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Themed Section: COVID-19

## Quality-Adjusted Life-Year Losses Averted With Every COVID-19 Infection Prevented in the United States

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### ABSTRACT

**Objective:** To estimate the overall quality-adjusted life-years (QALYs) gained by averting 1 coronavirus disease 2019 (COVID-19) infection over the duration of the pandemic.

**Methods:** A cohort-based probabilistic simulation model, informed by the latest epidemiological estimates on COVID-19 in the United States provided by the Centers for Disease Control and Prevention and literature review. Heterogeneity of parameter values across age group was accounted for. The main outcome studied was QALYs for the infected patient, patient's family members, and the contagion effect of the infected patient over the duration of the pandemic.

**Results:** Averting a COVID-19 infection in a representative US resident will generate an additional 0.061 (0.016-0.129) QALYs (for the patient: 0.055, 95% confidence interval [CI] 0.014-0.115; for the patient's family members: 0.006, 95% CI 0.002-0.015). Accounting for the contagion effect of this infection, and assuming that an effective vaccine will be available in 3 months, the total QALYs gains from averting 1 single infection is 1.51 (95% CI 0.28-4.37) accrued to patients and their family members affected by the index infection and its sequelae. These results were robust to most parameter values and were most influenced by effective reproduction number, probability of death outside the hospital, the time-varying hazard rates of hospitalization, and death in critical care.

**Conclusion:** Our findings suggest that the health benefits of averting 1 COVID-19 infection in the United States are substantial. Efforts to curb infections must weigh the costs against these benefits.

**Keywords:** contagion effect, COVID-19, family, prevention, QALYs, spillover effect.

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### Introduction

As the coronavirus disease 2019 (COVID-19) pandemic rages throughout the world, difficult decisions about how we can curb its spread come to the forefront. In the absence of a vaccine and a dearth of effective medications against the infections, public health measures such as wearing masks, sheltering, and maintaining physical distances becomes essential. Undoubtedly, these measures are inconvenient and sometimes harmful to economic growth and the mental health of many people in the community. Yet the consequences of not following these measures could be devastating as well. In this article, we shed light on one aspect of the potential devastation that the spread of COVID-19 can cause. Specifically, we estimate the magnitude of health loss generated by an additional infection in the community over the pandemic's longevity. We express this health loss in terms of quality-adjusted life-years (QALYs), which combine the impact from both the length of life and the quality-of-life losses.

Calculation of QALYs is standard in economic evaluation studies that compare the costs and benefits of medical and public health interventions.<sup>1</sup> Most recently, the Institute for Clinical and Economic Review attempted to model the costs and QALYs for remdesivir as

a treatment for COVID-19.<sup>2</sup> However, these and many other such economic evaluations tend to focus on the primary patients in measuring the health benefits. A recent review identifies 14 cost-effectiveness studies of antiviral treatments for pandemics and outbreaks of respiratory illnesses, including COVID-19. None of those studies included the quality of life of family members affected during such ordeal.<sup>3</sup> The approaches typically used produce a partial picture of society's realized total health benefits by averting or treating an infection. The Second Panel on Cost-Effectiveness and Health recommended including broader "spillover" effects of patients' health to family members and others in the society but called for more research work to show how to account for these spillovers.<sup>4,5</sup> The recent ISPOR Task force on valuing healthcare technologies has also highlighted the need to account for these spillover effects.<sup>6</sup> In the case of COVID-19, there are 2 specific spillovers to consider. One is the direct spillover to family members of the infected person; the other is the spillover to other society members through the contagion effect. We account for both these spillovers in this work.

Our work illustrates a modeling approach that considers competing risks of outcomes daily for a patient with COVID-19,

calibrates the model outputs to US-based estimates, and accounts for patients' and family members' QALYs throughout a pandemic affected by a single infection. We use our results to highlight and discuss issues that one should consider in economic evaluations of COVID-19 vaccines.

**Methods**

**Approach**

Infectious disease models typically use a structural dynamic Susceptible - Exposed - Infectious - Recovered - Susceptible type (SIR/SIRS/SEIR/SEIRS) approach to assess spread in the community. In contrast, in this article, we present an alternative "reduced form" modeling approach (which has not been used previously) to focus on a single patient and the sequelae of infections arising out of the single patient. Our estimates of the experience of this index patient calibrate with the existing knowledge about the disease. Although our model does not directly model the complicated and heterogeneous transmission processes, it does capture the transmission parameters in a "reduced form" approach through the effective reproduction ratio ( $R(t)$ ).  $R(t)$  is a direct function of an

