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Modeling the population-level impact of treatment on COVID-19 disease and SARS-CoV-2 transmission

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ABSTRACT

Different COVID-19 treatment candidates are under development, and some are becoming available including two promising drugs from Merck and Pfizer. This study provides conceptual frameworks for the effects of three types of treatments, both therapeutic and prophylactic, and to investigate their population-level impact, to inform drug development, licensure, decision-making, and implementation. Different drug efficacies were assessed using an age-structured mathematical model describing SARS-CoV-2 transmission and disease progression, with application to the United States as an illustrative example. Severe and critical infection treatment reduces progression to COVID-19 severe and critical disease and death with small number of treatments needed to avert one disease or death. Post-exposure prophylaxis treatment had a large impact on flattening the epidemic curve, with large reductions in infection, disease, and death, but the impact was strongly age dependent. Pre-exposure prophylaxis treatment had the best impact and effectiveness, with immense reductions in infection, disease, and death, driven by the robust control of infection transmission. Effectiveness of both pre-exposure and post-exposure prophylaxis treatments was disproportionately larger when a larger segment of the population was targeted than a specific age group. Additional downstream potential effects of treatment, beyond the primary outcome, enhance the population-level impact of both treatments. COVID-19 treatments are an important modality in controlling SARS-CoV-2 disease burden. Different types of treatment act synergistically for a larger impact, for these treatments and vaccination.

1. Introduction

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and associated Coronavirus Disease 2019 (COVID-19) continue to present a global health challenge (John Hopkins University Coronavirus resource center, 2021), a burden to healthcare systems (Legido-Quigley et al., 2020), and a cause of economic disruption (McKibbin and Fernando, 2020). While vaccination remains the fundamental solution for controlling and containing the pandemic (Makhoul et al., 2020), there are challenges to increasing vaccine coverage (Wouters et al., 2021; Schwarzingler et al., 2021), and emergence of variants of concern could reduce vaccine efficacy (World

Health Organization, 2021; Abu-Raddad et al., 2021; Chemaitelly et al., 2021; Tang et al., 2021). SARS-CoV-2 treatments may thus offer an additional tool to help control this pandemic and to reduce its disease burden, such as two promising drugs from Merck and Pfizer (Leonhardt, 2021; Merck and Ridgeback's, 2021; Mahase, 2021). Clinical trials are being conducted to assess efficacy and safety of various types of SARS-CoV-2/COVID-19 treatments, with different mechanisms of action (Rosa and Santos, 2020; Ito et al., 2020; Milken Institute Faster Cures, 2021; The New York Times, 2020). Experience with other infectious diseases, such as HIV (Granich et al., 2009; Cohen et al., 2011) and hepatitis C virus (Ayoub et al., 2020; Ayoub and Abu-Raddad, 2019), have demonstrated the utility of treatment programs as

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integral components of efforts to reduce infection transmission and associated disease burden.

Assessment of the potential population-level impact of candidate drug treatments through mathematical modeling is a component of drug development, licensure, decision-making, and treatment cost administration, just as it is for vaccines (Makhoul et al., 2020; McLean and Blower, 1995; Wells et al., 2015; Boily et al., 2012; Abu-Raddad et al., 2007; Michael et al., 2007; Alsallaq et al., 2010). In particular, modeling can be used to define the drug’s key preferred product characteristics, by estimating levels of efficacy and mechanisms of action that are necessary to generate the desired population-level impact and to identify priority populations for optimal effectiveness, thereby providing early guidance to developers, manufacturers, and regulators about candidates that are likely to maximize public health impact and cost-effectiveness, as is typically done for vaccines (Boily et al., 2012; Hill et al., 2019; Sah et al., 2019).

Against this background, the objectives of this study were to provide conceptual frameworks for potential effects of three types of treatments, both therapeutic and/or prophylactic, and to investigate the population-level impact of these treatment types. The overarching goal of the study was to provide scientific evidence that could inform and accelerate drug development and licensure, at a critical time for such development. The modeling was applied to the United States population as a relevant and illustrative example.

2. Methods

2.1. Mathematical models and parameterization

Age-structured deterministic compartmental models were constructed, building on our earlier calibrated models (Makhoul et al., 2020; Ayoub et al., 2020; Ayoub et al., 2020; Makhoul et al., 2021;

Abu-Raddad et al., 2021; Ayoub et al., 2021; Seedat et al., 2021; Ayoub et al., 2021; Abu Raddad et al., 2020; Ayoub et al., 2020) of SARS-CoV-2 transmission dynamics to include effects of potential treatments against this infection. The resulting models were based on current understanding of SARS-CoV-2 natural history and epidemiology and consisted of sets of coupled nonlinear differential equations that stratified the population into compartments according to age group (0–9, 10–19, ..., ≥80 years), infection status, infection stage (mild (including also asymptomatic), severe, and critical), COVID-19 disease stage (severe, critical), and treatment status.

Following a latency duration, infected individuals were modeled to develop mild (or asymptomatic) infection followed by recovery, or severe infection followed by severe disease and then recovery, or critical infection followed by critical disease and either recovery or mortality. Recovered individuals were assumed to be protected against reinfection (Abu-Raddad et al., 2020; Abu-Raddad et al., 2021; Abu-Raddad et al., 2021; Chemaitelly et al., 2021). Mixing between individuals in different age groups was described by an age-mixing matrix that allows a variety of mixing patterns. Assortativeness in mixing was assumed not to vary regardless of the presence or absence of public health restrictions. The degree of assortativeness was based on model fitting in mathematical modeling studies for SARS-CoV-2 infection (Abu-Raddad et al., 2021; Ayoub et al., 2021; Ayoub et al., 2021). All infections were assumed equally infectious regardless of the presence or absence of symptoms.

Detailed descriptions of each treatment model and associated schematic diagram are found in the Supplementary Materials (SM). Models were coded and analyzed using MATLAB R2019a (MATLAB®, 2019). Details of model parameters, values, and justifications are in Table S2.

2.2. Types of treatments

Impacts of three types of potential treatments were investigated: i)

Table 1
Summary of treatment types and scenarios investigated in this study.

Treatment type	Mechanism of action	Drug efficacy symbol/description	Explored scenarios	Illustration of mechanisms of action
Severe and critical infection treatment	Administered only to persons with severe and critical infection.	DE_{SC} : Treatment efficacy in preventing progression to severe or critical disease (the primary efficacy outcome for this treatment). DE_M : Treatment efficacy in preventing mortality among those with critical disease.	1) $DE_{SC} = 50\%$, but $DE_M = 0\%$ 2) $DE_M = 50\%$, but $DE_{SC} = 0\%$ 3) $DE_{SC} = DE_M = 50\%$ 4) Coverage was assumed to reach 80%	Fig. S1
Post-exposure prophylactic treatment	Administered to persons who are latently infected, but not yet infectious.	DE_{PostEP} : Post-exposure treatment efficacy in preventing progression of infection (the primary efficacy outcome for this treatment). DE_{SC} : Treatment efficacy in preventing progression to severe or critical infection/disease. DE_P : Treatment efficacy in reducing duration of infectiousness among those with mild (or asymptomatic) infection.	1) $DE_{PostEP} = 50\%$, but $DE_{SC} = 0\%$ and $DE_P = 0\%$ 2) $DE_{SC} = 50\%$, but $DE_{PostEP} = 0\%$ and $DE_P = 0\%$ 3) $DE_P = 50\%$, but $DE_{PostEP} = 0\%$ and $DE_{SC} = 0\%$ 4) $DE_{PostEP} = DE_P = 50\%$, but $DE_{SC} = 0\%$ 5) Coverage was assumed to reach 80%	Fig. S2
Pre-exposure prophylactic treatment	Administered to persons who are still susceptible and unexposed to the infection.	DE_{PreEP} : Pre-exposure treatment efficacy in preventing infection (the primary efficacy outcome for this treatment). DE_{SC} : Treatment efficacy in preventing progression to severe or critical infection/disease. DE_P : Treatment efficacy in reducing duration of infectiousness among those with mild (or asymptomatic) infection.	1) $DE_{PreEP} = 50\%$, but $DE_{SC} = 0\%$ and $DE_P = 0\%$ 2) $DE_{SC} = 50\%$, but $DE_{PreEP} = 0\%$ and $DE_P = 0\%$ 3) $DE_P = 50\%$, but $DE_{PreEP} = 0\%$ and $DE_{SC} = 0\%$ 4) $DE_{PreEP} = DE_P = 50\%$, but $DE_{SC} = 0\%$ 5) Coverage was assumed to reach 80%	Fig. S3

severe and critical infection treatment, ii) post-exposure prophylactic treatment, and iii) pre-exposure prophylactic treatment. Table 1 lists these types of treatment and their considered drug efficacies (that is product characteristics of candidate drugs), and Figs. S1-S3 provide conceptual and schematic illustrations of their effects and mechanisms of action.

