Cost-effectiveness of future lockdown policies against the COVID-19 pandemic

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Abstract
Aim: While the European Union (EU) has approved several COVID-19 vaccines, new variants of concern may be able to escape immunity. The purpose of this study is to project the cost-effectiveness of future lockdown policies in conjunction with a variant-adapted vaccine booster. The exemplary scenario foresees a 25% decline in the vaccine protection against severe disease. Methods: A decision model was constructed using, for example, information on age-specific fatality rates, intensive care unit (ICU) costs and outcomes, and herd protection threshold. The costs and benefits of a future lockdown strategy were determined from a societal viewpoint under three future scenarios—a booster shot's efficacy of 0%, 50%, and 95%. Results: The cost-effectiveness ratio of a lockdown policy in conjunction with a booster dose with 95% efficacy is €44,214 per life year gained. A lockdown is cost-effective when the probability of approving a booster dose with 95% efficacy is at least 48% (76% when considering uncertainty in input factors). Conclusion: In this exemplary scenario, a future lockdown policy appears to be cost-effective if the probability of approving a variant-adapted vaccine booster with an efficacy of 95% is at least 48%.

Keywords
COVID-19, Germany, revaccination, decision model

Introduction

The COVID-19 pandemic and the resulting containment measures have triggered the deepest economic recession in the history of the European Union (EU).[1] In this crisis, EU economies have been significantly impacted by a combined supply and demand shock. For example, gross domestic product (GDP) of Germany contracted by 4.9% in 2020.[2] The second and third wave of infections is expected to dampen the rebound to 3.5% this year. Assuming there is no permanent damage to productive capacity, Germany's economy is projected to continue to grow above potential in 2022 at 3.6% and complete its recovery to the pre-crisis levels.[2]

The contraction of the GDP has been essentially driven by three factors (adopted from Ref.[3]). First and unrelated to the German government's response, there has been a sharp reduction in global demand and a disruption in global supply chains. With exports comprising 47% of the German GDP,[4] Germany has not been able to escape this wider global slowdown. Second, as part of the response to the COVID-19 pandemic, the German government has maintained a partial shutdown and lockdown.[1] Third, there has been a productivity loss due to sick leave and quarantine orders (typically over 10–14 days) for symptomatic and asymptomatic COVID-19 cases and their contacts.[5]

The current pandemic situation in the EU is characterized by a high and increasing overall incidence.[6] Germany entered the fourth wave of the pandemic in August 2021. It successfully controlled the third wave by bringing the reproduction number (the average number of secondary infections due to a single infected person) below 1 while avoiding overwhelming its health care system, particularly its intensive care units (ICUs).

Several strategies have been taken to curb the pandemic. The strategy of "flattening the curve" aims to avoid exceeding ICU capacity by keeping the number of the severely ill below the capacity limit at peak demand. This strategy lowers infection rates through non-pharmacological interventions such as social distancing. A complementary strategy is to "raise the line," that is, to expand ICU capacity by increasing the number of ICU beds and other measures. However, under these two strategies and in the absence of an effective vaccine, the pandemic eventually infects most of the population. Accordingly, "flattening the curve" and "raising the line" by themselves can help achieve herd immunity only through natural infection. An alternative strategy consists in "squashing the curve" (suppression), which entails a total shutdown of all

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non-essential services. By bringing the reproduction number substantially below 1, most of the population can be protected from the infection. Other strategies including the mitigation strategy pursued by the German government impose more stringent measures than "flattening the curve" but do not extend to a total shutdown. Nevertheless, both "squashing the curve" and mitigation aim at achieving herd immunity by vaccination of the population.

In November 2020, the pharmaceutical companies Pfizer/Biontech and Moderna independently announced that their vaccine candidates against SARS-CoV-2 have demonstrated evidence of efficacy against COVID-19 in participants without prior evidence of SARS-CoV-2 infection. The case splits between vaccinated individuals and those who received the placebo indicated a vaccine efficacy rate above 90%. The European Commission approved the Biontech-Pfizer and Moderna vaccines for use across the 27 Member States on 21 December 2020 and 6 January 2021, respectively. The Commission has so far given the conditional marketing authorization for four vaccines.

The decision-making situation faced by policymakers during the coronavirus crisis is characterized by ignorance and difficult to quantify uncertainty.[7,8] Before the announcements about the efficacy of COVID-19 vaccines, decision-makers lacked information to determine the probability of one or more COVID-19 vaccines of getting approval, timing of approval, and efficacy particularly with regard to severe COVID-19 cases. Current uncertainties revolve around the ability of the vaccine(s) to prevent transmission of new variant strains, the benefits and harms in children, and whether new variant strains will render approved vaccines less effective.