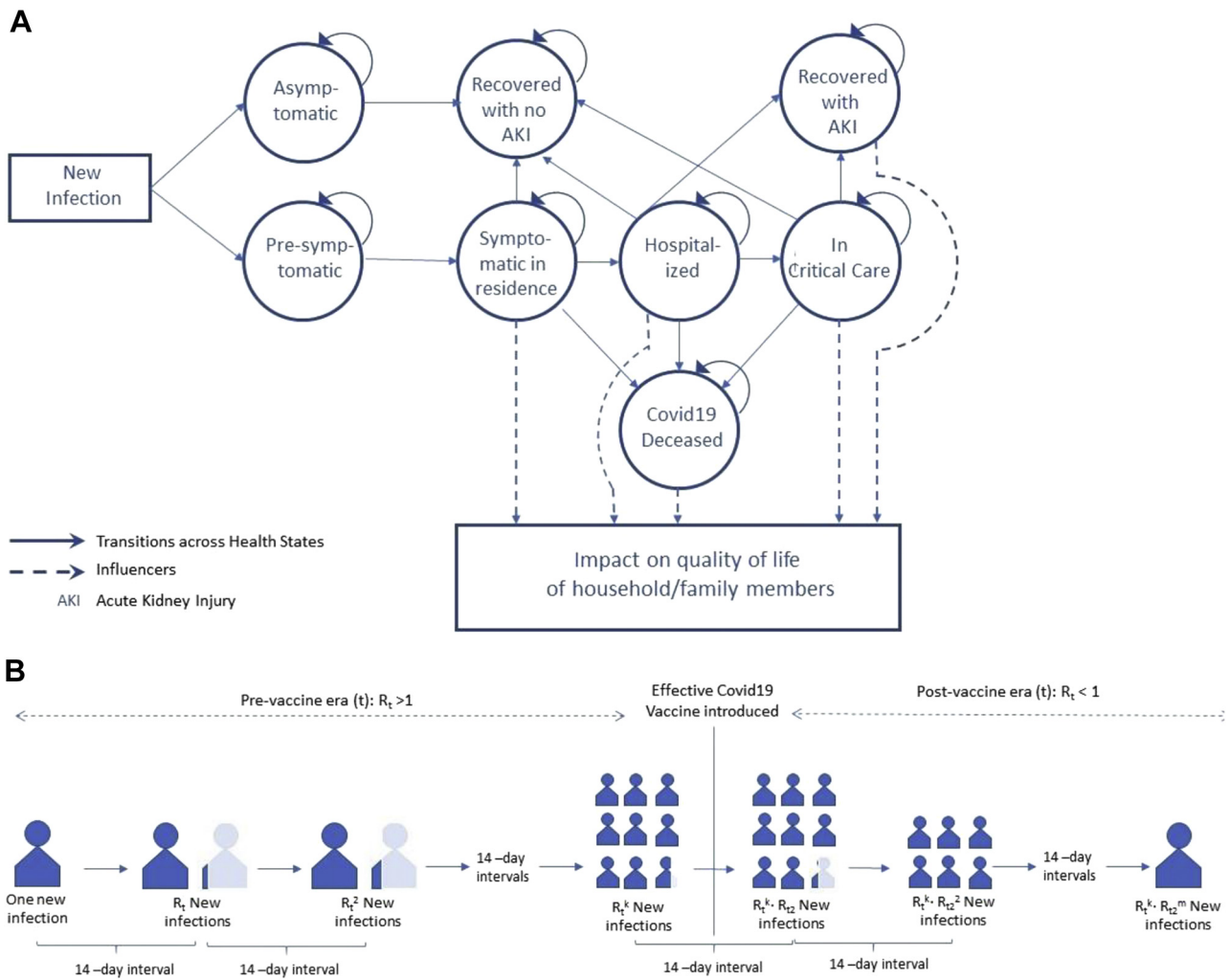
SEIR model's structural parameters. Uncertainty in those structural parameter estimates are captured through the uncertainty in  $R_t$ .<sup>7,8</sup> Moreover, our model also captures the reduced-form temporal trend in  $R_t$  after a vaccine is out.<sup>9</sup> Thus, our model presents an opportunity to assess the impact of a vaccine or treatment for COVID-19 validly and more straightforwardly by relying on reduced-form epidemiological parameters derived from a full-scale validated SEIR model.

Our patient-level model relies on a traditional Markov-type model structure, with time-varying transitions across competing risks, to capture the experience of a single patient with a COVID-19 infection. Such an approach also helps us follow the concomitant experiences of the family members in detail. Finally, the contagion effect of that single infection is captured by current and future estimates of the effective reproduction numbers.

**Simulation Model**

The experience of a representative patient with COVID-19 infection is illustrated in Figure 1A. At the onset, we recognize a nontrivial probability of a COVID-19 infection to remain asymptomatic, in which case no quality of life is lost for that patient and their family members. Emerging evidence suggests that there may

**Figure 1.** COVID-19 quality-adjusted life-years model. (A) Patient and family member experience. (B) Contagion model.



**Table 1.** Estimates for probability and hazard parameters for Figure 1.

Probability parameters	Distribution used	Notes
Asymptomatic infection	Beta(2,3)	Mean = .40, 5th percentile = .10; 95th percentile: .70. (CDC <sup>20</sup> )
Age distribution of symptomatic cases	Dirichlet(69703, 616457, 325277, 142129, 166921)	<18 years: 5.2%; 18-49 years: 46.7%; 50-64 years: 24.6%; 65-74 years: 10.8%; 75+ years: 12.7%; (CDC <sup>21</sup> )
Hospitalized   Symptoms	<18 years: $\text{logit}^{-1}(\ln(p_0/(1-p_0)))+\text{Normal}(1.60, .30)$ 18-49 years: $p_0 = \text{Beta}(1.5, 499)$ 50-64 years: $\text{logit}^{-1}(\ln(p_0/(1-p_0)))+\text{Normal}(1.30, .10)$ 65-74 years: $\text{logit}^{-1}(\ln(p_0/(1-p_0)))+\text{Normal}(2.16, .13)$ 75+ years: $\text{logit}^{-1}(\ln(p_0/(1-p_0)))+\text{Normal}(3.63, .20)$	18-49 years (Reference): .3% Odds ratio: <18 years: 4.96 (2.75-8.98); 50-64 years: 3.67 (3.01-4.48); 65-74 years: 8.7 (6.77-11.22); 75+ years: 37.87 (26.1-56.03); (CDC, <sup>22</sup> Petrilli et al <sup>23</sup> )
Death outside hospital   Symptoms	<18 years: 0 18-49 years: $p_0 = \text{Beta}(2.2, 1000)$ 50-64 years: Beta(2.2, 1000) 65-74 years: Beta(9.5, 1000) 75+ years: Beta(9.5, 1000)	<18 years: 0%; 18-49 years: 0.22%; 50-64 years: 0.22% (assumption); 65-74 years: 0.95%; 75+ years: 0.95%; Based on % of total deaths outside hospital = 36.6%, IFR ~ 0.6% and CDC planning estimates (CDC <sup>12,15</sup> )
Critical Care   Hospitalized	<18 years: Beta(113, 1000) 18-49 years: Beta(113, 1000) 50-64 years: Beta(113, 1000) 65-74 years: Beta(183, 1000) 75+ years: Beta(183, 1000)	<18 years: 11.3%; 18-49 years: 11.3%; 50-64 years: 11.3%; 65-74 years: 18.3%; 75+ years: 18.3%; Richardson et al (2020) <sup>34</sup>
Death without Critical Care   Hospitalized	<18 years: 0 18-49 years: Beta(19, 1000) 50-64 years: Beta(19, 1000) 65-74 years: Beta(265, 1000) 75+ years: Beta(265, 1000)	<18 years: 0; 18-49 years: 1.9%; 50-64 years: 1.9%; 65-74 years: 26.5%; 75+ years: 26.5%; Richardson et al (2020) <sup>12</sup>
Death   Critical Care	<18 years: 0 18-49 years: Beta(637, 1000) 50-64 years: Beta(637, 1000) 65-74 years: Beta(910, 1000) 75+ years: Beta(910, 1000)	<18 years: 0; 18-49 years: 63.7%; 50-64 years: 63.7%; 65-74 years: 91%; 75+ years: 91%; Richardson et al (2020) <sup>12</sup>
Acute Kidney Injury   Discharge from Critical Care	<18 years: Beta(111, 1000) 18-49 years: Beta(75, 1000) 50-64 years: Beta(75, 1000) 65-74 years: Beta(131, 1000) 75+ years: Beta(131, 1000)	<18 years: 11.1%; 18-49 years: 7.5%; 50-64 years: 7.5%; 65-74 years: 13.1%; 75+ years: 13.1%; Richardson et al (2020) <sup>12</sup>
Hazard parameters	Distribution used: Lognormal(mu, sigma)	Notes
Losing pre-symptomatic status	Mu~Uniform(1.51, 1.75) Sigma~Uniform(0.45, 0.55)	Mean days from exposure to symptom onset ~ 6 days (McAloon et al <sup>24</sup> )
Hospitalization   Symptoms	<18 years: mu~ Uniform(1, 2.5); sigma~(.15, .50) 18-49 years: mu~ Uniform(1,2.5); sigma~(.15, .50) 50-64 years: mu~ Uniform(1,2.5); sigma~(.15, .75) 65 - 74 years: mu~ Uniform(-.5,2); sigma~(.25, 1) 75+ years: mu~ Uniform(-.5,2); sigma~(.25, 1)	18-49 years: 6 (3, 9) days 50-64 years: 6 (2, 9) days ≥65 years: 3 (0, 7) days (CDC <sup>15</sup> )
Death outside hospital   symptoms	<18 years: NULL 18-49 years: mu~ Uniform(2,3); sigma~(.30, .70) 50-64 years: mu~ Uniform(2,3); sigma~(.30, .80) 65-74 years: mu~ Uniform(1.5,3); sigma~(.30, .75) 75+ years: mu~ mu~ Uniform(1.5,3); sigma~(.30, .75)	<18 years: NULL 18-49 years: 15 (9, 23) days 50-64 years: 15 (9, 25) days ≥65 years: 12 (7, 19) days (CDC <sup>25</sup> )

