Comparison of allocation strategies of convalescent plasma to reduce excess infections and mortality from SARS-CoV-2 in a US-like population

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Abstract

Background: While the use of convalescent plasma (CP) in the ongoing COVID-19 pandemic has been inconsistent, CP has the potential to reduce excess morbidity and mortality in future pandemics. Given constraints on CP supply, decisions surrounding the allocation of CP must be made.

Study Design and Methods: Using a discrete-time stochastic compartmental model, we simulated implementation of four potential allocation strategies: administering CP to individuals in early hospitalization with COVID-19; administering CP to individuals in outpatient settings; administering CP to hospitalized individuals and administering any remaining CP to outpatient individuals and administering CP in both settings while prioritizing outpatient individuals. We examined the final size of SARS-CoV-2 infections, peak and cumulative hospitalizations, and cumulative deaths under each of the allocation scenarios over a 180-day period. We compared the cost per weighted health benefit under each strategy.

Results: Prioritizing administration to patients in early hospitalization, with remaining plasma administered in outpatient settings, resulted in the highest reduction in mortality, averting on average 15% more COVID-19 deaths than administering to hospitalized individuals alone (95% CI [11%–18%]). Prioritizing administration to outpatients, with remaining plasma administered to hospitalized individuals, had the highest percentage of hospitalizations averted (22% [21%–23%] higher than administering to hospitalized individuals alone).

Discussion: Convalescent plasma allocation strategy should be determined by the relative priority of averting deaths, infections, or hospitalizations. Under conditions considered, mixed allocation strategies (allocating CP to both outpatient and hospitalized individuals) resulted in a larger percentage of infections and deaths averted than administering CP in a single setting.

Abbreviations: CP, Convalescent plasma; CCP, COVID-19 convalescent plasma; CI, confidence interval; COVID-19, Coronavirus disease 2019.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has resulted in over 267 million confirmed cases and more than 5.8 million deaths worldwide.[1] Among potential medical treatments for COVID-19, convalescent plasma (CP) was one of the earliest treatments considered. As early as January 2020, COVID-19 CP (CCP) from recovered COVID-19 patients was first used to treat patients with COVID-19.[2]

While studies of CCP treatment for COVID-19 have shown safety,[3] efficacy results are mixed. Multiple meta-analyses and systematic reviews of CCP among hospitalized patients have suggested no efficacy,[4-9] while others have suggested some clinical benefit.[10-18] It has been suggested that CCP use early in hospitalization within 7 days of symptom onset and when CCP is administered at high enough titer would be efficacious.[19,20] A study of the total number of units of CCP dispensed to US hospitals by blood banking organizations and hospital deaths occurring 2 weeks after admission showed a strong correlation between the two, which is consistent with the evidence of efficacy of CP among those with serious disease.[21] In outpatient settings, CCP shows promise; a multicenter randomized, controlled trial of over 1000 patients showed a 54% risk reduction in hospitalization within 28 days of receipt of high titer convalescent plasma.[22]

While monoclonal antibodies have been shown to be effective among both ambulatory patients and those with household exposures to SARS-CoV-2,[23,24] these have proved vulnerable to the evolution of variants.[25,26] In contrast, CCP is less vulnerable to the impact of viral evolution.[27] Collectively, these studies suggest that CCP therapy could serve as an effective COVID-19 prevention and treatment strategy.[13]

Use of convalescent plasma in major outbreaks of emerging viruses in the 21st century (SARS, MERS, H1N1, Ebola, and SARS-CoV-2)[28] suggests the possibility that convalescent plasma will be deployed again against future outbreaks until other therapies are available. In these outbreaks, as well as in future outbreaks of SARS-CoV-2 where full immunological escape variants may make vaccination less effective at protecting the population, it is critical to understand the optimal allocation of the scarce quantities of available plasma among patients treated in outpatient and hospitalized settings. To examine the difference in outcomes under different potential allocation strategies and identify whether a single strategy emerges as one averting the highest number of infections, hospitalizations, and deaths, we employ strategic models that mimic the dynamics of CP administration in a population experiencing an outbreak of a pathogen similar to SARS-CoV-2.

2 | MATERIALS AND METHODS

We developed a discrete-time, age-stratified stochastic compartmental model of SARS-CoV-2 transmission and disease progression, incorporating the infection dynamics, vaccination, and CP treatment. The full model is described in Supplementary materials.

2.1 | Base case transmission model

Individuals in the population are represented within susceptible (S), exposed (E), infectious asymptomatic (I_a), infectious mild / moderate (I_m), infectious severe (I_S) and recovered (R) compartments. I_S individuals proceed from early hospitalization to late hospitalization stage (I_{SL}). Individuals exit the population only through death from COVID-19. Each day, susceptible individuals may transition to being exposed at a rate determined by their age and occupation-specific contact matrix, which impacts the force of infection. Contact matrices were derived using the "socialmixr" package of R,[29] which estimates the social contact matrices by age groups from the Polymod study.[30]

Partial schema of stochastic dynamics is presented in Figure 1.