Assuming antigenically similar strains, it has been predicted[9] that even without immune boosting, a significant proportion of individuals may maintain long-term protection from severe infection. Nevertheless, new variants of concern may be able to escape immunity, induced by natural infection or vaccines. If variants of concern with either a substantial transmission advantage over resident variants, or the ability to evade vaccine-derived and prior immunity become dominant, they are expected to generate a wave of infections and hospitalizations comparable to those seen in the winter 2020–2021 wave.[10] If escape variants occur, vaccines need to be adapted. Depending on the platform technology used, the time needed to make such changes may vary from 3 to 9 months.[11] To approve the modified vaccine, the European Medicines Agency[12] does not require large-scale safety and efficacy studies, however. The time to produce a batch of the Pfizer/Biontech vaccine has been estimated to require 2 months even incorporating recent optimizations.[13]

The purpose of this study is to present a model for decision-making under ignorance in the coronavirus crisis. Assuming future COVID-19 outbreaks due to new variant strains that render vaccines less effective (vaccine escape), this study projects the cost-effectiveness of future lockdown policies combined with an adapted vaccine against a COVID-19 variant. In particular, it determines the minimum probability of a successful revaccination that makes a lockdown policy worthwhile. Uncertainty around booster shot's efficacy results particularly from the fact that clinical trials for adapted vaccines are not mandatory. Given the uncertainty around future variants of concern and waning protection, the study is exemplary in nature and primarily intends to demonstrate the applicability of decision-analytic tools to infectious disease preparedness.

Methods

Conceptual framework

All methods were carried out in accordance with relevant guidelines and regulations. The analysis takes a societal viewpoint. Thus, it includes direct medical costs, indirect/productivity costs, and consumption costs.

A decision model was constructed based on a previously developed and validated model.[14] The latter model determines the gain in life years of a strategy that is successful in "squashing the curve" compared to the situation before the pandemic. It is based on a life-table model that summarizes the age-specific mortality impact of the SARS-CoV-2 pandemic. The base case calculation relies on an independence assumption, implying that individuals not dying from COVID-19 have the same probability of death as all individuals before the rise of the pandemic. Given that patients who die from COVID-19 tend to have more comorbidities,[15] I assumed a harvesting effect in a sensitivity analysis. This approach presumes that those who die from COVID-19 are sicker and would have died any-way. In fact, a short-term harvesting effect (a lower number of deaths than expected) was observed in February and March 2021 after the peak at the turn of the year 2020/21,[16] suggesting that a portion of those who died would have died in the short term. In this scenario, I assumed for age groups with excess mortality associated with COVID-19 (the difference between observed and pre-pandemic mortality rates) that except for COVID-19, there are no other causes of death in the forthcoming 12 months. To account for the age distribution of the population, the model weights age-specific life-expectancy changes by age-specific population sizes.

Comparators

This study considered a future lockdown strategy similar to the COVID-19 mitigation policy chosen by the German government during the second and third wave. The response strategy included compulsory face masks, physical distancing, and quarantine directives but also a shutdown of businesses (overall, a partial lockdown/shutdown). Given that a surge of cases in an unmitigated future wave was predicted to result in a similar level as the mitigated second and third

waves (cf. Ref. 10), the lockdown was assumed to be able to suppress a future wave.

A future lockdown strategy ends with a successful large-scale rollout of a vaccine adapted to variants, by lifting the restrictions. In the absence of a successful revaccination program, a lockdown policy was assumed to either end or to continue. Under continuation, future SARS-CoV-2 pandemic waves were assumed to peak in winter and re-turn yearly, thus imposing regular lockdowns.

As an add-on to the lockdown policy, I considered "raising the line" by providing additional staffed beds in the ICU. This strategy accounts for the possibility of a surge of COVID-19 cases that would overwhelm the existing ICU capacity. While the addition of ICU capacity is heavily constrained by labor supply and other input factors, I analyzed the addition of up to 20,000 beds to show the range of possible costs and benefits.

The comparator of a future COVID-19 lockdown policy is "no intervention." "No intervention" does not impose a lockdown/shutdown and results in herd immunity through natural infection in the subpopulation with waning immunity or no immunization. I did not adjust the number of life years gained for a possible deferral of elective procedures assuming that ICU capacity is sufficient.

In agreement with other authors who foresaw a high probability of a second and third SARS-CoV-2 pandemic wave under no intervention strategy (e.g., Refs. 17 and 18) I assumed two remaining pandemic waves under no intervention in the base case.

Time horizon

Assuming that efficacy of a booster shot will be maintained over 1 year (cf. Ref. 19) the time horizon of a lockdown policy was set to 1 year in the base case. In the event of vaccine failure, the study assumed the enactment of annual relockdowns. The time horizon was set to 5 years reflecting the expected maximum acceptable period of relockdowns.

