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RESEARCH ARTICLE

Impact of Vaccination and Nonpharmaceutical Interventions With Possible COVID-19 Viral Evolutions Using an Agent-Based Simulation

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Introduction: The COVID-19 pandemic continues with highly contagious variants and waning immunity. As the virus keeps evolving to be more infectious and immune evasive, some question whether the COVID-19 pandemic can be managed through sustainable public health measures.

Methods: We developed an agent-based simulation to explore the impact of COVID-19 mutations, periodic vaccinations, and nonpharmaceutical interventions on reducing COVID-19 deaths. The model is calibrated to the greater Seattle area by observing local epidemic data. We perform scenario analyses on viral mutations that change infectiousness, disease severity, and immune evasiveness from previous infections and vaccination every 6 months. The simulation is run until the end of year 2023.

Results: Variants with increased infectivity or increased immune evasion dominate previous strains. With enhanced immune protection from a pancoronavirus vaccine, the most optimistic periodic vaccination rate reduces average total deaths by 44.6% compared with the most pessimistic periodic vaccination rate. A strict threshold nonpharmaceutical intervention policy reduces average total deaths by 71.3% compared with an open society, whereas a moderate nonpharmaceutical intervention policy results in a 33.6% reduction.

Conclusions: Our findings highlight the potential benefits of pancoronavirus vaccines that offer enhanced and longer-lasting immunity. We emphasize the crucial role of nonpharmaceutical interventions in reducing COVID-19 deaths regardless of virus mutation scenarios. Owing to highly immune evasive and contagious SARS-CoV-2 variants, most scenarios in this study fail to reduce the mortality of COVID-19 to the level of influenza and pneumonia. However, our findings indicate that periodic vaccinations and a threshold nonpharmaceutical intervention policy may succeed in achieving this goal. This indicates the need for caution and vigilance in managing a continuing COVID-19 epidemic.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic continues to ravage populations around the world. Several factors influence this situation, including the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOCs) such as the Omicron variant that is highly infectious and immune evasive;[1] changes in the level of nonpharmaceutical interventions (NPIs), such as reduced mask use and social distancing; and public reluctance to be vaccinated. Understanding the impact of vaccination and NPI policies on COVID-19 incidence and deaths is needed to guide effective interventions.

The immune response to SARS-CoV-2, including VOCs such as Alpha, Delta, and Omicron variants that have resulted in increased viral loads; disease severity; and/or resistance to immunity conferred by previous infection or vaccination,[1] is complex. Studies have shown that immunity wanes over time, and the degree of waning may differ by vaccine, time since vaccination or infection, variant type, and demographic factors.[2–6] The immune response to SARS-CoV-2 confers differential protection against infection, severe disease, or death.[7–10] Protection against reinfection declines faster for the Omicron variant than for the original Wuhan, Alpha, and Delta variants. However, protection against severe disease remains high for all variants, including the Omicron variant.[11]

Questions have been raised about the need for periodic COVID-19 vaccinations and which population groups should receive them. The Centers for Disease Control and Prevention now recommends the updated bivalent COVID-19 booster vaccine to all individuals aged ≥12 years, with at least a 2-month interval since their last dosage. Evidence has shown that it provides better protection against the Omicron variant than older vaccines without additional safety concerns.[12] Nevertheless, repeated vaccinations may result in reduced effectiveness and durability of protection.[11,13] The effects of periodic vaccination should be explored under various immune scenarios, especially given the emergence of SARS-CoV-2 variants that may impact the efficacy.

In this article, our objective is to understand the role of emerging variants, vaccination, and NPI policies on COVID-19 infections and deaths. We aim to identify scenarios in which COVID-19 can be managed such that the death rate from COVID-19 becomes comparable with the combined annual mortality rate from influenza and pneumonia. As a case study for a large urban area, we simulate COVID-19 transmission in King County, Washington, (greater Seattle) using an agent-based simulation model. Calibrated to local epidemiologic data, our study uses detailed synthetic population data and includes interactions between vaccination and specific NPIs while considering waning immunity and emergence of variants. Virus mutation scenarios include 12 combinations of infectivity, disease severity, and immune evasiveness. A highly effective pancoronavirus vaccine that works against all strains is considered an optimistic scenario.

METHODS

Population-based Simulation Model

Agent-based simulation has been employed in studies[14–17] to account for heterogeneous individual behaviors and contact networks. Our agent-based model is based on the open-source FRED (A Framework for Reconstructing Epidemics Dynamics) model.[18] As in Lee et al.,[19] we modified the FRED model to simulate SARS-CoV-2 transmission in King County, Washington, with approximately 1.9 million individuals. The NPIs that we model include social distancing, face mask use, school closures, home quarantine, testing, and contact tracing as in Lee et al.[19] Our natural history of COVID-19 follows a SEIRS (susceptible-exposed-infected-recovered-susceptible) model framework, including SARS-CoV-2 variants, vaccination, and immunity from natural infection or vaccination. As shown in Figure 1, each disease compartment is stratified by variant type as superscript x, individuals' vaccination history as subscript v, and previous infection history as subscript p. The model is also stratified by age and comorbidities. These factors affect disease progression, including the probabilities of infection, disease severity, and death. Values for all parameters and calibration are given in Appendix Section 1 (available online), and detailed transmission equations are given in Appendix Section 2 (available online).

SARS-CoV-2 variants. We consider SARS-CoV-2 variants that show different infectivity, disease severity, and/or immune evasive properties after previous infection or vaccination. We sequentially introduce 3 variants that are the most widespread SARS-CoV-2 VOCs, specifically, the Alpha, the Delta, and the B.1.1.529 Omicron variants. The variants have evolved to be more infectious while either decreasing or increasing disease severity.[20–24] The level of natural and vaccine immunity against the Alpha and the Delta variants is assumed to be the same as that of the original Wuhan strain, whereas the B.1.1.529 Omicron variant has been found to more easily evade the immunity acquired from vaccine or prior infection.[25] We refer to the original Wuhan, the Alpha, and the Delta variants as pre-Omicron strains. In the scenario analyses presented in the section on Parameter Settings for

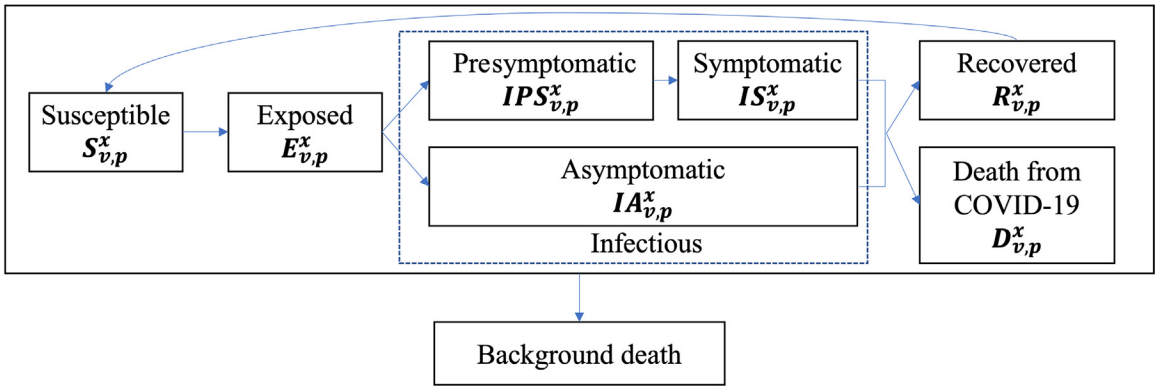

Figure 1. Natural history model of COVID-19.
In each compartment (S, E, IPS, IS, IA, R, D), the superscript x implies a variant type, and subscripts v and p imply the most recent vaccination and previous infection date, respectively.

