whereby efficacious tracking of the asymptomatic individuals has been shown to arrest the progression of the spread of the virus.[70, 71] High detection rates can be realized with aggressive contact tracing strategies that can identify stranger contacts in addition to close contacts.[72] At the same time, while it is reasonable that most people who develop symptoms or are informed of exposure to an infected individual will isolate, and possibly test, detecting asymptomatic individuals could become progressively more difficult, especially with general decline in social distancing practices and lifting of mandatory testing by many employers and institutions.[13]

While insightful, our results are not free from limitations. Though calibrated in real data, the high granularity of our model comes at a cost of a series of assumptions. Importantly,

immunity due to vaccination was modeled based on educated guesses due to limited data availability. Except for waning immunity benefits from vaccination, all the parameters in our simulations were time-invariant; in real settings factors such as NPIs or testing coverage are likely to change in response to emerging situations[73, 74] and, likewise, vaccination rates to dynamically change. Moreover, we tested the general, uninfected population in a non-random fashion, and contact tracing guidelines within our model were more conservative than those currently in-place.

Concerning the timing and profile of waning immunity, in our study we made several assumptions based on the knowledge available at the time of writing the paper. We acknowledge that the scientific community has yet to reach complete consensus. Specifically, we set immunity benefits from vaccination to start to gradually wane after a period of eight months from peak-level immunity. This is in accordance with recent studies on the humoral and cellular immune responses, which indicates eight-months as a lower-bound on this period.[36, 37] However, other studies suggest different, and potentially shorter, timings,[38, 39] thereby conclusive evidence is yet to be established.[43] Similar uncertainty seems to be present on the duration of natural immunity,[50, 51, 52, 53] which, in this work, was chosen to last for six months. To partially address these uncertainties, we performed a parametric study that is reported in the Supporting Information, which ensure that our qualitative findings and observations are robust to changes in the timing and profile of the waning immunity.

The study design was based on information about the pandemic gathered during summer 2021. In particular, in the original (August 2021) schedule, booster shots were planned to be available to all the adults in the U.S. eight months after they took their second vaccine dose.[2] This schedule has changed several times, as currently COVID-19 vaccine booster shots are available for some categories of people who completed their initial series at least six months ago (for Pfizer and Moderna), or two months ago (for Johnson&Johnson).[75] New changes to such a plan are expected in the near future, as the "President Biden's COVID-19 Plan" suggests "to quickly get booster shots into the arms of eligible Americans once approved."[67] As scenarios are rapidly changing in the U.S. and throughout the globe, we have opted to adhere to the original CDC guidelines for our simulations. We believe that the additional simulations in the Supporting Information (Figs. S3–S4) provide some in-

sights into this issue, suggesting that the rate of vaccination is more important than its actual timing, to avoid potential, resurgent outbreaks in late winter/spring 2022.

The need to administer booster shots must also be put in context with respect to medical, social, and moral concerns .[3, 76] First, the waning of immunity is still not confirmed with certainty[43], and the health effects of an additional dose remain, to some extent, unexplored.[3] It cannot be excluded that an additional dose may only selectively boost the efficacy for individuals who are immunocompromised or whose initial vaccination had low efficacy.[77] Also, any adverse effects of the booster dose may have a negative impact to the vaccine acceptance.[77] Second, with less than 5% of the populations in low income countries being fully vaccinated, the World Health Organization has deemed every booster shot as "ethically questionable" and warned that unmitigated COVID-19 pandemic in those areas will continue yielding new variants.[76, 78] Despite these concerns, countries have already started their booster shot campaigns in an attempt to curb the risk of new surges and restrictions.[79] These decisions are likely driven by the Delta variant, which dilutes the herd-immunity thresholds estimated for the wild-type strain.[80, 81, 82, 83]

Supporting information

Supporting Information is available from the Wiley Online Library or the corresponding author. The complete computational framework, including code needed to reproduce the study is openly available. The database is accessible in Zenodo at `https://doi.org/10.5281/zenodo.5659785`, the agent-based model in Github at `https://github.com/Dynamical-Systems-Laboratory/ABM-COVID-revac`.

Author contributions

Conceptualization—AT, LZ, SB, AR, MP; data curation—AT; methodology—AT, LZ, SB, AR, MP; software—AT, SB; validation—AT; formal analysis—all the authors; investigation—all the authors; resources—MP; writing—original draft preparation—AT, LZ, SB, AR, MP; writing—review and editing—EC, ZPJ; visualization—AT; supervision—SB, EC, ZPJ, AR, MP; project administration—MP; funding acquisition—SB, ZPJ,AR, MP.

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Conflict of interest

The authors declare no conflict of interest.

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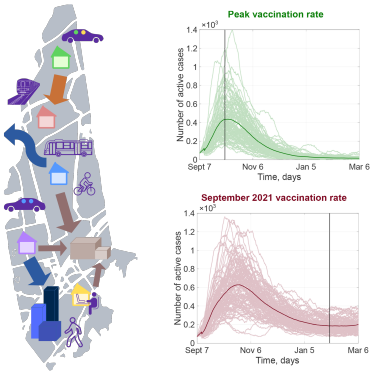

Mathematical models have proven to be indispensable in our fight against COVID-19. This paper expands on a high-resolution agent-based model published previously in this journal to study the effectiveness of the booster shot campaign in preventing a new wave in the town of New Rochelle, NY during this Fall and the coming Spring.