Cost analysis

The incremental costs of a future lockdown policy versus "no intervention" are the contribution of the lockdown/shutdown to the total economic burden of the SARS-CoV-2 pandemic. Whereas from the perspective of static efficiency the GDP drop associated with the lockdown/shutdown until today can be considered sunk, from the perspective of dynamic efficiency, which sets incentives for innovation (e.g., for vaccines in future pandemics), it is still relevant. As vaccine development and distribution in future pandemics is likely to occur only in conjunction with a shutdown strategy, considering the full shutdown cost avoids introducing excessive incentives for innovation. Therefore, a dynamic efficiency perspective was considered in the base case.

The savings in health care expenditures by enacting a future lockdown (compared to "no intervention") were not added to the GDP estimate because the savings were assumed to be offset by higher health expenditures for elective procedures and emergency and physician visits for unrelated medical conditions. That is, in case of a natural spread, providers and patients were assumed to reduce utilization of elective procedures as well as emergency and physician visits for unrelated medical conditions.

Conversely, productivity gains from avoiding sickness were added to the GDP estimates. They were calculated by multiplying the proportion of symptomatic patients with the duration of sickness and the daily productivity loss. For the latter calculation, a few simplifying assumptions were made. First, all undiagnosed but symptomatic infections were assumed to be mild. This assumption is indirectly supported by official data on excess mortality in Germany[16] showing that the peak in excess mortality in the first half of April 2020 and in December 2020 both coincided with surges in COVID-19 deaths (thus essentially ruling out deaths due to undiagnosed COVID-19 cases). Second, the number of quarantined contact persons per diagnosed case reached the maximum in August 2020 and cannot increase further due to labor and technological constraints in local public health departments. Third, infected and quarantined individuals are representative of the general population.

If revaccination is not successful, one scenario foresees that the lockdown policy ends by lifting the restrictions. The suspension results in costs associated with health care spending, productivity loss, and voluntary social distancing due to the spread of the infection. However, as these costs also incur under no intervention, they cancel out in an incremental calculation. The alternative scenario assumes continuation of the lockdown policy over the time horizon considered.

To determine the costs of "raising the line," I used an estimate of the societal costs of providing additional ICU beds for ICU candidates based on the above-mentioned model.[20] The time horizon is the remaining lifetime. The cost estimate includes not only the initial ICU stay but also rehospitalizations occurring in the first year after discharge from the ICU, hospital copayments, as well as future consumption and unrelated care during added life years. Hospital costs of treating COVID-19 patients include operating and infrastructure costs.

Concerning vaccination costs, I considered the costs of (i) the vaccine itself, (ii) the logistical management and clinical administration, and, in agreement with a dynamic efficiency perspective, (iii) scientific research failures. Regarding the costs of the vaccine, I considered prices that do not include a markup above the marginal costs of production and distribution. This is in agreement with the economic principle that drug prices need to be adjusted for producer surplus, as it presents a gain in societal welfare.[21] The level of efficacy was assumed to be independent of the marginal costs of production and distribution. For the costs of scientific research failures, I considered the probability of success of clinical trials of vaccines. In this regard, it is important to mention that

Germany has several companies developing a COVID-19 vaccine. While part of the upfront costs faced by vaccines producers have been already financed in the form of advance purchase agreements, they are still relevant from the perspective of dynamic efficiency.

Vaccine efficacy and duration of protection

Vaccine efficacy refers to vaccine protection measured in clinical trials.[22] While the terms vaccine efficacy and effectiveness are often used interchangeably in the scientific literature, vaccine effectiveness refers strictly to vaccine efficacy in field conditions. Vaccine efficacy/effectiveness (VE) can be measured by comparing the frequency of illness in the vaccinated and unvaccinated (placebo) groups[22,23]:

$$VE = 1 - \left(\frac{AR_V}{AR_V} \right), \qquad (1)$$

where AR_V and AR_U are the attack rates among vaccinated and unvaccinated individuals, respectively. The attack rate is the proportion of individuals infected in the specific risk group over a nominated period. Vaccine efficacy can also be defined based on the frequency of only severe cases.[24]

The herd immunity threshold is calculated based on an inversely proportional relationship with vaccine efficacy (in terms of attack rate)[25]:

$$\varphi = \frac{1}{\epsilon} \left(1 - \frac{1}{R_0} \right), \qquad (2)$$

where φ refers to the herd immunity threshold, ϵ is vaccine efficacy, and R_0 is the basic reproduction number of a disease.