We assumed that severe and critical infection treatment was administered to only persons with severe or critical SARS-CoV-2 infection. Treatment thwarts development of severe or critical COVID-19 disease with drug efficacy DE_{SC} (the primary efficacy outcome for this treatment). However, those successfully treated were assumed not to have acquired protective immunity against reinfection, as such treatment may interfere with development of natural immunity. For those who progress to critical disease despite treatment, treatment is still beneficial in preventing disease mortality, with efficacy DE_M . This treatment thus reduces development of full-blown disease, or reduces disease mortality of those with critical disease.

We further assumed that post-exposure prophylactic treatment was administered to persons who had been exposed to SARS-CoV-2 to prevent further infection progression with efficacy DE_{PostEP} (the primary efficacy outcome for this treatment). Therefore, the mechanism of action is similar to that of other post-exposure prophylactic treatments, such as those for HIV (Siedner et al., 2018), influenza (Oxford, 2007), and hepatitis B virus (HBV) (Watanabe et al., 2015). However, those successfully treated were assumed not to acquire protective immunity against reinfection. For those in whom infection progresses despite treatment, treatment is still beneficial in preventing severe or critical disease, with efficacy DE_{SC} . Moreover, for those who ultimately develop a mild infection despite treatment, the duration of infectiousness is assumed shorter by a fraction DE_p (that is the treatment could accelerate resolution of the infection, as it does for influenza treatment with antivirals (Oxford, 2007)). Therefore, this type of treatment generally thwarts progression of infection, but in cases in which it does not, it reduces development of full-blown disease and accelerates resolution of mild infection.

Pre-exposure prophylactic treatment was assumed to have a mechanism of action similar to that of pre-exposure prophylactic (“PrEP”) treatment for HIV (Spinner et al., 2016; LeVasseur et al., 2018) or malaria (Baird et al., 2003). Treatment is administered to those who are still susceptible and unexposed to the infection and it prevents infection, as a vaccine does (Makhoul et al., 2020; Makhoul et al., 2021), with efficacy DE_{PreEP} (the primary efficacy outcome for this treatment). For those who are infected despite treatment, the treatment is still beneficial in preventing severe or critical disease, with efficacy DE_{SC} . Moreover, for those who develop a mild infection despite treatment, the duration of infectiousness is assumed shorter by a fraction DE_p . This type of treatment thus generally prevents infection as would a vaccine, but if not, it reduces development of full-blown disease and accelerates resolution of mild infections in “breakthrough” infections, that is infections acquired despite the treatment.

2.3. Analysis scenarios

To provide an example and proof-of-concept of the population-level impact of different treatment types, models were applied generically to a SARS-CoV-2 epidemic in a national population of the size and age structure of the U.S. population. Several scenarios were investigated for drug efficacies of each treatment type. These are summarized in Table 1. In all scenarios, and to assess optimal treatment potential, treatment was assumed to be scaled up at a fixed rate to reach the targeted coverage of 80% in the specific target population at the end of the epidemic cycle.

Two sets of analyses were conducted for each scenario, one assuming a basic reproduction number $R_0 = 3$, that is assuming a natural course of infection in the absence of social and physical distancing restrictions (He et al., 2020; MIDAS Online COVID-19 Portal, 2020), as one purpose of the treatments is to avoid such restrictions, and one assuming $R_0 = 1.5$, that is

in concert with social and physical distancing restrictions. Since the overall level of SARS-CoV-2 ever infection in the global population remains relatively low (Ayoub et al., 2021; Ayoub et al., 2021), baseline analyses were conducted assuming a generic case in which population immunity remains limited (set at 0%) at the onset of treatment interventions. Higher levels of population immunity were investigated in sensitivity analyses. Analyses were also conducted by targeting each treatment type to a specific age group, to investigate the age-dependency of the treatment impact. This was done by targeting the treatment to only one specific age group in the population at a time, while evaluating the impact of this age-targeted treatment in the entire population.

2.4. Measures of treatment impact

Population-level impact of different types of treatment was assessed by quantifying incidence, cumulative incidence, and reduction in incidence of infections, severe disease cases, critical disease cases, and deaths arising despite treatment, compared to the counter-factual scenario of no treatment. Treatment impact was further assessed by quantifying effectiveness, defined as the number of treatments (treated persons) needed to avert one infection or one adverse disease outcome (ratio of the number of treatments relative to that of averted outcomes). The latter measure is essentially a measure of cost-effectiveness, but with no costs included.

2.5. Sensitivity analyses

Sensitivity analyses were conducted to assess the impact of different values of the basic reproduction number (3 and 6), proportion of the population ever infected at onset of treatment (20% and 50%), treatment coverage (50% and 80%), and treatment efficacy (50% and 80%). Treatment effectiveness was also assessed by combining these values to yield the worst-case scenario and best-case scenario for treatment effectiveness. Additional univariable sensitivity analyses were performed to assess the range of outcomes by varying treatment efficacy over five-hundred model runs. In each run, Latin Hypercube sampling (Mckay et al., 1979; Sanchez and Blower, 1997) was applied to select the primary treatment efficacy of each treatment type within $\pm 30\%$ of its baseline value. The resulting distributions for treatment impact across all 500 runs were used to calculate predicted means and ranges of outcomes.

3. Results

Severe and critical infection treatment at $DE_{SC} = 50\%$ reduced the incidence peak of severe disease by 39.5%, critical disease by 39.4%, and mortality by 39.8% (Fig. 1A-C). Numbers of treatments needed to avert one severe disease case, one critical disease case, and one death were 2.5, 9.9, and 31.0, respectively. There was strong age-dependence in treatment effectiveness with fewer treatments needed to avert one death at older age (Fig. 1D). If, in addition to $DE_{SC} = 50\%$, there was auxiliary direct efficacy in preventing COVID-19 death ($DE_M = 50\%$), the impact of treatment in averting mortality nearly doubled (Fig. 1C) and only 20.8 treatments were needed to avert one death. The impact of this type of treatment in the absence (Fig. 1) or presence (Fig. S4) of social and physical distancing restrictions was similar.