continued on next page

Table 1. Continued

Hazard parameters	Distribution used: Lognormal( $\mu$ , $\sigma$ )	Notes
Recovery outside hospital   symptoms	First 7 days = 0; 7 days: uniform(0.3, .35)	Time to recovery ~ 10 days (CDC <sup>25</sup> )
Get critical care   Hospitalized	<18 years: $\mu$ ~ Uniform(-0.5,1.2); $\sigma$ ~(.95, 1.5) 18-49 years: $\mu$ ~ Uniform(-0.5,1.2); $\sigma$ ~(.95, 1.5) 50-64 years: $\mu$ ~ Uniform(-0.5,2.3); $\sigma$ ~(.5, 1.5) 65-74 years: $\mu$ ~ Uniform(-1.8,1.8); $\sigma$ ~(.75, 1.9) 75+ years: $\mu$ ~ Uniform(-1.8,1.8); $\sigma$ ~(.75, 1.9)	<18 years: 3 (2, 5) days 18-49 years: 3 (2, 5) days 50-64 years: 6 (2, 11) days $\geq$ 65 years: 3 (1, 7) days (CDC <sup>14,15</sup> )
Death without critical care   Hospitalized	Same as Death outside hospital   symptoms	
Discharge without critical care   Hospitalized	<18 years: $\mu$ ~ Uniform(-0.5,1.7); $\sigma$ ~(.75, 1.5) 18-49 years: $\mu$ ~ Uniform(-0.5,1.2.); $\sigma$ ~(.95, 1.5) 50-64 years: $\mu$ ~ Uniform(-0.5,1.7); $\sigma$ ~(.75, 1.5) 65-74 years: $\mu$ ~ Uniform(.3,2.2); $\sigma$ ~(.5, 1.3) 75+ years: $\mu$ ~ Uniform(.3,2.2); $\sigma$ ~(.5, 1.3)	<18 years: 4 (2, 7) days 18-49 years: 3 (2, 5) days 50-64 years: 4 (2, 7) days $\geq$ 65 years: 6 (3, 10) days (CDC <sup>15</sup> )
Death   Critical Care	<18 years: $\mu$ ~ NULL 18-49 years: $\mu$ ~ Uniform(1.5,2.7); $\sigma$ ~(.2, .6) 50-64 years: $\mu$ ~ Uniform(1.9,2.5); $\sigma$ ~(.1, .2) 65-74 years: $\mu$ ~ Uniform(1.75,2.6); $\sigma$ ~(.1, .3) 75+ years: $\mu$ ~ Uniform(1.75,2.6); $\sigma$ ~(.1, .3)	<18 years: NULL 18-49 years: 8 (5, 15) days 50-64 years: 9 (7, 12) days $\geq$ 65 years: 10 (6, 13) days (CDC <sup>15</sup> + 1 day (Richardson et al <sup>12</sup> ))
Discharge   Critical Care	<18 years: $\mu$ ~ $\mu$ ~ Uniform(1.2,2.6); $\sigma$ ~(.2, .6) 18-49 years: $\mu$ ~ Uniform(1.2,2.6); $\sigma$ ~(.2, .6) 50-64 years: $\mu$ ~ Uniform(1.8,2.4); $\sigma$ ~(.1, .2) 65-74 years: $\mu$ ~ Uniform(1.55,2.5); $\sigma$ ~(.15, .35) 75+ years: $\mu$ ~ Uniform(1.55,2.5); $\sigma$ ~(.15, .35)	<18 years: 7 (4, 14) days 18-49 years: 7 (4, 14) days 50-64 years: 8 (6, 11) days $\geq$ 65 years: 9 (5, 12) days (CDC <sup>15</sup> )

be some temporary lung damage in patients who are asymptomatic,<sup>10</sup> but how that affects quality of life remains unclear. However, patients who are asymptomatic will continue to have a contagion effect, similar to a symptomatic patient. If the infection is symptomatic, the patient starts in a presymptomatic phase and daily follows a hazard to become symptomatic. Once symptomatic, the patient has a chance to be hospitalized, or they can die or recover without being hospitalized. Once hospitalized, the patients could get critical care (defined as admission to intensive care unit [ICU] or be on a ventilator) or die or recover without getting critical care. Finally, if the patient receives critical care, they can die or recover. If the patient recovers after getting critical care, there is a chance that such recovery will happen with long-term complications. Although many such long-term complications are reported in the literature,<sup>11</sup> we only consider acute kidney injury as the most common long-term complication reported in US data.<sup>12</sup>