Break-even analysis

For the lockdown option, a break-even probability was calculated reflecting the minimum probability of a successful revaccination that makes a lockdown policy worthwhile. To this end, I used the net monetary benefit (NMB) as a payoff:

$$NMB = R \cdot \Delta e - \Delta c, \qquad (3)$$

where R is the willingness to pay for a health gain, Δe is the incremental health gain, and Δc is the incremental cost (GDP loss). The willingness to pay was borrowed from the cost-effectiveness ratio of new, innovative oncological drugs in Germany, as cancer reflects a condition with a similar morbidity and mortality burden in the general population in the short term as COVID-19.[14]

Given that the break-even point is defined as $NMB = 0$, we obtain:

$$0 = p \cdot NMB_{\text{success}} + (1 - p) \cdot NMB_{\text{no success}}. \qquad (4)$$

Solving for p yields:

$$\frac{1}{1 - NMB_{\text{success}} / NMB_{\text{no success}}} = p. \qquad (5)$$

Given that the uptake of a vaccine may be low due to public hesitancy, I also calculated the break-even probability for a given adoption rate ∂. Multiplying both sides of equation (5) with $\frac{1}{\partial}$ and rearranging it yields:

$$\frac{1}{1 - \partial \cdot R \cdot \Delta e_{\text{success}} - \Delta c_{\text{success}} / NMB_{\text{no success}}}$$
$$= \frac{1}{\frac{\partial}{p} - \partial + 1 - (\partial - 1) \cdot \Delta c_{\text{success}} / NMB_{\text{no success}}}. \qquad (6)$$

Hence, the break-even probability as a function of the uptake is obtained as follows:

$$p(\partial) = \frac{1}{\frac{\partial}{p} - \partial + 1 - (\partial - 1) \cdot \Delta c_{\text{success}} / NMB_{\text{no success}}}. \qquad (7)$$

Hurwicz decision rule

Under ignorance, the Hurwicz approach[26] attempts to find a middle ground between the extremes posed by the optimist and pessimist criteria. A recent article presented "a strong argument in favor of the Hurwicz criterion" for rational decision-making under ignorance.[27] Instead of assuming total optimism or pessimism, Hurwicz incorporates a measure of both by assigning a certain percentage weight to optimism and the balance to pessimism. That is, a weighted average is computed for every strategic alternative with an alpha weight α, called the coefficient of optimism ($0 \leq \alpha \leq 1$). An $\alpha = 1$ implies absolute optimism (maximax), while an $\alpha = 0$ implies absolute pessimism (maximin). The Hurwicz criterion (H) is formalized as follows:

$$H(d_i) = \alpha \cdot V_{\text{max},i} + (1 - \alpha) \cdot V_{\text{min},i}, \qquad (8)$$

where d denotes the decision alternative i and V refers to the payoff. In the decision-making situation in question, V_{max} and V_{min} are defined as scenarios with and without successful revaccination and are defined based on the NMB.

A break-even alpha weight was calculated based on equation (5), reflecting the minimum degree of optimism that makes waiting for a booster shot worthwhile.

Cost-effectiveness analysis

The incremental cost-effectiveness ratio (ICER) of a lockdown policy with and without expansion of ICU capacity compared to no intervention is calculated by dividing the sum of the incremental costs of a partial lockdown/shutdown, vaccination, and productivity loss by the incremental health gains.

Data

Cost data

A variant causing a drop in protection against severe disease was expected to generate a wave of infections and hospitalizations comparable to those seen in the winter 2020–21 wave (in the absence of non-pharmaceutical interventions).[10] Regarding the economic contraction due to another pandemic wave suppressed by a lockdown, I took the GDP contraction in the first quarter of 2021 (1.7%[28]), which was essentially driven by the second wave (and the concomitant lockdown policy). In terms of the GDP loss independent of the second wave, I took the GDP loss in 2020 (4.9%), accounted for the projected GDP increase in 2021 (3.5%),[2] and subtracted the GDP contraction of the second wave. However, this calculation assumes the absence of a pandemic in the counterfactual scenario, without considering the voluntary restrictions such as social distancing in view of the rapid spread of the virus in the population (cf. Ref. [29]). That is, individuals may take precautions even without the lockdown orders. Accounting for the latter would decrease the incremental cost of the lockdown/shutdown over no pandemic. In a sensitivity analysis I assumed the contribution of the lockdown/shutdown to the total loss of economic activities to be 10%, to account for the voluntary restrictions that may take place in the absence of a lockdown/shutdown. This estimate agrees with the one regarding the contribution of a shutdown to the loss of economic activities in Denmark, which was estimated to be 14% (=4%/29%).[30]

To determine the productivity gains resulting from a lockdown policy, as compared to no intervention, I used the data sources reported in Table A1 of the Appendix.

Concerning the costs of the vaccine itself, I considered prices of companies that declared not to strive for profits (i.e., Johnson & Johnson and AstraZeneca).[31] In the base case, I applied an estimate of €7 per person, which represents the costs of the Johnson & Johnson vaccine.[32] The price of the AstraZeneca vaccine, which requires two doses (each at €2.50) for full protection, was used in a sensitivity analysis. The marginal costs of producing and distributing the BioNTech/Pfizer and Moderna vaccines were not publicly available. The costs of failures were based on a failure rate of 70%, representing a weighted average of industry-sponsored and non-industry-sponsored vaccine development programs with end dates after 1 January 2000, and start dates before 7 January 2020.[33]

All costs are presented in euros, year 2020 values.