While the impact of severe and critical infection treatment was only in prevention of COVID-19 disease and death, post-exposure prophylactic treatment also impacted infection transmission significantly and flattened and slowed the epidemic time course (Fig. 2). Treatment coverage was assumed at 80%. This is an aspirational target coverage, motivated by the concept of effective contact tracing so that contacts are promptly given the treatment. However, admittedly, this target coverage is unlikely to be reached given our current knowledge of the epidemiology of this infection and the technical resources available at present for contact tracing. At $DE_{PostEP} = 50\%$, in the absence of social

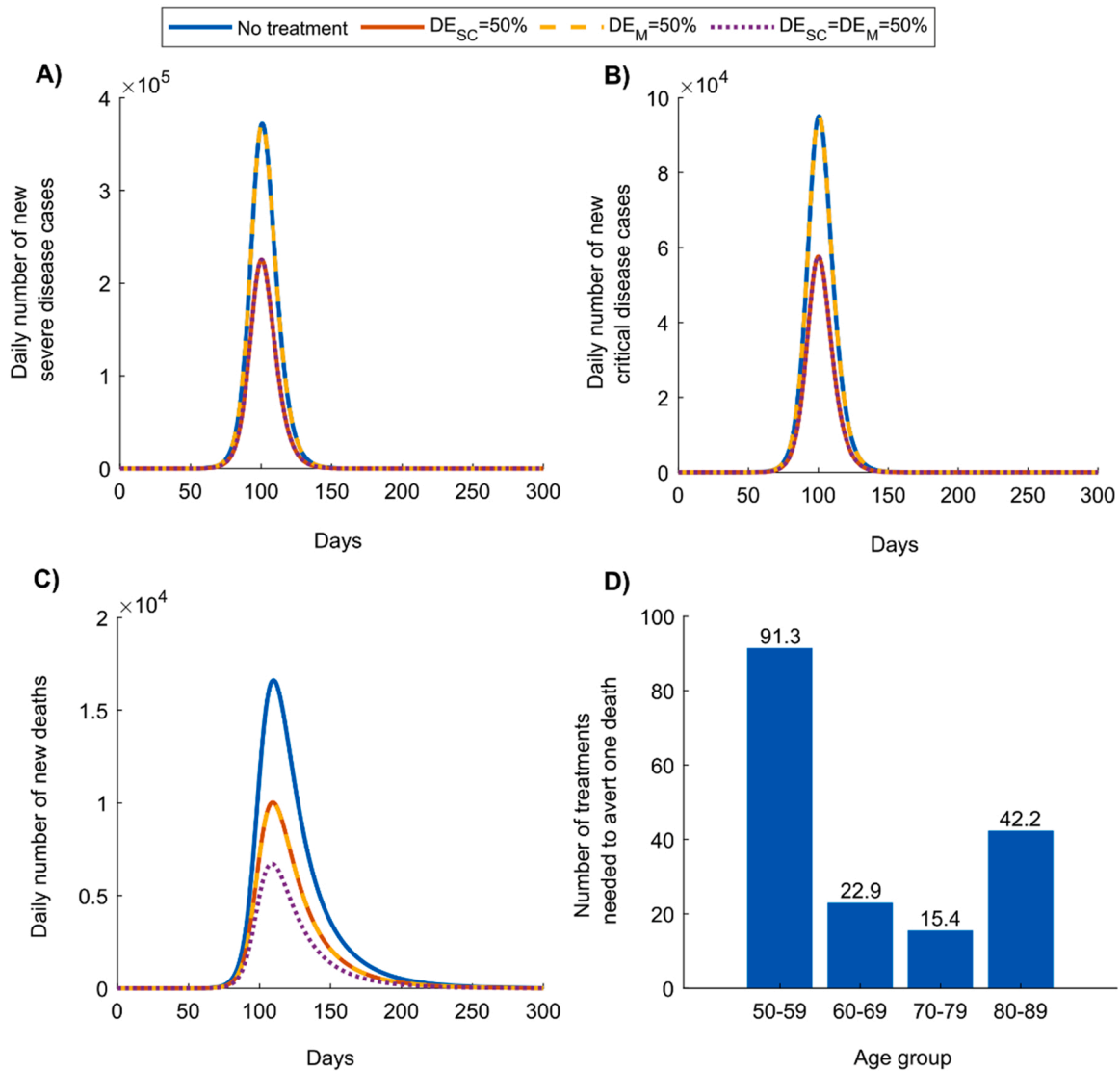


Fig. 1. Impact of SARS-CoV-2 severe and critical infection treatment. Impact of this treatment on the daily number of new A) severe disease cases, B) critical disease cases, and C) deaths at $DE_{SC} = 50\%$, $DE_M = 50\%$, and $DE_{SC} = DE_M = 50\%$ in the absence of social and physical distancing restrictions ($R_0 = 3.0$). D) The number of treatments needed to avert one death through age-group prioritization at $DE_{SC} = 50\%$. Results assuming social and physical distancing restrictions ($R_0 = 3.0$ reduced to $R_0 = 1.5$) are found in Fig. S4. Detailed description of these scenarios can be found in Table 1.

and physical distancing restrictions, peak incidence of infection, severe disease, critical disease, and death was reduced by 70.5%, 69.0%, 68.7%, and 59.0%, respectively, while cumulative numbers of infections, severe disease cases, critical disease cases, and deaths were reduced by 30.6%, 32.6%, 31.5%, and 33.5%, respectively. Additional potential efficacies of this treatment in reducing severe and critical disease (DE_{SC}) and accelerating resolution of mild infection (DE_P) also had a large impact in averting disease and reducing transmission, respectively (Fig. S5). Indeed, in the case of $DE_{PostEP} = DE_P = 50\%$ infection transmission was not sustainable, and the epidemic was fully contained. A similar large impact was found in presence of social and physical distancing restrictions (Fig. S6).

There was strong age-dependence in effectiveness of post-exposure prophylactic treatment, with fewer treatments needed to avert one disease or death outcome at older age, regardless of the absence (Fig. 3) or presence (Figure S7) of social and physical distancing restrictions. However, effectiveness was optimized when a larger segment of the population was targeted than when it was restricted to a specific age group, due to the disproportionately larger impact on reducing the onward transmission of the infection. By targeting the total population

with this treatment at $DE_{PostEP} = 50\%$ and 80% coverage, only 2.8, 94.0, 381.6, and 1112.7 treatments were needed to avert one infection, one severe disease case, one critical disease case, and one death, respectively.

Of the three types of treatments, pre-exposure prophylactic treatment had the best impact (Fig. 4) and effectiveness (Fig. 5). It largely controlled infection transmission and immensely reduced disease and death. At $DE_{PreEP} = 50\%$, even in the absence of social and physical distancing restrictions, peak incidence of each of infection, severe disease, critical disease, and death were reduced by 76.2%, 74.9%, 74.9%, and 67.5%, respectively (Fig. 4), while cumulative numbers of infections, severe disease cases, critical disease cases, and deaths were reduced by 51.8%, 52.6%, 52.1%, and 52.9%, respectively. Additional potential efficacies of this treatment in reducing severe and critical disease (DE_{SC}) and accelerating resolution of mild infection (DE_P) also helped significantly to avert disease and reduce transmission, respectively (Figure S8). In the case of $DE_{PreEP} = DE_P = 50\%$, infection transmission was not sustainable, and the epidemic was fully contained. A similar large impact occurred in the presence of social and physical distancing restrictions (Figure S9).