The timeline of our model for the index patients starts with the index infection and continues till the patient recovers from the

infection, unless they recover with acute kidney injury, in which case the timeline extends to the patient's lifetime.

### Quality-Adjusted Life-Years

Quality-adjusted life-years are calculated by accounting for the loss in quality-of-life weight for the specific health states that a patient experiences over its duration. We account for both the losses in QALYs experienced by the patient throughout a COVID-19 infection and the losses experienced by family members concomitant with the patient experiences (Fig. 1A). Based on the US national estimate of the average family size of 3.14 (and family size did not vary much across age),<sup>13</sup> we account for the spillover effect on 2 family members.

Disutilities for various health states were obtained from literature estimates of quality of life losses (Table 2). These quality of life losses were divided by 365 to calculate QALYs lost per day that a patient remains in a particular health state. For example, the quality of life loss for symptomatic nonhospitalized COVID-19 health state

**Table 2.** Quality of life utilities for patients with COVID-19 and their family members.

Health state	Patients QALY loss*	Notes	Family member QALY loss*	Notes
Symptomatic infection	Mean( $\Delta Q1$ ) = -0.43 $\Delta Q0$ -Uniform (-0.46, -0.40)	Hollman et al (2013) <sup>35</sup> Spain; EQ-5D; H1N1 outpatients, change from baseline	$\Delta Q4$ -Uniform (-0.10, -0.015)	Wittenberg et al (2019) <sup>36</sup>
Patient admitted to hospital	Mean( $\Delta Q2$ ) = -0.50 $\Delta Q2$ - Uniform (-0.60, -0.40)	Barbut et al (2019) <sup>37</sup> ICER Remdesivir Report <sup>38</sup>	Mean( $\Delta Q5$ ) = -0.125 $\Delta Q5$ -Uniform (-0.15, -0.10)	Interpolated between symptomatic patient and patient in ICU
Patient receiving critical care	Mean( $\Delta Q3$ ) = -.60 $\Delta Q3$ -Uniform (-0.80, -0.40)	Barbut et al (2019) <sup>37</sup> ICER Remdesivir Report <sup>38</sup> Hollman et al (2013) <sup>35</sup> Spain; EQ-5D; H1N1 inpatient, change from baseline	Mean( $\Delta Q6$ ) = -.18 $\Delta Q6$ -Uniform(-0.21, -0.15)	76% of family members of ICU patients showed signs of anxiety or depression (HAD scale, Pochard et al, 2005) <sup>39</sup> Whynes et al (2009) <sup>40</sup> (Eq-5D Disutility for either possible, other probable HADS-identified anxiety or depression ~ 0.24)
End-state	Lifetime QALE loss	Notes	Lifetime QALE loss	Notes
Patient with Acute Kidney Injury	$\Delta Q7 = x\%$ of $\Delta Q9$ <18: x = 10% (5% - 15%) 18-49: x = 12% (4% - 20%) 50-64: x = 19% (11% - 29%) 65-74: x = 22% (13%, 25%) 75+: x = 29% (17%, 43%) Beta distribution with a+b = 4000	Coca et al (2012) <sup>41</sup> HR for overall mortality after AKI vs no AKI: 1.6 (95% CI 1.3-2.1) (N = 4000)	$\Delta Q8$ : 10% (0, 20%) of $\Delta Q7$	Assumption.
Patient's death	$\Delta Q9$ : QALE Loss <18 years: 23.97 18-49 years: 18.99 50-64 years: 12.83 65-74 years: 8.84 75+ years: 4.51	Fryback et al. (2007) <sup>42</sup> US EQ-5D norm by age. 3% discounting. Vanness (2020) <sup>43</sup>	Mean( $\Delta Q8$ ) = -0.35 for 1 year $\Delta Q10 \sim$ uniform(-0.10, -0.60)	Comans et al (2013) <sup>44</sup> EQ-5D disutility for bereavement of a family member and 1 year follow-up.

QALY indicates quality-adjusted life-year.  
\*All QALY losses converted to quality-adjusted days loss by dividing by 365.

was estimated to be -0.43 based on H1N1 patients' experiences.<sup>14</sup> Therefore, the disutility per day would be -0.0012 QALYs.

### Contagion Effect

The contagion effect of a single infection is illustrated in Figure 1B. We rely on evidence coming from population-level epidemiologic models to estimate the effective reproduction ratio ( $R(t)$ ) and the uncertainty surrounding this estimate. Currently,  $R(t) < R_0$  (basic reproduction ratio) for COVID-19 due to a variety of individual-level protective behaviors (eg, wearing masks, practicing physical distancing) and policy levers (eg, shelter-in-place, business closures). While  $R_0$  for COVID-19 is estimated to be about 2.5,<sup>15</sup> the effective  $R(t)$  currently is closer to but greater than 1.<sup>16</sup> We account for uncertainty in this estimate using a uniform distribution (1, 1.2) and assume that this level will continue until an effective vaccine becomes available. To obtain a conservative estimate for the contagion effect,<sup>15</sup> we assume the "generation time," that is, time between an individual's infection and the transmission of that infection to another individual, to be 14 days. We also assume that an effective vaccine will be available in 90 days.