Epidemiological and clinical data

The analysis assumed a 25% decline in the protection against severe disease in individuals with immunity acquired by natural infection or by administration of a vaccine (in agreement with a scenario presented by[10]). Of note, this does not present an extreme-case scenario analyzed by the European Centre for Disease Prevention and Control (2021). In any case, the decline was varied in a sensitivity analysis. As a booster was assumed to make up only for this decline, it remains less effective than a vaccine, say, with 95% efficacy compared to no vaccine.

See Table 1 for further model input data.

To calculate the per capita gain in life years through a relockdown in conjunction with revaccination, I used an estimated COVID-19 infection fatality rate (IFR) of 0.83% until 12 December 2021[34] as a baseline, multiplied it with the mortality hazard ratio of the B.1.1.7 (Alpha) variant[35] (the relative mortality of the Delta variant was unclear at the time of writing the article), the decline in the protection against severe disease, and applied the resulting estimate to the previously developed model.[14] The IFR was adjusted upwards to account for the long-term mortality of ICU survivors. The per capita gain in life years incorporates a herd immunity effect once a certain percentage of the population has acquired immunity. In a sensitivity analysis, I explored structural uncertainty in the previously developed model. To this end, I performed a back-of-the-envelope calculation of the per capita gain in life years, by multiplying the IFR under "no intervention" with the average loss of life years and the decline in the protection against severe disease. Furthermore, given that the IFR is lower than the case fatality rate (CFR) in Germany, I adjusted the percentage of patients admitted to the ICU accordingly because a lower CFR also implies a lower percentage of cases admitted to the ICU.[14]

In both the Pfizer-Biontech and Moderna COVID-19 vaccines, efficacy in clinical trials in preventing confirmed (symptomatic) COVID-19 was approximately 95%. I took a 95% efficacy in preventing deaths and transmissions as the upper limit of efficacy of revaccinations. As the lower limit of vaccine efficacy against mortality, I took the minimum efficacy requested by the United States Food and Drug Administration (FDA),[36] which is 50% for the primary endpoint. As the FDA allows both SARS-CoV-2 infection and deaths associated with COVID-19 to be defined as primary endpoints, applying the 50% threshold to life years gained as a measure of vaccine efficacy is still valid.

In the base case, I assumed a vaccine uptake that is sufficient to achieve herd immunity with a vaccine efficacy of 95%. Based on equation (2) and a herd immunity threshold of 80% for natural infection,[37] the threshold is approximately 84% for a vaccine efficacy of 95%. As a vaccine efficacy of 50% cannot lead to sufficient herd immunity, the resulting productivity loss from viral spreading in the unprotected population was taken into consideration. In a sensitivity analysis, I considered an uptake of 50% for revaccinations.

Other data

The willingness to pay for an additional life year (€101,493 per life year gained) was calculated by dividing the incremental costs of new, innovative cancer drugs

Table 1. Input values and distributions used in the base case and sensitivity analysis.

Input	Mean (range)	Reference
Epidemiological and clinical data		
Probability of death by age and gender in Germany	see reference	[54]
Population size by age	see reference	[55]
IFR in Germany (without vaccine)	0.014 (0.011–0.017)	[34,35]
CFR in Germany (without vaccine)		[56]
Total population	0.017	
0–9 years	0.00013	
10–19 years	0.00002	
20–29 years	0.00010	
30–39 years	0.00026	
40–49 years	0.00087	
50–59 years	0.00302	
60–69 years	0.01554	
70–79 years	0.06305	
80–89 years	0.12154	
90 + years	0.15168	
Probability of ICU indication	0.03 (0.03–0.08)	[56,57]
False-positive ICU admissions	0.1 (0.1–0.2)	[58]
CFR in the ICU	0.23 (0.22–0.24)	[56]
CFR 1 year post ICU discharge	0.59 (0.47–0.73)	[59]
Herd protection threshold	0.80 (0.80–0.90)	[37]
Cost data		
GDP reduction per pandemic wave, %	1.7	[28]
GDP reduction in 2020/21 without a second wave, %	4.8	[2]
GDP drop attributable to shutdown versus voluntary restrictions, %	100 (10–100)	Estimate
Cost of a vaccine per individual, €	7 (5–7)	[32]
Construction and operation of vaccination centers, €	1,400,000,000	[60]
Vaccinations by primary care physicians, €	1,500,000,000	[61]
Transport, storage, syringes, and needles, €	231,000,000	[62]

CFR = case fatality rate, ICU = intensive care unit, IFR = infection fatality rate.

(€39,751) by the incremental survival benefit (0.39 life years).[14]

For a long-term lockdown policy following revaccination failure, the GDP drops associated with annual pandemic waves were discounted at an annual rate of 3%, based on the social rate of time preference derived from the Ramsey equation.[38] For health benefits of long-term lockdown, I applied a 2% discount rate, reflecting a 1% expected growth rate of the consumption value of health in Germany (cf. Ref. [39]). The costs and health benefits of providing additional ICU capacity were discounted at the same rates. All other costs and health benefits were not discounted because they refer to a time horizon of up to 1 year.