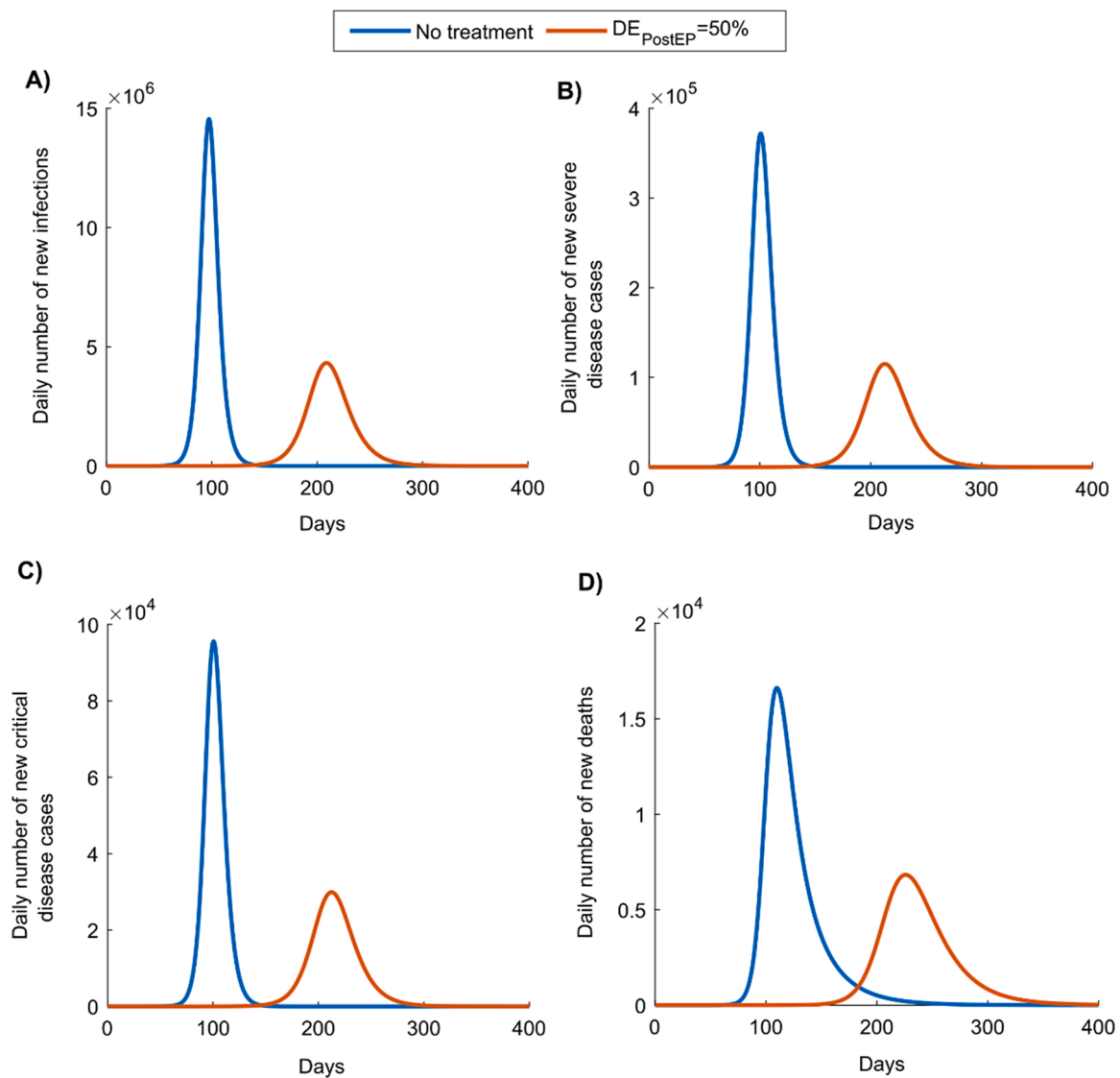


Fig. 2. Impact of SARS-CoV-2 post-exposure prophylactic treatment. Impact of this treatment on the daily number of new A) infections, B) severe disease cases, C) critical disease cases, and D) deaths at $DE_{PostEP} = 50\%$ in absence of social and physical distancing restrictions ($R_0 = 3.0$). Results including additional potential efficacies of $DE_{SC} = 50\%$ and $DE_p = 50\%$ are found in Fig. S5. Results assuming social and physical distancing restrictions ($R_0 = 3.0$ reduced to $R_0 = 1.5$) are found in Fig. S6. Detailed description of these scenarios can be found in Table 1.

There was strong age dependence in effectiveness of pre-exposure prophylactic treatment with fewer treatments needed to avert one disease or death outcome at older age, regardless of the absence (Fig. 5) or presence (Figure S10) of social and physical distancing restrictions. However, effectiveness was optimized when a larger segment of the population was treated than when a specific age group was targeted, due to the disproportionately larger impact on reducing onward transmission of the infection. By targeting the total population with this treatment at $DE_{PreEP} = 50\%$ and 80% coverage, only 1.6, 57.8, 228.3, and 708.8 treatments were needed to avert one infection, one severe disease case, one critical disease case, and one death.

The results of the sensitivity analyses assessing the impact of different values for the basic reproduction number, proportion of the population ever infected at onset of treatment, treatment coverage, and treatment efficacy, as well as worst-case scenario and best-case scenario for combination of these values, are shown in Table 2.

The results of the sensitivity analyses in assessing the range of outcomes by varying the primary treatment efficacy of each treatment type are shown in Figure S11.

4. Discussion

While vaccination remains the fundamental solution to the COVID-19 pandemic, the above results demonstrate that different types of COVID-19 treatments could also help to control this pandemic and its disease burden, provided that such treatments are widely deployed. Even the simplest type of treatment, severe and critical infection treatment, had a large impact in reducing severity and mortality. Post-exposure prophylactic treatment had a larger impact, as it affected not only disease, but also infection, thereby reducing onward transmission of the infection. Pre-exposure prophylactic treatment had the largest impact, as in reality, it is a form of vaccination.

These findings also demonstrated that these three types of treatment complement one another and act synergistically, as they are targeted to different populations. Severe and critical infection treatment is best targeted to persons at higher risk of developing severe or critical disease, such as persons > 50 years of age and those with multiple or specific comorbidities. Post-exposure prophylactic treatment can be targeted to those with suspected exposure to the infection, such as contacts of infected persons or individuals quarantined for other reasons. This type