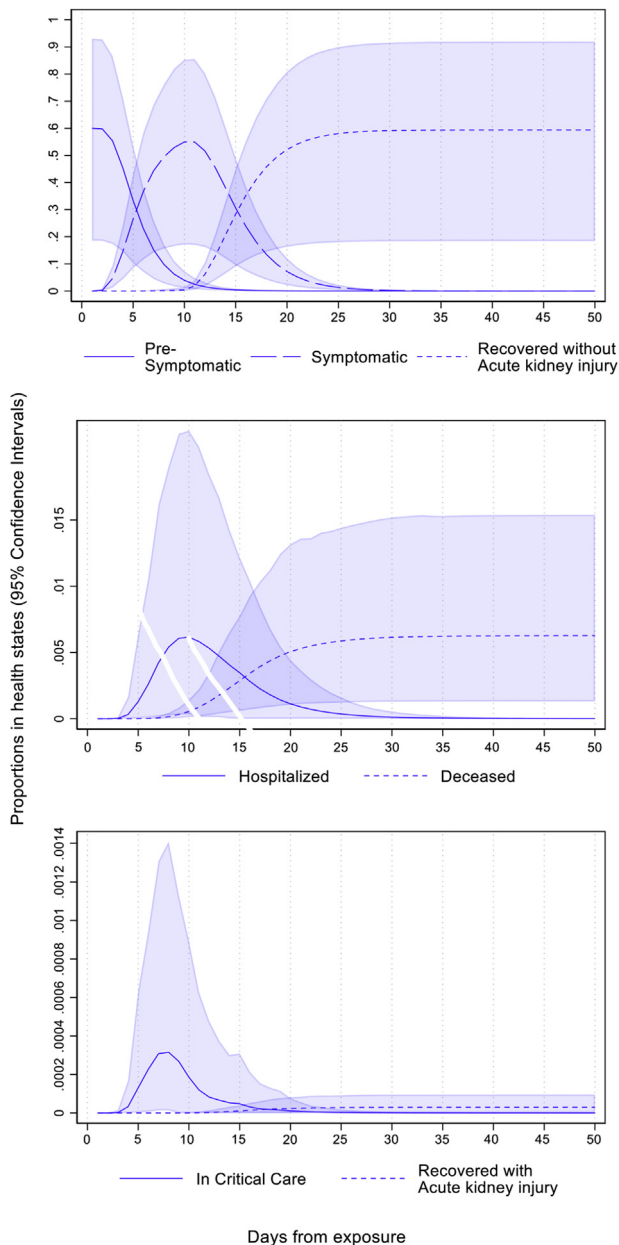
Vaccine efficacy can vary. We do not make any specific assumption on vaccine efficacy level except that a prophylactic

vaccine approved by the U.S. Food and Drug Administration is likely to have efficacy against acquisition of  $\geq 70\%$ . We allowed for a year for a non-perfect but suitable vaccine to help us reach herd immunity by the end of the year, which can be achieved by just 60% uptake. These estimates are in line with current modeling efforts with large SEIR models.<sup>17</sup> Therefore, after a vaccine becomes available, we allow  $R(t)$  to decrease linearly over 1 year to reach levels of herd immunity or  $R(t) \sim 0$ .<sup>8</sup> In total, we account for the growth in infections from the index infection date over the next 15 months, with each new infection experiencing the probabilistically similar QALY loss for the patient and their family members as our index case.

### Statistical Analysis

We carried out a probabilistic cohort-based simulation analysis of the model illustrated in Figure 1A. Of specific importance is to track different cohorts of infected individuals daily over the next set of competing risks that they face. For example, the cohort who would not remain asymptomatic will have a daily hazard of moving from presymptomatic to symptomatic status; those who become symptomatic will have competing risks of either dying outside hospital, recovering outside the hospital, or getting hospitalized; those who get hospitalized will face a daily competing

**Figure 2.** Proportion of initial cohort in different health states over days from exposure.



hazard of dying in the hospital without critical care, recovering without critical care, or getting critical care; and, finally, those who get critical care will face a daily hazard of death versus recovery. We used an event-specific probability and distribution approach to simulating competing risks, where we first simulated the proportion of cohort belonging to each competing risk and then applied the subhazard of the event to model the time of incidence for the event.<sup>18,19</sup> Where evidence exists, we stratified the probabilities and hazard estimates by age groups (Table 1). The infected person was followed until death or recovery. The resolution of final status occurred within 50 days in most of our simulations, but we followed through 180 days to capture any tails. Second-order (parameter) uncertainty for each parameter was propagated through the model using 10 000 deviates.

Univariate sensitivity analysis was carried out for this probabilistic model. We studied how our main results changed when, for each parameter, we used a deterministic value equal to the 2.5 or the 97.5 percentile of the parameter distribution while keeping all other parameters probabilistic.

## Results

The probabilistic experiences of a single representative infection are shown in Figure 2. There is about a 60% chance that an infected person will not remain asymptomatic. Among these, symptoms will appear for almost everyone within the first 15 days from the index day of infection (day 0) and most by the first 10 days. Close to 99% of those who become symptomatic (or 59.4% overall) recover without acute kidney disease. Almost all of these patients recover by day 25. The propensities to be in the hospital and critical care peak around the 10th day and the 7th day, respectively. This indicates that those who need critical care get hospitalized early. The probability of dying (corresponding to the infection fatality ratio) is 0.6%. Among those who become symptomatic, 0.005% recover with acute kidney injury. These estimates calibrate closely to existing evidence on COVID-19 in the United States.<sup>12,15,20–25</sup>

The main QALY results are shown in Table 3. The QALY loss to the infected patient and their family members accumulates to  $-0.061$  QALYs (95% confidence interval [CI]  $-0.129$  to  $-0.016$ ) for a single infection. Of this, 90% of the loss comes directly from patient experiences, and 10% from family members. Table 3 also shows the distribution of this loss between the patient and their family members by health states. When we applied this estimate of QALY loss for the index patient and their family members to account for the contagion effect, we found that over a 15-month period (with 3% discounting for the second year), where the vaccine arrives 3 months from now, the total QALY loss amounts to  $-1.51$  QALYs (95% CI  $-4.37$  to  $-0.28$ ).

Figure 3 illustrates the sensitivity analysis of our main results based on different parameters in our model. Our base case results remain robust against most parameters. The most influential parameters are identified by the largest difference in the mean QALY loss estimate from holding the parameter value to its 2.5 and 97.5 percentile (Fig. 3). These parameters were the effective reproduction number, probability of death outside the hospital, the time-varying hazard rates of death in critical care, and the time-varying hazard rates of hospitalization.