Results

A future lockdown policy avoids productivity losses due to symptomatic infections and quarantines of contact persons that are associated with an uncontrolled spread of the pandemic. Based on the results reported in Table A2 of the Appendix, the avoided productivity loss is predicted to amount to 1.2% of the GDP.

At the population level, costs of (i) the vaccine itself, (ii) the clinical administration, and (iii) scientific research failures correspond to 0.3% of the German GDP in 2019 assuming a level of uptake that achieves the herd immunity threshold.

As shown in Table 2, a successful lockdown policy requires a probability of 48% of approving a variant-adapted vaccine booster with 95% efficacy. However, when failure of approving a vaccine with a 95% efficacy would be followed by a long-term lockdown policy, a vaccine rollout would not be attempted because the NMB of a long-term lockdown policy is higher than that of revaccination. Nevertheless, a long-term lockdown policy, despite its favorable cost-effectiveness ratio, may not be affordable as it amounts to 10% of the GDP over 5 years and thus is projected to lead to economic stagnation or even decline. Decision-makers who are pessimistic concerning revaccination effectiveness would generally not accept a lockdown policy (Table 3).

Moreover, the largest Hurwicz value is predicted for a long-term lockdown policy without booster shots. As stated,

Table 2. Break-even probabilities (BEPs) of a successful COVID-19 revaccination in the base case.

	Successful revaccination		Revaccination failure		
	Costs (% GDP reduction)	Life years gained	Costs (% GDP reduction)	Life years gained	BEP
Vaccine efficacy 95%					
L_t vs. N	7.0	0.065	8.2	0	0.48
L_T vs. N	7.0	0.065	9.7	0.31	1.00
L + R versus N					
5000 additional beds	7.4	0.065	8.6	0.006	0.46
10,000 additional beds	7.7	0.065	8.9	0.008	0.45
15,000 additional beds	7.9	0.065	9.1	0.010	0.45
20,000 additional beds	8.1	0.065	9.3	0.011	0.45
Vaccine efficacy 50%					
L_t vs. N	7.8	0.034	8.2	0	1.00
L_T vs. N	7.8	0.0343	9.7	0.308	1.00
L_t + R versus N					
5000 additional beds	8.2	0.034	8.6	0.006	1.00
10,000 additional beds	8.4	0.034	8.9	0.008	1.00
15,000 additional beds	8.6	0.034	9.1	0.010	1.00
20,000 additional beds	8.8	0.034	9.3	0.011	1.00

R = 'raising the line', N = no intervention, L = lockdown, GDP = gross domestic product, t = current time period, T = time until the end of time horizon.

Table 3. Decision matrix based on a Hurwicz decision rule with an alpha weight of 0.5 and a break-even alpha weight. Calculation of the net monetary benefit (NMB) assumes a decision-maker who is neither pessimistic nor optimistic.

	Successful revaccination				Revaccination failure		Hurwicz decision rule			
	Vaccine efficacy 95%		Vaccine efficacy 50%							
	Costs (% GDP reduction)	Life years gained	Costs (% GDP reduction)	Life years gained	Costs (% GDP reduction)	Life years gained	Costs (% GDP reduction)	Life years gained	NMB (%GDP)	BEP(α)
Lt versus N	7.0	0.065	7.8	0.034	8.2	0.000	7.6	0.033	0.4	0.48
LT versus N	7.0	0.065	7.0	0.065	9.7	0.308	8.4	0.186	37.4	1.00
Lt + R versus N										
5000 additional beds	7.4	0.065	8.2	0.034	8.6	0.006	8.0	0.035	0.7	0.46
10,000 additional beds	7.7	0.065	8.4	0.034	8.9	0.008	8.3	0.037	0.8	0.45
15,000 additional beds	7.9	0.065	8.6	0.034	9.1	0.010	8.5	0.038	0.8	0.45
20,000 additional beds	8.1	0.065	8.8	0.034	9.3	0.011	8.7	0.038	0.7	0.45

R = 'raising the line', N = no intervention, L = lockdown, GDP = gross domestic product, NMB = net monetary benefit, BEP = break-even probability.

however, long-term lockdown measures may not be affordable. The second largest Hurwicz value is anticipated for a short-term COVID-19 lockdown policy in combination with booster shots and the addition of 10,000 ICU beds. Thus, expanding ICU capacity helps to "flatten the curve" in case of a failure of the lockdown policy and the booster shots. That is, bed expansion serves to hedge against a potential failure of a lockdown policy. Nevertheless, if overwhelming waves are not expected over the entire pandemic period, expanding ICU capacity leads to zero health benefit and increases the break-even probability of a lockdown policy.

As shown in the sensitivity analysis (see Figure 1), the break-even probability of approving a vaccine with 95% efficacy (and without a long-term response policy in the event of failure) varies between 5% and 76%.

