Global versus focused isolation during the SARS-CoV-2 pandemic- A cost-effectiveness analysis

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Abstract

Background: The novel coronavirus (SARS-CoV-2) pandemic is driving many countries to adopt global isolation measures in an attempt to slow-down its spread. These extreme measures are associated with extraordinary economic costs.

Objective: To compare the cost-effectiveness of global isolation of the whole population to focused isolation of individuals at high risk of being exposed, augmented by thorough PCR testing.

Design: We applied a modified Susceptible, Exposed, Infectious, Removed (SEIR) model to compare two different strategies in controlling the SARS-CoV-2 spread.

Data sources and target population: We modeled the dynamics in Israel, a small country with ~ 9 million people.

Time horizon: 200 days.

Interventions: 1. Global isolation of the whole population (strategy 1) 2. Focused isolation of people at high risk of exposure with extensive PCR testing (strategy 2).

Outcome measures: Number of deaths and the cost per one avoided death in strategy 1 vs 2.

Results of Base-Case analysis: The number of expected deaths is 389 in strategy 1versus 432 in strategy 2. The incremental cost-effectiveness ratio (ICER) in case of adhering to global isolation will be $ 102,383,282 to prevent one case of death.

Results of sensitivity analysis: The ICER value is between $ 22.5 million to over $280 million per one avoided death.

Conclusions: According to our model, global isolation will save ~43 more lives compared to a strategy of focused isolation and extensive screening. This benefit is implicated in tremendous costs that might result in overwhelming economic effects.

Limitations: Compartment models do not necessarily fit to countries with heterogeneous populations. In addition, we rely on current published parameters that might not reliably reflect infection dynamics.

***Introduction*:**

Since its identification at the very end of 2019, the novel coronavirus (SARS-CoV-2) has been spreading around the world at an extraordinary speed and is now officially declared as a pandemic (1). Following China, many countries around the world have adopted social distancing measures largely based on quarantine and travel bans, as well as on isolation of infected patients and their close contacts (2). Countries around the world are adding additional extreme distancing measures aiming to slow the rate of infections after watching the overwhelmed health systems of Italy and Spain which are suffering from rapidly spreading infections and a large number of fatalities (3). However, a few countries, such as South Korea, have succeeded in slowing the rate of infections without economically damaging lockdowns. Instead, South Korea applied early interventions that included identification and isolation of outbreak sources by a massive screening of infected patients and aggressive tracing and isolation of their contacts (4).

It is yet not clear whether the apparent success of South Korea could be applied to other countries in North America and Europe. It is, however, obvious that extreme non-selective measures are associated with tremendous economic costs that will result in a global financial crisis that will most likely affect public health and other essential aspects of our lives in the coming years. Therefore, decision-makers must balance public health concerns with economic considerations in fighting this epidemic.

In this study, we applied a modified Susceptible, Exposed, Infectious, Removed (SEIR) model (5), comparing two major strategies to control the virus spread: 1. Complete global quarantine of the whole population 2. Focused isolation of infected patients combined with relaxed isolation and massive screening of the population at high exposure risk. The study aimed to analyze the cost-effectiveness of these strategies to handle the SARS-CoV-2 spread. Our model refers to a small country with a population of ~ 9 million people, taking the current situation in Israel as an example.

***Methods*:**

A simulation model of SARS-CoV-2 transmission was constructed (Appendix Fig 1). The model includes five compartments (modified SEIR model (5)):

1. Susceptible (S): patients susceptible to SARS-CoV-2 infection.
2. Asymptomatic carriers (exposed) (E): patients infected with SARS-CoV-2 that do not have symptoms and are therefore not documented. They can transmit the virus to susceptible patients. These patients may be tested for SARS-CoV-2 and isolated accordingly.
3. Infected (I): patients with symptomatic disease. They will be tested for SARS-CoV-2, using a PCR test with close to 100% sensitivity. Patients with confirmed infection will be placed in strict isolation to prevent further transmission.
4. Recovered (R): Patients that were infected with SARS-CoV-2 and recovered (recovery does not confer lifelong immunity).
5. Death (D): Patients who died because of coronavirus disease 2019 (COVID-19) complications.

The mathematical ordinary differential equations (ODE) that illustrate our model are displayed in Appendix Figure 1.

β- transmission rate from carriers to the susceptible population. We assume that the transmission rates from the infectious population (I) and from the carrier population (E) are identical. However, if infectious subjects are isolated, the rate of transmission from "I" to the "S" population will decrease. If the size of the "I" population decreases by 50% due to isolation, the rate of transmission from "I" to "S" will decrease by 50% ($\beta 1=\beta x50\%$). Similarly, if we isolate the "E" population, the transmission rate from "E" to "S" will decrease accordingly (β2).

σ- transition rate from carrier state (exposed) to infected state (the time from exposure to symptom onset), assuming that the incubation period has an exponential distribution.

δ - mortality rate of the infected population

γ- recovery rate of the infected population

α - transmission rate from the recovered population to the susceptible population

Ro – (Reproductive Number) is the expected number of secondary infections from an infected individual. If Ro<1, then the pathogen will be cleared from the population. Otherwise, the pathogen will be able to infect the whole susceptible population. Note that Ro= $\frac{\beta}{\gamma}$.

There are few actions that can influence the epidemiological dynamics. For example, isolation of the infectious (I) population decreases the rate of transmission. We define three levels of isolation:

1. Strict isolation - 95% of this population does not have any contacts.
2. Relaxed isolation - 85% of this population does not have any contacts.
3. Quarantine - 70% of this population does not have any contacts.

In this study we compare the cost-effectiveness of two strategies:

Strategy 1: Strict isolation of all infectious individuals and relaxed isolation for two weeks of subjects at high-risk of contact with infected or carrier individuals (high risk group). In addition, quarantine of the susceptible population.

