Assessing the Combined Public Health Impact of Pharmaceutical Interventions on Pandemic Transmission and Mortality: An Example in SARS CoV-2

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To assess the combined role of anti-viral monoclonal antibodies (mAbs) and vaccines in reducing severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) transmission and mortality in the United States, an agent-based model was developed that accounted for social contacts, movement/travel, disease progression, and viral shedding. The model was calibrated to coronavirus disease 2019 (COVID-19) mortality between October 2020 and April 2021 (aggressive pandemic phase), and projected an extended outlook to estimate mortality during a less aggressive phase (April–August 2021). Simulated scenarios evaluated mAbs for averting infections and deaths in addition to vaccines and aggregated non-pharmaceutical interventions. Scenarios included mAbs as a treatment of COVID-19 and for passive immunity for postexposure prophylaxis (PEP) during a period when variants were susceptible to the mAbs. Rapid diagnostic testing paired with mAbs was evaluated as an early treatment-as-prevention strategy. Sensitivity analyses included increasing mAb supply and vaccine rollout. Allocation of mAbs for use only as PEP averted up to 14% more infections than vaccine alone, and targeting individuals ≥65 years averted up to 37% more deaths. Rapid testing for earlier diagnosis and mAb use amplified these benefits. Doubling the mAb supply further reduced infections and mortality. mAbs provided benefits even as proportion of the immunized population increased. Model projections estimated that ~42% of expected deaths between April and August 2021 could be averted. Assuming sensitivity to mAbs, their use as early treatment and PEP in addition to vaccines would substantially reduce SARS-CoV-2 transmission and mortality even as vaccination increases and mortality decreases. These results provide a template for informing public health policy for future pandemic preparedness.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Novel monoclonal antibodies (mAbs) developed against the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) spike protein provide treatment for presymptomatic or symptomatic infections and can reduce the magnitude and duration of viral shedding.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Because multiple mitigation strategies are ongoing concomitantly and it is difficult to generate clinical trial data to understand their combined benefits, the effects of mAbs on top of vaccine and non-pharmaceutical interventions were evaluated using a modeling approach.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Higher availability and utilization of mAbs as well as earlier treatment resulted in greater effects in reducing infections and deaths. The incremental benefit of mAbs as a strategy persists even if the deployment of other strategies such as vaccine rollout are intensified.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These results suggest an expanded role for mAbs for reducing SARS-CoV-2 transmission and deaths.

Received March 4, 2022; accepted August 15, 2022. doi:10.1002/cpt.2728

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Severe acute respiratory coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), continues to have a devastating impact on individuals and economies worldwide. From the beginning of the pandemic, there has been extensive implementation of non-pharmaceutical interventions (NPIs), such as masking and social distancing, and rapid development of diagnostic tests, vaccines, and new therapeutic modalities, including monoclonal antibodies (mAbs) in an effort to treat COVID-19 and control SARS-CoV-2 transmission.

Whereas the extent to which NPIs can reduce SARS CoV-2 transmission is dependent on behavior changes and adherence,[1,2] the additional deployment of vaccines, which require development of active immunity to COVID-19 over time, represents a long-term strategy for pre-exposure prevention. Concurrently, mAbs against the SARS-CoV-2 spike protein were developed for both the treatment and prevention of COVID-19 by conferring immediate and long-lasting passive immunity. Such mAbs may be useful as both pre- and postexposure prophylaxis, especially for individuals exposed to COVID-19 who have not been vaccinated, cannot receive a vaccine, or fail to respond to a vaccine. Provided that they can neutralize variants of concern (VOC), public health benefits of mAbs are likely to increase as logistical challenges associated with their clinical use are addressed. Moreover, mAbs may provide further benefits in reducing the pandemic burden under conditions where vaccination uptake is low.

Monoclonal antibodies are effective in asymptomatic, presymptomatic, and symptomatic infections for the prevention of further progression of COVID-19 including to more severe disease, and may be useful as both postexposure and preexposure prophylaxis.[3–7] The mAbs that have been granted Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) for use in specific populations include the combinations of bamlanivimab plus etesevimab (developed by Eli Lilly),[8] casirivimab plus imdevimab (developed by Regeneron),[9] and tixagevimab plus cilgavimab (developed by AstraZeneca),[10] as well as the monotherapy sotrovimab (developed by GlaxoSmithKline).[11] However, in January 2022, both casirivimab plus imdevimab and bamlanivimab plus etesevimab had their EUAs revised by the FDA to exclude treatment of those infected with the Omicron VOC.[12]

The mAbs can contribute to reducing transmission and overall pandemic burden when used early in a treatment-as-prevention (TasP) strategy, because they reduce the magnitude and duration of viral shedding in addition to reducing risk of COVID-19 progression in ambulatory patients.[3,4] Furthermore, mAbs can serve as a bridge to immunity shortly after vaccination, or as an alternative to vaccination for people who cannot respond to a vaccine.

To date, use of mAbs to prevent COVID-19 transmission has not been fully delineated with respect to public health planning. The objective of this study was to quantitatively explore the role that therapeutic mAbs as passive immunization may play in reducing the pandemic burden when used in conjunction with the standard management strategies of NPIs and vaccination. Understanding this role can provide a template to inform public health policy for meeting the challenges of pandemic preparedness for future outbreaks of SARS-CoV-2 and emerging infectious diseases with similar transmission characteristics.

Because multiple COVID-19 prevention strategies are ongoing concomitantly, it is difficult to generate real-time, controlled, clinical trial data to understand the benefits of a specific intervention or a combination of interventions in the real-world setting. Compartmental models, such as Susceptible-Exposed-Infectious-Recovered (SEIR), evaluate dynamics of infectious disease transmission, including under conditions that use mitigation strategies. However, limitations of the SEIR models are that they assume homogenous infectiousness and do not account for social contact networks or movement within the population. Social networks are especially relevant to the COVID-19 pandemic because of the potential for transmission from presymptomatic and asymptomatic individuals[13,14] and the substantial rate of household transmission.[15,16]

To overcome the limitations associated with SEIR models, we developed an agent-based model to characterize the individual-level heterogeneity of SARS-CoV-2 transmission in the US population.[17–19] This model enabled simulation of various pandemic scenarios, relative to a base case that assumed implementation of an aggregate of NPIs. These scenarios included vaccine and the mAbs casirivimab plus imdevimab on top of vaccine. The mAbs were used as active treatment and as passive immunity for postexposure prophylaxis (PEP). We also assessed rapid diagnostic testing paired with mAb interventions as an early TasP strategy.