We initialized the model with a population of $N = 1000,000$, comprised of general population (95%) and healthcare workers (5%), with age structure resembling that of the US population.[31] To capture dynamics of early stages of the outbreak, where dynamics are not driven by endemic states, we began the simulations with 20% of population in the recovered compartment, and 1.1% of population split equally between the exposed and infectious compartments. This is roughly equivalent to early March 2021 in the US during the COVID-19 pandemic.[32] A table of parameter values for disease transmission, CCP, and vaccination, as well as a description of the Polymod study and distribution of population in age groups, is provided in Supplementary materials.
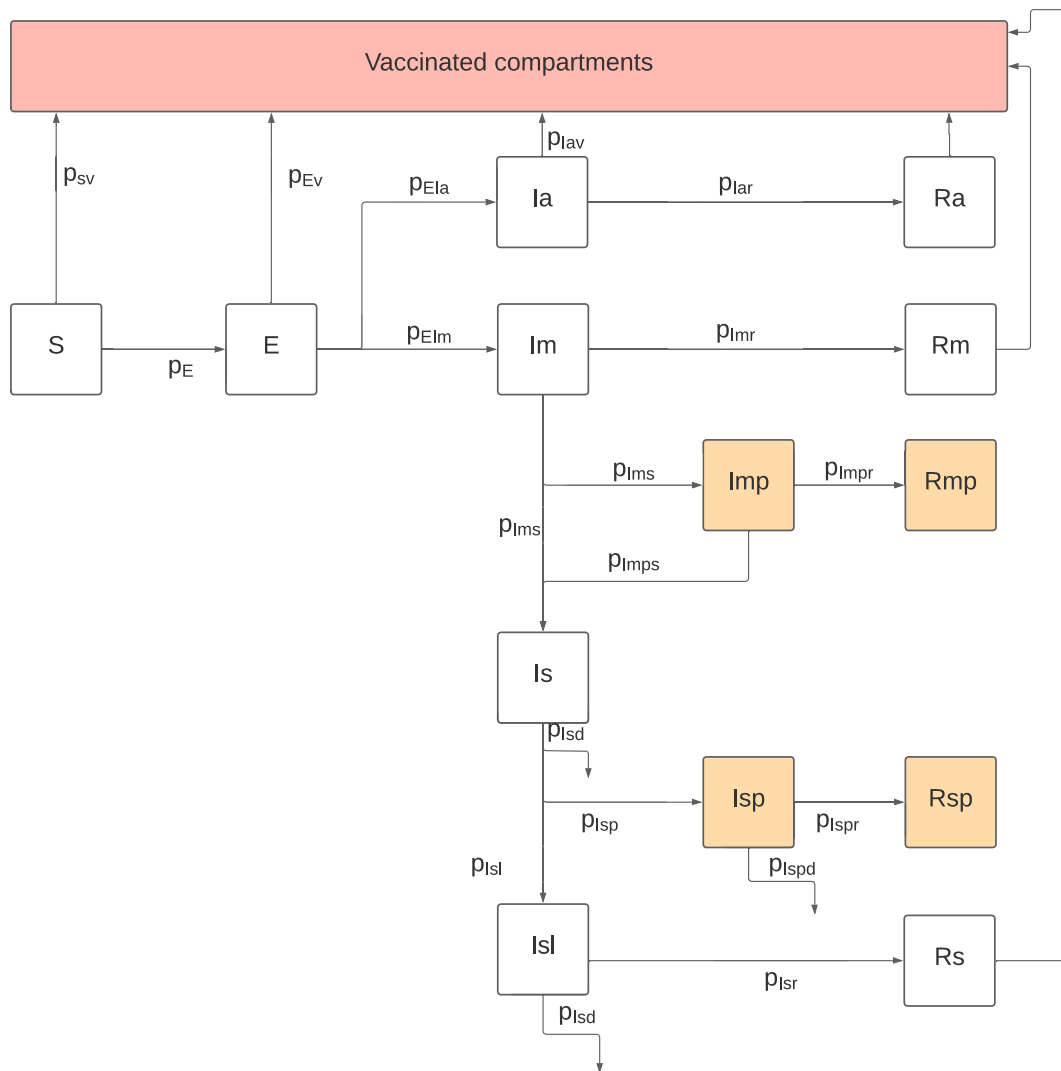
FIGURE 1 Schema for transitions between susceptible (S), exposed (E), infectious asymptomatic (Ia), infectious mild/moderate (Im), and infectious severe (Is) compartments. Individuals with mild / moderate or severe symptoms receiving COVID-19 convalescent plasma (CCP) move to Imp and Isp compartments, respectively, while those recovering move to Ra, Rm, Rmp, Rs, and Rsp compartments, with the subscript indicating the severity of disease and presence or absence of treatment with CCP. Please note that this is only a partial schema, which does not depict movement of vaccinated individuals, or the process of donation of CCP. A comprehensive schema is provided in S1. [Color figure can be viewed at wileyonlinelibrary.com]

2.2 | CCP strategies

We assume that CCP is administered to infected individuals with mild/moderate (i.e., outpatient) or severe (i.e., hospitalized) disease, the latter only receiving CCP if they are in the early stages of hospitalization (I_S). We assume that part of CCP is high titer and part is low; specifically, 50%, 60%, and 80% of CCP collected from individuals recovered from asymptomatic, mild/moderate, and severe infections are high titer. Only high-titer CCP is administered (i.e., it is tested prior to administration), and all available units of CCP can be administered at that time step (no CCP is reserved for future administration). Treatment of individuals in the I_M with CCP reduces recovery time in half when compared to untreated

individuals ($\gamma_{mt} = \gamma_m * 2$), and the probability of moving on to I_S compartment (becoming hospitalized) is also reduced in half.[22] When administered to hospitalized individuals in the early stage of hospitalization, high-titer CCP is assumed to reduce mortality rate by 30%, which falls within the range of estimates from published studies where CCP is administered early in hospitalization.[13,33,34] CCP is not administered to individuals in late hospitalization.