Scenario Analysis, we introduce potential new variants that mutate every 6 months after the B.1.1.529 Omicron variant on the basis of data indicating that the previous VOC appearance interval is between 4 and 8 months[26] (details are presented in Appendix Section 1.3, available online).

Vaccination. Vaccination parameters, including effectiveness in preventing infection and death, are primarily based on the first-generation Pfizer-BioNTech COVID-19 vaccine. In the primary vaccination series (available from January 1, 2021), 2 doses are administered, with the second dose following the first dose by 21 days. Additional vaccines after the second dose may be administered every 6 months. We introduced vaccines to the simulation using age-specific eligibility dates and prioritization policy in Washington State[27,28] (details are presented in Appendix Section 1.5, available online).

Immune response. SARS-CoV-2 variants may evade the immune system and increase the probability of infection.[29] We refer to this as immune evasion. Immunity gained from natural infection or vaccination wanes over time and differs by variant types.[4,25,30] From clinical studies, we fit a linear regression model to estimate immune evasion.[2,7,31–33] The immunity level has a continuous value ranging from 0 to 1 that depends on individuals' latest infection date, vaccination date, and variant type. In estimating immune evasion, we distinguish whether the immunity was obtained from previous infections or from vaccinations because research[2,4,8] shows that levels of immune evasion vary depending on its source. When an individual has immunity from both previous infection and vaccination, we multiplied their effects on the basis of studies[4,9,34] that a hybrid immunity increases protection against reinfection. If an individual is infected, the severity of the disease (probability of dying from disease) may be reduced with previous infection or vaccination. We refer to this as immune protection. We fit a linear regression model to estimate immune protection against death[7,30,35] (the equations are presented in Appendix Section 1.4, available online).

Mortality. Deaths from COVID-19 and background mortality are considered. We assume that the infection fatality ratio of COVID-19 depends on individuals' age and comorbidity status.[36,37] The ratio can decrease when an individual has immune protection against death from previous infections or vaccinations (Appendix Section 2.3, available online). In the agent-based simulation, once an individual dies, the person is removed from each active location (household, neighborhood, school, and/or workplace) and no longer influences future transmission. Background death rate is based on sex and age.[38]

Calibration Procedure with Parameter Settings

We calibrate the model to data for the greater Seattle area from January 15, 2020, to December 31, 2020, by targeting basic reproduction number (R_0) and reported deaths. We fit previous compliance history to NPIs by observing Seattle's sequence of interventions. Parameters that we calibrate include COVID-19 transmissibility, contact rates at each location (household, neighborhood, school, and workplace), and default home quarantine percentage of symptomatic individuals (the calibration procedure and detailed model description are presented in Appendix Section 1.6, available online).

Our simulation period spans 4 years, from January 15, 2020, (reported first day of infection in King County) to December 31, 2023. The period from January 15, 2020, to December 31, 2020, is used to calibrate parameters.

Table 1. Parameter Settings for Virus Mutation Scenario Analyses

Mutation scenarios	Changes in infectivity compared with previous variant	Changes in disease severity compared with previous variant	Changes in immune evasion compared with previous variant
S1	50% more infectious	Same	Pessimistic immune evasion
S2	50% more infectious	Same	Neutral immune evasion
S3	50% more infectious	Same	Optimistic immune evasion
S4	50% more infectious	50% less severe	Pessimistic immune evasion
S5	50% more infectious	50% less severe	Neutral immune evasion
S6	50% more infectious	50% less severe	Optimistic immune evasion
S7	Same	Same	Pessimistic immune evasion
S8	Same	Same	Neutral immune evasion
S9	Same	Same	Optimistic immune evasion
S10	Same	50% less severe	Pessimistic immune evasion
S11	Same	50% less severe	Neutral immune evasion
S12	Same	50% less severe	Optimistic immune evasion

Note: The changes in immune evasion compared with previous variant have 3 characterizations: pessimistic immune evasion indicates that the virus mutates to be 25% more immune evasive than is acquired from vaccination or previous infection, neutral immune evasion indicates that the virus mutates to have the same immune evasiveness as B.1.1.529 Omicron, and optimistic immune evasion indicates that the virus mutates to have the same immune response as B.1.1.529 Omicron when it is acquired from previous infection but enhanced immune response when it is acquired from vaccination (details are presented in Appendix Section 1.4, available online).

From January 1, 2021, to December 31, 2023, (3 years), we perform a scenario analysis by simulating different virus mutations as in Table 1 and policy scenarios as in Table 2. In all analyses and calibration, we replicate 50 simulation runs. The scenario analysis used common random seeds for variance reduction.

Mutation parameters. As listed in Table 1, we introduce 12 new variants with mutation scenarios labeled S1−S12 that vary in infectivity, disease severity, and immune evasion on June 4, 2022, after the B.1.1.529 Omicron variant. We label each mutation scenario as S1−S12. For ease of explanation, we name the 3 immune evasion parameter settings as pessimistic, neutral, and optimistic immune evasion. In the optimistic scenario, we assume that a pancoronavirus vaccine is always available for all strains, and the vaccine effects always show the same level as against pre-Omicron strains. This provides stronger and more lasting immune protection than our base, first-generation vaccine, which is less effective against B.1.1.529 Omicron strains.

Once 1 of the 12 new variants is introduced to society, we mutate it every 6 months. The mutation parameters follow the same pattern every 6 months for simplicity. For example, if the virus evolves to increase infectivity by 50% with the same disease severity and immune evasiveness, then 6 months later, the second generation (December 2022−June 2023) of the new strain will have a 50% further increase in infectivity compared with the first generation (June 2022−December 2022) of the mutated strain. A third generation (June 2023−December 2023) mutates once more after 6 months (details are provided in Appendix Sections 1.3 and 1.4, available online).

Table 2. Parameter Settings for Policy Scenario Analyses

Policy scenarios	Parameter settings
Reduction in vaccine willingness for each additional dose (fourth or higher)	50% less, 25% less, same
NPI policy	Timeline 1, Timeline 2, threshold

NPI, nonpharmaceutical intervention.

Vaccination parameters. After the third vaccine dose, a periodic vaccination program (fourth or higher) is scheduled for every 6 months until the end of the simulation. The periodic vaccination program runs from January 23, 2022, to December 31, 2023. When receiving periodic vaccinations, vaccine willingness may decline by 50% or 25% or remain constant for each additional vaccination in the scenario analyses, as listed in Table 2. Individuals' vaccine willingness for primary and booster vaccination depends on their age from King County data.[28] It is assumed that vaccine supply is enough to cover the population, although there may be some delays due to daily limits.