Strategy 2: Strict isolation of all infected individuals and a 14-day relaxed isolation for all the individuals who are at high-risk of exposure. These individuals will be repeatedly tested using PCR every three days. Under this strategy, only the high risk group will be quarantined, while most of the susceptible population will go back to the workforce. The specific individuals that are at high-risk of contact with infected or carrier subjects will be located using detailed epidemiological tracing and/or using mobile phone and satellite technology. In addition, extensive PCR testing will identify carriers and infected individuals within the population and will prevent unnecessary isolation of non-infected individuals. Subjects with two sequential negative PCR results will be removed back into the workforce. We estimated that the length of isolation in the high risk population will decrease from two weeks to an average of 7 days which is within the range of the average incubation period (6-8).

We estimated the number of deaths and the total cost of each strategy described above and calculated the cost per one avoided death (denoted by incremental cost-effectiveness ratio (ICER)). The costs were based on the Gross Domestic Product (GDP) per capita in Israel ($40,270) or per GDP per capita per day i.e. $130. In the model, we estimated that the cost of isolating one person per day is $70.

In addition to the two main strategies mentioned above, we estimated the number of deaths and the size of the infectious population, in another hypothetical strategy:

Strategy 3: No intervention. No isolation (even for infectious (I) population) and no testing.

The time horizon in the model was 200 days.

The list of parameters in the model as well as the low and high values that were used for sensitivity analysis are presented in Table 1.

Parameter estimation:

The following parameter estimates were used to construct the model (Table 1):

Carriers (C0) were defined as the number of infected individuals that are currently undocumented. For our basic model we estimated 10,000 undocumented carriers. This estimate is based on the number of infected individuals in Israel when constructing the model and the published estimation that 86% of the carriers are undocumented (9). The initial number of the infected individuals (I0) was determined according to the Israeli ministry of health publications. The number of susceptible individuals was defined as a rounded approximation of the population in Israel (9 million) after subtracting the infected and undocumented carriers. Global isolation refers to infected individuals that are hospitalized (including individuals in intensive care units) or quarantined in a dedicated facility. The isolation costs are calculated using an estimation of the price of lost workdays and hospitalization. Relaxed isolation refers to self-isolation at home and thus the estimated costs include only the price of lost workdays.

To calculate the recovery rate (γ), an estimation of 26 days with a range of 21 to 32 days for the time from symptom onset to recovery was taken, compatible with several recent studies (8, 10-12). The average incubation period $\boldsymbol{\sigma}$ was approximated to be 5.1 (6-8).

We used R_0=2.4 (range 1.4-3.9) (13), we assumed that the recovery time is 26 days, thus the transmission rate from infected (carrier) patients to susceptible population (β) was 0.09 (range 0.031 to 0.186)(13). According to the data of the number of infected people in Israel, published by the Israeli Ministry of Health, the transmission rate would be higher, β=0.22, or R_0=5.7, which is unlikely. The main reason for the discrepancy is that the number of infected people in Israel includes imported cases. As all subjects coming to Israel from abroad are isolated, in the model we did not include imported cases. Case fatality rates vary between different countries ranging from 7.2% in Italy to 0.2% in Germany (14). Thus, for the rate of death (**δ**) in our basic model we considered a moderate estimate of 2.6% or 0.001 per day over 26 days of infection.

RR1-3 represents the estimated part of the population which does not have any contacts in each type of isolation.

The assumptions used for the two strategies are described in Table 2. In strategy 1, r1_HR_c represents the proportion of the population under relaxed isolation due to a high risk of contact with SARS-CoV-2 patients (0.7%). Under strategy 1, we estimated the proportion of the susceptible population under quarantine (r_S) to be 50%, while the proportion of carrier (r1_E) population that is under relaxed isolation was estimated at 80%. In contrast, under strategy 2 (r2_HR_c) the proportion of the population under relaxed isolation will be lower (0.3%) due to repeated testing. Under strategy 2, the number of susceptible individuals under quarantine (r2_S) will be 0, while the proportion of carriers (r1_E) that are under relaxed isolation will remain 80%. The time horizon was 200 days and therefore the discount rate was 0. In addition, favoring strategy 1, we assumed that the cost of isolation is only for 14 days.

The analysis was performed using MATLAB.

***Results*:**

Base case results

We first tested our model under a situation in which no intervention is being undertaken (strategy 3, see methods section). Starting with a baseline of 10,000 carriers and 3,000 infected individuals without any interventions, the maximal number of infected individuals, 2.4 million (Fig. 1, I), will be reached after 114 days and about 200,000 people will die (Fig. 1, D). In case we start with a smaller number of initially infected individuals (10) and 100 carriers, the total numbers of infected individuals and of fatalities will not change, but the maximal number of infected individuals will be reached after 190 days.

We next tested our model with a strategy of strict isolation of all infected individuals, relaxed isolation for two weeks of the high-risk group and a global quarantine of the susceptible population (strategy 1). Applying this strategy will yield a peak of 9,350 people infected followed by a rapid decline (Fig. 2, I) with a total of 14,995 infected patients over the 200 days period. Under this strategy, the maximal number of deaths is expected to be 389 (Fig. 2, D) and it will be reached after ~ 100 days. Our second proposed strategy includes a focused isolation of all infected individuals while using relaxed isolation and repeated PCR testing of high-risk individuals every four days. Under these conditions, the maximum number of infected individuals will be slightly increased to 9,713, with a total of 16,658 infected patients over the 200 days period (Fig. 3, I). The total number of deaths will increase to 432 (Fig. 3, D).

Table 3 summarizes the costs and number of deaths in each strategy. Factoring the cost of workday loss, isolation costs (in a dedicated facility or under hospitalization) and the PCR tests costs enabled us to calculate the ICER as follows:

$$ICER = \frac{4{,}495{,}734{,}526-64{,}442{,}372}{432-389} = \frac{4{,}431{,}292{,}153}{43} = 102{,}383{,}282$$

Under these conditions, the cost of preventing one case of death is \$ 102,383,282.