Recovered individuals may donate plasma up to two times, with a different probability of donation based on the severity of infection. Effectiveness of CCP also depends on the severity of the donor's infection prior to recovery. To verify our assumptions about rate of CCP donation across age groups and severity of disease, we

allowed for collection of CCP from recovered individuals. The proportion of plasma collected by population age sub-group resembles that collected by Vitalant between June and December 2020 (Table S2), which suggests that our assumptions are plausible.

We set the initial number of CCP units to 300.

We consider the following four scenarios for plasma allocation: (1) Administer all available plasma units to early hospitalized individuals only (Scenario A); (2) Administer all available plasma units in outpatient setting only (Scenario B); (3) Administer available plasma units to patients in both early hospitalized and outpatient settings, prioritizing early hospitalized patients; that is, each day, administer plasma to early hospitalized individuals first, and administer any remaining plasma units to outpatient setting (Scenario C); and (4) Administer available plasma to patients in both early hospitalized and outpatient settings, prioritizing outpatients; that is, each day, administer plasma to outpatients first, and administer any remaining plasma units to early hospitalized individuals (Scenario D).

No non-pharmaceutical interventions were considered, and no new variants or other changes in transmissibility were introduced.

Finally, we consider a "flooding the market" strategy, where the number of units of CCP is effectively unlimited (initial number of available units is 1000,000). This is equivalent to administering CCP to all eligible individuals in early hospitalized and outpatient settings.

2.3 | Model analyses

2.3.1 | Comparison of outcomes

We first examined the outcomes of alternative strategies, specifically the cumulative incidence of SARS-CoV-2 infections, hospitalizations, and deaths from COVID-19 disease over the entire 180-day period. Strategies were compared using bootstrapped simulations ($n = 100$ per option) using the mean, 2.5% and 97.5% bounds. A scenario where CCP was administered to hospitalized individuals only was used as a reference scenario when comparing outcomes. While these uncertainty intervals are not quite the same as confidence intervals, we report them as "CI" in results for convenience.

2.3.2 | Identification of optimal strategies

To assess how a decision-maker's relative valuation of COVID-19 fatalities and SARS-CoV-2 infections affects the recommended scenario, we constructed a composite

measure of COVID-19 burden under each scenario as the weighted sum of averted deaths and SARS-CoV-2 infections under the scenario and as follows:

weighted health benefit $=$ deaths averted$*$

(relative weighted value of death)

$+$ infections averted$*$

$(1-$ relative weighted value of death$)$

$$(1)$$

where *relative weighted value of death* represents the planner's relative valuation of COVID-19 fatalities and ranges from 0 to 1.

In addition, we also calculated cost per weighted health benefit as

cost per weighted health benefit

$$= \frac{\text{number of doses of CCP used}}{\text{weighted health benefit}} \quad (2)$$

We then compared scenarios against each other along the gradient of relative valuation weights to identify dominant strategies.

3 | RESULTS

We present results from the *base case scenario*, in which individuals progress across disease states including vaccination, but CCP is not administered. Next, we present findings from *CCP allocation scenarios*, where the amount of plasma doses available at the beginning of the simulation period is limited. We then present the results of the *"flooding the market" scenario*, where CCP is unlimited. Finally, we present the *weighted health benefits of different allocation strategies*.

3.1 | Base case scenario (no CP)

The base case scenario without CP administration resulted in a final outbreak size of 481,000 SARS-CoV-2 infections (95% confidence interval [CI]: [477,000–485,000]), 71,200 hospitalizations (95% CI: [70,400–72,000]), and 4000 deaths (95% CI: [3900–4100]) over 180 days (Table 1). The epidemic curve of daily incident infections peaks at day 76, while the highest number of new deaths peaks at day 94. The epidemic continues under this strategy with over 500 daily incident infections and more than 10 new daily COVID-19-related fatalities on average at the end of the simulation (Figure S2).

TABLE 1 Final infection size, peak prevalent and cumulative hospitalizations, and cumulative number of deaths from COVID-19 under base case scenario of no convalescent plasma administration and four convalescent plasma allocation strategies

	Final infection size mean [95% CI]	Infections averted mean [95% CI]	Peak infections day mean [95% CI]	Final number of hospitalizations mean [95% CI]	Peak prevalent hospitalizations mean [95% CI]	Hospitalizations averted mean [95% CI]	Final deaths mean [95% CI]	Deaths averted mean [95% CI]	Peak deaths day mean [95% CI]	Individuals treated with CP mean [95% CI]	Percent of CP used mean [95% CI]
No plasma	481,000 [477,000, 485,000]	N/A	76 [70; 82]	71,200 [70,400; 72,000]	2200 [2200; 2300]	N/A	4000 [3900; 4100]	N/A	94 [73; 115]	0	0%
Scenario A	473,000 [468,000; 476,000]	Ref	77 [71; 83]	69,800 [68,800; 70,600]	1300 [1300; 1400]	Ref	3200 [3100; 3300]	Ref	93 [69; 115]	26,300 [25,9300; 26,700]	9% [9%; 9%]
Scenario B	454,000 [449,000; 459,000]	4% [3%; 5%]	76 [69; 83]	54,900 [54,000; 55,700]	1600 [1500; 1700]	21% [20%; 23%]	3200 [3100; 3300]	0% [−6%; 5%]	90 [70; 112]	71,000 [70,000; 72,000]	27% [26%; 27%]
Scenario C	455,000 [452,000; 459,000]	4% [3%; 5%]	74 [69; 81]	57,000 [56,200; 57,700]	1000 [1000; 1100]	18% [17%; 20%]	2700 [2600; 2800]	15% [11%; 18%]	87 [63; 106]	80,300 [79,500; 81,100]	30% [29%; 30%]
Scenario D	452,000 [447,000; 456,000]	4% [3%; 6%]	76 [70; 83]	54,600 [53,800; 55,200]	1600 [1500; 1700]	22% [21%; 23%]	2900 [2800; 3000]	9% [6%; 14%]	84 [65; 102]	80,400 [79,300; 81,500]	30% [30%; 31%]

