MODEL STRUCTURE

The model (Figure 1, main text) advances in discrete, 1-day time steps for 2.5 years (the longest epidemic duration across scenarios included in this study). On any given day, each individual in the model is in 1 of 5 mutually exclusive COVID-19 coronavirus compartments: (1) susceptible (S, not infected and able to become infected), (2) exposed (E, infected, but not able to transmit to others), (3) infectious and asymptomatic (I_a, infected, but without symptoms, and able to transmit to others), (4) infectious and symptomatic (I_s, infected, showing symptoms, and able to transmit to others), or (5) recovered/immune (R, not infected and unable to become infected). On day 1, a set number of individuals start in the 'I_a' and 'I_s' compartments (i.e., seed coronavirus); the remainder start in the 'S' compartment. Each day, individuals interact with each other randomly, and an infectious person can potentially transmit the virus to a susceptible person. If a susceptible person comes in contact with an infectious person, he/she moves from the 'S' to the 'E' compartment. The following equation determines the number of susceptible individuals who became exposed each day: $\beta*S*Is + \beta*S*Ia$. Beta (β) is a function of the basic reproduction number (R_0; the average number of secondary cases generated by 1 infectious case) divided by the infectious period duration and the number of individuals in the population, 'S' and 'I' represent the number of susceptible and infectious persons, respectively, on any given day. Exposed individuals remain in the 'E' compartment for the latent period duration (i.e., time between exposure and ability to transmit) before becoming infectious and moving to the 'I' compartment (at the rate of 1/latent period duration). As individuals can transmit the virus prior to disease onset,[1] they could transmit 1 day prior to symptom onset. Each individual moving to the 'I' compartment has a probability of being symptomatic, which governs if they are in the 'I_s' or 'I_a' compartment. Each person draws an infectious period duration from a distribution (range:

4–15 days, including the day prior to symptom onset). Infectious individuals remain in the 'I state' until they recover and are no longer infectious, moving from the 'I' to the 'R' compartment (at the rate of 1/infectious period duration), where they remained for the rest of the simulation.

Each symptomatically infected person (i.e., COVID-19 case, regardless of formal diagnosis) travels through a probability tree of different sequential age-specific outcomes.[2,3] An infected person showing symptoms starts with a mild infection and has a probability of either seeking ambulatory care or calling his/her physician. This person then has a probability of progressing to severe disease requiring hospitalization (regardless of ambulatory care or telephone consult). If this person has only mild illness and is not hospitalized, he/she self-treats with over-the-counter medications and misses productivity days. If this person is hospitalized, he/she has a probability of developing severe pneumonia or severe non-pneumonia symptoms and has a probability of intensive care unit admission. This patient then has a probability of having either sepsis or acute respiratory distress syndrome (ARDS), with or without sepsis. If this patient has ARDS, he/she requires the use of a ventilator. If the person is hospitalized, he/she has a probability of dying. The person accrues relevant costs and health effects as he/she travels through the model.

DATA SOURCES

Appendix Table 1 shows key model input parameters, values, and sources. All costs, clinical probabilities, and durations were age-specific when available and come from scientific literature or nationally representative data sources [e.g., Healthcare Cost and Utilization Project (HCUP), Centers for Medicare and Medicaid Services (CMS)]. In the absence of literature, data from the Centers for Disease Control and Prevention (CDC) was preferred. Age-specific COVID-19 data

are specific to the U.S. context as of May 30, 2020 and come from the CDC.[4] When multiple sources were used for a parameter value (e.g., health state utility, probability of ARDS), input values are the average and standard deviation or median and range across reported values. In the absence of specific data, the probability of diagnosis given symptoms, derived from seroprevalence surveys and case reports, served as a proxy for the probability of seeking ambulatory care for symptoms.[5] Utility weights, derived from sources using preference-based measures, accounted effects on the quality of life but not for effects on productivity. All costs are reported in 2020 values, inflating all past and discounting all future costs using a 3% annual rate. As cost data come from several sources published across different years, we utilized a standard 3% rate to inflate all past costs, regardless of year, to 2020 values, per recommendations from the Panel of Cost-Effectiveness in Health and Medicine.[6,7] We also explored the impact of using a daily discount rate.