If a vaccine with 50% efficacy is approved, the ICER of a lockdown policy with and without expansion of ICU capacity is projected to lie between €93,113 and €105,711 per life year gained (Table 4). Hence, a lockdown in conjunction with a revaccination at 50% efficacy would not be a clearly cost-effective investment. For a vaccine with 95% efficacy, ICERs are lower (between €44,214 and €50,845 per life year gained depending on the level of ICU expansion) because the lockdown policy is able to enable larger health gains. With a successful revaccination, the additional ICU bed capacity will remain unused and thus increases the ICER.
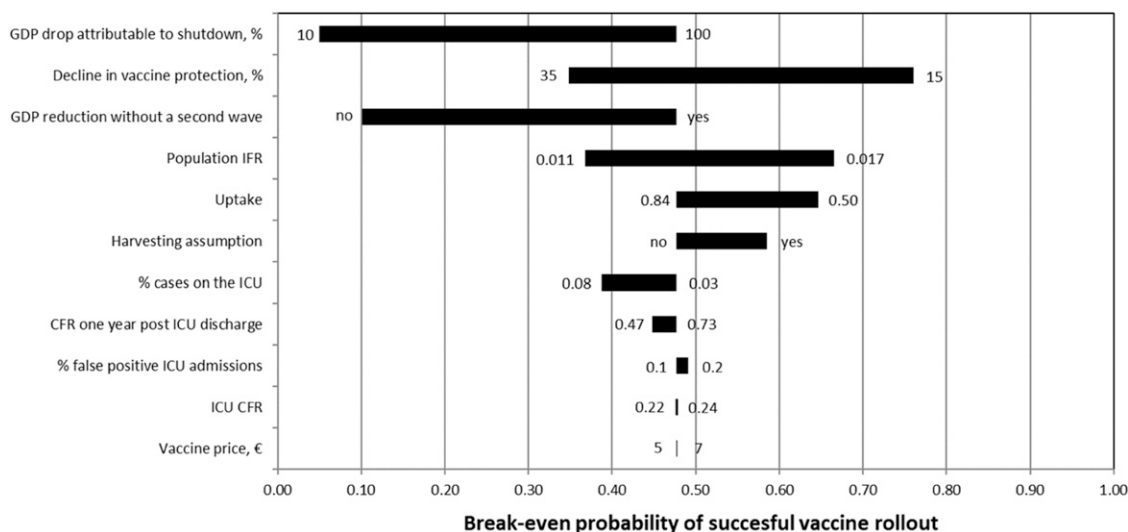
Figure 1. Tornado diagram demonstrating the results of the one-way sensitivity analysis. The variables are ordered by the impact on the break-even probability of a successful COVID-19 revaccination (95% efficacy). The numbers indicate the upper and lower bounds. CFR = case fatality rate, GDP = gross domestic product, ICU = intensive care unit, IFR = infection fatality rate.

Table 4. Base case. Incremental costs, effects, and cost-effectiveness ratio of a lockdown policy that leads to a successful revaccination compared to no intervention. All costs are in Euro.

	Costs (% GDP reduction)	Life years	ICER
Vaccine efficacy 95%			
L versus N	2885	0.07	44,214
L + R versus N			
5000 additional beds	3042	0.07	46,626
10,000 additional beds	3150	0.07	48,281
15,000 additional beds	3239	0.07	49,637
20,000 additional beds	3317	0.07	50,845
Vaccine efficacy 50%			
L versus N	3197	0.03	93,113
L + R versus N			
5000 additional beds	3355	0.03	97,696
10,000 additional beds	3463	0.03	100,840
15,000 additional beds	3551	0.03	103,416
20,000 additional beds	3630	0.03	105,711

ICER = incremental cost-effectiveness ratio, R = 'raising the line', N = no intervention, L = lockdown, GDP = gross domestic product.

Discussion

The results obtained from this exploratory study, which takes a future viewpoint after efficacy of the existing COVID-19 vaccines has been diminished by 25%, can be summarized as follows. A lockdown in conjunction with a variant-adapted vaccine booster expected to yield a 50% efficacy may not be clearly cost-effective. But even future revaccination with 95% efficacy is less cost-effective than a long-term lockdown policy. However, the latter strategy may not be sustainable on psychological and economic grounds because it leads to economic stagnation or even decline. Therefore, if expanding ICU capacity is not impeded by labor supply and other input constraints, a lockdown policy plus ICU bed expansion strategy is the preferred strategy and the probability of re-vaccination failure can be as high as 55%. The possibility that a mutation of the virus could overcome the immune response triggered by the booster shots may thus be a reason for a pessimistic decision-maker not to impose a lockdown.