Note: Scenario A includes vaccination and allocation of convalescent plasma to hospitalized individuals only. Scenario B includes vaccination and administration of convalescent plasma in the outpatient setting only. Scenario C includes vaccination and administration of convalescent plasma to both hospitalized individuals and those in an outpatient setting, prioritizing hospitalized individuals. Scenario D includes vaccination and administration of convalescent plasma to both hospitalized and outpatient individuals, prioritizing those in the outpatient setting. Infections, hospitalizations, and deaths averted are calculated with Scenario A as reference.

3.2 | CCP allocation strategies

Results suggest that scenarios that allocate the available units of plasma to patients in both hospital and outpatient settings are more effective in reducing final outbreak size (i.e., cumulative incident infections) and deaths than those allocating plasma to a single setting. Prioritizing plasma administration to outpatient infected individuals is more effective in reducing infections by reducing transmission through reducing recovery time, whereas prioritizing administration in a hospital setting is more effective in reducing deaths when a mixed allocation strategy is considered (Table 1).

When administering CCP in a single setting (either to early hospitalized individuals, or in an outpatient setting only), the two allocation strategies are comparable in averting deaths. Compared to Scenario A, Scenario B led to 0% more deaths averted (95% CI: [−6%–5%]). However, in the outpatient-only allocation, 4% more infections were averted than in the hospitalized allocation (95% CI: [3%–5%]). In contrast, CCP administration to patients in both outpatient and hospital settings, while prioritizing those in outpatient settings (Scenario D) reduces a similar amount of infections compared to Scenario A as Scenario B and C (4% reduction; 95% CI: [3%–6%]), and 9% higher reduction in deaths (95% CI: [6%–14%]). Prioritizing hospitalized individuals while administering remaining CCP to outpatient individuals (Scenario C) reduces infections by 4% more than administering to hospitalized individuals alone (95% CI: [3%–5%]) while reducing deaths by 15% compared to Scenario A (95% CI: [11%–18%]). In both of the mixed scenarios, a larger number of individuals were treated with CCP.

No scenario significantly shifts the timing of peak incidence; the peak days ranged from day 74 (95% CI: [69–81]) (Scenario C) to day 77 (95% CI: [71–83]) (Scenario A) (Figure 2, Table 1). However, the timing of peak for fatalities shifts widely across scenarios. Under Scenario A, the peak for mean incident deaths is reached on day 93 (95% CI: [69–115]), whereas under Scenario D, the peak occurs on day 84 (95% CI: [65–102]).