MODEL CALIBRATION AND VALIDATION

We parameterized the number of individuals starting in the 'Ia state' and 'Is state' on day 1 (i.e., coronavirus seed) such that simulated cases reflected case data reported as of March 24, 2020[8] for any given R_0 drawn from the distribution, and an epidemic occurred. This was equivalent to 130 symptomatic cases and 70 asymptomatic cases, which has a ratio of symptomatic to asymptomatic persons based on the probability of having symptoms. As predicting the specific course of the current pandemic can be challenging with such variations in the application of social distancing measures and face mask use policies as well as variations in the types and efficacy of face masks, we simulated general non-pharmaceutical intervention (NPI) use. We parameterized NPI effectiveness (i.e., combination of efficacy of NPIs and compliance with

NPIs) such that (in the absence of vaccination) the simulated prevalent cases reflected the reported number of prevalent cases as of October 8, 2020,[9] simulated over a similar duration. This was equivalent to an effectiveness of 0.3825, which generated 7,554,912 prevalent cases in the model by day 242, which corresponds to the reported 7,583,200 prevalent cases based on total SARS-CoV-2 case counts.

We also performed model validation including face validity and criterion validity. We achieved face validity as the progression of the simulated unmitigated epidemic proceeded in a trend following widely accepted epidemiological trends. For example, the peak number of cases per day (e.g., the peak of the epidemic curve) occurred when the population achieved herd immunity, which aligns with previously demonstrated trends in population infection control. For criterion validation, we compared the number of simulated age-stratified infections with and without NPIs to CDC age-stratified data from day 246. Day 246 corresponds to the most recent date of available COVID-19 data from the CDC (October 12, 2020[10,11]), assuming that community spread began in the U.S. at the beginning of February. Appendix Table 2 shows the age-stratified simulated data compared to the available CDC data. To note, there are a number of limitations to the CDC data when making comparisons. The hospitalization and ICU admission data have many missing data points (including all data for ages 80+) and has a 15-day lag. Additionally, an overall limitation of surveillance data is the inability to capture the cases in individuals who do not seek testing. Given these limitations, we expect there to be some discrepancy between model simulated data and CDC reported data, but the overall trends and patterns hold. To note, results for this study are based on comparisons between modeled scenarios (e.g., cases averted when varying timing of vaccination onset and vaccine efficacy).

RESULTS OF SENSITIVITY ANALYSES

Overall, the duration of the infectious period, followed by vaccine efficacy and vaccination coverage are the largest drivers of total cases and third-party paper costs when vaccinating (Appendix Figure 1). Hourly wage, then vaccine efficacy, followed by the duration of infectiousness are the largest drivers of total societal costs when vaccinating.

While changes in coverage does not affect the situations in which waiting reduces total cases and costs, the magnitude of impact between vaccination scenarios changes (Appendix Figure 2). For example, if there is a vaccine with a 50% efficacy when 10% of the population have been infected, waiting until 40% are infected for an 80% efficacy results 1.95 million additional cases with a 25% coverage and 23.3 million more with a 75% coverage. Varying vaccination cost had little impact on total costs as vaccination costs are a small fraction of total costs compared to COVID-19 medical costs (e.g., ±$40 in vaccination cost varies total third-party payer costs by -2.7% to 3% and total societal costs by –1.1% to 2.4%; Appendix Figure 3). Ambulatory care had little impact on direct medical costs due to illness (e.g., vaccinating with 20% vaccine efficacy when 25% have been infected results in $277.8 billion when patients can seek ambulatory care and $275.7 billion when all have a telephone consult).