Nonpharmaceutical intervention parameters. NPIs include social distancing, face mask use, school closure, home quarantine, testing, and contact tracing. We simulate different levels of compliance to social distancing, school closure, and face mask use by aggregating the 3 factors under one concept—the NPI stage (Figure 2). As

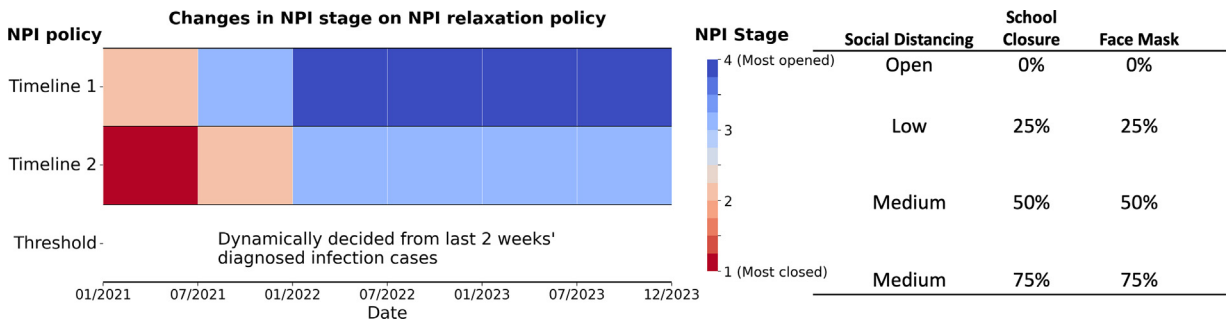

Figure 2. Definitions of NPI stages and timeline NPI policies.
Date is in month/year.
NPI, nonpharmaceutical intervention.

illustrated in Figure 2, we consider 4 levels of NPIs ranging from a fairly closed society (stage 1) to a fully open society (stage 4). We consider 3 NPI policies as listed in Table 2 that consist of different stages and timing as shown in the left panel of Figure 2. Timeline 1 gradually opens from 2021 to a fully open society in 2022, whereas Timeline 2 is a moderate NPI policy that opens more slowly and maintains some level of NPIs through 2023. We also introduce a threshold NPI policy in which the NPI stage is dynamically determined by the last 2 weeks' diagnosed infection cases. Under this policy, the society is in stage 1 if diagnosed cases are higher than 350 cases per 100,000 population for a 14-day rolling period; in stage 2 if there are 200−349 cases per 100,000; in stage 3 if there are 100−199 cases per 100,000; and in stage 4 if there are <100 cases per 100,000. We fix compliance parameters for home quarantine, testing, and contact tracing at the same level as those at the end of 2020. Combining the 9 policy scenarios with the 12 mutation scenarios yields 108 scenarios, with parameter values given in Tables 1 and 2.

Measures for Scenario Analysis

We explore the impact of viral mutation, vaccination, and NPI policies on SARS-CoV-2 infections and deaths due to COVID-19. Because new variants after B.1.1.529 Omicron are introduced from June 4, 2022, we focus on deaths that occur from June 4, 2022, to December 31, 2023. Given that the severity of the disease influences public perception and response, we identify scenarios for which COVID-19 deaths can be reduced to or below the mortality rate from influenza and pneumonia, which was 12.6 per 100,000 population in Washington State in 2017.[39] This number converts into 374 total deaths from June 4, 2022, to December 31, 2023, or 0.65 person deaths per day in the region.

RESULTS

Increased infectivity and immune evasion are the main drivers of new variants' capacity to dominate other strains.[14,40] Figure 3 presents the number of daily infections by variants under mutation scenarios S1−S3 with increased infectivity and S10−S12 with reduced disease severity from Table 1. The first row of Figure 3 shows that when variants mutate to increase infectivity, the new variants dominate the previous strain. When the variants become more immune evasive (S1, pessimistic immune evasion), the outbreak size is much higher than the outbreak from B.1.1.529 Omicron (Figure 3A). If the immune evasion scenario is neutral (S2) or optimistic (S3), the outbreak size is reduced, and its peak is delayed (Figure 3B and C). When variants retain the same infectivity with reduced disease severity, dominance of new variants depends on evolution in immune evasion (Figure 3D−F). With pessimistic immune evasion (S10), the new variants slowly dominate its previous strain with a lower peak size than B.1.1.529 Omicron (Figure 3D). However, if variants show the same infectivity and immune evasiveness as B.1.1.529 Omicron (S11, neutral immune evasion) or with better vaccination immune protection (S12, optimistic immune evasion), new variants do not dominate B.1.1.529 Omicron (Figure 3E and F).

Figure 4 presents simulated results for total deaths. The 12 graphs in Figure 4 represent mutation scenarios S1−S12 in Table 1, where the 4 rows represent changes in infectivity and disease severity, and the 3 columns represent immune evasion characteristics. Each of the 12 graphs have 3 markers (squares, circles, and triangles) for vaccine willingness impacting periodic vaccination rate. The 3 NPI policies are plotted on the horizontal axis, and total deaths (in 1,000s) are plotted on the vertical axis.

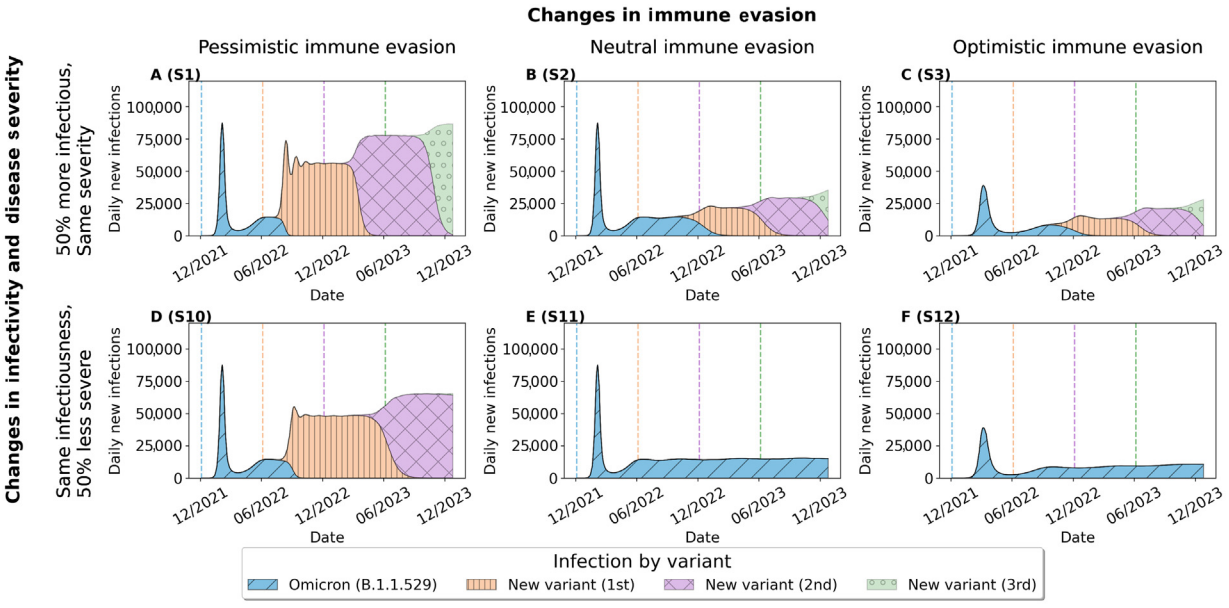

Figure 3. Impact of viral mutation on SARS-CoV-2 infections while varying infectivity and immune evasion.
Note: Virus mutation scenarios are listed in the upper left corner of each graph. Subfigures A, B, and C represent scenarios S1, S2, and S3. Subfigures D, E, and F represent scenarios S10, S11, and S12. Colored lines in each graph indicate the first imported date of each variant. Periodic vaccination willingness is assumed to reduce by 25% for each additional dose. NPI policy is assumed to be Timeline 1 policy (the results of 12 mutation scenarios from January 15, 2020 are presented in Appendix Section 3, available online).
NPI, nonpharmaceutical intervention.