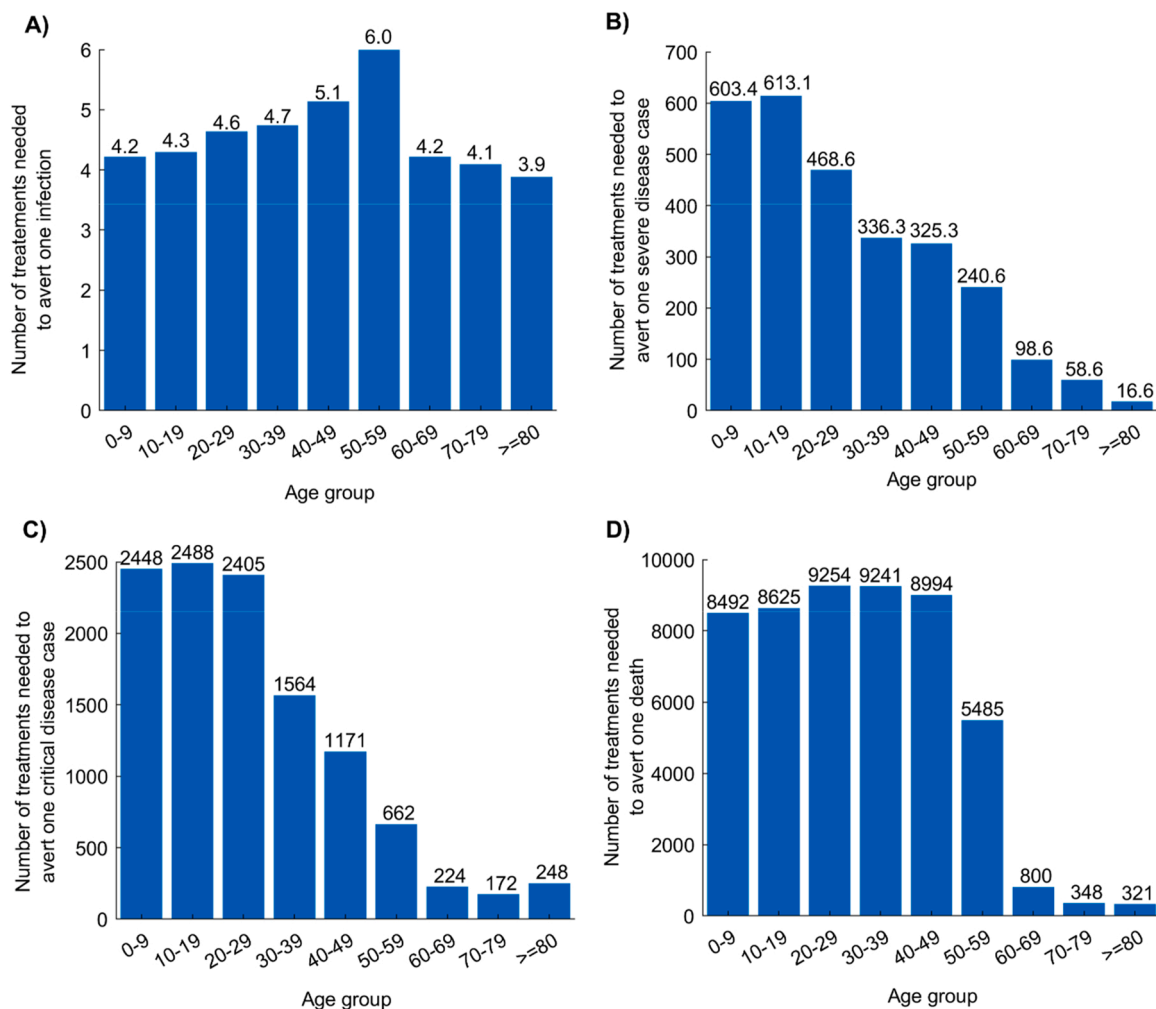


Fig. 3. SARS-CoV-2 post-exposure prophylactic treatment effectiveness by age group. The number of treatments that are needed for each age group to avert one A) infection, B) severe disease case, C) critical disease case, and D) death at $DE_{\text{PostEP}} = 50\%$ in the absence of social and physical distancing restrictions ($R_0 = 3.0$). Results assuming social and physical distancing ($R_0 = 3.0$ reduced to $R_0 = 1.5$) are found in Fig. S7. Detailed description of these scenarios can be found in Table 1.

of treatment, in a protocol that also includes real-time polymerase chain reaction (RT-PCR) testing, may even alleviate the need for quarantine, or at least reduce its duration, thereby minimizing the burden of quarantine measures on societies and economies. Pre-exposure prophylactic treatment can be used by those at higher risk of developing severe or critical disease if infected, especially at times of high incidence or during an ongoing outbreak, to minimize the likelihood of their acquiring the infection and developing COVID-19 disease. It can be further used as a form of travel medicine for those traveling to areas of high incidence, or more broadly used as a form of intervention to reduce infection acquisition and transmission in the population, just as a vaccine.

With the tepid scale-up of vaccination worldwide (Bloomberg, 2021), vaccine hesitancy (Wouters et al., 2021; Schwarzingler et al., 2021; BioSpace, 2021), and the circulation of variants of concern with evidence for lower vaccine efficacy against them (World Health Organization, 2021; Abu-Raddad et al., 2021; Chemaitelly et al., 2021; Tang et al., 2021; Abu-Raddad et al., 2021; European Centre for Disease Prevention and Control, 2020), it is possible that this pandemic may last for years, highlighting the need for treatment as an additional strategy to complement vaccination and to reduce disease burden. The emergence of variants of concern with higher infectiousness (World Health Organization, 2021; Abu-Raddad et al., 2021; Chemaitelly et al., 2021; Tang et al., 2021; Abu-Raddad et al., 2021; European Centre for Disease Prevention and Control, 2020) indicates that R_0 of this infection is probably increasing, leading to a higher threshold for herd immunity

(Anderson et al., 2020; Britton et al., 2020; Jeremijenko et al., 2021; Al-Thani et al., 2021). Perhaps as much as 90% of the population would have to be immune, thereby complicating efforts to fully control the infection. It seems not likely that vaccine coverage will reach the level needed for herd immunity, or that real-world vaccine effectiveness will ever be high enough, given the expanding number of variants of concern and waning of vaccine protection (Abu-Raddad et al., 2021; Chemaitelly et al., 2021; Tang et al., 2021; Abu-Raddad et al., 2021; Chemaitelly et al., 2021). This further affirms the need to continue development of novel treatments per the three types modeled in this study.

While treatments are likely to be developed for a specific primary outcome, such as efficacy in reducing COVID-19 severity and mortality or acquisition of infection, they may also have other downstream auxiliary effects (Table 1), just as for vaccines that can reduce infectiousness and change disease progression, in addition to preventing acquisition of infection (Makhoul et al., 2020; Abu-Raddad et al., 2007; Ayoub et al., 2020). The presence of these additional effects is supported by our growing knowledge of the natural history and immunology of this infection (Sette and Crotty, 2021). In the present study, we investigated the impact of such additional effects (note, for example, Fig. 1 and Figures S5 and S8). Their large impact suggests that the population-level impact of each treatment could be even higher than expected, considering only the primary treatment outcome. This further supports the role of treatment as an important approach to confronting this pandemic.

One finding of this study is that treatment coverage is an important

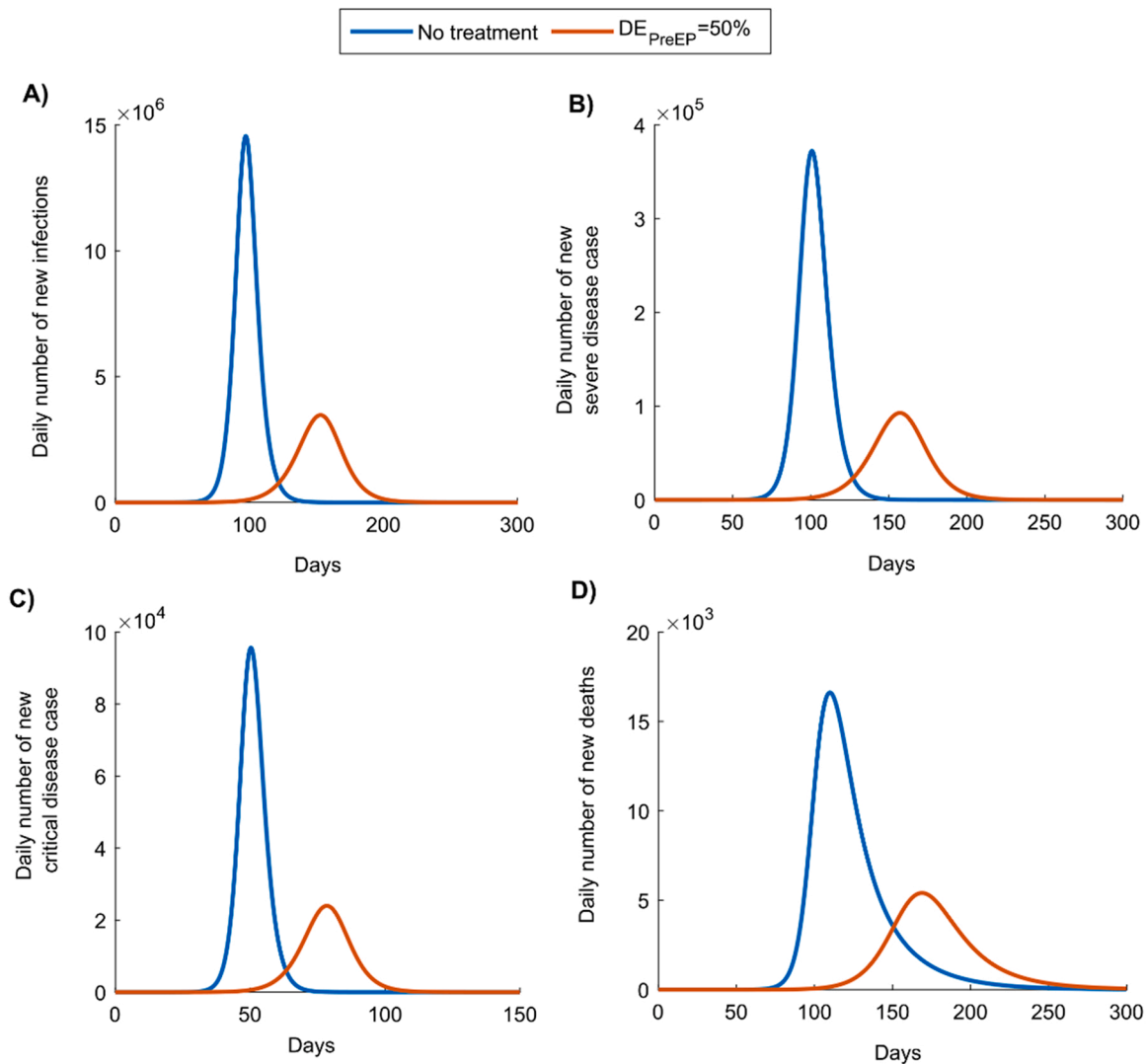


Fig. 4. Impact of SARS-CoV-2 pre-exposure prophylactic treatment. The impact of this treatment on the daily number of new A) infections, B) severe disease cases, C) critical disease cases, and D) deaths at $DE_{preEP} = 50\%$ in the absence of social and physical distancing restrictions ($R_0 = 3.0$). Results including additional potential efficacies of $DE_{SC} = 50\%$ and $DE_p = 50\%$ are found in Fig. S8. Results assuming social and physical distancing restrictions ($R_0 = 3.0$ reduced to $R_0 = 1.5$) are found in Figure S9. Detailed description of these scenarios can be found in Table 1.