Applying a daily discount rate had little impact on the resulting savings garnered by vaccinating with the first available vaccine. For example, if there is a 35% efficacious vaccine when 20% have been infected, waiting until 45% are infected for a vaccine with a 50% efficacy results in $14.1 billion more in direct medical costs and $13.9 billion more in productivity losses

(compared to $14.2 billion and $14.0 billion more respectively when discounting annually). As another example, if there is a vaccine with a 50% efficacy available when 25% of the population have been infected, waiting until 50% become infected for an 80% efficacious vaccine results in $21.3 billion more in direct medical costs and $18.5 billion more in productivity losses (compared to $21.7 billion and $18.8 billion more with discounting annually). Given the high variability of when cases show symptoms, seek care, and may be hospitalized and that costs will accrue on different days based on this, we use an annual discount rate for all presented results.

Appendix Table 1. Model Input Parameters, Values, and Sources

Parameter	Distribution type	Mean or median	SE or range	Source
COVID-19 coronavirus transmission				
R_0	Triangular	2.5	2.0–3.5	12–15
Latent period (days)	Triangular	5.2	4.1–7.0	12
Infectious period (days)	Uniform	–	3–14	16–19
Costs (2020 US$)				
Annual wages (all occupations)	Beta Pert	40,993	21,950–104,403[a]	20
Ambulatory care visit	Uniform		110.43–148.33	21
Telephone consult	Point estimate	14.80	–	22
Over the counter medications, daily				
0–12 years old[b]	Gamma	3.87	2.10	23
≥13 years old[c]	Gamma	0.46	0.17	23
Hospitalization for pneumonia[d]				
0–17 years old	Gamma	12,502.30	1,508.04	24
18–44 years old	Gamma	10,627.15	1,045.06	24
45–64 years old	Gamma	13,718.14	1,238.76	24
65–84 years old	Gamma	12,264.39	478.40	24
≥85 years old	Gamma	10,982.73	518.29	24
Hospitalization for severe non-pneumonia (all ages)[e]	Gamma	6,886.53	1,182.99	24
Hospitalization for sepsis[f]				
0–17 years old[g]	Gamma	22,694.30	1,861.33	24
18–44 years old	Gamma	43,778.39	5,382.40	24
45–64 years old	Gamma	38,734.24	2,725.10	24
65–84 years old	Gamma	30,308.29	1,367.91	24
≥85 years old	Gamma	22,694.30	1,861.33	24
Hospitalization for ARDS[h]				

0–17 years old	Gamma	42,350.58	4,198.97	[24]
18–44 years old	Gamma	26,210.96	1,558.61	[24]
45–64 years old	Gamma	19,863.98	453.92	[24]
65–84 years old	Gamma	18,718.55	335.69	[24]
≥85 years old	Gamma	16,559.75	754.12	[24]
Hospitalization for Guillain-Barre Syndrome[i]	Gamma	39,953.81	1,122.69	[24]
Hospitalization for allergic reaction/anaphylaxis[j]	Triangular	7,527.55	6,774.80–8,280.31[k]	[24]
Probabilities				
Non-pharmaceutical intervention (NPI) effectiveness	Point estimate	0.3825	–	Calibrated
Side effects due to vaccination				
Minor	Uniform	–	0.33–0.42	[25–27]
Severe: Guillain-Barre Syndrome[l]	Uniform	–	0.000001–0.000003	[28]
Severe: allergic reaction/anaphylaxis[l]	Triangular	0.0000015	0.0000009–0.0000025	[29]
Asymptomatic infection	Triangular	0.35	0.315–0.385[k]	[15]
Relative infectiousness of asymptomatic infection	Point estimate	1	–	[15]
Missing work/school	Point estimate	1.0	–	Assumption
Ambulatory care	Triangular	0.15	0.06–0.26	[5]
Telephone consult	–	1-probability of ambulatory care	–	Assumption
Hospitalization, given infection				
0–17 years old	Beta pert	0.031	0.028–0.034[k]	[4]
18–44 years old	Beta pert	0.056	0.051–0.062[k]	[4]
45–64 years old	Beta pert	0.140	0.126–0.154[k]	[4]
≥65 years old	Beta pert	0.300	0.270–0.330[k]	[4]