Impact of viral mutation on SARS-CoV-2 deaths

In most cases, increased infectivity yields more deaths than mutations that maintain the same infectivity. When the variants' disease severity remains the same and infectivity increases, total mortality increases by 44.7% (Figure 4A and G), 93.1% (Figure 4B and H), and 112.7% (Figure 4C and I) when averaged over vaccine willingness and NPI policies. When the virus mutates to reduce disease severity and the immune evasion scenario is pessimistic, total deaths increase by 16.7% (Figure 4D and J). In contrast, when the immune evasion scenario is neutral or optimistic, the total number of deaths decreases by 7.0% (Figure 4E and K) and 8.3% (Figure 4F and L), respectively. This is because the new variants with higher infectivity dominate the previous strains, resulting in more infections, but the reduced disease severity leads to fewer deaths.

Similarly, reduced disease severity typically leads to fewer deaths than the same severity. When the virus mutates to increase infectivity, reduced disease severity decreases total mortality by 59.4% (Figure 4A and D), 52% (Figure 4B and E), and 56.9% (Figure 4C and F) when averaged over vaccine willingness and NPI policies. Although the reduced disease severity decreases total deaths by 51.1% (Figure 4G and J) in the pessimistic immune evasion scenario, the impact of reduced disease severity is negligible when infectivity is the same, and the immune evasion scenario is neutral or optimistic. The mortality reduces by 0.3% (Figure 4H and K) in the neutral immune case and increases by 0.1% (Figure 4I and L) in the optimistic case. This is because the new variants, which do not mutate to increase infectivity or immune evasiveness, do not replace previous variants as demonstrated in Figure 3E and F. Thus, the decreased disease severity of these new variants does not result in a reduction of deaths.

In all instances, increased immune evasion results in a higher death toll. Viruses with a pessimistic immune evasion strategy (first column of Figure 4) cause 3,867 average deaths. When the viruses exhibit neutral immune evasion (second column of Figure 4), the average total mortality rate decreases by 14.9% from the first column setting. With optimistic immune evasion (third column of Figure 4), the death toll further decreases by 30.9% from the second column setting.

Impact of periodic vaccination rate on SARS-CoV-2 deaths

The effect of increasing periodic vaccination coverage heavily depends on new variants' immune evasion property. An effective pancoronavirus vaccine (S3, S6, S9, and S12) and the most optimistic periodic vaccination rate (same vaccination willingness as the booster vaccination rate) yield 1,590 average total deaths, reducing total deaths by 44.6% compared with the most

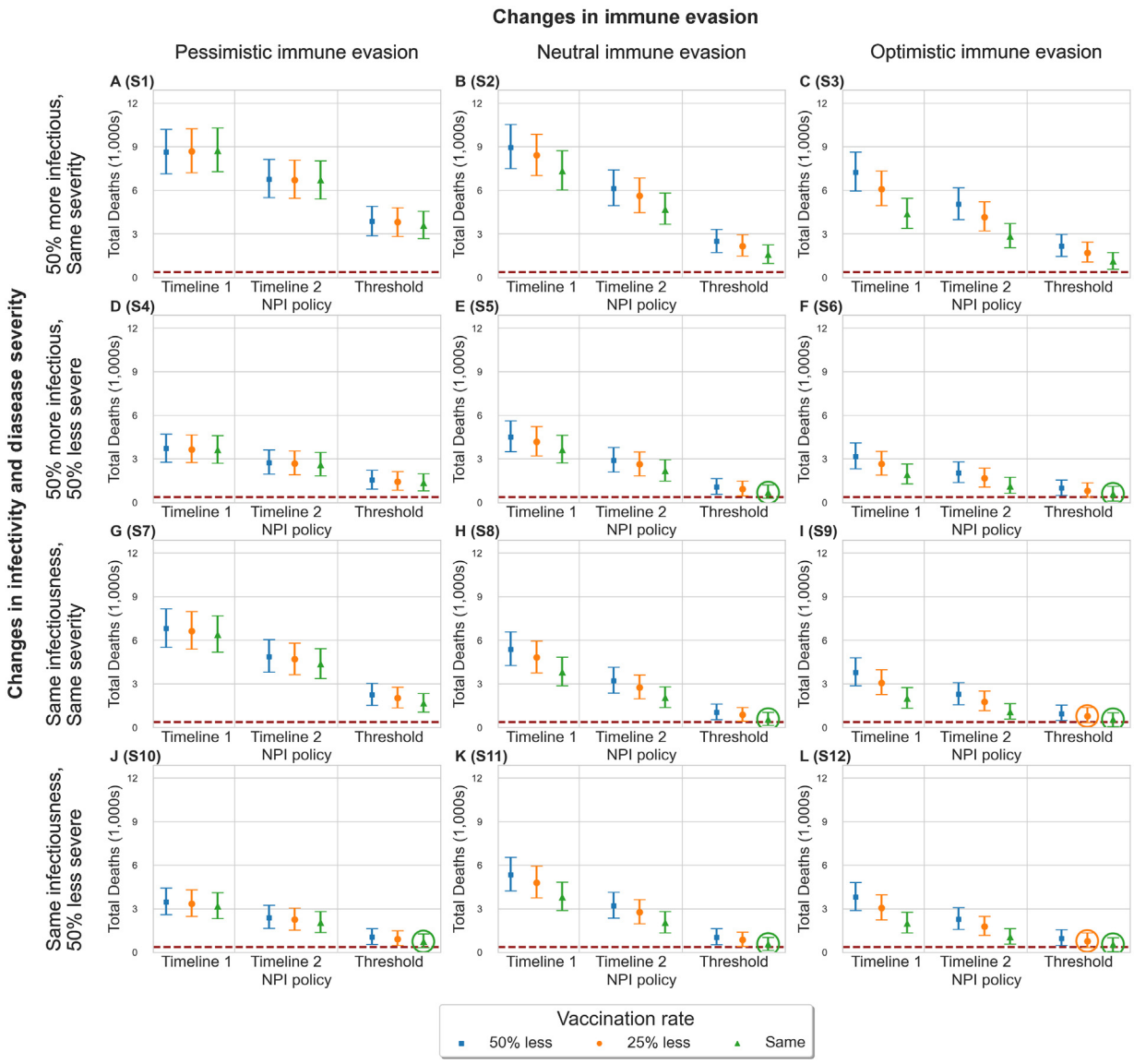

Figure 4. Impact of periodic vaccination rate and NPI policies on deaths from June 4, 2022, (first date of viral mutation after B.1.1.529 Omicron is imported to the society) to December 31, 2023, with varying mutation scenarios on infectivity, disease severity, and immune evasion.

Note: Virus mutation scenario numbers are listed in the upper left corner of each graph. Subfigures A-L represent scenarios S1-S12 respectively. Error bars represent the 25th and 75th percentile values of total deaths, with the dot at the 50th percentile. In each virus mutation graph, red dotted lines represent the number of total deaths from influenza and pneumonia in Washington state in 2017, which is calculated to be 374 deaths during the simulation period. Scenarios with error bars that overlap the objective are circled.