Without CP administration, the average peak number of prevalent hospitalizations is 2242 (95% CI: [2161–2319]). The biggest reduction in peak prevalent hospitalizations is observed under Scenario C (mean number of peak prevalent hospitalizations is 1044 (95% CI: [1003–1094])) (Table S4). However, the highest reduction in the number of prevalent hospitalizations averted occurs under Scenario D, followed very closely by Scenario B, with 22% (95% CI: [21%–23%]) and 21% (95% CI: [20%–23%]) hospitalizations averted compared to under Scenario A, respectively (Table 1).
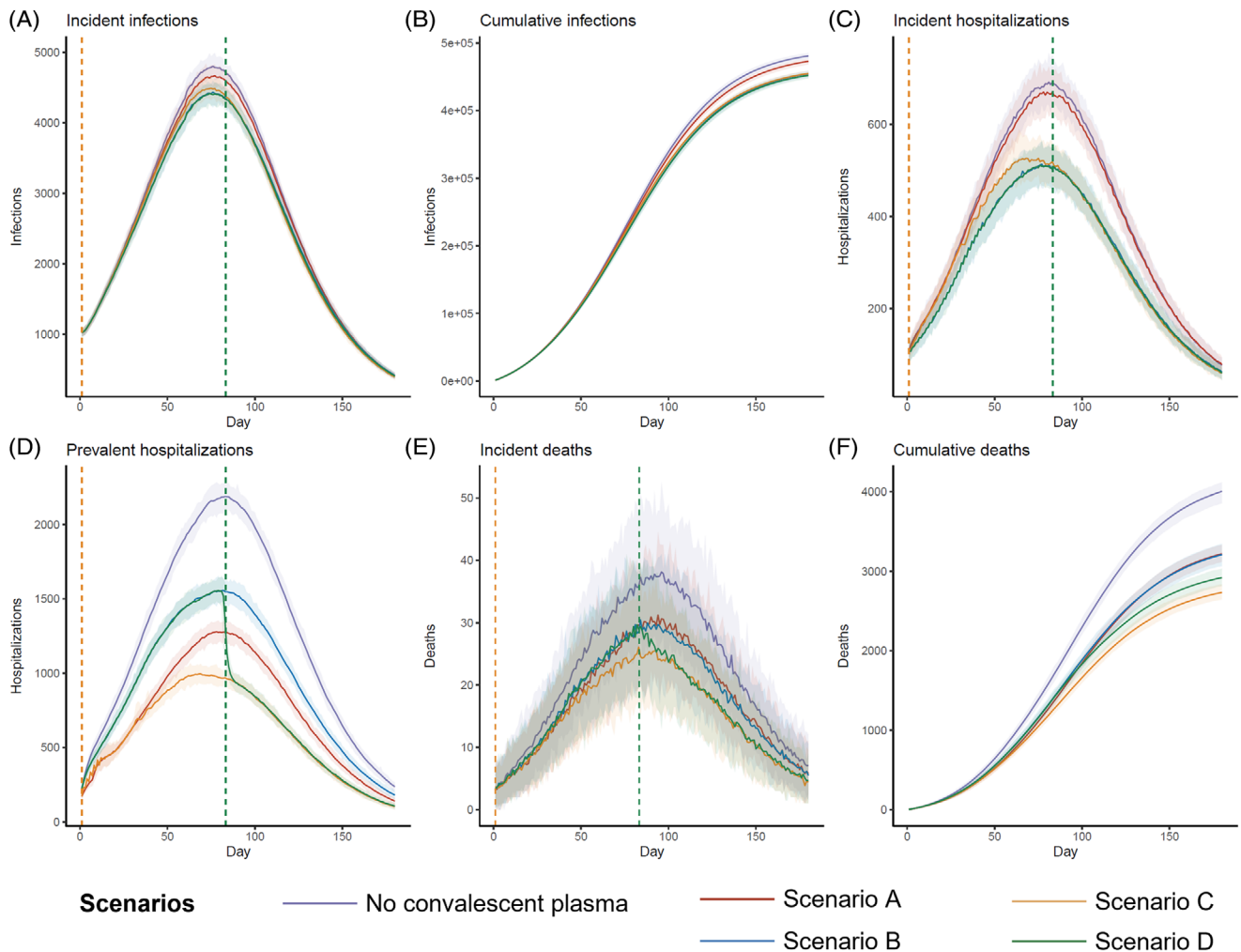
FIGURE 2 New and cumulative SARS-CoV-2 infections from COVID-19 over the course of 180 days under different allocation scenarios. (A) Incident infections. (B) Cumulative infections. (C) Incident hospitalizations. (D) Prevalent hospitalizations. (E) Incident deaths. (F) Cumulative deaths. Reference scenario is one with no plasma administration to any population groups. In scenario A, convalescent plasma is administered only to hospitalized individuals. In scenario B, convalescent plasma is administered only to outpatients. In scenario C, plasma is administered to hospitalized individuals; any leftover plasma is then administered to outpatients. In scenario D, plasma is administered to outpatients first; any leftover plasma is then administered to hospitalized individuals. Dashed lines indicate mean days when the first outpatient individuals receive CCP in scenario C (1; 95% CI [1; 1]) and when the first hospitalized individuals receive CCP in scenario D (82; 95% CI [80; 83]).

3.3 | "Flooding the market" strategy

In the scenarios above, the supply of CCP was limited by the rate of donation, number of individuals eligible to donate, and supply of plasma available at the beginning of the simulation. Potentially, donations of CCP from outside of a population and a health campaign to increase donations could remove constraints on the availability of CCP. While this may be difficult to achieve, this scenario shows the "best" situation for using CCP and acts as an upper bound to what we could expect to occur. Removing constraints on the availability of CCP at the beginning of the simulation results in 8% infections averted (95% CI: [7%–9%]), 26% hospitalizations averted

(95% CI: [25%–28%]), and 37% deaths averted (95% CI: [33%–40%]) (Table 2, Figure 3).

3.4 | Weighted health benefits of CP allocation strategies

To identify the optimal strategy for the planner at various relative valuations of COVID-19 fatalities relative to infections, we calculated the weighted health benefits of each strategy, following the approach described in the methods section (Equation 1). The results suggest that Scenario D is the optimal strategy among all strategies considered when the decision-maker's relative valuation

	Final infection size mean [95% CI]	Infections averted mean [95% CI]	Percent infections averted mean [95% CI]	Final number of hospitalizations mean [95% CI]	Percent hospitalizations averted mean [95% CI]	Final deaths mean [95% CI]	Deaths averted mean [95% CI]	Percent deaths averted mean [95% CI]
No plasma	480,800 [476,500; 484,500]	–	–	71,100 [70,400; 72,000]	–	4000 [3800; 4200]	–	–
Flooding the market	443,600 [439,500; 447,700]	37,600 [31,300; 43,200]	8% [7%; 9%]	52,500 [51,700; 53,200]	26% [25%; 28%]	2500 [2400; 2600]	1500 [1300; 1700]	37% [33%; 40%]

of deaths is below about 0.9 (see Figure 4A). However, while the mean is slightly lower, Scenarios C and B are essentially equivalent given the confidence intervals. At the highest relative values of death, Scenario C has the highest weighted health benefit. Scenario A consistently results in the lowest relative health benefits.