METHODS

Components of the agent-based model

An agent-based model can simulate behaviors of individuals (i.e., "agents") and the interactions among them to better characterize transmission dynamics of infectious diseases in a large population. Such a model is flexible enough to simulate scenarios that assess virus transmission and the impact of different mitigation strategies across the US population. Our model (**Figure 1**) linked component modules that are integral to evaluating pandemic spread. See **Supplementary Information** for detailed methods.

The population and social network module was structured to resemble the US population, and was mapped based on population density to different locations across the United States using aggregated data from US Census Bureau (**Table S1**). Because SARS-CoV-2 can be transmitted by presymptomatic and asymptomatic individuals[13,20] with substantial secondary infection risk in households, the primary transmission pathway in the social networks was household,[15,16] and other transmission pathways included the workplace, school, neighborhood, and community (**Figure 1**).

The movement and travel module focused on propagation of COVID-19 inside the United States, assuming the risk from imported cases would be negligible. Data were derived from the US Department of

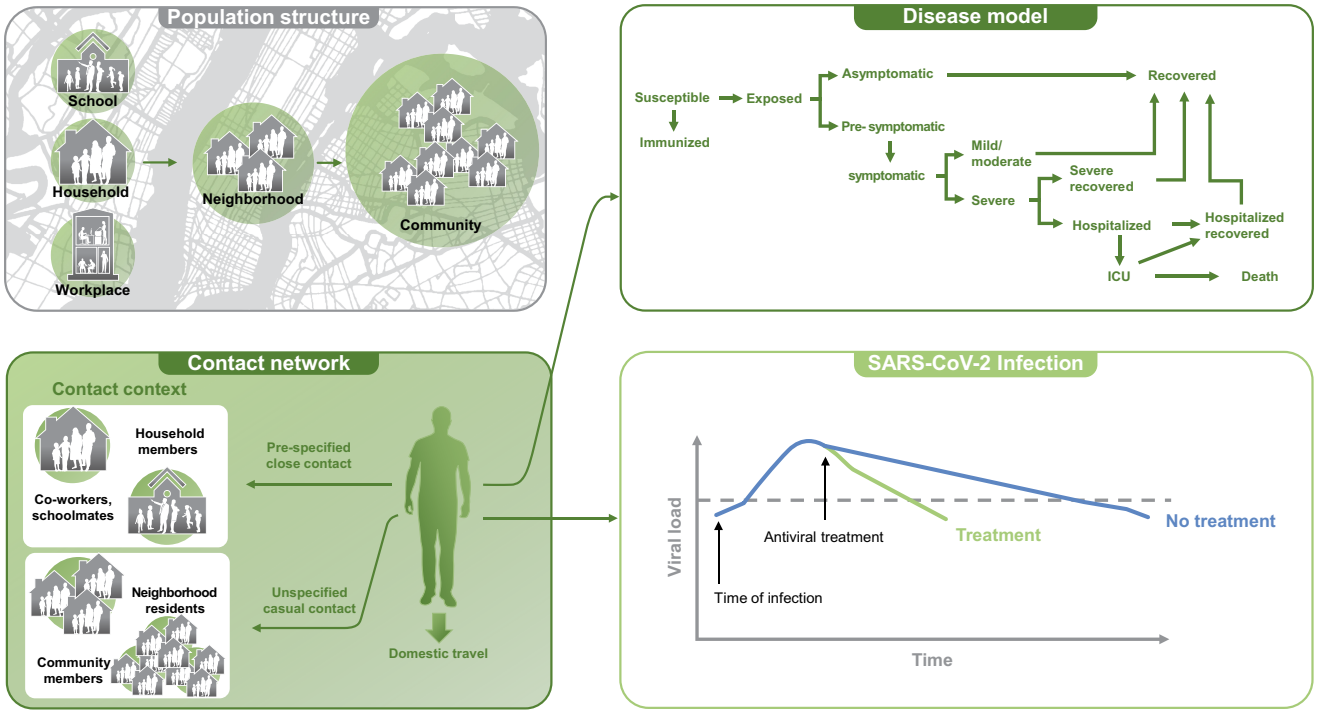


Figure 1 Components of the COVID-19 agent-based model. Development of the model incorporated 7 modules to allow for simulation of mitigation strategies for the COVID-19 pandemic. Components of the model consisted of the US population structure, a base social network, movement/travel within the United States, virus transmission, a disease model, use of non-pharmaceutical interventions, and pharmaceutical interventions. COVID-19, coronavirus disease 2019.

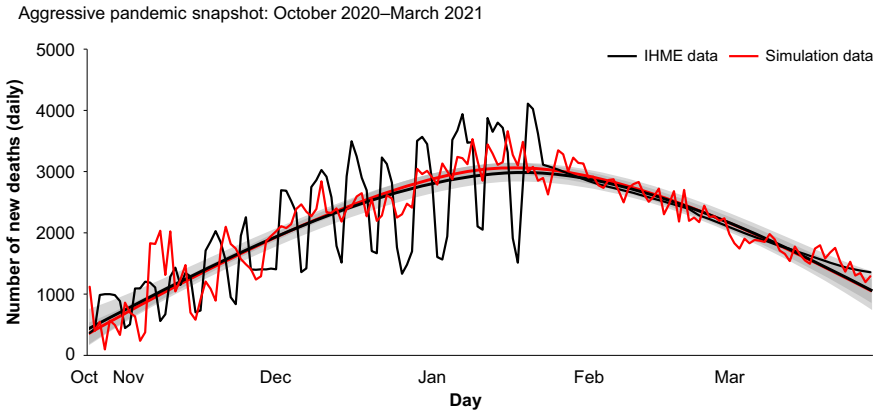


Figure 2 Calibration of the model using real-world mortality data. The model was calibrated to capture the daily distribution of deaths over a time period that reflected a more aggressive pandemic phase, from October 26, 2020–April 4, 2021. When fit to the observed distribution of deaths, the model tracked to the observed mortality curve. The oscillating lines represent raw mortality data, and the straight lines denote smoothed mortality curves, with the shaded bands indicating the 95% confidence interval for the smoothed curves. Observed data are from the Institute for Health Metrics and Evaluation (IHME).

Transportation and the US Travel Association (**Table S3**) and accounted for duration of population mixing.

The virus transmission module was based on person-to-person transmission.[17,21] The probability of transmission to a susceptible individual was calculated according to **Eq. S2** described in the **Supplementary Methods**.

The health status of each individual in the model (**Figure 1**) was evaluated at each simulation time step (1 day). We differentiated between presymptomatic and symptomatic individuals and between mild/moderate and severe disease so that the natural history of COVID-19 infections is realistically described and reflects how transmission forces change during the disease course.