ICU admission, given hospitalization				
0–17 years old	Beta pert	0.171	0.154–0.1881[k]	[4]
18–44 years old	Beta pert	0.152	0.137–0.1675[k]	[4]
45–64 years old	Beta pert	0.186	0.168–0.2047[k]	[4]
≥65 years old	Beta pert	0.148	0.133–0.163[k]	[4]
Mortality, given hospitalization				
0–17 years old	Uniform	–	0.0054–0.0215[l]	[4]
18–44 years old	Uniform	–	0.0186–0.0745[l]	[4]
45–64 years old	Uniform	–	0.0519–0.2076[l]	[4]
≥65 years old	Uniform	–	0.1517–0.6068[l]	[4]
Pneumonia, given hospitalization	Beta	0.79	0.711–0.869[m]	[30]
ARDS, requiring ventilator use in ICU	Beta	0.771	0.053	[31–35]
Age-group, given infection				
0–17 years old	Point estimate	0.05	–	[4]
18–44 years old	Point estimate	0.39	–	[4]
45–64 years old	Point estimate	0.33	–	[4]
≥65 years old	Point estimate	0.23	–	[4]
Durations (days)				
Minor side effects	Uniform	–	1–2	Assumption[n]
Ambulatory care	Point estimate	0.5	–	Assumption
Duration of symptoms with mild illness	Triangular	7	3–17	[18,36,37]
Duration of symptoms prior to hospital admission	Triangular	7	3–9[o]	[38,39]
Hospitalization, not admitted to ICU				
0–49 years old	Gamma	3.9	3.7	[15]
50–64 years old	Gamma	4.9	4.3	[15]
≥65 years old	Gamma	6.2	5.7	[15]
Hospitalization, ICU (all ages)	Gamma	9	4–17[m]	[33–35,40]
Hospitalization, ventilator use	Gamma	9	5–12[m]	[33,34,41]

Hospitalization, Guillain-Barre Syndrome[i]	Gamma	11.5	0.33	[24]
Hospitalization, allergic reaction/anaphylaxis[j]	Gamma	2.3	2.1–2.5	[24]
Utility weights				
Healthy QALY				
<17 years old	Point estimate	1	–	[42]
18–64 years old	Point estimate	0.92	–	[42]
≥65 years old	Point estimate	0.84	–	[42]
Mild non-specific symptoms[p]	Beta	0.648	0.103	[43–52]
Hospitalized, non-pneumonia symptoms[q]	Beta	0.514	0.089	[45,52,53]
Pneumonia	Beta	0.496	0.17	[54–58]
Sepsis	Beta	0.467	0.18	[58–64]
ARDS	Triangular	0.10	0.08–0.15	[65]
Sensitivity analyses				

Parameter	**Values**	**Source**
Vaccine efficacy	20%–80%	Assumption
Percent of population exposed prior to vaccination onset	5%–50%	Assumption
Vaccination coverage	25%–75%	Assumption
Vaccination cost	$45–$125	Assumption[66,67]
NPI use	No, Yes	Assumption
Probability of ambulatory care	Baseline distribution–0%	Assumption[5]

[a]Values are 95% CI.
[b]Assumes 5 to 10 mg/kg of ibuprofen orally every 6 to 8 hours as needed OR 10 to 15 mg/kg of acetaminophen orally every 4 to 6 hours as needed.
[c]Assumes 200 mg of ibuprofen or acetaminophen orally every 4 to 6 hours as needed.
[d]Uses ICD-10 code #J13 Pneumonia due to Streptococcus pneumoniae.
[e]Uses ICD-10 code #J11.89 Influenza due to unidentified influenza virus with other manifestations.
[f]Uses ICD-10 code #R65.21 Severe sepsis with septic shock.
[g]Data for age-group unavailable and uses lowest values of all age-groups as a proxy.