## Discussion

We developed a simulation model to comprehensively capture a COVID-19 infected patient's experiences and their family members in the United States. We quantified these experiences using the loss in QALYs incurred. We then applied these estimates to account for the contagion effect of the index infection during the pandemic. We model the contagion effect under a conservative scenario where an effective vaccine becomes available in 3 months, following which it takes a year to achieve herd immunity.<sup>26</sup> To our knowledge, this is the first instance where both patients' and family members' QALYs were modeled throughout a pandemic.

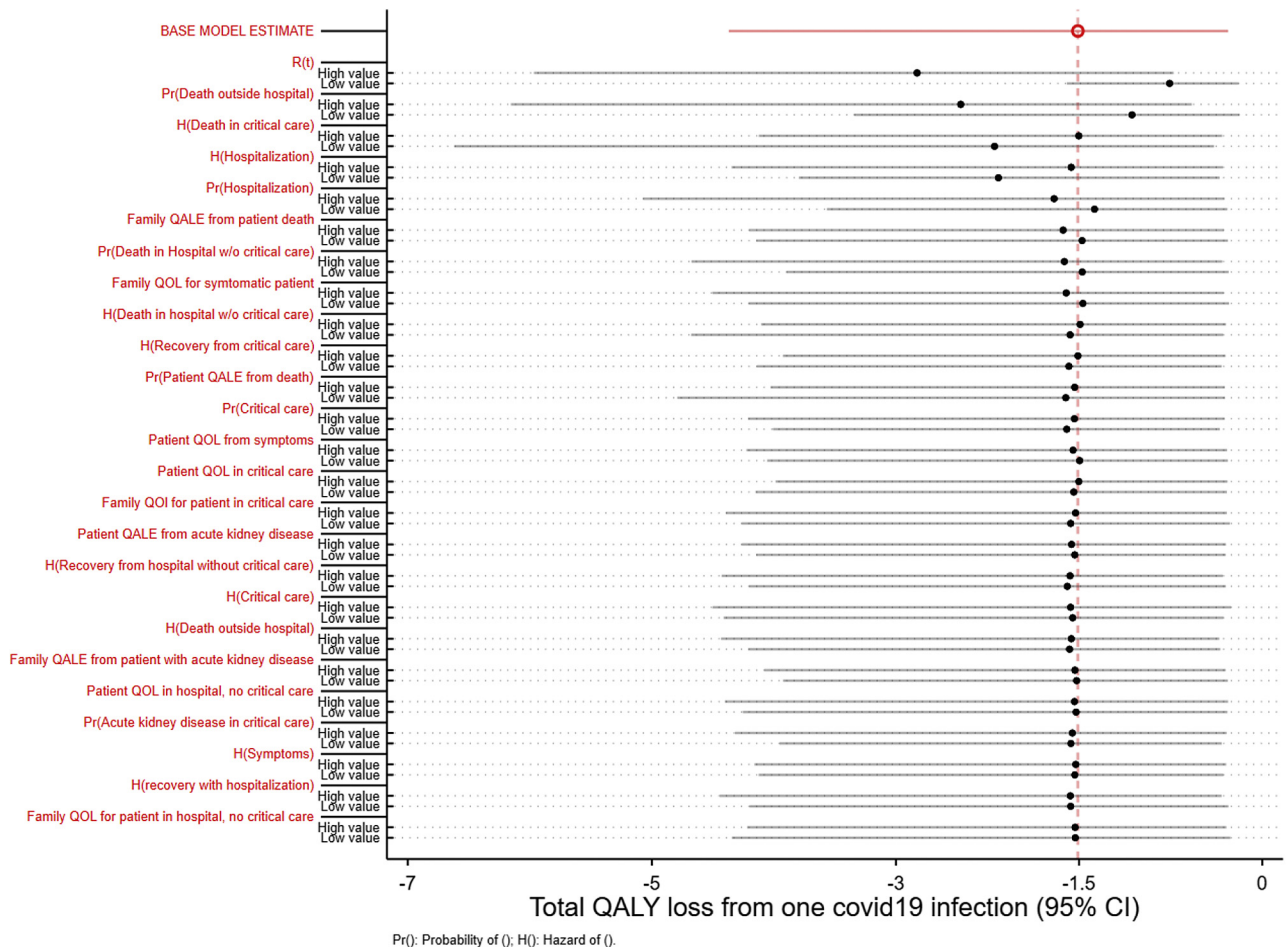
Our results show the QALY loss from 1 COVID-19 infection is substantial. To put this loss in perspective, we use the Tufts CEVR CEA registry<sup>27</sup> to identify the incremental QALYs reported for other US interventions since 2008 across all possible scenarios (eg, perspective, time duration). Of the 1900 US-based incremental cost-effectiveness ratio estimates we identified, the potential gain in QALYs that could be achieved by preventing 1 COVID-19 infection

**Table 3.** QALYs lost due to 1 representative COVID-19 infection and its distribution by health states.

Health states	QALY loss to patients (% of total loss) [95% CI]	QALY loss to family members (% of total loss) [95% CI]	Total QALY loss (% of total loss) [95% CI]
Symptomatic nonhospitalized	-0.007 (11.5%) [-0.011 to -0.002]	-0.002 (3.3%) [-0.004 to -0.001]	-0.009 (14.8%) [-0.014 to -0.003]
Hospitalized, not in critical care	-0.00009 (0.15%) [-0.00028 to -0.00001]	-0.00004 (0.07%) [-0.00015 to 0]	-0.00013 (0.21%) [-0.00043 to -0.00001]
In critical care	-0.000003 (0.005%) [-0.00001 to -0.0000002]	-0.000002 (0.003%) [-0.000006 to -0.0000001]	-0.000005 (0.008%) [-0.000016 to -0.0000003]
Recovered with acute kidney diseases	-0.00005 (0.08%) [-0.00018 to -0.000003]	-0.000011 (0.02%) [-0.00004 to -0.000001]	-0.000065 (0.11%) [-0.00021 to -0.000004]
Death	-0.048 (78.7%) [-0.106 to -0.011]	-0.004 (6.6%) [-0.012 to -0.001]	-0.052 (85.2%) [-0.115 to -0.011]
<b>TOTAL</b>	<b>-0.055 (90.2%)</b> <b>[-0.115 to -0.014]</b>	<b>-0.006 (9.8%)</b> <b>[-0.015 to -0.002]</b>	<b>-0.061 (100%)</b> <b>[-0.129 to -0.016]</b>

QALY indicates quality-adjusted life-year.