factor in its impact, with disproportionately larger impact for higher coverage—the indirect effects on onward transmission are larger the more closely the population approaches the threshold of $R_0 = 1$. Treatment effectiveness was optimized when a larger segment of the population was targeted than when treatment was restricted to a specific age group. For instance, only 1.6 pre-exposure prophylactic treatments would be needed to avert one infection if this treatment achieves coverage of 80% in the wider population, but ≥ 2 treatments would be needed by targeting only a specific age group (Fig. 5).

The impact of treatment was investigated for a generic population to provide a “proof-of-concept” for the population-level impact of investigated types of treatment. Actual impact, however, can also depend on the epidemic phase in each country. The conceptual frameworks and modeling tools provided here can be applied to generate specific predictions for specific countries, factoring the actual epidemic phase at any given time.

5. Limitations of the study

Model estimations are contingent on the validity and generalizability of input data and parameters. While we used available evidence for

SARS-CoV-2 natural history and epidemiology, our understanding of its epidemiology is still evolving. We provided a conceptual framework for the potential effects of each type of treatment, but actual effects of each specific treatment will be clarified only after each drug product is developed and tested. Development of novel treatments may not also necessarily translate into broad use, as costs and logistics could be barriers to benefits from any novel COVID-19 intervention, especially in resource-limited settings. Despite these limitations, the developed models are sufficiently sophisticated to factor different potential effects for each type of treatment, for broad future use and applications, but still parsimonious enough to be tailored to available data.

In conclusion, COVID-19 therapeutic and prophylactic treatments can play an important role in controlling SARS-CoV-2 transmission and reducing COVID-19 disease burden, in a manner that complements vaccination and other interventions. Different types of treatment can act synergistically for a larger impact. With the likelihood that this pandemic may become protracted for years, investment in development of novel treatments of different effects may prove essential to reduce the burden of this infection and its toll on societies and economies.

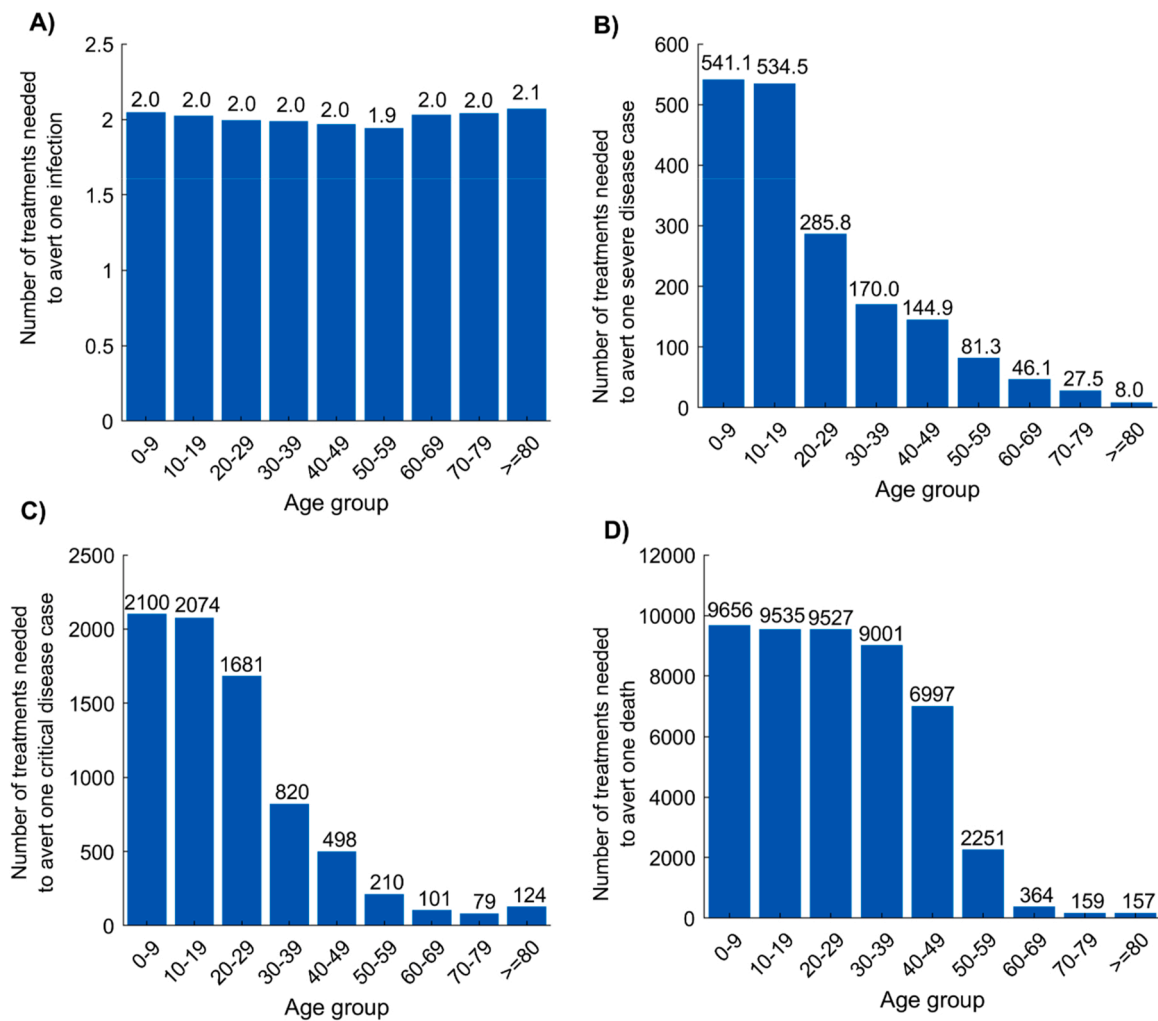


Fig. 5. SARS-CoV-2 pre-exposure prophylactic treatment effectiveness by age group. The number of treatments needed for each age group to avert one A) infection, B) severe disease case, C) critical disease case, and D) death at $DE_{PreEP} = 50\%$ in the absence of social and physical distancing restrictions ($R_0 = 3.0$). Results assuming social and physical distancing ($R_0 = 3.0$ reduced to $R_0 = 1.5$) are found in Fig. S10. Detailed description of these scenarios can be found in Table 1.

Table 2

Sensitivity analyses assessing the effectiveness of three types of SARS-CoV-2 treatments. For each treatment type, effectiveness is assessed at two different values of the basic reproduction number (3 and 6), proportion of the population ever infected at onset of treatment (20% and 50%), treatment coverage (50% and 80%), and treatment efficacy (50% and 80%). Treatment effectiveness is also assessed by combining these values to yield the worst-case scenario and best-case scenario for treatment effectiveness.