Sensitivity analyses

The results of univariable sensitivity analyses are displayed in Fig 4. Across broad variation in the ranges of each parameter, the ICER remained between \$ 22.5 million to over \$280 million per one avoided death. The two variables with the strongest influence on ICER were the virus transmission rate (β) and the rate of death per day (δ).

One-way sensitivity analyses of these parameters are displayed in Appendix Figure 2.

Next, sensitivity analyses were performed on the number of deaths expected for strategy 1 and strategy 2. As shown in Appendix Figure 3, the initial number of infected individuals and the rate of death per day (δ) was the most influential parameters on the death rate. Notably, all other parameters examined had only a negligible influence on the death rate.

***Discussion*:**

SARS-CoV-2 infection is now a pandemic with possible serious clinical consequences and a substantial death rate, affecting more than 177 countries around the world. So far, this epidemic has affected around 665,000 people globally and claimed the lives of more than 30,500 individuals (15, 16). "Flattening the curve" of new infections, thereby enabling the local health systems to handle the growing mass of seriously ill patients that need hospitalization and intensive care, is a priority.

In countries that were late in taking drastic steps, the rapid spread of the disease has been accompanied by a high death toll, imposing extraordinary and sustained demands on the public health system that necessitated controlled distribution and use of scarce medical resources (17). In China, where the pandemic has first emerged, drastic measures of social distancing and global isolation have successfully controlled virus spread enabling now a gradual release of the population from quarantine (18). However, global adoption of these extreme measures is implicated in unprecedented social and economic costs that might, directly and indirectly, affect the health system, among many other aspects of our life, in the years to come. Therefore, there is an urgent need to find a more pragmatic and balanced strategy that will enable countries under a similar condition to handle this situation.

In this study, we implemented cost-effectiveness analysis tools of two distinct strategies to slow-down the virus spread in Israel, a small country with a population of 9 million. We show that a complete quarantine of the whole population (strategy 1) will result in a total of ~14,995 infected people and around 389 deaths over a period of 200 days. An alternative strategy of "trace, isolate, test and treat approach" (strategy 2) in which only individuals who are defined as being at high-risk for being exposed are isolated (relaxed isolation) and repeatedly tested will result in a total of 16,658 infected people with 432 deaths. Overall, strategy 1 is expected to save ~43 more lives, but with a cost of $102,383,282 to prevent one case of death, compared to a more focused approach. As usual ICER in cost-effectiveness analyses relates to cost per Quality-adjusted life year (QALY), and in our study the ICER was measured as cost per one avoided death, we suggest an easy transformation from the ICER in this study to the conventional ICER in cost-effectiveness analyses. Assuming that one case of death is equivalent to a loss of 10 QALYs, the ICER would be $102,383,282 divided by 10, resulting in $10.2 million per QALY. This number is extremely higher than the $150,000 per QALY, recommended by Neumann et al. as the threshold of willingness to pay (19).

A key component of the "trace, isolate, test and treat" strategy is massive and repeated testing of the population at high risk of exposure. We assumed that this should require four PCR tests for each high-risk individual during the 14 days of isolation, and therefore ~10,000-15,000 tests will be needed daily for a country the size of Israel. This number translates to ~1666 tests per million people. As a comparison, South Korea performs 4 times more tests daily (14). Of note, serological tests, when available, might also be used as a part of this strategy. These tests would most likely improve its efficiency due to their larger window of detecting infection and thus fewer tests would be needed per high-risk individual (11).

One of the major concerns of the health authorities is that the number of patients needing intensive care and mechanical ventilation will overcome the local health care system capacity. This is the rationale underlying the efforts to "flatten the curve" thereby avoiding a narrow and high peak of infected patients that is necessarily accompanied by a substantial number of patients in severe condition. According to our model, a strategy of avoiding any active step to contain the virus will result in an unacceptable number of infected people (7.65 million) and an extremely high death rate (~200,000 people), and therefore is not realistic. In contrast, the difference in the peak number of infected patients between the two main strategies tested is ~360 patients, in favor of strategy 1. Assuming that 10% of patients are at risk for developing severe disease, this translates to an additional 36 potential hospitalizations and mechanical ventilation at the peak, an acceptable extra burden for the local health system.

One major limitation of compartment models is that they assume a homogeneous population, which is not the case in many countries including Israel. In Israel, for example, the reproductive number (R_0) is most probably higher among some religious groups. Such pockets with high levels of infection might alter the infection dynamics and affect the outcome of the model.

As with similar models, the validity of this model is based on the correct assumption of the various parameters the model is based on. Since SARS-CoV-2 is a new virus and the exact infection rates in the population are still unknown, these parameters are subjected to variations and may change over time.

Our sensitivity analysis indicates that β (transmission rate) is the most influential parameter. β relies on R_0, which might change, and on the recovery time that will most likely remain the same. However, since a similar R_0 is used for modeling both strategies, we believe that the difference in the number of deaths and ICER will largely remain similar.

Obviously, strategy 2 of "trace, isolate, test and treat", largely representing the steps successfully undertaken by South Korea to handle the situation, demands two major components, critical to its success: 1. Intensive epidemiological investigations of infected patients combined with surveillance to trace possible interactions with infected individuals. 2. Availability of enough testing kits and facilities enabling a large number of daily PCR tests to isolate high-risk subjects.

Obviously, intensive epidemiological investigations, necessary to define people at high risk of exposure who must be isolated and repeatedly tested, are implicated in massive use of mobile phone and satellite technology thereby violating citizens' privacy rights. Therefore, decision-makers must carefully weigh their options with the knowledge that avoiding those extreme steps and choosing global quarantine strategies comes with a very high economical price that might seriously threaten the nation's economy.