Model calibration

Using US daily deaths reported by the Institute for Health Metrics Evaluation (IHME) and infection fatality ratio from the Centers for Disease Control and Prevention (CDC; **Table S21**), the model was calibrated to assure that it represents real-world conditions. Our model assumed total infections, and calibration was based on daily mortality and the infection fatality ratio rather than confirmed infections, which is used by the CDC and may result in undercounting as infections can be presymptomatic or asymptomatic. The calibration spanned the period during the winter months from October 26, 2020, to April 4, 2021 (**Figure 2**), which was considered an aggressive phase of the pandemic because of high

Table 1 Summary of main assumptions in simulation scenarios

Parameters		Sources
Antiviral therapy		
Average time to treatment (day) of active treatment	3 (SD = 1.4) days post symptom onset	Assumption
Average time to treatment (day) for postexposure prophylaxis	3 (SD = 1) days post infection	Assumption
Length of protection for prophylaxis	30 days	Assumption
Efficacy of postexposure prophylaxis when administered to susceptible agent (probability of being completely immune to infection after treatment)	81%	28
Effectiveness of contact tracing (proportion of close contacts reached)	100% for household members; 40% for colleagues and classmates	Assumption
Proportion of postexposure prophylaxis administered to confirmed cases	25% without rapid test; 100% with rapid test	Assumption
Sensitivity and specificity of rapid test (rapid diagnostics)	No assumption around test sensitivity or specificity (assume any test approved by FDA would have reasonable performance)	
Average time to rapid test (day)	Assumed that the rapid test was administered the same day as drug administered as post-exposure prophylaxis	
Reduction of infectiousness	Modulated via viral load values, dependent on time of treatment initiation as described in "Antiviral treatment module"	
Reduction of disease progression	Modulated by reducing the probability of progressing to the following worse disease stage, consistent with clinical trial information, as described in "Antiviral treatment module"	
Disease progression		
The time from infection to symptom onset (day)	5	26
Duration of being exposed (E in **Figure S8**) and not infectious (day)	2	25
Duration of being pre-symptomatic (Incu in **Figure S8**) and infectious (day)	3	Time from infection to symptom onset – duration of being exposed and not infectious
Duration of being asymptomatic (A in **Figure S8**)	7	Based on the simulated viral load values (100 control profiles as described in "Antiviral treatment module") multiplied by a factor of 75%
Duration of being symptomatic with mild symptoms (day), mild in **Figure S8**	6	38
Duration of being symptomatic with severe symptoms before hospitalization (day), severe in **Figure S8**	5	39
Time needed to recover from severe symptoms if not hospitalized (day), Severe_rec in **Figure S8**	2	Assumed as equal to hospital stay before ICU
Duration of hospitalization if ICU not required (day)	9	39
Duration of hospitalization before critical care admission (day), Hosp in **Figure S8**	2	39
Time needed to recover from hospitalization (day), Hosp_rec in **Figure S8**	7	Hospitalization duration if ICU not required – duration of hospitalization before ICU
Duration of ICU stay (day), ICU in **Figure S8**	10	38
Probability of disease progression	**Table S6**	Results obtained from model calibration

FDA, US Food and Drug Administration; ICU, intensive care unit.

mortality and overburdened healthcare systems, and during which time vaccines became available. The observed data show that mortality peaked from late October 2020 through January 2021. The calibrated model tracked closely to the actual number of deaths over time and cumulative mortality (**Figure 2**). Similarly, our values for the infection fatality ratio (**Table S19**) are close to those estimated by the CDC (**Table S12**).

Evaluating impact of mAbs on infections and mortality

Using our model assumptions (**Table 1**), simulations were conducted to determine the effects of various mitigation strategy scenarios during a more aggressive phase of the pandemic. Because multiple NPIs (e.g., travel bans, school and workplace closure, restriction of visitors to nursing homes, social distancing, facemasks, staying at home, and contact

tracing) have been implemented in the United States, the aggregate impact of NPIs on cumulative infections and deaths in the absence of any pharmaceutical intervention comprised the base case. Subsequent simulations evaluating vaccine and mAbs were conducted on a background of NPIs; the mAbs were evaluated on top of vaccines to reflect real-world mitigation strategies. Administration of mAbs was exclusively to unvaccinated individuals, as vaccines are used to prevent infection, and mAb efficacy is reduced in subjects with previous initiation of the endogenous immune response (e.g., vaccination).[3,7]

All simulations with vaccines, including scenarios with mAbs, assumed a vaccine dosing interval of 25 days with efficacy of 52% and 95% after the first and second doses, respectively[22]; vaccine protection was assumed to start 7 days after the first dose. Individuals were prioritized who are either ≥ 65 years of age, living in nursing homes, or are medical workers; additional vaccine doses are distributed to those ≥ 60 years of age or critical workers with greater social mixing.

Viral load served as proxy for infectiousness,[23] and SARS-CoV-2 infectiousness was assumed to be proportional to the decimal logarithm of viral load in excess of 100 copies/mL, beginning 2 days following the first 2 days postinfection (latent period).[24,25] A similar approach has been used for influenza.[18,19] A viral kinetic model captured the population variability of viral load profiles,[26] with the assumption that viral loads were highest at symptom onset, consistent with studies indicating that presymptomatic individuals are responsible for a large proportion of virus transmission.[13,14] In the simulations, the median duration of infectivity in the absence of treatment was 9 days (range of 2–18 days). The impact of mAbs on median duration of infectivity varies with time of treatment; the reduction is 88% if administered 1 day after infection, 38% if treated at day 5 (time to symptom development), and 0% at day 10 (**Table S10**). For symptomatic patients, we assumed 71% reduction in hospitalization and mortality risk.[27]

The simulations assumed full utilization of 300,000 doses per month (10,000 doses/day) starting in January 2021, for a total of 900,000 doses with homogenous drug access across the United States (i.e., equal opportunity of unvaccinated individuals to receive drug whenever eligible regardless of county or region). A sensitivity analysis was also conducted to interrogate the impact of 600,000 per month for a total of 1.8 million doses.

Assuming a 15% vaccine rollout, scenarios were simulated with mAbs as both active treatment and PEP, with doses allocated in a ratio of 1:2 (active treatment:PEP); PEP was defined as empiric administration to an unvaccinated person exposed to the virus through close contact but who does not present with symptoms and is of unknown COVID-19 status. Use of mAbs as PEP and early TasP also assumed use of the more convenient subcutaneous formulation.[28] Because the proportion of the US population vaccinated is increasing over time, a sensitivity analysis evaluated the impact of increasing vaccine rollout from 15% to 30% and 47%, while keeping mAb supply constant at 300,000 and 600,000 doses per month, regardless of the increase in vaccinations.[3,4] A sensitivity analysis was also conducted assuming 0% vaccination to clarify the benefits of mAbs and characterize their potential role under conditions relevant to a pre-vaccine pandemic preparedness scenario.