[h]Uses ICD-10 code #J96.22 Acute and chronic respiratory failure with hypercapnia for 18 years and older and ICD-10 code #J96.20 Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia for 0 to 17-year olds.
[i]Uses ICD-10 code #G61.0 Guillain-Barre syndrome.
[j]Uses ICD-10 code #T78.2 Anaphylactic shock, unspecified.
[k]Values are a relative +/– 10% of the mean or median value.
[l]Maximum value is value reported in data, minimum value is a relative 75% reduction of the reported value.
[m]Values are IQR.
[n]Uses data from influenza vaccinations as a proxy.
[o]Values are 10%–90%.
[p]Uses influenza without hospitalization as a proxy.
[q]Uses influenza with hospitalization as a proxy.

ICU, intensive care unit; ARDS, acute respiratory distress syndrome; QALY, quality adjusted life year.

Appendix Table 2. Number of Model-Generated Clinical Outcomes and CDC Reported Data Through Day 246

Variable	SARS-CoV-2 infections	Symptomatic cases	Mild infections	Hospitalizations [b]	Intensive care unit stays[b]	Number deaths
Model-generated outcomes						
Unmitigated pandemic						
All ages	299,653,942	194,775,062	167,734,933	27,040,129	4,372,271	6,469,707
0 to 17 years		9,738,753	9,439,897	298,856	51,260	4,015
18 to 44 years		75,962,274	71,671,373	4,290,901	653,504	199,781
45 to 64 years		64,275,771	55,264,308	9,011,463	1,677,033	1,169,221
≥65 years		44,798,264	31,359,355	13,438,909	1,990,474	5,096,691
With non-pharmaceutical interventions (NPIs)						
All ages	7,855,478	5,106,060	4,397,199	708,861	114,620	169,604
0 to 17 years		255,303	247,468	7,835	1,344	105
18 to 44 years		1,991,364	1,878,877	112,487	17,132	5,237
45 to 64 years		1,685,000	1,448,763	236,237	43,964	30,651
≥65 years		1,174,394	822,091	352,303	52,181	133,611
CDC reported data (note different age groups and for which missing data in reported)						
Total[a]	7,787,548					
0 to 17 years	493,455					96
18 to 49 years	3,121,724					7,832
50 to 64 years	1,151,425					24,013
≥65 years	840,858					122,291
0 to 19 years				209	35	
20 to 49 years				33,459	3,791	
50 to 69 years				78,907	9,862	
70-79 years				11,936	1,804	

Notes: Cases and death counts reported by CDC as of October 12, 2020[10]; hospitalizations and ICU admissions reported by CDC through September 30, 2020.[11]

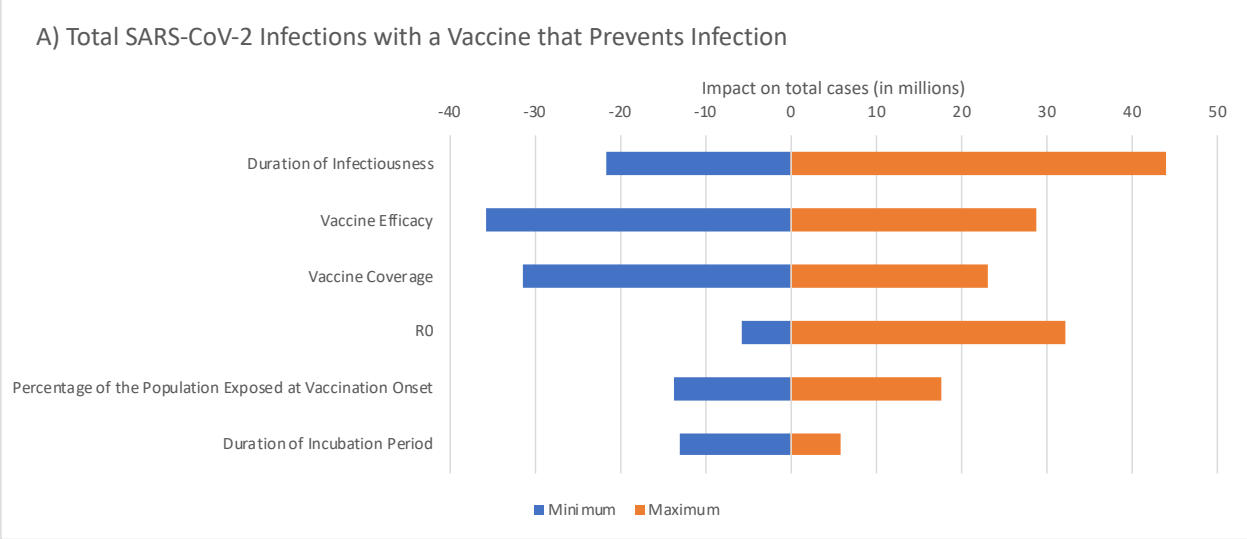
[a]Age group not available for 4% of cases.