In summary, in this cost-effectiveness analysis based on a modified SIER model, we show that a strategy of global quarantine over time is modestly superior over a strategy of focused isolation and repeated testing in terms of reducing death rates, but this is implicated in extremely high costs to prevent one case of death.

Acknowledgements

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Table 1. General assumptions.

	Base	**Low**	**High**	**comments**
C0	10,000	5000	50,000	initial number of carriers
I0	3,000	1,000	5,000	initial number of infected individuals
R0	50	0	100	initial number of recovered individuals
D0	0	0	10	initial number of deaths
Cost of global isolation (including hospitalization and ICU, US$)	250	150	400	
Cost of relaxed isolation or quarantine (US $)	70	50	120	
Cost of PCR test (US $)	50	20	75	
R_0	2.4	1.4	3.9	
γ (gamma)	0.038	0.031	0.048	1/time to recovery (21 to 32 days)
β (beta)	0.092	0.044	0.186	Calculated $R_0 \times \gamma$
σ (sigma)	0.2	0.0833	0.2500	1/incubation time (4 to 12 days)
δ (delta)	0.001	0.0005	0.003	rate of deaths per day
RR1	0.95	0.9	0.99	proportion of population with no contacts - strict isolation
RR2	0.85	0.8	0.9	proportion of population with no contacts - relaxed isolation
RR3	0.7	0.6	0.8	proportion of population with no contacts - quarantine

Table 2: Assumptions regarding strategy.

Strategy 1	**Base**	**Low**	**High**	**comments**
r1_HR_c	0.007	0.005	0.01	proportion of the population under relaxed isolation due to high-risk of contact
r1_S	0.5	0.3	0.8	proportion of S population under quarantine
r1_E	0.8	0.6	0.9	proportion of carrier (E) population under relaxed isolation
Strategy 2	**Base**	**Low**	**High**	**comments**
r2_HR_c	0.003	0.001	0.05	proportion of relaxed isolation due to high risk of contact
r2_S	0	0.05	0.1	proportion of S population under quarantine
r2_E	0.8	0.5	0.9	proportion of E population under relaxed isolation

Table 3: Summary of the costs and number of deaths in each strategy.

	Deaths	**Cost ($)**
Strategy 1	389	4,495,734,526
Strategy 2	432	64,442,372

Figure legends:

Figure 1: Infection dynamics without interventions. The five graphs display the dynamics in the 5 compartments over time. Susceptible (S, blue); Infected (I, red); Carrier (Yellow, E); Recovered (R, Green), Dead (D, Black).

Figure 2: Infection dynamics under global isolation (strategy 1). Graphs are labeled as described under Fig. 1.

Figure 3: Infection dynamics during isolation of high-risk groups and extensive testing (strategy 2). Graphs are labeled as described under Fig. 1.

Figure 4: Sensitivity analysis (tornado diagram) of the incremental cost effectiveness ratio (ICER) between the two strategies. Red bar indicates that the value was produced by the Lower Bound (Low), and a dark blue bar indicates that the value was produced by the Upper Bound (High).

Appendix Figure 1. An illustration of the modified SIER model applied in this study.

Appendix Figure 2. Sensitivity analyses of the transmission rate (β) (upper panel) and mortality rate (δ) (lower panel) (ICER- incremental cost effectiveness ratio)

Appendix Figure 3. Tornado analyses of the number of deaths according to strategy 1 (upper panel) and strategy 2 (lower panel).