We also simulated scenarios with rapid diagnostic testing for use in the home setting, such as the one from Ellume, which has been approved for emergency use in the United States.[29] The assumption was that patients would test themselves multiple times until getting a perfect test result within 3 days (±1 day) of exposure and, if positive for COVID-19, would initiate mAb treatment the same day. With such testing, PEP may be more appropriately considered an early TasP strategy.

Projected outlook

Predicted mortality data from the IHME have indicated that although the number of deaths will continue to decrease, 58,368 deaths were still expected to occur between April 13 and August 1, 2021.[30] To further explore how the model can be used, a model simulation calibrated to these predictions was conducted to project the number of deaths that could be averted during this less aggressive phase of the pandemic when the rate of mortality was declining. The model projections assumed deployment of 1.25 million doses of mAbs with prioritization to those ≥ 65 years old and use of 75% of the total drug supply during the first 50 days to temporally coincide with the peak of mortality.

RESULTS

In the base case, there were ~ 103 million cumulative infections and 338,000 cumulative deaths over the simulation time period. Vaccine rollout of 15% averted almost 6 million infections and 43,000 deaths (**Figure 3**, blue bar), corresponding to reductions of ~ 6% and 13% in infections and mortality, respectively. In an analysis that increased the dosing interval from 25 to 60 and 90 days, these effects were relatively constant (Table **S22**), suggesting that real-world deviations from the assumed dosing interval are unlikely to affect model predictions.

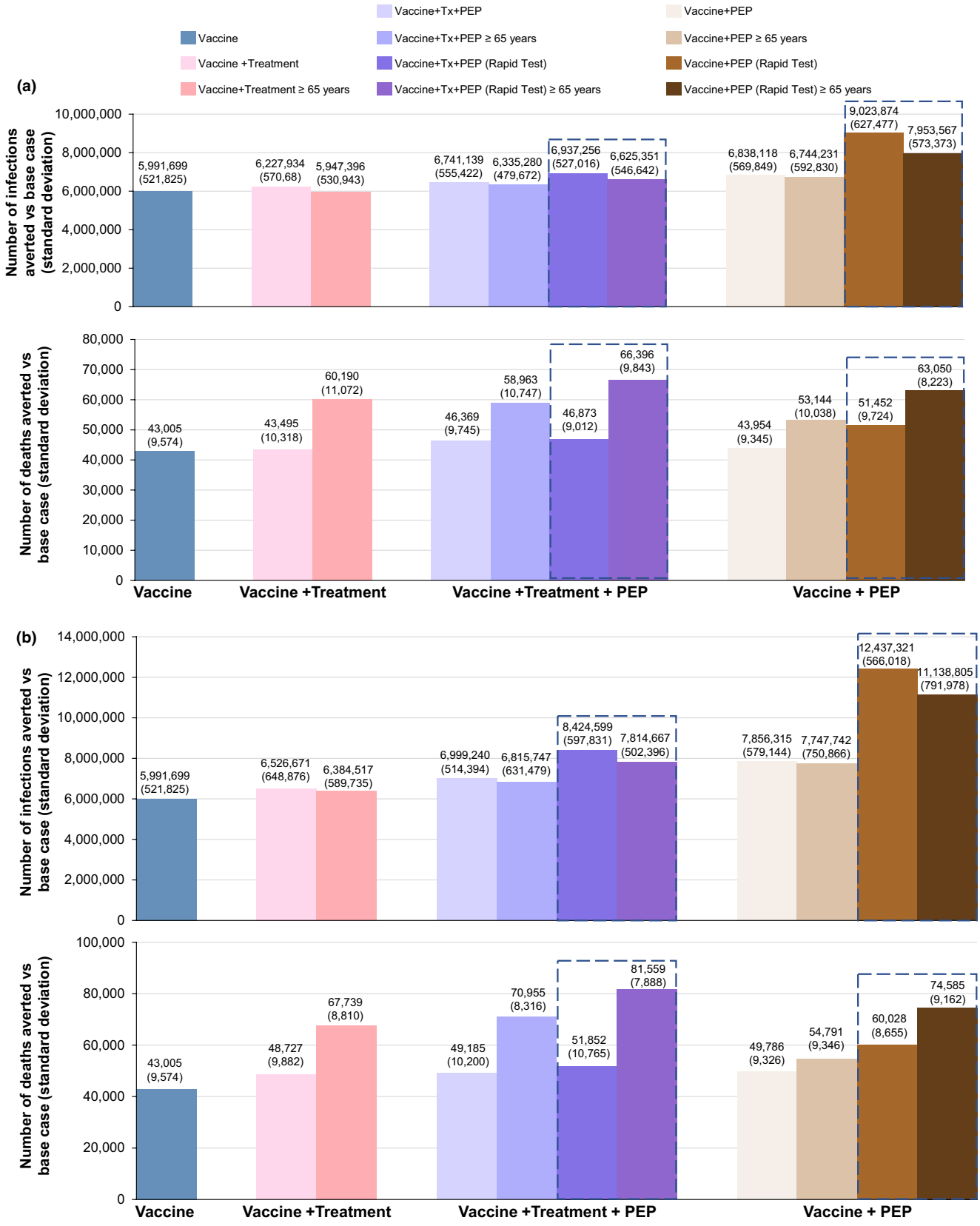
The mAbs as active treatment combined with vaccines (**Figure 3a**, pink bars) show overall effects that are similar to vaccine alone. However, specifically targeting this active treatment on top of a vaccine program to those ≥ 65 years of age results in ~ 60,000 deaths averted, 40% more than with vaccine alone.

The mAbs as both active treatment and PEP (**Figure 3a**, purple bars) provide an incremental benefit of 8% relative to vaccine in the cumulative number of averted infections. However, targeting individuals ≥ 65 years of age results in a 37% increase in the number of averted deaths over vaccine.

Shifting allocation of mAbs solely for use as PEP instead of only as treatment further increased the benefits in the overall population (**Figure 3a**, brown bars); the number of averted infections (6.8 million) was ~ 14% higher than vaccine (6 million), while at the same time reducing mortality by 2%. When an older population is specifically targeted, a 24% reduction in mortality (53,000 averted deaths) is achieved relative to vaccine (43,000 averted deaths), although additional benefits did not extend to infections averted.