	Basic reproduction number		Proportion of the population ever infected at onset of treatment		Treatment coverage		Primary treatment efficacy		Worst scenario ^a Combination	Best scenario ^b Combination
	3.0	6.0	20%	50%	50%	80%	50%	80%		
Number of treatments needed to avert one severe or critical disease case										
Severe and critical infection treatment	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.3	2.0	1.3
Post-exposure prophylactic treatment	81.4	231.5	48.0	25.6	100.0	81.4	81.4	22.2	183.7	25.1
Pre-exposure prophylactic treatment	46.1	50.8	43.1	47.4	51.3	46.1	46.1	24.4	46.8	30.2

^a Combination of parameter values to yield the worst-case scenario for treatment effectiveness.

^b Combination of parameter values to yield the best-case scenario for treatment effectiveness.

Disclose funding received for this work

Others.

CRedit authorship contribution statement

M.M. constructed, coded, and parameterized the mathematical model, conducted the analyses and wrote the first draft of the paper. F.A supported model construction and parametrization. L.J.A. conceived and led the design of the study, construct, and parameterization of the mathematical model, and co-wrote the first draft of the article. All authors contributed to discussion and interpretation of the results and to the writing of the manuscript. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no competing interests.

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Data and materials availability

All data are available within the manuscript and its [supplementary materials](#). The codes programmed in MATLAB can be obtained by contacting the authors.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.epidem.2022.100567](https://doi.org/10.1016/j.epidem.2022.100567).

References

- Abu Raddad, L.J., 2020. Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic, 2020.2007.2016.20155317v20155312 (non-peer-reviewed preprint). medRxiv. <https://doi.org/10.1101/2020.07.16.20155317>.
- Abu-Raddad, L.J., 2020. Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting. *Clin. Infect Dis.* <https://doi.org/10.1093/cid/ciaa1846>.
- Abu-Raddad, L.J., 2021. Introduction and expansion of the SARS-CoV-2 B.1.1.7 variant and reinfections in Qatar: a nationally representative cohort study. *PLoS Med.* 18, e1003879 <https://doi.org/10.1371/journal.pmed.1003879>.
- Abu-Raddad, L.J., 2021. Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic (Available from). *Scientific Reports* 11 (6233). <https://doi.org/10.1038/s41598-021-85428-7> (Available also from). (<https://www.medrxiv.org/content/10.1101/2020.07.16.20155317v2>).
- Abu-Raddad, L.J., 2021. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. *EClinicalMedicine* 35, 100861. <https://doi.org/10.1016/j.eclinm.2021.100861>.
- Abu-Raddad, L.J., Boily, M.C., Self, S., Longini Jr., I.M., 2007. Analytic insights into the population level impact of imperfect prophylactic HIV vaccines. *J. Acquir Immune Defic Syndr.* 45, 454–467. <https://doi.org/10.1097/QAI.0b013e3180959a94>.
- Abu-Raddad, L.J., Chemaitelly, H., Butt, A.A., National Study Group for Covid Vaccination, 2021. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. *N. Engl. J. Med.* 385, 187–189. <https://doi.org/10.1056/NEJMc2104974>.
- Alsallaq, R.A., 2010. Population level impact of an imperfect prophylactic HSV-2 vaccine. *Sexually Trans. Dis.* 37, 290.
- Al-Thani, M.H., 2021. SARS-CoV-2 infection is at herd immunity in the majority segment of the population of Qatar. *Open Forum Infect Dis.* 8, ofab221. <https://doi.org/10.1093/ofid/ofab221>.
- Anderson, R.M., Heesterbeek, H., Klinkenberg, D., Hollingsworth, T.D., 2020. How will country-based mitigation measures influence the course of the COVID-19 epidemic? *Lancet* 395, 931–934. [https://doi.org/10.1016/S0140-6736\(20\)30567-5](https://doi.org/10.1016/S0140-6736(20)30567-5).
- Ayoub, H.H., 2020. Characterizing key attributes of COVID-19 transmission dynamics in China's original outbreak: model-based estimations. *Glob Epidemiol* 2, 100042. <https://doi.org/10.1016/j.gloepi.2020.100042>.
- Ayoub, H.H., 2020. Characterizing key attributes of the epidemiology of COVID-19 in China: model-based estimations, 2020.2004.2008.20058214 medRxiv. <https://doi.org/10.1101/2020.04.08.20058214>.
- Ayoub, H.H., 2020. Age could be driving variable SARS-CoV-2 epidemic trajectories worldwide, 2020.2004.2013.20059253 medRxiv. <https://doi.org/10.1101/2020.04.13.20059253>.
- Ayoub, H.H., 2021. Estimates of global SARS-CoV-2 infection exposure, infection morbidity, and infection mortality rates, 2021.2001.2024.21250396 medRxiv. <https://doi.org/10.1101/2021.01.24.21250396>.
- Ayoub, H.H., 2021. Mathematical modeling of the SARS-CoV-2 epidemic in Qatar and its impact on the national response to COVID-19. *J. Glob. Health* 11, 05005. <https://doi.org/10.7189/jogh.11.05005>.
- Ayoub, H.H., 2021. Estimates of global SARS-CoV-2 infection exposure, infection morbidity, and infection mortality rates in 2020. *Glob. Epidemiol.* 3, 100068 <https://doi.org/10.1016/j.gloepi.2021.100068>.
- Ayoub, H.H., 2021. Epidemiological impact of prioritising SARS-CoV-2 vaccination by antibody status: mathematical modelling analyses. *BMJ Innov.* 7, 327–336. <https://doi.org/10.1136/bmjinnov-2021-000677>.
- Ayoub, H.H., Abu-Raddad, L.J., 2019. Treatment as prevention for hepatitis C virus in Pakistan: mathematical modelling projections. *BMJ Open* 9, e026600. <https://doi.org/10.1136/bmjopen-2018-026600>.
- Ayoub, H.H., Chemaitelly, H., Kouyoumjian, S.P., Abu-Raddad, L.J., 2020. Characterizing the historical role of parenteral antischistosomal therapy in hepatitis C virus transmission in Egypt. *Int. J. Epidemiol.* 49, 798–809. <https://doi.org/10.1093/ije/dyaa052>.
- Ayoub, H.H., Chemaitelly, H., Abu-Raddad, L.J., 2020. Epidemiological Impact of Novel Preventive and Therapeutic HSV-2 Vaccination in the United States: Mathematical Modeling Analyses. In: *Vaccines*, 8. Basel., <https://doi.org/10.3390/vaccines8030366>.
- Baird, J.K., Fryauff, D.J., Hoffman, S.L., 2003. Primaquine for prevention of malaria in travelers. *Clin. Infect Dis.* 37, 1659–1667. <https://doi.org/10.1086/379714>.
- BioSpace. 47% of Americans Still Hesitant to Get COVID-19 Vaccine, New Poll says. Available from: (<https://www.biospace.com/article/47-percent-of-americans-still-hesitant-to-get-covid-19-vaccine-new-poll-says/>). Accessed on March 2, 2021. (2021).
- Bloomberg. More Than 271 Million Shots Given: COVID-19 Tracker. Available from: (<https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution/#global>). Accessed on March 3, 2021.
- Boily, M.-C., Brisson, M., Masse, B. & Anderson, R. (eds WJW Morrow, NA Sheikh, CS Schmidt, & DH Davies) 480–508 (Wiley-Blackwell, 2012).
- Britton, T., Ball, F., Trapman, P., 2020. A mathematical model reveals the influence of population heterogeneity on herd immunity to SARS-CoV-2. *Science* 369, 846–849. <https://doi.org/10.1126/science.abc6810>.
- Chemaitelly, H., 2021. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N. Engl. J. Med.* 385, e83 <https://doi.org/10.1056/NEJMoa2114114>.
- Chemaitelly, H., 2021. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. *Nat. Med.* 27 (1614–1621) <https://doi.org/10.1038/s41591-021-01446-y>.
- Chemaitelly, H., Bertolini, R., Abu-Raddad, L.J., National Study Group for Covid Epidemiology, 2021. Efficacy of natural immunity against SARS-CoV-2 reinfection with the beta variant. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMc2110300>.
- Cohen, M.S., 2011. Prevention of HIV-1 infection with early antiretroviral therapy. *New England J. Med.* 365, 493–505. <https://doi.org/10.1056/NEJMoa1105243>.
- European Centre for Disease Prevention and Control. Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom – 20 December 2020. *ECDC: Stockholm*; 2020.
- Granich, R.M., Gilks, C.F., Dye, C., De Cock, K.M., Williams, B.G., 2009. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *The Lancet* 373, 48–57.
- He, W., Yi, G.Y., Zhu, Y., 2020. Estimation of the basic reproduction number, average incubation time, asymptomatic infection rate, and case fatality rate for COVID-19: Meta-analysis and sensitivity analysis. *J. Med. Virol.* <https://doi.org/10.1002/jmv.26041>.
- Hill, E.M., Petrou, S., de Lusignan, S., Yonova, I., Keeling, M.J., 2019. Seasonal influenza: modelling approaches to capture immunity propagation. *PLoS Comput Biol.* 15, e1007096 <https://doi.org/10.1371/journal.pcbi.1007096>.
- Ito, K., Ohmagari, N., Mikami, A., Sugiura, W., 2020. Major ongoing clinical trials for COVID-19 treatment and studies currently being conducted or scheduled in Japan. *Global Health Med.* 2, 96–101. <https://doi.org/10.35772/ghm.2020.01034>.
- Jeremijenko, A., 2021. Herd Immunity against severe acute respiratory syndrome coronavirus 2 infection in 10 communities, Qatar. *Emerg. Infect Dis.* 27, 1343–1352. <https://doi.org/10.3201/eid2705.204365>.
- John Hopkins University Coronavirus resource center. *COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)*. Available from: (<https://coronavirus.jhu.edu/map.html>). Accessed on January 11, 2021.