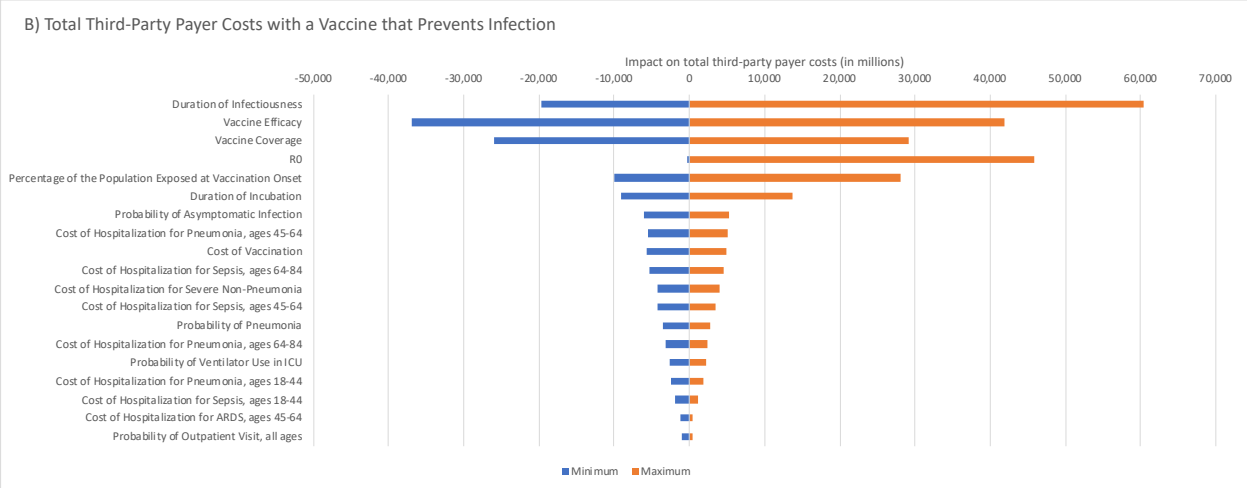
[b]Hospitalizations/Intensive care unit stays: data not available for 80+; 922,846 missing/unknown data points for ICU stays; 487,404 missing/unknown data points for hospitalization. Questions that have been left unanswered (blank) on the case report form are re-