When mAbs were used as both treatment (i.e., symptomatic infections) and PEP under conditions of rapid testing, the number

Figure 3 Simulations of the impact of monoclonal antibody treatment and prophylaxis among unvaccinated individuals in combination with a vaccine program (15% rollout). Simulations were conducted using the model to determine the contributions of different mitigation strategies on disease transmission (cumulative infections and deaths) during the aggressive phase of the pandemic (October 26, 2020–April 4, 2021). Monoclonal antibody supply from January 2021 was 300,000 doses/month (a) and 600,000 doses/month (b; sensitivity analysis), with total supply of 900,000 and 1.8 million doses, respectively. Results are presented as the number of infections or deaths averted relative to a base case of an aggregate of non-pharmaceutical interventions, which was characterized by 102,946,388 cumulative infections and 338,222 cumulative deaths over the time period. The colored columns reflect distinct paradigms, with shading indicating different scenarios within the paradigm. The columns enclosed by broken lines additionally incorporate the use of rapid diagnostic tests. PEP, postexposure prophylaxis; Tx, treatment.



of averted infections was 16% higher than vaccine, and when mAb allocation was shifted exclusively to PEP the number of averted infections was 51% higher (Figure 3a). While targeting those ≥ 65 years of age provided benefits of 11%–33% in reducing transmission, the number of averted deaths increased by 47%–54% (Figure 3a).

Doubling the supply of mAbs from 300,000 to 600,000 per month (**Figure 3b**) with full utilization resulted in incremental benefits on top of vaccine that were greater than observed at the lower drug supply (**Figure 3a**). Using rapid testing and allocating mAb to PEP at the higher supply averted more than twice the number of infections (12.4 million) than with vaccine, with a 40% reduction in mortality (**Figure 3b**). Similarly, targeting the elderly averted almost twice as many deaths and 86% more infections than vaccine (**Figure 3b**).

Vaccine effects on reducing infections were proportional to the extent of vaccine rollout within the ranges we considered (**Figures 3, 4, Figure S13**); infections averted increased from ~6 million to 12 and 18 million as vaccinations increased from 15% to 30% and 47%, respectively. However, mAbs on a vaccine background consistently avert more infections and deaths than vaccine alone regardless of the proportion of the population vaccinated (**Figures 3, 4, Figure S13**). The same pattern was observed in all scenarios: higher numbers of averted infections and deaths when mAb allocation is shifted to PEP, amplified effects when combined with rapid testing, and a sensitivity to mAb utilization. For example, even at 47% vaccine rollout (**Figure S13**), monthly mAb supplies of 300,000 and 600,000 used as early TasP (i.e., PEP combined with rapid testing) resulted in incremental benefits of 1.88 million and 3.85 million more averted infections, respectively, than vaccine. Similarly, using this scenario and targeting an older population results in ~11,600 and 18,800 more averted deaths at the two mAb supply levels, respectively.

As shown in **Figure 5**, trends in averting infections and mortality relative to a background of NPIs only (i.e., 0% vaccine) were similar to the other simulations; mortality reductions were greatest when targeting those ≥65 years old, and shifting mAb allocation to PEP, especially combined with rapid testing, incrementally reduced transmission. Transmission reduction was also closely related to mAb supply, with an approximate two-fold increase in averted infections when mAb availability was doubled (**Figure 5**).

In the projected outlook for the less aggressive pandemic phase, simulations calibrated to the IHME mortality predictions suggest that use of the mAbs could avert 24,650 of the 58,368 predicted deaths. These projections represent an ~42% reduction in mortality during this time period.

DISCUSSION

Insights on the effectiveness of concomitant mitigation strategies are increasingly important from the perspectives of public health and policy decision-making given the rapid course of the current pandemic, advances in treatment and vaccination, and the likelihood of other emerging infectious diseases. We therefore implemented a modeling and simulation approach to quantitatively evaluate the benefits of mAbs in reducing COVID-19 infections and mortality among unvaccinated individuals in a real-world dynamic setting where other mitigation strategies are being used concurrently. Although the use of mAbs as treatment has generally focused on reducing the risk of COVID-19 disease progression at the level of the individual patient, our results suggest an expanded role for mAbs. This role encompasses their empirical use as PEP for reducing overall transmission and deaths, and when combined with rapid diagnostic testing suggests an effective early TasP intervention.

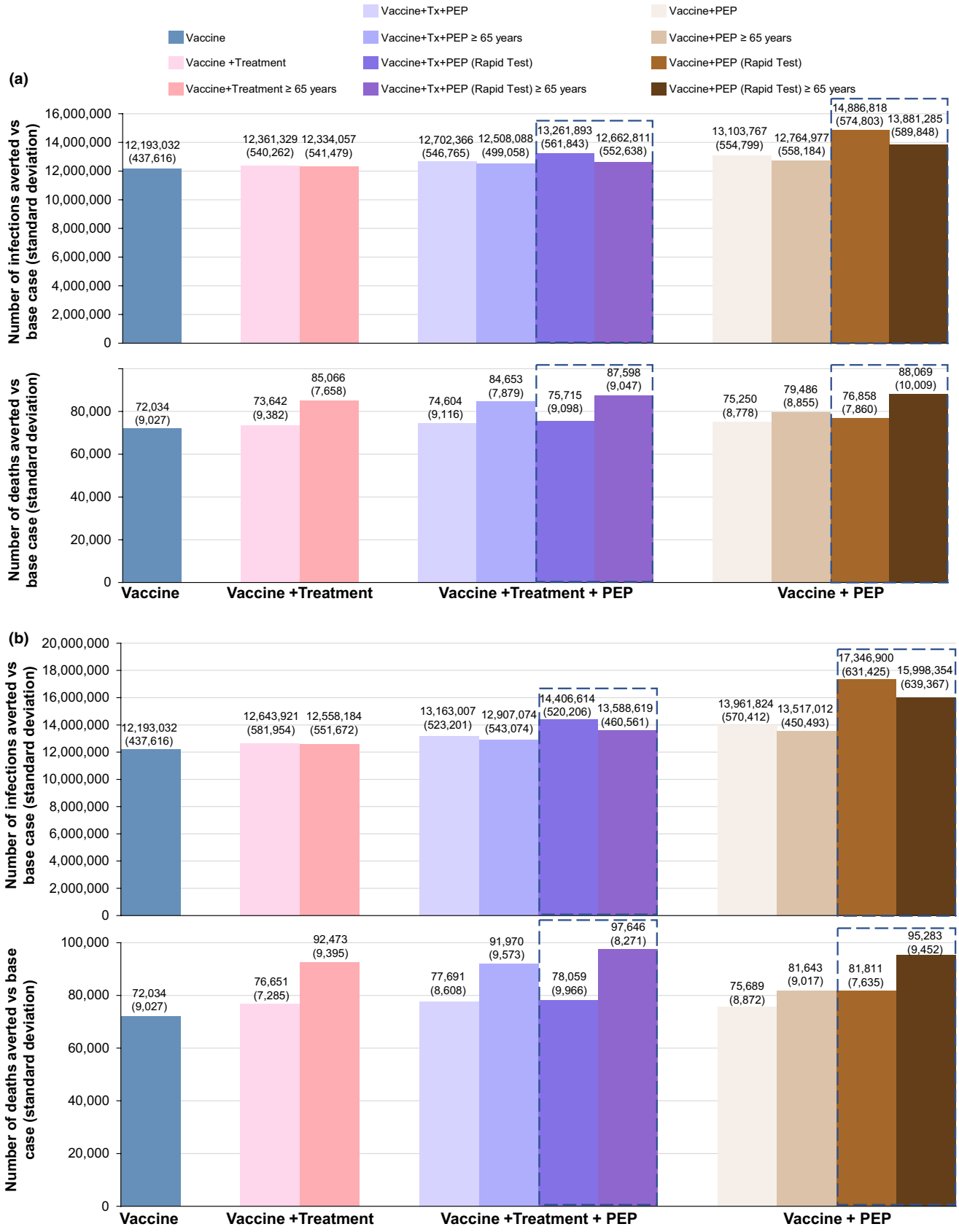
Our base case was the aggregate impact of NPIs. While NPIs can reduce or stop transmission,[1,2] they require strict and prolonged adherence that may be difficult to implement nationally due to potential social and economic consequences, suggesting the importance of additional strategies to reduce transmission even in the presence of vaccines. Widespread vaccination remains an essential component of COVID-19 management strategy, and our results confirm a vaccine program provides additional reductions in infections and deaths in the setting of continued use of NPIs. Other modeling studies have provided evidence of reduced transmission with this paradigm and have also emphasized the importance of adherence to NPIs even when implementing a vaccine program.[31,32]