- Legido-Quigley, H., et al., 2020. Are high-performing health systems resilient against the COVID-19 epidemic? *Lancet* 395, 848–850. [https://doi.org/10.1016/S0140-6736\(20\)30551-1](https://doi.org/10.1016/S0140-6736(20)30551-1).
- Leonhardt, D. *Covid Treatments Are Coming! The New York Times*. Available from: (<https://www.nytimes.com/2021/12/03/briefing/covid-treatments-pfizer-merck.html>) (Dec 2021).
- LeVasseur, M.T., Goldstein, N.D., Tabb, L.P., Olivieri-Mui, B.L., Welles, S.L., 2018. The effect of PrEP on HIV incidence among men who have sex with men in the context of condom use, treatment as prevention, and seroadaptive practices. *J. Acquir Immune Defic. Syndr.* 77, 31–40. <https://doi.org/10.1097/qai.0000000000001555>.
- Mahase, E., 2021. Covid-19: molnupiravir reduces risk of hospital admission or death by 50% in patients at risk. *MSD reports*. *BMJ*. (<https://doi.org/10.1136/bmj.n2422>).
- Makhoul, M., et al., 2020. Epidemiological impact of SARS-CoV-2 vaccination: mathematical modeling analyses. *Vaccines* 8, 668.
- Makhoul, M., Chemaitelly, H., Ayoub, H.H., Seedat, S., Abu-Raddad, L.J., 2021. Epidemiological differences in the impact of COVID-19 vaccination in the United States and China. *Vaccines* 9, 223.
- MATLAB®. The Language of Technical Computing. The MathWorks, Inc. (2019).
- Mckay, M.D., Beckman, R.J., Conover, W.J., 1979. A comparison of three methods for selecting values of input variables in the analysis of output from a computer code. *Technometrics* 21, 239–245. <https://doi.org/10.2307/1268522>.
- McKibbin, W., Fernando, R., 2020. The global macroeconomic impacts of COVID-19: Seven scenarios. *Asian Economic* 1–55.
- McLean, A.R., Blower, S.M., 1995. Modelling HIV vaccination. *Trends Microbiol.* 3, 458–462. [https://doi.org/10.1016/S0966-842X\(00\)89010-1](https://doi.org/10.1016/S0966-842X(00)89010-1).
- Merck and Ridgeback's investigational oral antiviral molnupiravir reduced the risk of hospitalization or death by approximately 50 percent compared to placebo for patients with mild or moderate covid-19 in positive interim analysis of phase 3 study. Available from: (<https://www.merck.com/news/merckand-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderate/>) (Oct 2021).
- Michael, E., Malecela-Lazaro, M.N., Kazura, J.W., 2007. Epidemiological modelling for monitoring and evaluation of lymphatic filariasis control. *Adv. Parasitol.* 65, 191–237. [https://doi.org/10.1016/S0065-308X\(07\)65003-9](https://doi.org/10.1016/S0065-308X(07)65003-9).
- MIDAS Online COVID-19 Portal. COVID-19 parameter estimates: basic reproduction number. Available from: (https://github.com/midas-network/COVID-19/tree/master/parameter_estimates/2019_novel_coronavirus). Accessed on: May 19, 2020. (2020).
- Milken Institute Faster Cures. COVID-19 Treatment and Vaccine Tracker. Available from: (<https://covid-19tracker.milkeninstitute.org>). Accessed on January 19, 2021.
- Oxford, J.S., 2007. Antivirals for the treatment and prevention of epidemic and pandemic influenza. *Influenza Other Respir. Viruses* 1, 27–34. <https://doi.org/10.1111/j.1750-2659.2006.00006.x>.
- Rosa, S.G.V., Santos, W.C., 2020. Clinical trials on drug repositioning for COVID-19 treatment. *Rev. Panam Salud Publica* 44, e40. <https://doi.org/10.26633/RPSP.2020.40>.
- Sah, P., et al., 2019. Future epidemiological and economic impacts of universal influenza vaccines. *Proc. Natl. Acad. Sci. U S A* 116, 20786–20792. <https://doi.org/10.1073/pnas.1909613116>.
- Sanchez, M.A., Blower, S.M., 1997. Uncertainty and sensitivity analysis of the basic reproductive rate - Tuberculosis as an example. *Am. J. Epidemiol.* 145, 1127–1137.
- Schwarzinger, M., Watson, V., Arwidson, P., Alla, F., Luchini, S., 2021. COVID-19 vaccine hesitancy in a representative working-age population in France: a survey experiment based on vaccine characteristics. *The Lancet Public Health*.
- Seedat, S., 2021. SARS-CoV-2 infection hospitalization, severity, criticality, and fatality rates in Qatar. *Sci. Rep.* 11, 18182. <https://doi.org/10.1038/s41598-021-97606-8>.
- Sette, A., Crotty, S., 2021. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell* 184, 861–880. <https://doi.org/10.1016/j.cell.2021.01.007>.
- Siedner, M.J., Tumarkin, E., Bogoch II, H.I.V., 2018. post-exposure prophylaxis (PEP). *Bmj* 363, k4928. <https://doi.org/10.1136/bmj.k4928>.
- Spinner, C.D., 2016. HIV pre-exposure prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in humans. *Infection* 44, 151–158. <https://doi.org/10.1007/s15010-015-0850-2>.
- Tang, P., 2021. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. *Nat. Med.* 27, 2136–2143. <https://doi.org/10.1038/s41591-021-01583-4>.
- The New York Times. Coronavirus Drug and Treatment Tracker. Available from: (<https://www.nytimes.com/interactive/2020/science/coronavirus-drugs-treatments.html>). Accessed on: March 1, 2021. (2020).
- Watanabe, T., 2015. Postexposure prophylactic effect of hepatitis B virus (HBV)-active antiretroviral therapy against HBV infection. *Antimicrob. Agents Chemother.* 59, 1292–1298. <https://doi.org/10.1128/aac.04459-14>.
- Wells, C., 2015. Harnessing case isolation and ring vaccination to control Ebola. *PLoS Negl. Trop Dis.* 9, e0003794. <https://doi.org/10.1371/journal.pntd.0003794>.
- World Health Organization. Tracking SARS-CoV-2 variants. Available from: (<https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>). Accessed on: June 5, 2021. (2021).
- Wouters, O.J., et al., 2021. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. *The Lancet*.