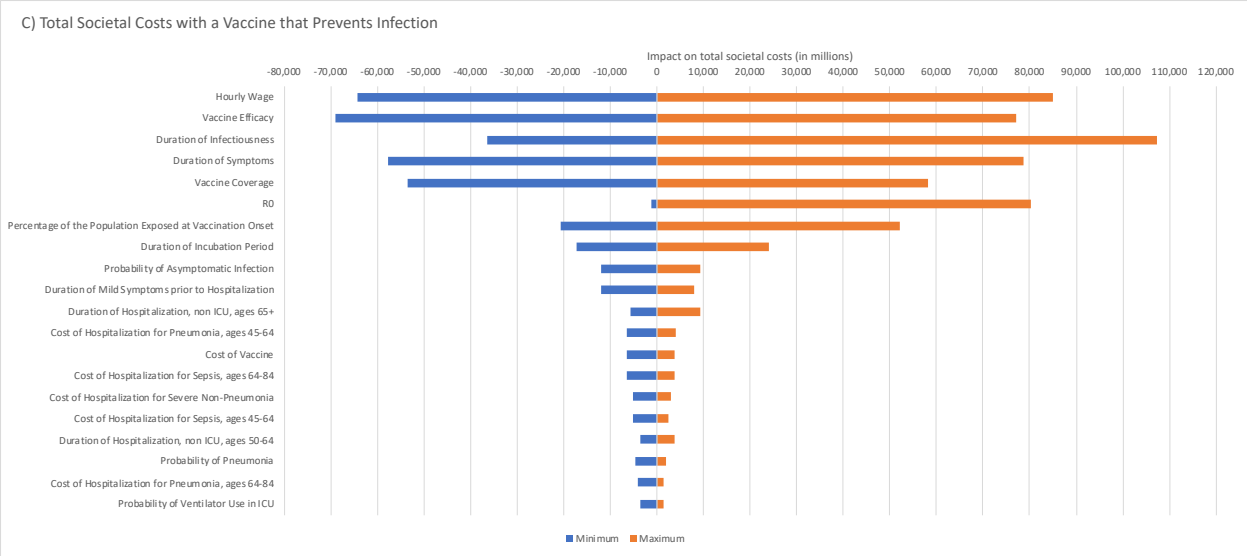
classified to a Missing value, if applicable to the question. For example, in the question *Was the patient hospitalized?*, where the possible answer choices include *Yes*, *No*, or *Unknown*, the missing value is re-coded to Missing if the respondent did not answer the question.[11]

CDC, Centers for Disease Control and Prevention.

Appendix Figure 1. Impact of model parameters on (A) Total SARS-CoV-2 infections with a vaccine that prevents infection and NPIs implemented, (B) Total third-party payer costs with a vaccine that prevents infection and NPIs implemented, and (C) Total societal costs with a vaccine that prevents infection and NPIs implemented.