NPI, nonpharmaceutical intervention.

pessimistic periodic vaccination (50% reduction in vaccine willingness for each additional dose). If such a pancoronavirus vaccine does not exist, and a virus shows neutral immune evasion (second column of Figure 4), the average total death reduction is 27.2%. If the virus mutates to evade immunity more easily (first column of Figure 4), the death toll reduction is 6.5% when comparing the most optimistic with the most pessimistic vaccination rate. Figure 5 illustrates the impact of periodic vaccination on daily deaths when the virus mutation scenario is S1−S3 with increased infectivity and S10−S12 with reduced disease severity. The figure illustrates an example in which the benefit of increased periodic vaccination is more apparent when the immune evasion scenario is optimistic.

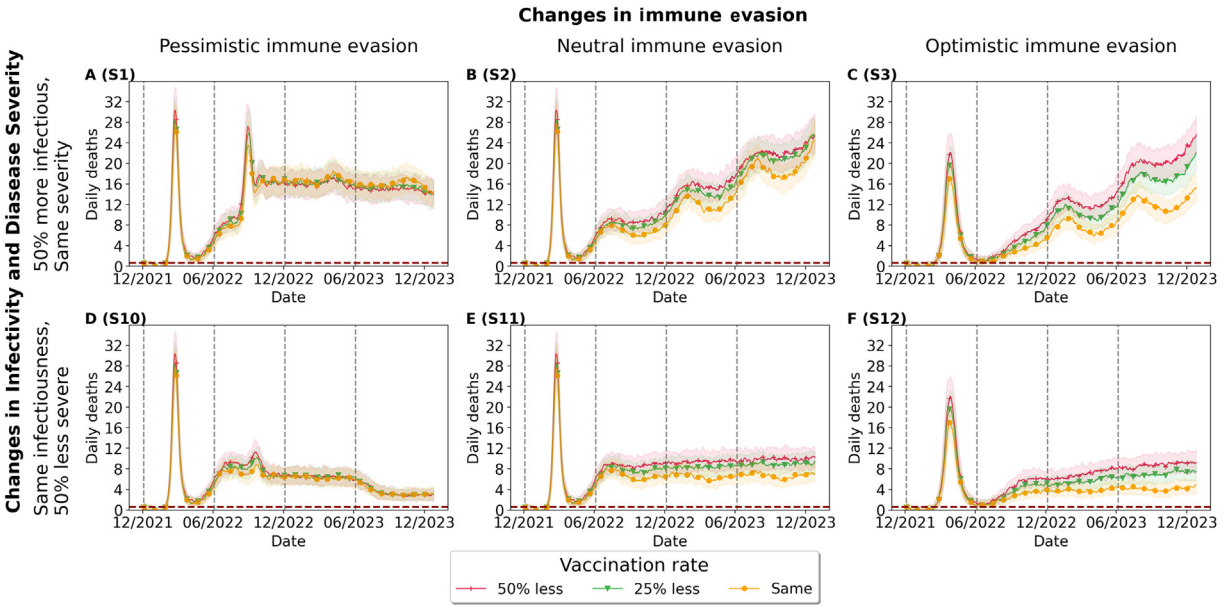

Figure 5. The impact of periodic vaccination rate on daily deaths is shown in subfigures A–C for scenarios S1–S3, and shown in subfigures D–F for scenarios S10–S12.

The NPI policy is assumed to follow Timeline 1. The shaded area in each line indicates the 25th and 75th percentile values of daily deaths. In each graph, the vertical gray line indicates the first imported date of each variant (the B.1.1.529 Omicron and a new variant that mutates twice more). The red dotted lines represent the number of daily deaths from influenza and pneumonia in Washington state in 2017, which is calculated to be 0.65 deaths per day (the results of all 12 mutation scenarios from January 15, 2020, are presented in Appendix Section 4, available online).
NPI, nonpharmaceutical intervention.

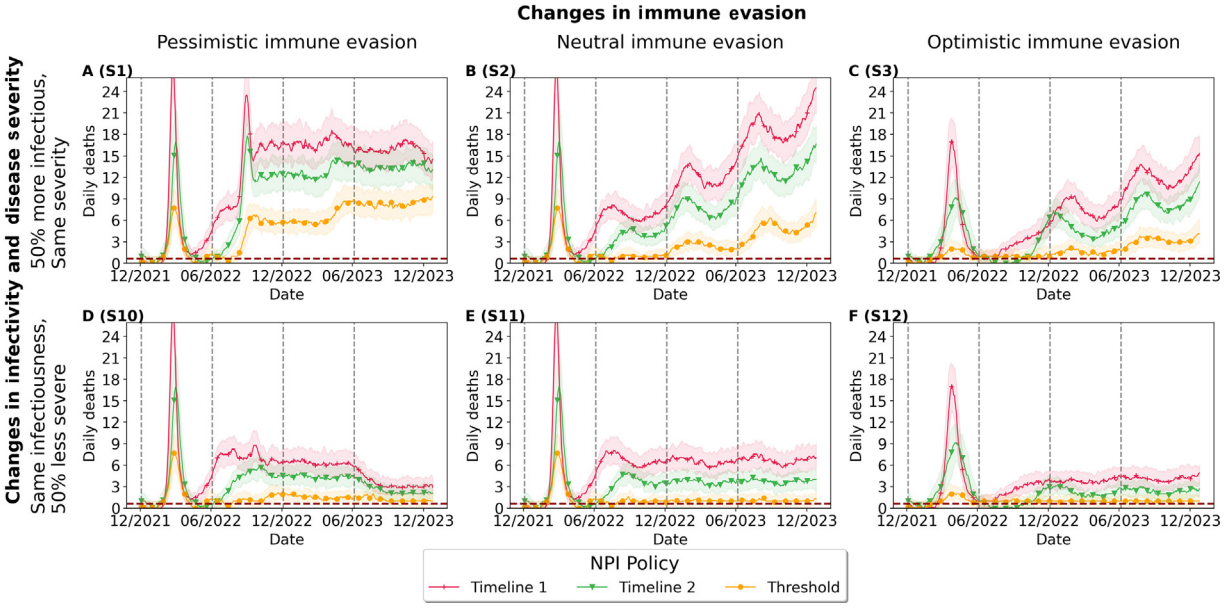

Figure 6. The impact of NPI policies on daily deaths is shown in subfigures A–C for scenarios S1–S3, and shown in subfigures D–F for scenarios S10–S12.

Periodic vaccination willingness is assumed to reduce by 25% for each additional dose. The shaded area in each line indicates the 25th and 75th percentile values of daily deaths. In each graph, the vertical gray line indicates the first imported date of each variant (the B.1.1.529 Omicron and a new variant that mutates twice more). Red dotted lines represent the number of daily deaths from influenza and pneumonia in Washington state in 2017, which is calculated to be 0.65 deaths per day (the results of 12 mutation scenarios from January 15, 2020, are presented in Appendix Section 4, available online).
NPI, nonpharmaceutical intervention.