Reducing infections with use of mAbs (and, by extension, potential use of other effective pharmaceutical interventions) was shown to be critically dependent on logistics, including time to treatment initiation. This time factor was exemplified by the use of mAbs in conjunction with rapid diagnostic testing, which further amplified the benefits of mAbs through earlier time-to-treatment. However, mAb administration outside of our assumption of treating the same day as positive test results would be expected to decrease the benefits, and a sensitivity analysis around such a delay between test results and treatment would be useful to evaluate in future model iterations.

Pairing testing with a readily accessible PEP regimen offers substantial impact on both disease transmission and clinical outcomes by identifying and treating presymptomatic individuals who are major contributors to transmission.[13,15,16,20] Earlier treatment consistently resulted in greater reductions in transmission and mortality, as also indicated by the increasing numbers of averted infections and deaths as mAb allocation shifted from active treatment alone, to treatment + PEP, to use only as PEP. This shift further suggests how mitigation strategies and implementation of TasP may be adapted as different modalities become available for treatment and prevention.

When targeted to those ≥65 years of age, the benefits of mAbs were greater on mortality than on transmission, with similar patterns observed at all levels of vaccine rollout. This differential

Figure 4 Sensitivity analysis of the impact of monoclonal antibody treatment and prophylaxis among unvaccinated individuals in combination with a 30% vaccine rollout. Simulations with the model were conducted under the same conditions as the main analysis but assuming a 30% vaccine rollout that was prioritized to those who are ≥65 years of age, living in nursing homes, or are medical workers, with additional doses distributed to those ≥60 years of age or essential workers with greater social mixing. Results are presented as the number of infections or deaths averted relative to a base case of an aggregate of non-pharmaceutical interventions (102,946,388 cumulative infections and 338,222 cumulative deaths) based on monoclonal antibody supply from January 2021 of 300,000 doses/month (**a**) and 600,000 doses/month (**b**). The colored columns reflect distinct paradigms, with shading indicating different scenarios within the paradigm. The columns enclosed by broken lines additionally incorporate the use of rapid diagnostic tests. PEP, postexposure prophylaxis; Tx, treatment.


(a)
Vaccine
Vaccine +Treatment
Vaccine+Treatment ≥ 65 years
Vaccine+Tx+PEP
Vaccine+Tx+PEP ≥ 65 years
Vaccine+Tx+PEP (Rapid Test)
Vaccine+Tx+PEP (Rapid Test) ≥ 65 years
Vaccine+PEP
Vaccine+PEP ≥ 65 years
Vaccine+PEP (Rapid Test)
Vaccine+PEP (Rapid Test) ≥ 65 years
Number of infections averted vs base case (standard deviation)
16,000,000
14,000,000
12,000,000
10,000,000
8,000,000
6,000,000
4,000,000
2,000,000
0
12,193,032 (437,616)
12,361,329 (540,262)
12,334,057 (541,479)
12,702,366 (546,765)
12,508,088 (499,058)
13,261,893 (561,843)
12,662,811 (552,638)
13,103,767 (554,799)
12,764,977 (558,184)
14,886,818 (574,803)
13,881,285 (589,848)
Number of deaths averted vs base case (standard deviation)
80,000
60,000
40,000
20,000
0
72,034 (9,027)
73,642 (9,382)
85,066 (7,658)
74,604 (9,116)
84,653 (7,879)
75,715 (9,098)
87,598 (9,047)
75,250 (8,778)
79,486 (8,855)
76,858 (7,860)
88,069 (10,009)
Vaccine
Vaccine +Treatment
Vaccine +Treatment + PEP
Vaccine + PEP
(b)
Number of infections averted vs base case (standard deviation)
20,000,000
18,000,000
16,000,000
14,000,000
12,000,000
10,000,000
8,000,000
6,000,000
4,000,000
2,000,000
0
12,193,032 (437,616)
12,643,921 (581,954)
12,558,184 (551,672)
13,163,007 (523,201)
12,907,074 (543,074)
14,406,614 (520,206)
13,588,619 (460,561)
13,961,824 (570,412)
13,517,012 (450,493)
17,346,900 (631,425)
15,998,354 (639,367)
Number of deaths averted vs base case (standard deviation)
100,000
80,000
60,000
40,000
20,000
0
72,034 (9,027)
76,651 (7,285)
92,473 (9,395)
77,691 (8,608)
91,970 (9,573)
78,059 (9,966)
97,646 (8,271)
75,689 (8,872)
81,643 (9,017)
81,811 (7,635)
95,283 (9,452)
Vaccine
Vaccine +Treatment
Vaccine +Treatment + PEP
Vaccine + PEP

effect is not unexpected, because older patients are at higher risk of death but less likely to transmit the virus. However, because this population is prioritized for vaccination, the incremental difference in averted deaths relative to vaccine was diminished as the vaccine rollout increased.