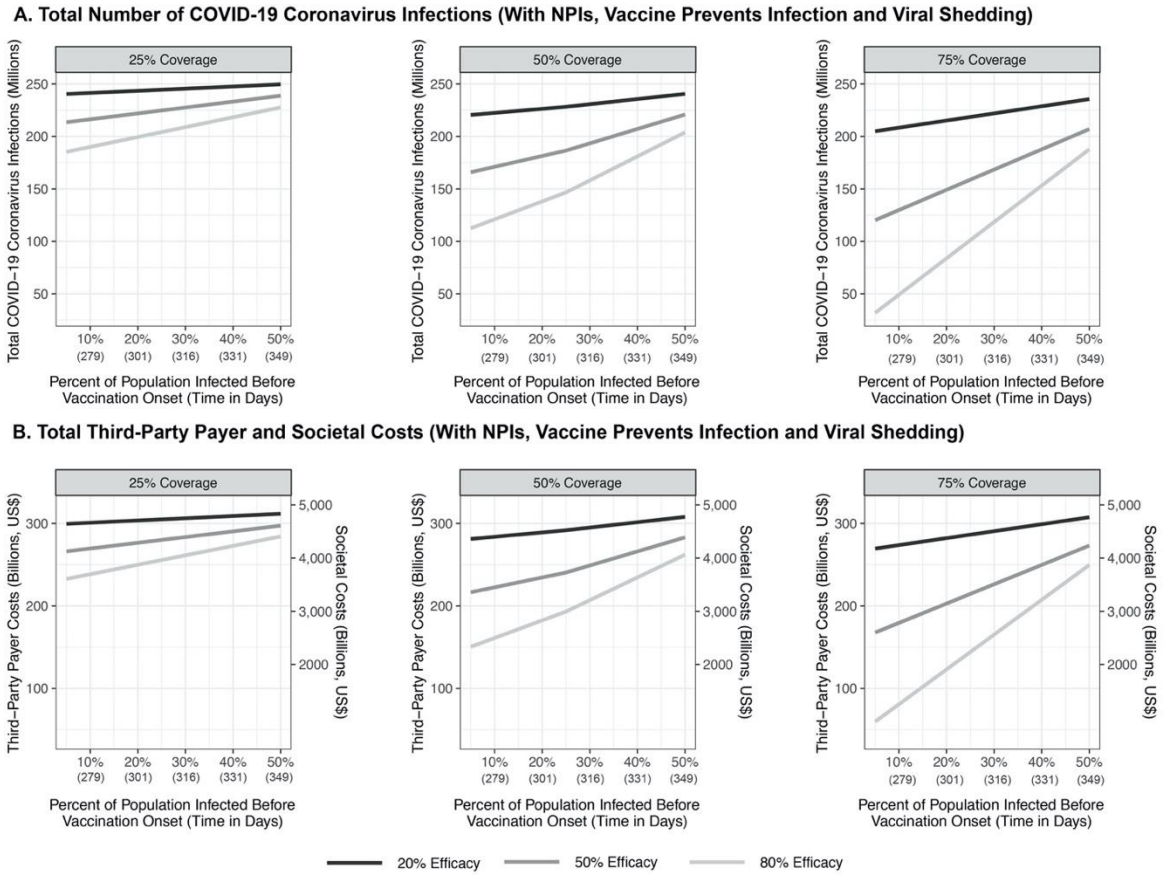




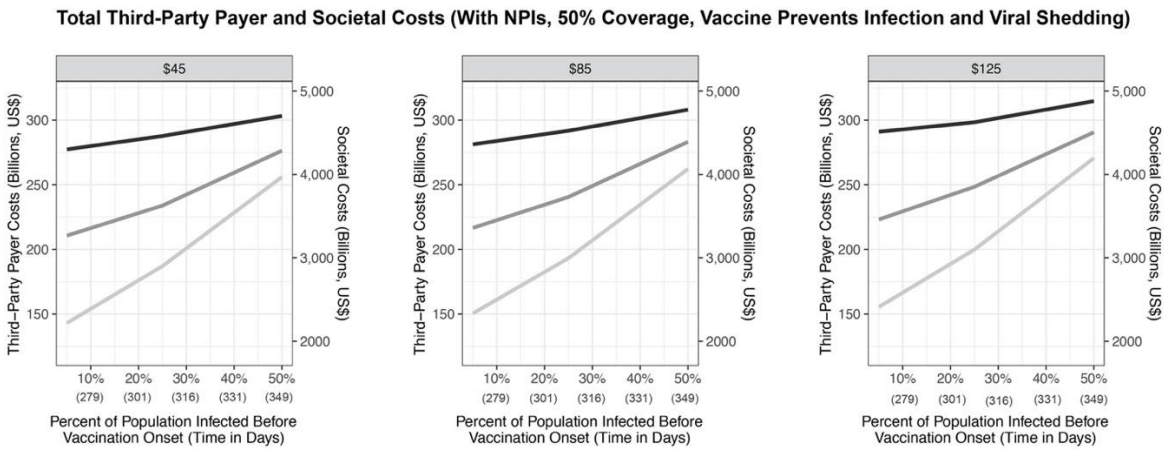


Notes: The x-axis shows the magnitude of the impact when parameters are varied to the minimum and maximum ends of their ranges; zero indicates the point for the target result at which all variables on the y-axis are held at their midpoint values. The width of the bar shows the range of impact that each parameter had when varied from its minimum to maximum value. To note, plots of total cases only include those parameters that affect this number (e.g., costs of hospitalization, etc. are not included) while plots of costs only include the top 20 parameters that impacted this value.

Appendix Figure 2. Impact of vaccine efficacy and timing of vaccination onset (percent of the population exposed to COVID-19 coronavirus prior to vaccination onset) on (A) the total number of COVID-19 coronavirus cases and (B) total third-party payer and societal costs during the course of the pandemic for a vaccine that prevents infection, varying with vaccination coverage ($85 vaccination cost), when non-pharmaceutical interventions (NPIs) similar to current U.S. measures implemented.



Appendix Figure 3. Impact of vaccination cost and timing of vaccination onset (percent of the population exposed to COVID-19 coronavirus prior to vaccination onset) on total third-party payer and societal costs during the course of the pandemic for a vaccine that prevents infection, assuming 50% coverage, when non-pharmaceutical interventions (NPIs) similar to current U.S. measures implemented.



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