Impact of nonpharmaceutical intervention policies on SARS-CoV-2 deaths

NPI policies always reduce the death toll regardless of mutation scenarios, as shown in Figure 6. Compared with the Timeline 1 NPI policy, which fully opens the society from January 2022, the Timeline 2 policy maintains NPI stage 3 from January 2022 to the end of 2023 (Figure 2). With constant moderate NPI policies in Timeline 2, the average total death toll is reduced by 33.6% compared with that of Timeline 1. The reduction ranges from 21.8% to 47.2% depending on the mutation scenarios. The threshold policy, which dynamically decides the NPI stage according to the number of cases in a 14-day rolling period, reduces the death toll by 71.3% compared with Timeline 1. The reduction ranges from 55% to 85% depending on mutation scenarios. When the threshold policy is applied, the NPI stage 1 policy is selected in early 2022 with the rapid spread of B.1.1.529 Omicron variant and remains in NPI stage 1 in most virus mutation scenarios. Even in the case where the virus mutates to be milder and exhibits the same infectivity and a pancoronavirus vaccine is available (S12), the society is generally in NPI stage 2, which involves a medium level of social distancing (Appendix Section 5, available online).

Reducing annual deaths from SARS-CoV-2 to the levels of influenza and pneumonia

Our objective is to find scenarios that reduce COVID-19 deaths to the levels of influenza and pneumonia, which is 374 total deaths during the simulation period in the region. Of 108 scenarios, 9 scenarios (with virus mutations S5, S6, and S8−S12) satisfy the objective within the error bar limits, as indicated by the circled markers in Figure 4. All 9 scenarios have threshold NPI policies. Of the 9 scenarios, 7 scenarios have the same periodic vaccination willingness as the rate of the third booster vaccination. The remaining 2 scenarios have a 25% reduced periodic vaccination rate (with virus mutations S9 and S12). In Figure 6F, in which the virus mutation is S12, the periodic vaccination rate is reduced by 25%, and the threshold NPI policy is applied, the lower error bar also satisfies the objective when converted to daily numbers, equating to 0.65 daily deaths in the simulation period.

DISCUSSION

In this study, we explore the role of hypothetical virus mutation, periodic vaccination, and NPI policies on COVID-19 in a large urban area, King County, Washington, using an agent-based simulation model. Our study highlights that the impact of increased periodic vaccination coverage on mortality is heavily dependent on the concomitant evolution of immune evasion and is not significant when SARS-CoV-2 mutates to substantially increase immune evasion. In contrast, the effect of strengthening NPI policy is robust to viral mutation. Few scenarios meet the objective of reducing COVID-19 mortality to or below the influenza and pneumonia mortality levels by the end of 2023. This raises concerns about managing ongoing COVID-19 community spread using strategies analogous to those for seasonal influenza.

Consistent with other modeling studies,[14,40] our results demonstrate that a novel SARS-CoV-2 strain dominates its previous strain and drives new waves of infections when it has sufficiently increased infectivity or immune evasiveness. Our model indicated that changes in relative infectivity and immune evasiveness determine the dominance of new SARS-CoV-2 strains, irrespective of the mutation scenario. Furthermore, even with changes in vaccination rates and NPIs, the same dominance was observed, although the time to domination varied.

Our study finds that the majority of deaths come from people aged ≥65 years, accounting for 67.4%−81.9% of all deaths in our scenarios. This is in line with the Centers for Disease Control and Prevention's initial decision to recommend the fourth booster vaccine to individuals at high health risk. Furthermore, we observed that increasing the rate of periodic vaccination can reduce the death toll by 27%−45% as long as the immune evasiveness of new variants remains the same or less than that of the B.1.1.529 Omicron variant. An effective pancoronavirus vaccine can reduce immune evasiveness and improve protection. The implementation of updated bivalent COVID-19 vaccines, which are believed to provide improved immune response,[12,41] is likely to contribute to reducing the death toll to some extent.

As the COVID-19 pandemic continues, many are fatigued and reluctant to follow restrictive NPI measures, such as social distancing and mask wearing. Now that the COVID-19 pandemic is in its fourth year, our threshold NPI policy that mostly returns to NPI stage 1, a strict policy, or from late 2022 is likely to be impractical. The criterion in our threshold policy is based on the number of diagnoses suggested by the Washington government before the widespread distribution of vaccination.[42] Now that the disease severity of SARS-CoV-2 is lower, easing the threshold criteria to implement a more relaxed threshold policy might be a practical alternative.

Agent-based simulation has been employed in studies[14−17] to account for heterogeneous individual behaviors and contact networks. Our model accounts for real-world evidence of immune response to SARS-CoV-2 so

that individuals' level of immune response depends on previous infection and vaccination history as well as variant type and disease outcomes (i.e., infection or death). Moreover, our agent-based model captures individual heterogeneity in behaviors such as mask wearing and compliance with social distancing and risk factors such as age and comorbidity. Rather than approximating the impacts of NPIs as a single variable that changes the force of infection, a method commonly used in mathematical models for simplicity,[43–45] we separately model specific NPIs, including social distancing, face mask use, school closure, testing, contact tracing, and home quarantine.

Limitations

Limitations exist in our model. Some of the virus mutation scenarios may not be biologically feasible. For example, our most pessimistic mutation scenario (S1) that assumes that the virus keeps mutating to increase infectivity, increase immune evasiveness, and have the same disease severity may be considered extreme. Our model assumes that the virus follows the same mutation path every 6 months, ignoring interactions between other factors. Research shows that high SARS-CoV-2 incidence rates[46] or infections in immunocompromised individuals[47] could impact the pace and nature of mutation. Recent research has challenged our assumption that hybrid immunity provides stronger protection than immunity generated through either infection or vaccination.[48,49] Another study suggests that the presence of neutralizing antibodies, that is, exposure to the current strain of the virus, is a crucial determining factor in the level of immunity.[50,51]

Our model has simplified some individual behaviors. Individuals' compliance with NPIs such as face mask use or social distancing are assumed to be independent of vaccination behavior, which might not be true in reality.[52,53] Future research should consider dynamic human behavior for vaccination and NPIs. Our individuals' vaccine willingness was based on their age and location, but inclusion of other demographic characteristics such as educational status, sex, and political affiliation may be beneficial for a more comprehensive analysis. Although some research[54,55] highlights sex differences in behavioral responses and clinical characteristics, our study primarily focused on age as a predominant factor influencing human behavior, including vaccination and disease progression.[36,56] Owing to the vast number of possible individual NPI scenarios, we had to aggregate the NPIs to manage a feasible number of scenarios for analysis. We used our previous research[19] to create reasonable aggregated NPIs and timelines.

Although we count deaths due to COVID-19 in the simulation, counting excess deaths may give different insights. Our results could overestimate mortality if better antiviral treatments are developed. Seasonal changes in transmissibility or contact patterns might affect the shape of the infection waves. Our calibration was based on the original Wuhan virus, and other variants' disease characteristics were based on literature review. We did not calibrate to the current time because our objective was to deliver a broad message on the impact of changes in virus mutation scenarios and vaccination and NPI policies on death toll rather than predicting the exact outcomes in an urban area.