Our simulations were conducted as vaccination was being rolled out, reflecting a particular time point in the pandemic. During this period, the benefits of mAbs for reducing the pandemic burden were robust at three levels of vaccine rollout (15%, 30%, and 47%), especially when mAbs were used as early TasP or specifically targeted to an older population, who may also serve as a proxy for other high-risk groups (i.e., younger individuals with multiple risk-related comorbidities). The observed relationship between vaccine rollout and averted infections is consistent with the reported association between vaccination and reduced transmission in a community setting.[33] Regardless of the proportion vaccinated, mAbs reduced infections and mortality relative to vaccine, although the magnitude of the difference was attenuated as the proportion of population vaccinated increased. The results under conditions of 0% vaccination showed that, not surprisingly, vaccination is the overall driver of averted infections. However, in the absence of a vaccination program, mAbs reduced mortality relative to NPIs when targeted to those ≥ 65 years old and substantially reduced transmission, especially when combined with rapid diagnostic testing. These results emphasize the utility of mAbs regardless of the proportion vaccinated, and have public health implications regardless of the pandemic source; as the effective reproductive number, $R(t)$, approaches 1, incremental benefits from an antiviral may still provide momentum in further reducing infections, thereby bringing $R(t)$ below 1. Recent evidence also suggests that receiving a mAb for COVID-19 prophylaxis does not affect the immune response that results from subsequent vaccination,[34] strengthening the combined role for these strategies in pandemic management.

The estimated impact is also sensitive to the mAb supply, with additional supply leading to larger benefits, which was especially noted in the 0% vaccine simulation. There are several implications regarding this observation. First, reducing logistical barriers to access and use will amplify reductions in transmission and improve patient outcomes. Although we assumed homogenous drug access across the United States, population heterogeneity was already accounted for by the model, as drug use would be driven by the rate of infection, which is in turn driven by the population interaction and density. Currently, mAbs are underutilized for treatment and are approved for prophylaxis only in specific populations. This underutilization may arise from several sources, including lack of clarity of their potential contribution to reducing transmission. Our analysis suggests that broader use of mAbs for PEP and early TasP can specifically contribute to reducing the pandemic burden when included as part of current mitigation policies. Second, the simulations provide guidance on allocation of resources and lay a groundwork that can be applied to determine strategies for future pandemic preparedness. While mAbs provide an example of how an anti-viral therapy can be used as a mitigation strategy, the results are applicable to any intervention that can be used adjunctively with vaccination and are relevant for potentially guiding use of mAbs with similar characteristics for management of other outbreaks. Third, the relationship between mAb availability and reduced transmission in the absence of a vaccine program suggests the importance for pandemic preparedness of maintaining an infrastructure that enables production scalability and deployment of diagnostics and treatments while vaccines may still be in the developmental stage.

This study evaluated the effects of mAbs during two time periods that are relevant to pandemics in general; an aggressive phase, and a less aggressive period projected to be associated with a decreasing rate of mortality, which also reflects reduced transmission. Both periods showed that mAbs conveyed substantial benefits, suggesting that even as the pandemic may be tapering, mortality may still be averted with utilization of appropriate strategies. Such information is also relevant for strategic planning for potential regional or seasonal outbreaks and the emergence of VOC that remain sensitive to treatment. In this regard, the results may be generalizable to the Delta variant (B.1.617.2),[35] but are not applicable to conditions under which the Omicron variant (B.1.1.529) is prevalent. There is much yet to be learned about mutant emergence and the role of mAbs. However, such emergence may be considered less likely with dual mAbs than a single mAb, and selective pressure for mutational emergence derives from multiple sources, including vaccines and NPIs. Nevertheless, the model provides a template that, by modifying the input parameters as new data on next generation mAbs become available, can be applied for evaluating how implementation of management strategies can mitigate transmission and outcomes.

We recognize that the current analysis reflects the US public health system, and that extrapolation to other health systems may require case-by-case evaluation. Similarly, whereas we conducted sensitivity analyses on key factors that may impact mAb use and outcomes, identifying the factors having the greatest impact on outcomes was beyond scope of the current study but should be considered for future investigation.

There are several limitations to this analysis, including that the simulations reflect specific time periods of the US epidemic, although, as mentioned, results from the projected outlook indicate a substantial reduction in mortality even as overall mortality is decreasing. We also made assumptions around vaccine effectiveness after the first dose, despite recent studies suggesting that it may be higher.[36,37] Although our assumption was based on data available at the time of model development, the sensitivity analysis on increased vaccine rollout, which also serves as a proxy for higher proportions of immunized individuals in the population, provides additional evidence of the incremental benefits that may still be achieved with mAbs. Another limitation is that the contact structure in the model did not specifically consider superspreader events that can contribute to transmission. However, these events are stochastic, and although our analysis took the national population perspective rather than a local geographic perspective, the model may be amenable to more granularity with regard to local geography where a substantial proportion of secondary cases may result from superspreading of a small number of index cases. Such granularity at the local level would require a separate analysis that was not an