**Figure 3.** One-way sensitivity analysis for a probabilistic COVID-19 quality-adjusted life-years model.





was found to be greater than 90th percentile of the distribution of these estimates. There are many reasons for this. In general, the contagion effect of infection in a pandemic would account for a substantial portion of the value of prevention. Moreover, most, if not all, of the incremental cost-effectiveness ratios documented in the Tufts CEVR CEA registry do not account for the spillover effects of patients' health on family members.

Our results also have implications for the evaluation of the upcoming COVID-19 vaccines. For the first vaccine that enters the market, its cost-effectiveness evaluation must compare the reduction and time profile of  $R(t)$  achieved by that vaccine versus the likelihood that  $R(t)$  initially stays high but starts declining due to its entry competitor vaccine in the future. This control arm for the evaluation of the first vaccine is illustrated in our present work, although in the case of an actual evaluation, one would model the entry of the competitor vaccine probabilistically. Finally, our model also suggests that there is a distinct first-mover advantage for a vaccine manufacturer. The first vaccine that comes to the market can show a larger effect from preventing infection than subsequent vaccines due to changing  $R(t)$ 's baseline levels ( $t$ ).

Evaluation of vaccine should also account for any existing treatments of patients with COVID-19. The use of dexamethasone is already commonplace in the clinical care of patients who are hospitalized<sup>28</sup>; therefore, all our current estimates incorporate the effects of such uses. Recent trials have shown modest effects of remdesivir on the hazard of recovery of a patient who is hospitalized.<sup>29</sup> Remdesivir did not significantly affect overall mortality,<sup>30</sup> and most of its impact on time to recovery was concentrated among patients who did not need critical care at baseline. Consequently, the effect of remdesivir could be incorporated into our model by altering the hazard of recovery for hospitalized patients without critical care.<sup>29</sup> However, as Figure 3 shows, our results are not sensitive to this parameter. Therefore, even though remdesivir may benefit some patients, it likely will have little influence on the overall value of a vaccine. In general, the value of prevention always hinges on the effectiveness of treatments. If effective treatments that can substantially reduce mortality become available in the future, the value of prevention can be revisited.

Existing evidence suggests the disproportionate toll of COVID-19 among minority communities. Our model would readily be extended to study the burden of an infection within separate communities, given detailed data on the distribution of infections by age group, alternate progression parameters, and effective reproduction ratios are established with these communities. However, substantial evidence gaps remain on these issues.

There are several limitations to our analysis. We believe that all of these drawbacks indicate that our estimate of the effect of preventing an additional COVID-19 infection is conservative. First, we account for acute kidney injury as the long-term complication of getting critical care with COVID-19. Emerging evidence suggests that there may be additional long-term complications associated with severe infections.<sup>11</sup> Of specific concern is the evidence on the involvement of the heart (eg, myocarditis) in several recovered patients.<sup>31</sup> However, the long-term consequences of these manifestations are yet to be established.<sup>32</sup> Second, we assume that patients return to normal health immediately after recovery from infection. Some evidence suggests that return to normalcy may take many more days even after a patient becomes infection-free.<sup>33</sup> Third, we assume the probability of death in patients below 18 years to be zero. There have been reports of about 90 COVID-19 deaths in the United States among children.<sup>15</sup> For each of these cases, as more evidence accumulates, incorporating the effects would likely increase the impact of preventing a COVID-19 infection. Finally, our estimates of quality-of-life weights do not directly come from patients with COVID-19, but rather patients

experiencing severe influenzas or H1N1. Further works to assess the quality of life among patients with COVID-19 will be helpful.

Our model provides an alternate way to model the full impact of COVID-19 infection on QALYs of patients, family members, and the contagion effect. Efforts to curb COVID-19 infections must weigh the costs against these benefits.

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## REFERENCES

- Sanders GD, Maciejewski ML, Basu A. Overview of cost-effectiveness analysis. *JAMA*. 2019;321(14):1400–1401.
- Whittington MD, Campbell JD. Alternative pricing models for remdesivir and other potential treatments for COVID-19. [https://icer-review.org/wp-content/uploads/2020/06/ICER-COVID\\_Revised\\_Report\\_20200624.pdf](https://icer-review.org/wp-content/uploads/2020/06/ICER-COVID_Revised_Report_20200624.pdf). Accessed August 14, 2020.
- Dawoud DM, Soliman KY. Cost-effectiveness of antiviral treatments for pandemics and outbreaks of respiratory illnesses, including COVID-19: a systematic review of published economic evaluations [e-pub ahead of print]. *Value Health*. 2020. <https://doi.org/10.1016/j.jval.2020.07.002>. Accessed August 14, 2020.
- Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016;316(10):1093–1103.
- Neumann PJ, Kim DD, Trikalinos TA, et al. Future directions for cost-effectiveness analyses in health and medicine. *Med Decis Making*. 2018;38(7):767–777.
- Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care: a health economics approach: an ISPOR Special Task Force Report [3]. *Value Health*. 2018;21(2):131–139.
- van den Driessche P. Reproduction numbers of infectious disease models. *Infect Dis Model*. 2017;2(3):288–303.
- Hong HG, Li Y. Estimation of time-varying reproduction numbers underlying epidemiological processes: a new statistical tool for the COVID-19 pandemic. *PLoS One*. 2020;15(7):e0236464.
- Nishiura H, Chowell G. The effective reproduction number as a prelude to statistical estimation of time-dependent epidemic trends. *Math Stat Est Approach Epidemiol*. 2009:103–121.
- Long Q, Tang X, Shi Q, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med*. 2020;26:1200–1204.
- Potere N, Valeriani E, Candeloro M, et al. Acute complications and mortality in hospitalized patients with coronavirus disease 2019: a systematic review