CONCLUSIONS

In summary, our study provides estimated impacts of virus mutation, SARS-CoV-2 vaccination, and NPI policies on COVID-19 outcomes using an agent-based simulation. The development of pancoronavirus vaccines with increased durability and protection has a high potential to reduce the death toll. NPIs are important not only because of their direct impact on reducing COVID-19 infections and deaths but also because of their indirect impact on hindering the emergence of variants by reducing transmission. A dynamic, threshold approach to NPI policy is more effective than fixed policies, implying the need to strengthen surveillance systems for timely reporting of SARS-CoV-2 infections and other communicable diseases with pandemic potential. Few scenarios reduce deaths from COVID-19 to or below the levels of influenza and pneumonia by the end of 2023. However, periodic vaccinations coupled with dynamic NPI policies may succeed in managing COVID-19 as an endemic disease that is similar to seasonal influenza.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.focus.2023.100155.

REFERENCES

1. Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.htm. Updated September 1, 2023. Accessed September 14, 2022.
2. Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. *Nat Med.* 2022;28(5):1063–1071. https://doi.org/10.1038/s41591-022-01753-y.
3. Mazzoni A, Maggi L, Capone M, et al. Heterogeneous magnitude of immunological memory to SARS-CoV-2 in recovered individuals. *Clin Transl Immunology.* 2021;10(5):e1281. https://doi.org/10.1002/cti2.1281.
4. Goldberg Y, Mandel M, Bar-On YM, et al. Protection and waning of natural and hybrid immunity to SARS-CoV-2. *N Engl J Med.* 2022;386(23):2201–2212. https://doi.org/10.1056/NEJMoa2118946.
5. Centers for Disease Control and Prevention. Science brief: SARS-CoV-2 infection-induced and vaccine-induced immunity. https://stacks.cdc.gov/view/cdc/111167. Published October 20, 2021. Accessed September 14, 2022.
6. Antia R, Halloran ME. Transition to endemicity: understanding COVID-19. *Immunity.* 2021;54(10):2172–2176. https://doi.org/10.1016/j.immuni.2021.09.019.
7. UK Health Security Agency. COVID-19 vaccine surveillance report - week 24. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1083443/Vaccine-surveillance-report-week-24.pdf. Published June 16, 2022. Accessed September 14, 2022.
8. Altarawneh HN, Chemaitelly H, Ayoub HH, et al. Effects of previous infection and vaccination on symptomatic omicron infections. *N Engl J Med.* 2022;387(1):21–34. https://doi.org/10.1056/NEJMoa2203965.
9. Nordström P, Ballin M, Nordström A. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. *Lancet Infect Dis.* 2022;22(6):781–790. https://doi.org/10.1016/S1473-3099(22)00143-8.
10. World Health Organization. Interim statement on hybrid immunity and increasing population seroprevalence rates. https://www.who.int/news/item/01-06-2022-interim-statement-on-hybrid-immunity-and-increasing-population-seroprevalence-rates. Published June 1, 2022, Accessed October 5, 2022.
11. COVID-19 Forecasting Team. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. *Lancet.* 2023;401(10379):833–842. https://doi.org/10.1016/S0140-6736(22)02465-5.
12. Chalkias S, Harper C, Vrbicky K, et al. A bivalent omicron-containing booster vaccine against Covid-19. *N Engl J Med.* 2022;387(14):1279–1291. https://doi.org/10.1056/NEJMoa2208343.
13. Chemaitelly H, Ayoub HH, Tang P, et al. Long-term COVID-19 booster effectiveness by infection history and clinical vulnerability and immune imprinting. *medRxiv.* 2022. 11.14.22282103. https://doi.org/10.1101/2022.11.14.22282103.
14. Le Rutte EA, Shattock AJ, Chitnis N, Kelly SL, Penny MA. Modelling the impact of Omicron and emerging variants on SARS-CoV-2 transmission and public health burden. *Commun Med (Lond).* 2022;2:93. https://doi.org/10.1038/s43856-022-00154-z.
15. Sanz-Leon P, Hamilton LHW, Raison SJ, et al. Modelling herd immunity requirements in Queensland: impact of vaccination effectiveness, hesitancy and variants of SARS-CoV-2. *Philos Trans A Math Phys Eng Sci.* 2022;380(2233):20210311. https://doi.org/10.1098/rsta.2021.0311.
16. Vilches TN, Sah P, Moghadas SM, et al. COVID-19 hospitalizations and deaths averted under an accelerated vaccination program in northeastern and southern regions of the USA. *Lancet Reg Health Am.* 2022;6:100147. https://doi.org/10.1016/j.lana.2021.100147.
17. Tatapudi H, Das R, Das TK. Impact assessment of full and partial stay-at-home orders, face mask usage, and contact tracing: an agent-based simulation study of COVID-19 for an urban region. *Glob Epidemiol.* 2020;2:100036. https://doi.org/10.1016/j.gloepi.2020.100036.
18. Grefenstette JJ, Brown ST, Rosenfeld R, et al. FRED (a Framework for Reconstructing Epidemic Dynamics): an open-source software system for modeling infectious diseases and control strategies using census-based populations. *BMC Public Health.* 2013;13:940. https://doi.org/10.1186/1471-2458-13-940.
19. Lee S, Zabinsky ZB, Wasserheit JN, Kofsky SM, Liu S. COVID-19 pandemic response simulation in a large city: impact of nonpharmaceutical interventions on reopening society. *Med Decis Making.* 2021;41(4):419–429. https://doi.org/10.1177/0272989X211003081.
20. Fort H. A very simple model to account for the rapid rise of the alpha variant of SARS-CoV-2 in several countries and the world. *Virus Res.* 2021;304:198531. https://doi.org/10.1016/j.virusres.2021.198531.
21. Earnest R, Uddin R, Matluk N, et al. Comparative transmissibility of SARS-CoV-2 variants Delta and Alpha in New England, USA. *Cell Rep Med.* 2022;3(4):100583. https://doi.org/10.1016/j.xcrm.2022.100583.
22. Jalali N, Brustad HK, Frigessi A, et al. Increased household transmission and immune escape of the SARS-CoV-2 Omicron variant compared to the Delta variant. *Nat Commun, 13.* 2022.
23. Fisman DN, Tuite AR. Evaluation of the relative virulence of novel SARS-CoV-2 variants: a retrospective cohort study in Ontario, Canada. *CMAJ.* 2021;193(42):E1619–E1625. https://doi.org/10.1503/cmaj.211248.
24. Ulloa AC, Buchan SA, Daneman N, Brown KA. Estimates of SARS-CoV-2 omicron variant severity in Ontario, Canada. *JAMA.* 2022;327(13):1286–1288. https://doi.org/10.1001/jama.2022.2274.
25. Reiner B. COVID-19 model update: omicron and waning immunity. Institute for Health Metrics and Evaluation. https://www.healthdata.org/special-analysis/omicron-and-waning-immunity. Published December 22, 2021. Accessed September 14, 2022.
26. Washington State Department of Health. SARS-CoV-2 sequencing and variants in Washington State. https://doh.wa.gov/sites/default/files/2022-02/420-316-SequencingAndVariantsReport.pdf?uid=63179ee18bd2e. Published September 27, 2023. Accessed October 29, 2023.
27. Washington State Department of Health. Washington's COVID-19 vaccine phases. https://www.doh.wa.gov/Portals/1/Documents/1600/coronavirus/VaccinationPhasesInfographic.pdf. Updated March 31, 2021. Accessed June 1, 2021.
28. Washington State Department of Health. Summary of COVID-19 vaccination among King County residents. https://kingcounty.gov/depts/health/covid-19/data/vaccination.aspx. Accessed July 6, 2022.
29. Lucas M, Karrer U, Lucas A, Klenerman P. Viral escape mechanisms-escapology taught by viruses. *Int J Exp Pathol.* 2001;82(5):269–286. https://doi.org/10.1046/j.1365-2613.2001.00204.x.
30. Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19—associated emergency department and urgent care encounters and hospitalizations