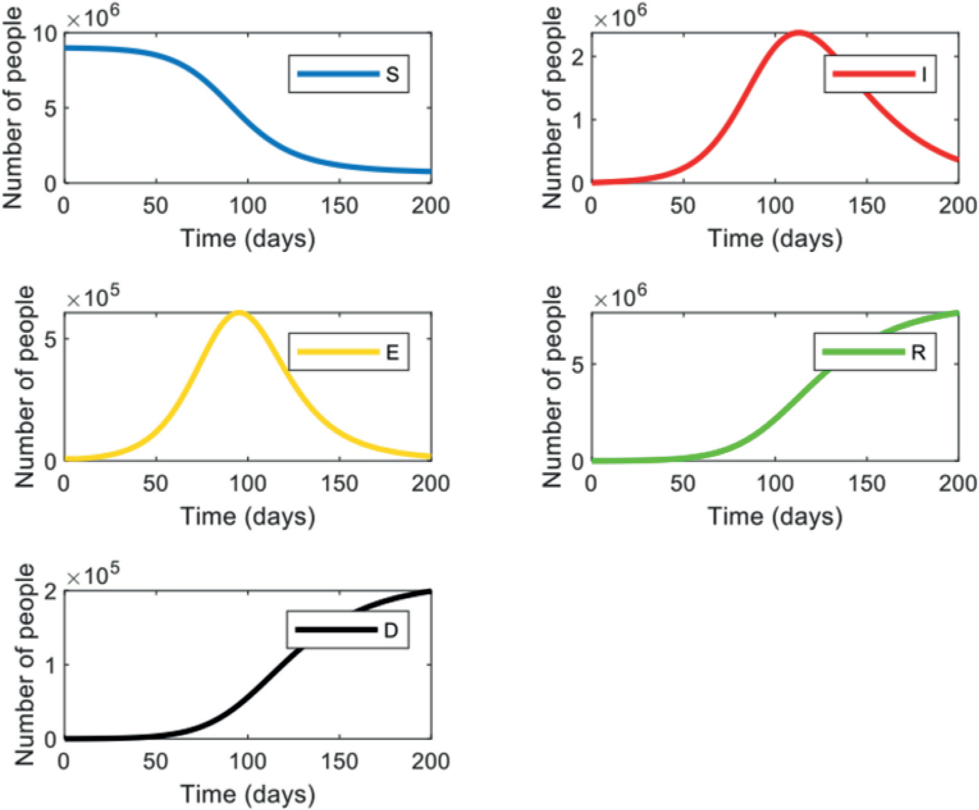

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Fig 1

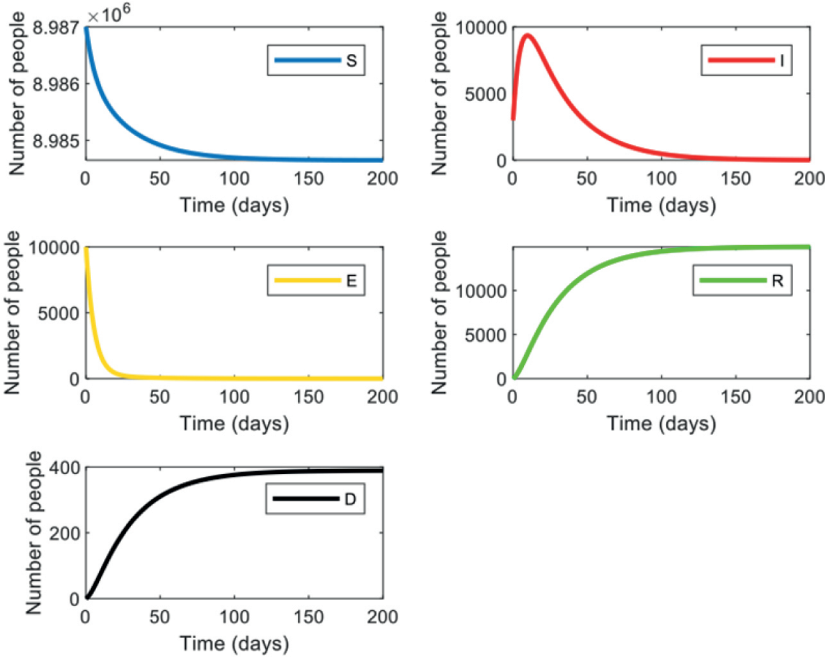
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Fig 2