For relative weighted values of death below 0.8, Scenario B has the lower cost per weighted health benefit, calculated according to (Equation 2), although results are very close for Scenarios B, C, and D, and 95% uncertainty intervals overlap (Figure 4B). Below 0.8, Scenario A has the highest cost per weighted health benefit, although confidence intervals overlap. For the highest relative weighted value of deaths, Scenario A has the lowest cost per weighted health benefit, followed by Scenario C, Scenario D, and Scenario B.

While Scenario B has the highest mean number of infections averted per 100 units of plasma, given the wide confidence intervals, the scenarios are not significantly different from each other (Figure 4C). However, Scenario A has the highest number of deaths averted per 100 units of plasma, followed by Scenario C.

4 | DISCUSSION

Decisions to prioritize the administration of CCP to COVID-19 patients in a hospital versus outpatient settings have ramifications for the epidemiological impact (infections and fatalities) of the SARS-CoV-2 pandemic. In this study, we considered four allocation strategies for the administration of CCP in the stages of the epidemic corresponding to early 2021 in the United States, using a discrete-time stochastic SEIR model to simulate the outbreak in a US-like setting over the course of 6 months. Using a cumulative number of infections and deaths occurring at the end of the simulation period, we compared the number of deaths and infections averted under each of the plasma allocation scenarios, as well as weighted health benefits and costs, compared to the base transmission scenario with no CP administration. Our results suggest that prioritization of early hospitalized patients for plasma administration results in the largest reduction in COVID-19 deaths, with a substantially lower required quantity of CP units per death averted, thus implying that this strategy may be the most efficient strategy among all strategies considered for reducing COVID-19 fatalities. In contrast, prioritizing plasma administration to patients in outpatient settings first, and administering the remaining plasma to early hospitalized individuals, results in the largest reductions in infections and hospitalizations, although strategies do not significantly differ in their efficiency in averting infections
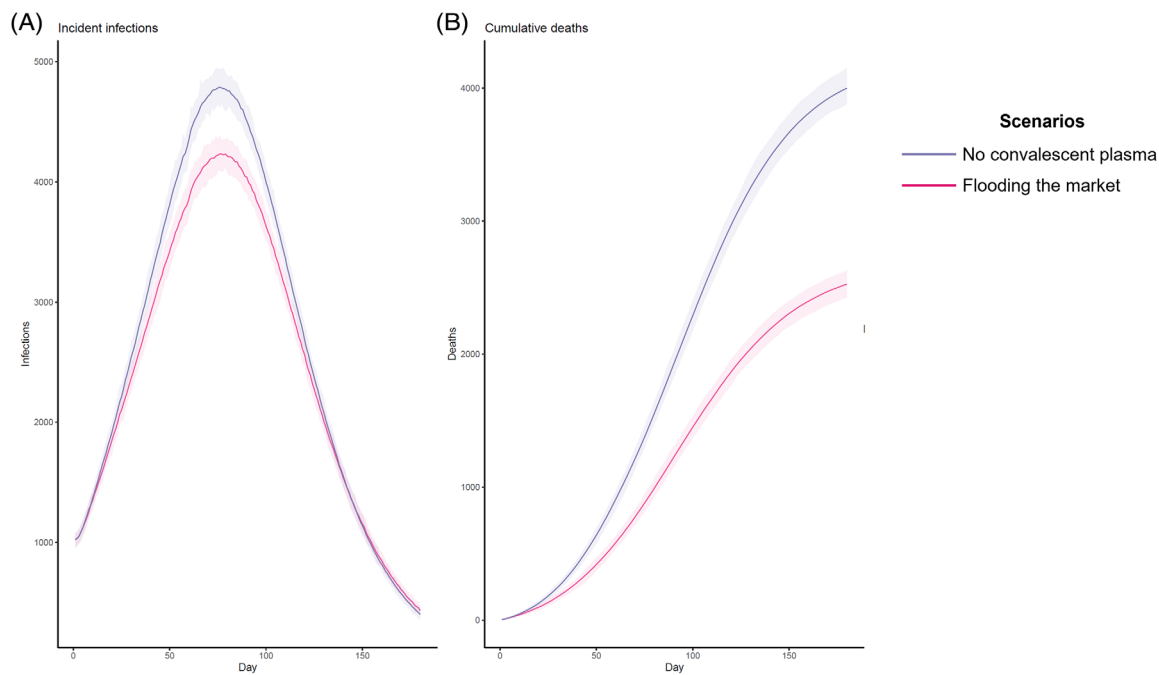
FIGURE 3 Incident infections and cumulative deaths from SARS-CoV-2 in the base case scenario (no convalescent plasma administration) and "flooding the market" strategy

(Table S3; Table 1). The determination of the optimal strategy depends on the decision-maker's relative valuation of fatalities and infections averted.