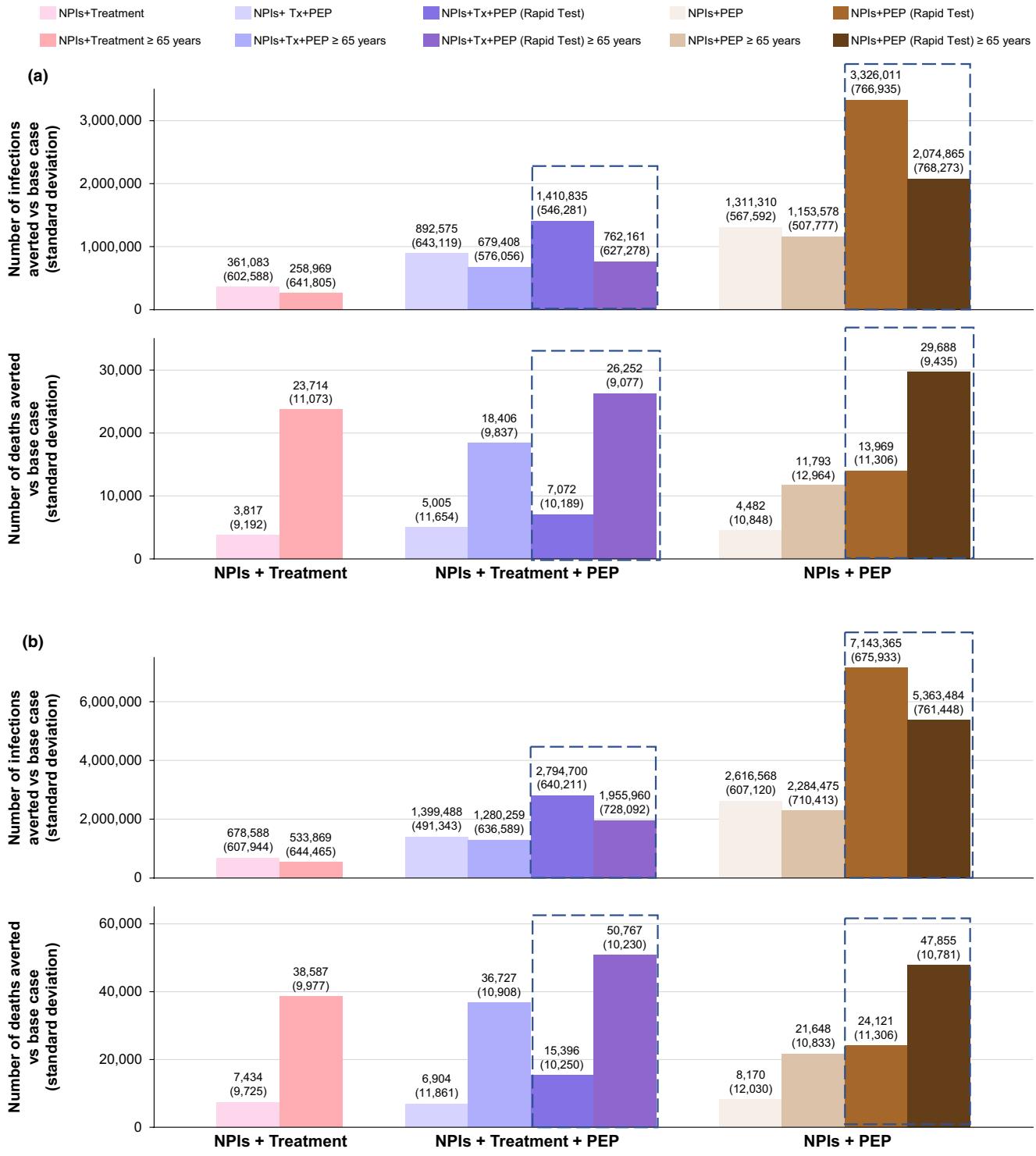


Figure 5 Simulations of the impact of monoclonal antibody treatment and prophylaxis on a background of non-pharmaceutical interventions (NPIs) in the absence of a vaccination program. Simulations were conducted using the model to determine the contributions of different mitigation strategies on disease transmission (cumulative infections and deaths) during the aggressive phase of the pandemic (October 26, 2020–April 4, 2021). Monoclonal antibody supply from January 2021 was 300,000 doses/month (**a**) and 600,000 doses/month (**b**), with total supply of 900,000 and 1.8 million doses, respectively. Results are presented as the number of infections or deaths averted relative to a base case of an aggregate of NPIs, which was characterized by 102,946,388 cumulative infections and 338,222 cumulative deaths over the time period. The colored columns reflect distinct paradigms, with shading indicating different scenarios within the paradigm. The columns enclosed by broken lines additionally incorporate the use of rapid diagnostic tests. PEP, postexposure prophylaxis; Tx, treatment.

objective of the current study. Although reductions in infections have implications for an overburdened healthcare system by potentially reducing hospitalizations and use of intensive care, this was beyond the scope of the current analysis and would need additional calibration of the model on relevant data. Finally, we did not consider potential VOC when simulating the impact of mitigation strategies on the pandemic. As mutated viruses are indicative of a form of rapid, multistage evolutionary jumps (saltational evolution), this is an important component that will need to be characterized as data become available. The modular nature of the model makes it amenable to the potential occurrence of saltational evolution in this and future pandemics, for example, by inclusion of a "viral resistance module."

CONCLUSION

We demonstrate how anti-viral mAbs may be used to suppress SARS-CoV-2 virus transmission and improve clinical outcomes even as the proportion of the population vaccinated increases and mortality decreases. These findings can be extrapolated to other anti-viral interventions with similar efficacy profiles to anti-spike mAbs. Although vaccines may provide long-term benefits, our results suggest that the near-term use of mAbs for early treatment and PEP provides additional public health benefits by reducing SARS-CoV-2 transmission and related mortality in the real-world setting. Increasing drug supply and utilization while lowering logistical barriers to access are integral to such mitigation strategies in addition to targeting specific populations at high risk (e.g., ≥ 65 years of age) and increasing use of rapid testing. The benefits of mAbs appeared to be robust even as the vaccine rollout increased, and these benefits are likely to be enhanced in scenarios where rapid uptake of vaccine is not feasible. These results may help guide resource allocation and health policy decisions for COVID-19 management, and can serve as a template for strategic planning to enable future pandemic preparedness for emerging infectious diseases of similar transmission characteristics.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

Writing support during manuscript development was provided by E. Jay Bienen, PhD, and was funded by Regeneron Pharmaceuticals. The authors thank Prime, Knutsford, United Kingdom, for manuscript formatting, which was funded by Regeneron Pharmaceuticals.

FUNDING

The study was sponsored by Regeneron Pharmaceuticals, Inc.

CONFLICTS OF INTEREST

M.A.K., A.K., M.H., H.E.H., M.K.T., D.J.C., N.A.-H., and M.O'B. are employees and shareholders of Regeneron Pharmaceuticals, Inc. L.Q., K.P., T.O., R.C., and P.F.S. are employees of Certara, which received financial support from Regeneron Pharmaceuticals, Inc. for this work. W.W. is an employee of Certara, which received financial support from Regeneron Pharmaceuticals, Inc. for this work; is a Statistics and Modeling Advisor for 1Day Sooner, a COVID-19 human challenge trials advocacy group; and a consultant, working on COVID-19 modeling, for University of Chicago Development Innovation Lab. M.S.C. is co-chair of the HPTN and CoVPN supported by NIH research funding. In addition, the author serves on an advisory board for Aerium, Atea and GSK. R.V.B. declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

M.K., A.K., L.Q., W.W., K.P., and P.S. designed and performed the research. All authors analyzed the data and wrote the manuscript.

DATA AVAILABILITY STATEMENT

All data are available in the main text or the **Supplementary Materials**.

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