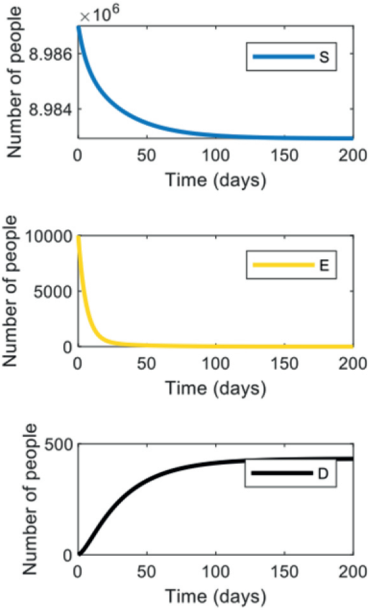

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Fig 3

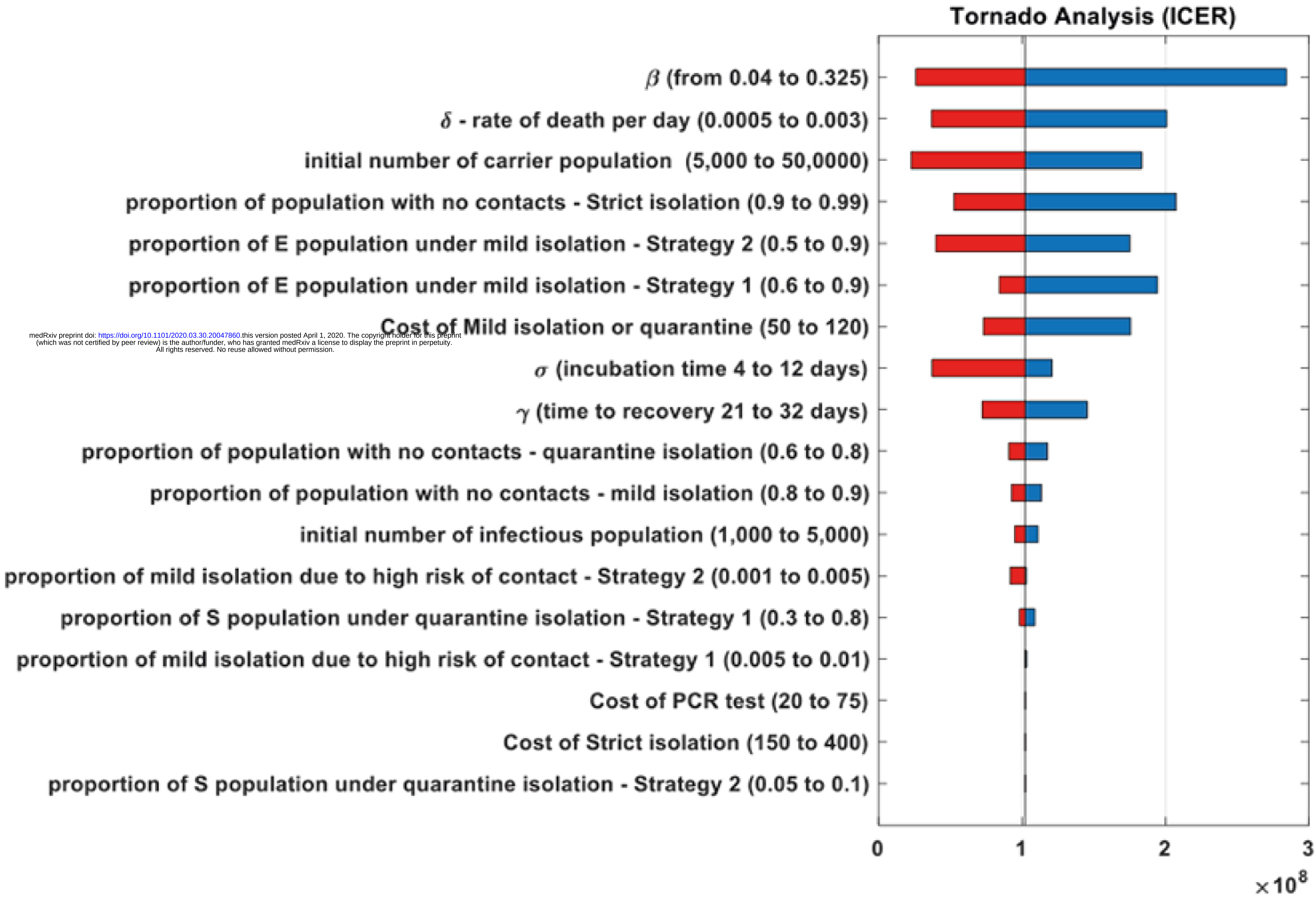
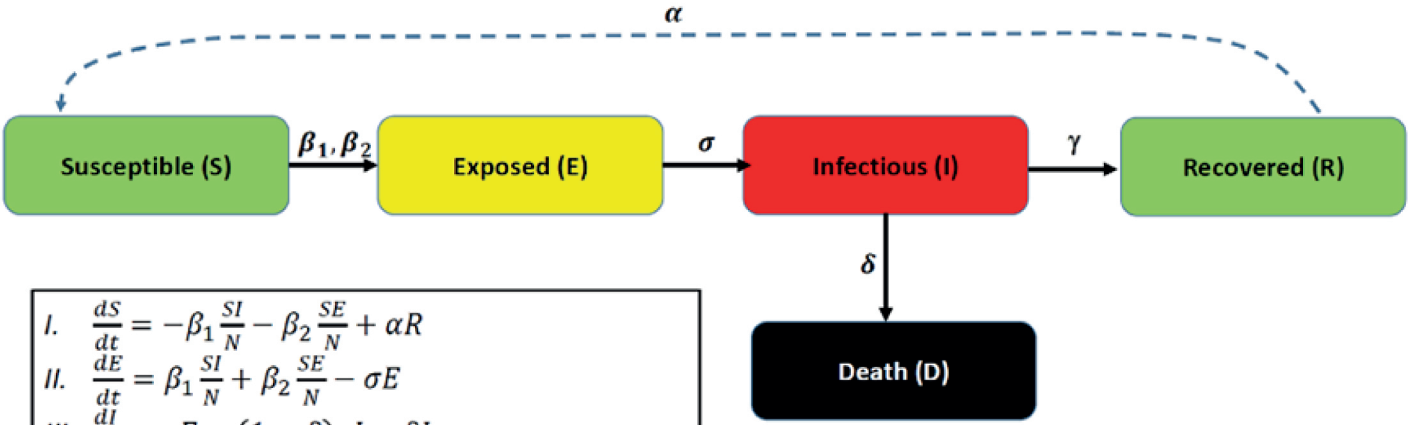

Tornado Analysis (ICER)
β (from 0.04 to 0.325)
δ - rate of death per day (0.0005 to 0.003)
initial number of carrier population (5,000 to 50,0000)
proportion of population with no contacts - Strict isolation (0.9 to 0.99)
proportion of E population under mild isolation - Strategy 2 (0.5 to 0.9)
proportion of E population under mild isolation - Strategy 1 (0.6 to 0.9)
Cost of Mild isolation or quarantine (50 to 120)
σ (incubation time 4 to 12 days)
γ (time to recovery 21 to 32 days)
proportion of population with no contacts - quarantine isolation (0.6 to 0.8)
proportion of population with no contacts - mild isolation (0.8 to 0.9)
initial number of infectious population (1,000 to 5,000)
proportion of mild isolation due to high risk of contact - Strategy 2 (0.001 to 0.005)
proportion of S population under quarantine isolation - Strategy 1 (0.3 to 0.8)
proportion of mild isolation due to high risk of contact - Strategy 1 (0.005 to 0.01)
Cost of PCR test (20 to 75)
Cost of Strict isolation (150 to 400)
proportion of S population under quarantine isolation - Strategy 2 (0.05 to 0.1)
0
1
2
3
×10^8

Fig 4



I. $\frac{dS}{dt} = -\beta_1 \frac{SI}{N} - \beta_2 \frac{SE}{N} + \alpha R$

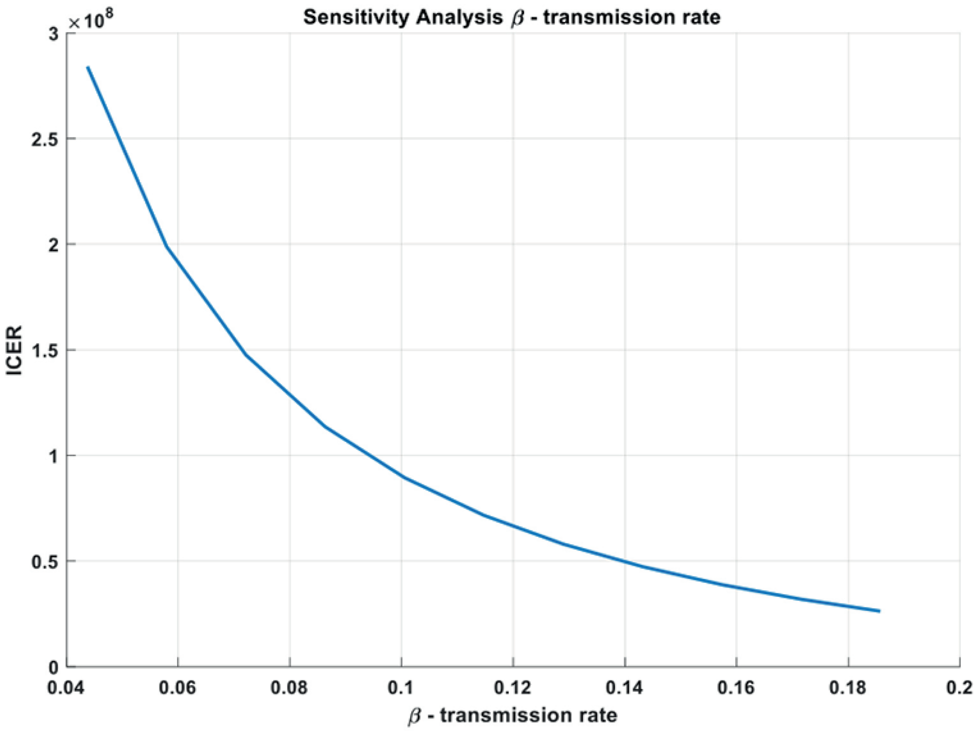
II. $\frac{dE}{dt} = \beta_1 \frac{SI}{N} + \beta_2 \frac{SE}{N} - \sigma E$