Limitations

As a word of caution, given the time constraints and the rapid inflow of new information on the SARS-CoV-2 pandemic while conducting the study and writing this manuscript, which made it necessary to update the projections continuously, this decision-analytic study has several cayaveats. First, there are reasons why the study overestimates the projected health benefits and cost-effectiveness of a lockdown. For example, the study does not consider the deaths and loss of health-related quality of life associated with the shutdown and social distancing, e.g., due to depressive or anxiety disorders, suicides, unemployment, domestic violence, and fewer emergency and regular visits to physicians for unrelated medical conditions. Nevertheless, as mentioned in the Methods section, official data on excess mortality in Germany[16] show that the peak in excess mortality in the first half of April 2020 and in December 2020 both coincided with the surges in COVID-19 deaths, thus indicating that excess mortality was driven by COVID-19 and not by other causes.

Furthermore, unaffected individuals may experience a loss of personal freedom[40] and autonomy under lockdown. Moreover, when "raising the line" ICU survivors may suffer from a loss of quality of life.[41] Besides, if rationing decisions in the ICU disfavor patients with less prospects of survival, the health benefits of "raising the line" or a lockdown are reduced (cf. Ref. [42]). In addition, lockdown measures and social distancing can lead to productivity loss due to pre-senteeism. For example, a U.K. survey during the first lockdown showed that 26% of university staff and 40% of students had experienced problems doing their work or studying because of psychological or physical symptoms.[43] Finally, distance learning during lockdown hinders students' access and success in higher education and reduces the income potential of the young generation as a whole, but especially of low-performing students and those from educationally disadvantaged families. Therefore, there may be costs in the long term in the form of a reduction of accumulated human capital and greater educational inequality.[44] Hanushek and Wößmann[45] caution, however, that "reactions to the pandemic do, however, open the possibility of moving in directions that improve school quality and thus offer hope of eliminating the learning gap faced by today's students."

Conversely, there are reasons to believe that the health benefits and cost-effectiveness of COVID-19 policy response may be underestimated. First, decreased economic activity can save lives, among other reasons, because it reduces air pollution, traffic accidents,[46] and accidents on construction sites.[47] Second, social distancing may reduce deaths due to non–COVID-19 flu. Third, reducing the number of deaths prevents grief among caregivers. Fourth, a lockdown policy may prevent COVID-19 infection with long-haul symptoms and save direct (non-)medical costs and indirect costs associated with nonfatal COVID-19 cases. Some of the biases listed in this and the previous paragraph may cancel each other out. Perhaps, the most fundamental tradeoff exists between an increase in the psychological burden on the one hand and the avoidance of the long COVID syndrome on the other hand.

Regarding the transferability and relevance of the results and conclusions of this study to other countries the usual caveats apply. The reasons for caution include between-country differences in clinical and epidemiological data, costs, and the willingness to pay for health benefits. In addition, between-country differences in culture norms may exist that impact compliance with social distancing rules, e.g., mobility choices.[48]

Conclusion

This article demonstrates the applicability of decision-analytic tools to infectious disease preparedness and response planning under ignorance. In an exemplary scenario that foresees a 25% decline in the vaccine protection against severe disease a future lockdown policy appears to be cost-effective if a variant-adapted vaccine booster is likely to achieve an efficacy of 95%. Growing information about the level of waning immunity and the transmissibility of new variants in the forthcoming months require an adjustment of the model to real-world conditions and a re-appraisal of the cost-effectiveness.

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Notes

1. The terms lockdown and shutdown are often used interchangeably. Strictly speaking, however, lockdown refers to mass quarantine while shutdown denotes the closing of a factory, business, or piece of machinery, either permanently or for a short time (https://de.wikipedia.org/wiki/Massenquarant%C3%A4ne).

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Appendix

Table A1. Input data used for calculating the productivity loss due to an uncontrolled infection in the absence of a vaccine.

Input	Mean (range)	Reference
Epidemiological		
IFR in Germany	0.014 (0.011–0.017)	[34,35]
Percent of infections that are asymptomatic	0.4	[49]
Percent of diagnosed infections that are asymptomatic	0.38	[45,50]
Percent of diagnosed infections that are hospitalized	0.07	[50]
Quarantined contact persons per diagnosed case	5	[51]
Number of newly diagnosed cases in Aug 2020	33,683	[52]
Cost data		
Hours worked per head and year in the population	753.3	[53]
Labor productivity per hour, €	55.1	[53]

IFR = infection fatality rate.

Table A2. Individual and population productivity loss due to an uncontrolled spread of the infection in the absence of a vaccine.

Case description	Estimate	Per person productivity loss (€)	Population productivity loss (€)
Undiagnosed asymptomatic, %	0.25	0	0
Undiagnosed mild, %	0.38	798	17,633,418,328
Diagnosed asymptomatic, %	0.14	798	6,385,827,347
Diagnosed hospitalized, %	0.03	1596	2,352,673,233
Diagnosed mild, %	0.20	798	9,242,644,844
Quarantine of contacts, *n*	1,178,905	798	941,011,720
Total			36,555,575,471