None of the convalescent plasma strategies examined significantly "flattened" the curve, which is not surprising as CCP is a therapeutic treatment that aims to reduce the severity of outcome rather than stem transmission. Even removing the restriction on the amount of plasma available by "flooding" the market, we observed only a 15% reduction in cumulative incident infections. This is comparable to stay-at-home orders in the US, which were found to be associated with a 15% reduction in effective reproductive number.[35] In contrast, under assumptions made, CCP markedly reduced COVID-19 fatalities and hospitalizations. Administering plasma in a single setting (hospitalized vs. outpatient) resulted in a similar reduction of deaths; however, administration in outpatient setting (Scenario B) resulted in a 21% reduction in hospitalizations and a 4% reduction in infections compared to administration in hospitalized setting only (Scenario A). Administration in mixed settings (hospitalized and outpatient) resulted in additional reductions in deaths averted. In the best-case scenario (Scenario C), 15% more deaths were averted as compared to Scenario A, although this scenario resulted in slightly less additional hospitalizations averted than both Scenarios B and D (18% additional reduction compared to Scenario A, compared to 21% and 22%, respectively).

In all scenarios, a potential additional reduction in the number of infections and hospitalizations averted could be impacted by robust contact tracing with CCP administered to infected persons including ones not experiencing symptoms. Furthermore, if endogenous antibody testing is made a precursor to CCP administration, whence CCP will only be administered to individuals who do not show evidence of endogenous antibodies, the allocation strategies may become further refined.

The tradeoff between allocation strategies is highlighted when taking into account the cost in units of plasma per weighted health benefit. When we prioritize averting infections over deaths, the scenario administering plasma to outpatients and administering remaining plasma to hospitalized patients results in the lowest cost per weighted health benefit, although not significantly, with almost identical cost as the scenario where plasma is administered to both hospitalized and outpatient settings, with outpatients receiving CCP first. However, when prioritizing averting deaths over infections, administering CCP to hospitalized individuals only becomes more cost-effective (Figure 4). Furthermore, depending on the health care infrastructure, planners may want to minimize occupied hospital beds at any particular time. In such a case, Scenario C results in the least amount of prevalent hospitalized patients and may avoid overwhelming hospital capacity, allowing for other non-COVID-19 care to be maintained.

The findings should be carefully interpreted in light of assumptions made about model parameters, especially with mixed results on the efficacy of CCP among
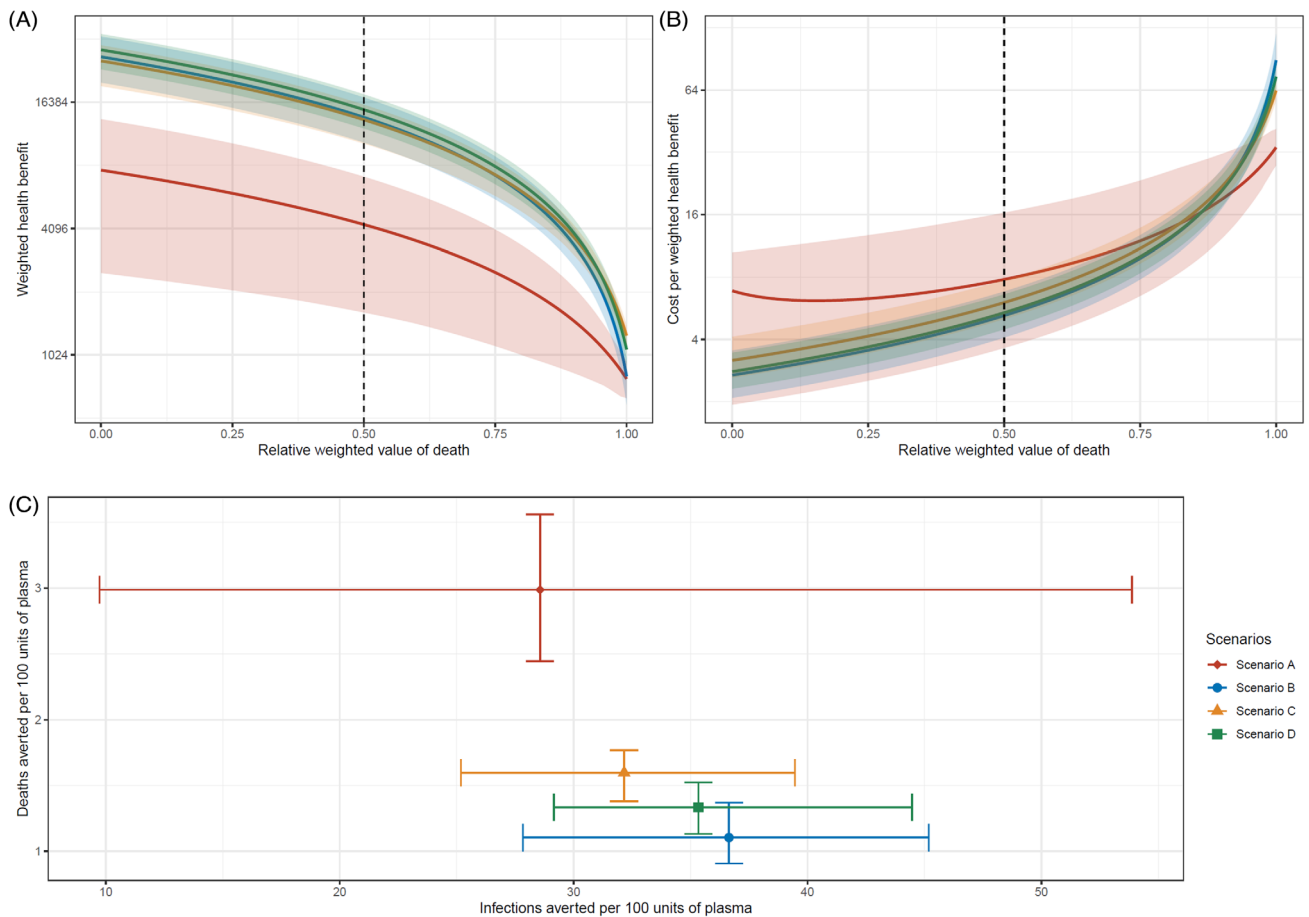
FIGURE 4 Weighted health benefits of COVID-19 convalescent plasma (CCP) allocation strategies. (A) Weighted health benefit by the relative weighted value of death. Weighted health benefit is obtained by summing (deaths avoided * relative weighted value of death) and (infections avoided * [1 – relative weighted value of death]). A higher deaths averted weight corresponds to a higher relative value assigned to a death averted as compared to an infection averted. The dashed vertical line in panel (A) represents the line of indifference, where the relative weighted value of death is equal to the relative weighted value of infection. In scenario A, CCP is administered only to hospitalized individuals. In scenario B, CCP is administered only to outpatients. In scenario C, plasma is administered to hospitalized individuals; any leftover plasma is then administered to outpatients. In scenario D, plasma is administered to outpatients first; any leftover plasma is then administered to hospitalized individuals. Weighted health benefit (y-axis) is presented on log scale. (B) Relative weighted value of death against the cost in units (doses) of plasma administered per weighted health benefit. (C) Number of infections averted per 100 units of CCP on the x-axis, and mean number of deaths averted per 100 units of CCP on the y-axis, with 95% uncertainty intervals presented as bars.