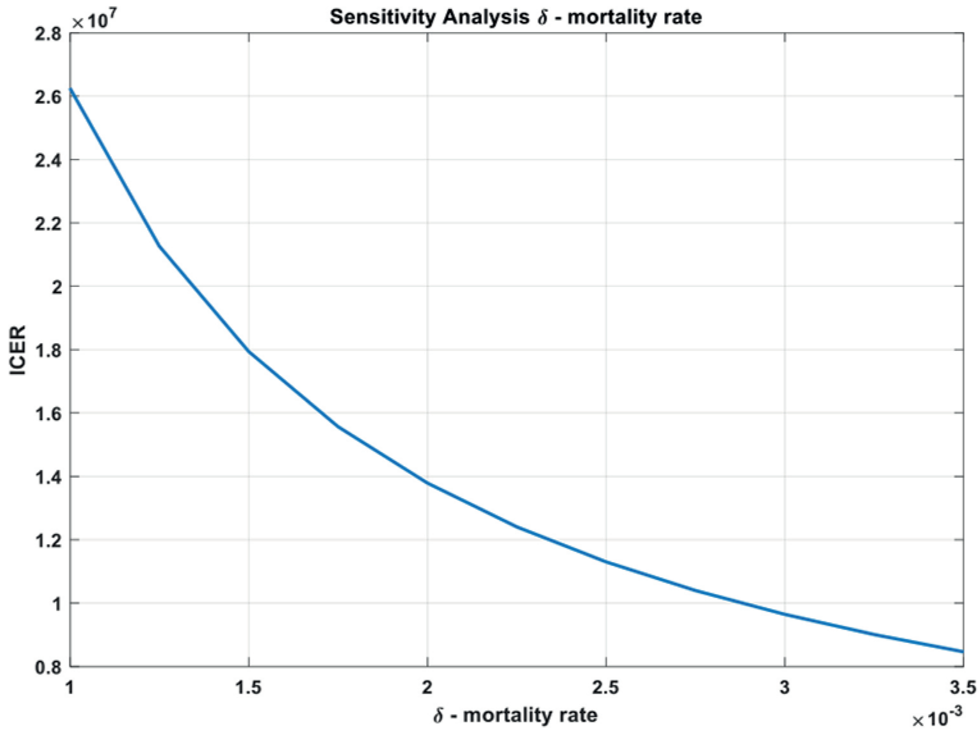
III. $\frac{dI}{dt} = \sigma E - (1 - \delta)\gamma I - \delta I$