among adults during periods of Delta and Omicron variant predominance—VISION Network, 10 states, August 2021–January 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(7):255–263. https://doi.org/10.15585/mmwr.mm7107e2.
31. Sheehan MM, Reddy AJ, Rothberg MB. Reinfection rates among patients who previously tested positive for coronavirus disease 2019: a retrospective cohort study. *Clin Infect Dis.* 2021;73(10):1882–1886. https://doi.org/10.1093/cid/ciab234.
32. Fowlkes AL, Yoon SK, Lutrick K, et al. Effectiveness of 2-dose BNT162b2 (Pfizer BioNTech) mRNA vaccine in preventing SARS-CoV-2 Infection among children aged 5–11 years and adolescents aged 12–15 years—PROTECT Cohort, July 2021–February 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(11):422–428. https://doi.org/10.15585/mmwr.mm7111e1.
33. Altarawneh HN, Chemaitelly H, Hasan MR, et al. Protection against the omicron variant from previous SARS-CoV-2 infection. *N Engl J Med.* 2022;386(13):1288–1290. https://doi.org/10.1056/NEJMc2200133.
34. Bobrovitz N, Ware H, Ma X, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. *Lancet Infect Dis.* 2023;23(5):556–567. https://doi.org/10.1016/S1473-3099(22)00801-5.
35. UK Health Security Agency. COVID-19 vaccine surveillance report - week 11. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1061532/Vaccine_surveillance_report_-_week_11.pdf. Published March 17, 2022. Accessed September 14, 2022.
36. Clark A, Jit M, Warren-Gash C, et al. How many are at increased risk of severe COVID-19 disease? Rapid global, regional and national estimates for 2020. *medRxiv.* 2020. https://doi.org/10.1101/2020.04.18.20064774.
37. FAIR Health. Risk factors for COVID-19 mortality among privately insured patients: a claims data analysis. https://s3.amazonaws.com/media2.fairhealth.org/whitepaper/asset/Risk%20Factors%20for%20COVID-19%20Mortality%20among%20Privately%20Insured%20Patients%20-%20A%20Claims%20Data%20Analysis%20-%20A%20FAIR%20Health%20White%20Paper.pdf. Published November 11, 2020. Accessed September 13, 2022.
38. Flagg LA, Anderson RN. National Vital Statistics Reports. Unsuitable underlying causes of death for assessing the quality of cause-of-death reporting. Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/data/nvsr/nvsr69/nvsr69-14-508.pdf. Published January 11, 2021. Accessed September 14, 2022.
39. Centers for Disease Control and Prevention. Stats of the state of Washington. https://www.cdc.gov/nchs/pressroom/states/washington/washington.htm. Updated April 9, 2018. Accessed September 14, 2022.
40. Dyson L, Hill EM, Moore S, et al. Possible future waves of SARS-CoV-2 infection generated by variants of concern with a range of characteristics. *Nat Commun.* 2021;12(1):5730. https://doi.org/10.1038/s41467-021-25915-7.
41. Lin DY, Xu Y, Gu Y, et al. Effectiveness of bivalent boosters against severe omicron infection. *N Engl J Med.* 2023;388(8):764–766. https://doi.org/10.1056/NEJMc2215471.
42. Washington State Department of Health. Healthy Washington: road map to recovery metrics. https://bloximages.newyork1.vip.townnews.com/yakimaherald.com/content/tncms/assets/v3/editorial/5/0f/50f96c14-13f0-5805-a52f-8b331f33841b/6074f05b40ce8.pdf.pdf. Published April 12, 2021. Accessed June 20, 2021.
43. Viana J, van Dorp CH, Nunes A, et al. Controlling the pandemic during the SARS-CoV-2 vaccination rollout. *Nat Commun.* 2021;12(1):3674. https://doi.org/10.1038/s41467-021-23938-8.
44. Reeves DB, Bracis C, Swan DA, et al. Rapid vaccination and partial lockdown minimize 4th waves from emerging highly contagious SARS-CoV-2 variants. *Med.* 2021;2(5):573–574. https://doi.org/10.1016/j.medj.2021.04.012.
45. Borges ME, Ferreira LS, Poloni S, et al. Modelling the impact of school reopening and contact tracing strategies on Covid-19 dynamics in different epidemiologic settings in Brazil. *Glob Epidemiol.* 2022;4:100094. https://doi.org/10.1016/j.gloepi.2022.100094.
46. Thompson RN, Hill EM, Gog JR. SARS-CoV-2 incidence and vaccine escape. *Lancet Infect Dis.* 2021;21(7):913–914. https://doi.org/10.1016/S1473-3099(21)00202-4.
47. Choi B, Choudhary MC, Regan J, et al. Persistence and evolution of SARS-CoV-2 in an immunocompromised host. *N Engl J Med.* 2020;383(23):2291–2293. https://doi.org/10.1056/NEJMc2031364.
48. Cerqueira-Silva T, de Araujo Oliveira V, Paixão ES, et al. Vaccination plus previous infection: protection during the omicron wave in Brazil. *Lancet Infect Dis.* 2022;22(7):945–946. https://doi.org/10.1016/S1473-3099(22)00288-2.
49. Walls AC, Sprouse KR, Bowen JE, et al. SARS-CoV-2 breakthrough infections elicit potent, broad, and durable neutralizing antibody responses. *Cell.* 2022;185(5):872–880.e3. https://doi.org/10.1016/j.cell.2022.01.011.
50. Gruell H, Vanshylla K, Weber T, Barnes CO, Kreer C, Klein F. Antibody-mediated neutralization of SARS-CoV-2. *Immunity.* 2022;55(6):925–944. https://doi.org/10.1016/j.immuni.2022.05.005.
51. Lucas C, Vogels CBF, Yildirim I, et al. Impact of circulating SARS-CoV-2 variants on mRNA vaccine-induced immunity. *Nature.* 2021;600(7889):523–529. https://doi.org/10.1038/s41586-021-04085-y.
52. Woodcock A, Schultz PW. The role of conformity in mask-wearing during COVID-19. *PLOS ONE.* 2021;16(12):e0261321. https://doi.org/10.1371/journal.pone.0261321.
53. Buckley J. Unlocking the World. EU digital Covid certificate: everything you need to know. CNN. https://www.cnn.com/travel/article/eu-covid-certificate-travel-explainer/index.html. Updated June 9, 2021. Accessed September 14, 2022.
54. Mukherjee S, Pahan K. Is COVID-19 gender-sensitive? *J Neuroimmune Pharmacol.* 2021;16(1):38–47. https://doi.org/10.1007/s11481-020-09974-z.
55. Santos JV, Gomes da Costa J, Costa E, Almeida S, Cima J, Pita-Barros P. Factors associated with non-pharmaceutical interventions compliance during COVID-19 pandemic: a Portuguese cross-sectional survey. *J Public Health (Oxf).* 2023;45(1):47–56. https://doi.org/10.1093/pubmed/fdac001.
56. Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med.* 2020;26(8):1205–1211. https://doi.org/10.1038/s41591-020-0962-9.