hospitalized patients.[12] Sensitivity analysis, presented in Supplementary materials, suggests the results are robust to parameter uncertainties and stochasticity. However, with the changing landscape of SARS-CoV-2 variants, persistent inequity in vaccine coverage, breakthrough infections, and change in contact patterns and behaviors, emerging data should be incorporated into the model to more accurately reflect the dynamics in the population of interest.

We further assumed that, prior to administration of CCP, units are screened and only high titer plasma is administered. Relaxing this assumption (e.g., administering all available units of CCP, regardless of their titer) would reduce the effectiveness of CCP, and likely reduce the difference between scenarios.

Collectively, these findings suggest that CCP allocation strategies should be determined by the relative priority of averting deaths or averting infections. These may change depending on resources available, availability of treatment, infection prevention measures and policies, population behaviors, SARS-CoV-2 variants, population health characteristics, vaccine availability and acceptability, and underlying disparities that deepen negative outcomes in some populations. For example, availability of treatment effective at curbing deaths from COVID-19 among hospitalized individuals may favor CCP strategies that are more efficient at reducing infections (Scenarios B, C, and D). On the other hand, in populations with high levels of comorbidities and high risk of mortality from COVID-19, we may prioritize Scenarios C

and D, which prioritize administration of CCP in both outpatient and hospitalized settings. Another prioritization setting where this allocation may be preferable is in the context of high vaccination levels, under the assumption that vaccination reduces the probability of severe disease, or high rates of breakthrough infections, where, similar to the Omicron wave across the world, infection rate is high, but a lower percentage of cases are severe. Different prioritization strategies may be considered in settings with a high proportion of high-risk individuals. This study provides a framework by which decision-makers can evaluate allocation strategies, taking into account absolute reductions in infections and deaths, as well as the cost-effectiveness of CCP in each approach when taking into account the relative valuation of infections and deaths averted.

CCP can be especially beneficial in settings where alternatives such as vaccines are not yet available, are scarce, or are not widely accepted. In the US, even as vaccination is widely available, evolution of variants is leading to breakthrough infections, particularly among immunosuppressed individuals who may not mount an effective response post-vaccination. Inequity in distribution of vaccines across the world resulted in a stark gap in vaccination coverage, with only 11% of the population in Africa receiving at least one dose of a vaccine, compared to 72% in the US and Canada as of December 7, 2021.[37] In the US and elsewhere, use of CCP may be more accepted than vaccination in some populations, as evidenced by the high uptake of monoclonal antibodies among vaccine-hesitant individuals.[38] In these contexts, CCP can serve as an additional tool in mitigating the effects of the pandemic. However, results of this research may not be directly transferable to other settings where population structure, such as age distribution, is markedly different from the US.

Our findings could apply to future outbreaks. If CP is deployed in other outbreaks, similar models can be implemented to identify optimal strategies of allocating CP, conditional on pathogen characteristics, availability of other interventions, population susceptibility, and relative valuation of infections versus deaths averted. Optimizing CP allocation may increase its cost-effectiveness and may better contribute to reducing excess morbidity and mortality due to an infectious pathogen. Notably, coupling CP with other interventions, such as effective contact tracing and reduction of time to seek care, will likely increase cost-effectiveness and overall impact in mitigating negative outcomes.

In the constantly changing context of the SARS-CoV-2 pandemic or in future outbreaks, CP may be an effective option to complement other interventions to reduce excess morbidity and mortality. The relatively low barriers to collection, storage, and administration of CP as compared to treatments like monoclonal antibodies, as well as its long history of use, may make it particularly appealing in some contexts. However, CP is a limited resource. The choice of its allocation strategy has significant implications on the impact it can achieve. Careful consideration of priorities—whether prioritizing reduction of deaths or reduction of infections – should guide strategies for CP administration.

CONFLICT OF INTEREST
The authors have disclosed no conflicts of interest

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.