IV. $\frac{dR}{dt} = (1 - \delta)\gamma I - \alpha R$

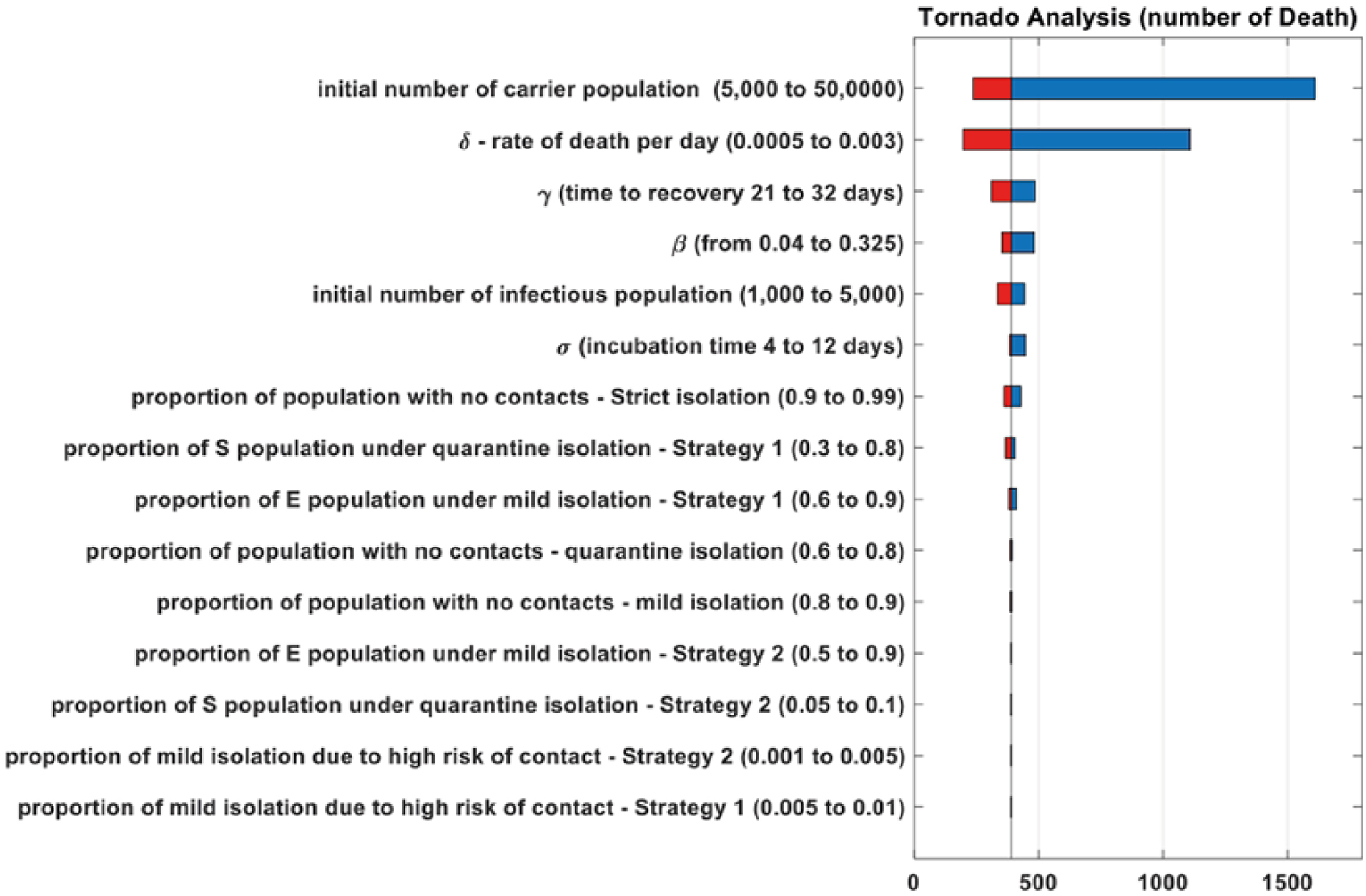
V. $\frac{dD}{dt} = \delta I$

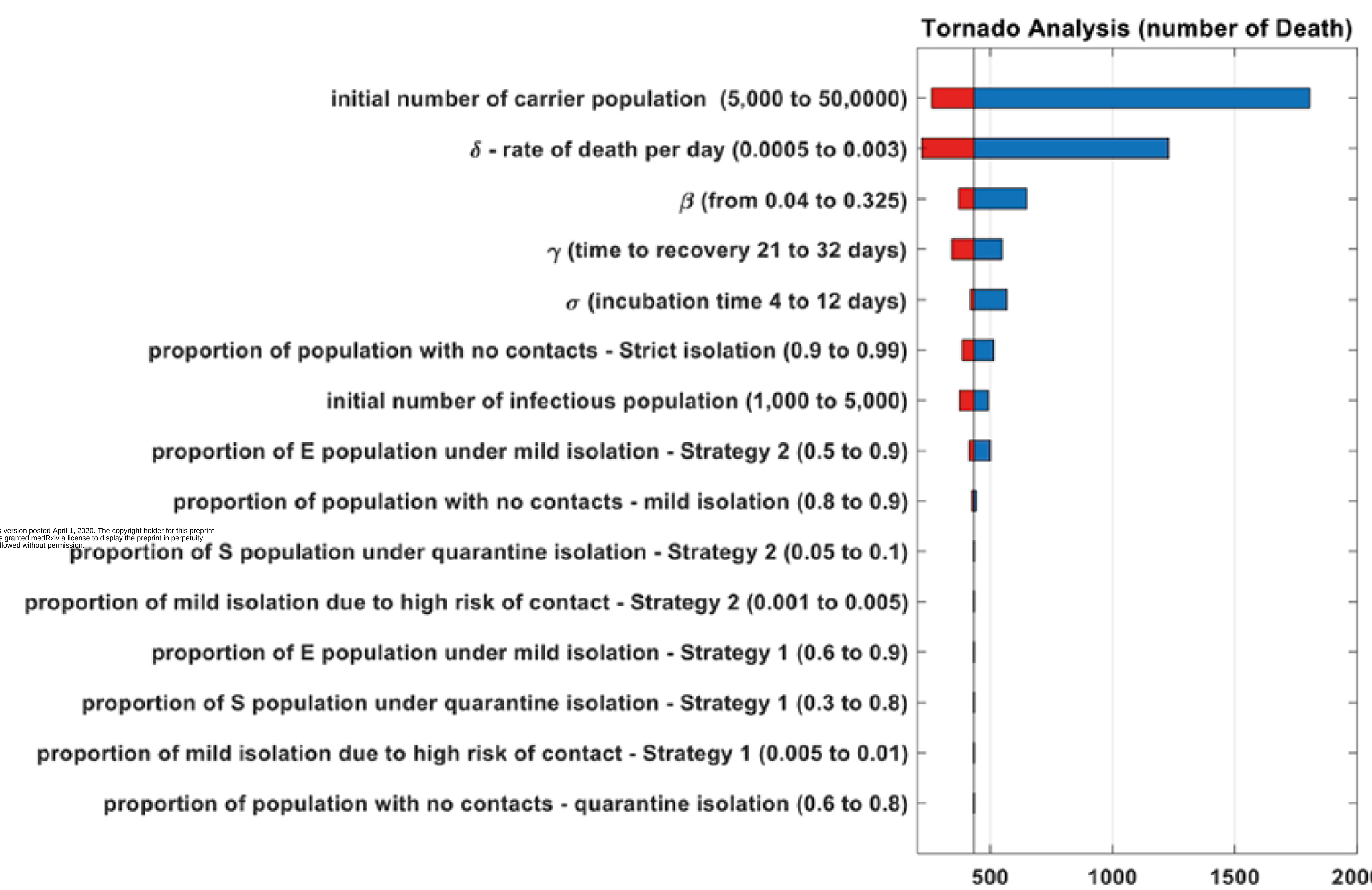
Appendix Fig 1





Appendix Fig 2





Appendix Fig 3