- and meta-analysis. *Crit Care*. 2020;24:389. recovered patients: is it mandatory? *Sci Total Environ*. 2020;729:139021.
12. Provisional COVID-19 death counts by place of death and state. Atlanta, GA: Centers for Disease Control and Prevention (US), National Center for Health Statistics (MD). <https://www.cdc.gov/nchs/nvss/vsrr/covid19/index.htm>. Accessed August 14, 2020.
  13. United States Census Bureau. America's families and living arrangements: 2019. <https://www.census.gov/data/tables/2019/demo/families/cps-2019.html>. Accessed August 14, 2020.
  14. Centers for Disease Control and Prevention. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 - Georgia, March 2020. <https://www.cdc.gov/mmwr/volumes/69/wr/mm6918e1.htm>. Accessed August 18, 2020.
  15. American Academy of Pediatrics. Children and COVID-19: state-level data report. <https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/>. Accessed August 16, 2020.
  16. Abbott S, Hellewell J, Thompson RN, et al. Estimating the time-varying reproduction number of SARS-CoV-2 using national and subnational case counts [version 1; peer review: awaiting peer review]. <https://wellcomeopenresearch.org/articles/5-112>. Accessed August 14, 2020.
  17. Makhoul M, Ayoub HH, Chemaitelly H, et al. Epidemiological impact of SARS-CoV-2 vaccination: mathematical modeling analyses. *medRxiv*. 2020. <https://doi.org/10.1101/2020.04.19.20070805>.
  18. Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. *Health Technol Assess*. 2004;8(11):104.
  19. Degeling K, Koffijberg H, Franken MD, Koopman M, Ijzerman MJ. Comparing strategies for modeling competing risks in discrete-event simulations: a simulation study and illustration in colorectal cancer. *Med Decis Making*. 2019;39(1):57-73.
  20. Centers for Disease Control and Prevention. COVID-19 pandemic planning scenarios. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html>. Accessed August 18, 2020.
  21. Centers for Disease Control and Prevention. Coronavirus disease 2019 case surveillance: United States, January 22–May 30, 2020. [https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm?s\\_cid=mm6924e2\\_w#T2\\_down](https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm?s_cid=mm6924e2_w#T2_down). Accessed August 18, 2020.
  22. Centers for Disease Control and Prevention. Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States: 2018–2019 influenza season. <https://www.cdc.gov/flu/about/burden/2018-2019.html>. Accessed August 18, 2020.
  23. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 2020;369:m1966.
  24. McAloon CG, Collins A, Hunt K, et al. The incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. *BMJ Open*. 2020;10:e039652.
  25. Centers for Disease Control and Prevention. Duration of isolation and precautions for adults with COVID-19. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html>. Accessed August 18, 2020.
  26. Jena AB, Worsham CM. If we want to beat COVID-19, we need to get a lot better at vaccinating people. <https://www.washingtonpost.com/opinions/2020/07/07/if-we-want-beat-covid-19-we-need-get-lot-better-vaccinating-people/>. Accessed August 15, 2020.
  27. CEVR Tuft Medical Center. CEA registry. <https://cevr.tuftsmedicalcenter.org/databases/cea-registry>. Accessed September 18, 2020.
  28. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related *Strongyloides* hyperinfection. *JAMA*. 2020;324(7):623-624.
  29. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19: preliminary report. *N Engl J Med*. 2020:NEJMoa2007764.
  30. Pan H, Peto R, Karim QA, et al. WHO Solidarity trial consortium. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results [e-pub ahead of print]. *medRxiv*. 2020. <https://doi.org/10.1056/NEJMoa2023184>. Accessed August 14, 2020.
  31. Li LQ, Huang T, Wang YQ, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol*. 2020;92(6):577-583.
  32. Mitrani RD, Dabas N, Goldberger JJ. COVID-19 cardiac injury: implications for long-term surveillance and outcomes in survivors. *Heart Rhythm*. 2020. S1547-5271(20)30625-1.
  33. Balachandrar V, Mahalaxmi I, Subramaniam M, et al. Follow-up studies in COVID-19
  34. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City. *JAMA*. 2020;323(20):2052-2059.
  35. Hollmann M, Garin O, Galante M, Ferrer M, Dominguez A, Alonso J. Impact of influenza on health-related quality of life among confirmed (H1N1) 2009 patients. *PLoS One*. 2013;8(3):e60477.
  36. Wittenberg E, James LP, Prosser LA. Spillover effects on caregivers' and family members' utility: a systematic review of the literature. *Pharmacoeconomics*. 2019;37:475-499.
  37. Barbut F, Galperine T, Vanhems P, et al. Quality of life and utility decrement associated with *Clostridium difficile* infection in a French hospital setting. *Health Qual Life Outcomes*. 2019;17:6.
  38. Whittington MD, Campbell JD. Alternative pricing models for remdesivir and other potential treatments for COVID-19. Institute for Clinical and Economic Review Report. [https://icer-review.org/wp-content/uploads/2020/06/ICER-COVID\\_Initial\\_Abstract\\_05012020.pdf](https://icer-review.org/wp-content/uploads/2020/06/ICER-COVID_Initial_Abstract_05012020.pdf); May 1, 2020. Accessed August 5, 2020.
  39. Pochard F, Darmon M, Fassier T, et al. Symptoms of anxiety and depression in family members of intensive care unit patients before discharge or death: a prospective multicenter study. *J Crit Care*. 2005;20(1):90-96.
  40. Whyne DK, TOMBOLA Group. Responsiveness of the EQ-5D to HADS-identified anxiety and depression. *J Eval Clin Pract*. 2009;15(5):820-825.
  41. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int*. 2012;81(5):442-448.
  42. Fryback DG, Dunham NC, Palta M, et al. US norms for six generic health-related quality-of-life indexes from the National Health Measurement study. *Med Care*. 2007;45(12):1162-1170.
  43. Vanness D. Quality-adjusted life expectancies in the US. Private Communications.
  44. Comans T, Visser V, Scuffham P. Cost-effectiveness of a community-based crisis intervention program for people bereaved by suicide. *Crisis*. 2013;34(6):390-397.