# **OPTIMISING TIME-LIMITED NON-PHARMACEUTICAL INTERVENTIONS FOR COVID-19 OUTBREAK CONTROL**

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## **ABSTRACT**

Retrospective analyses into the non-pharmaceutic interventions (NPIs) used to combat the ongoing COVID-19 outbreak has highlighted the potential of optimising interventions. These interventions allow for policy makers to manage the duration, introduction and strength of NPIs to minimise the human health impacts of both COVID-19 and the intervention itself. Here, we use a susceptible-infectious-recovered (SIR) mathematical model to explore the feasibility of optimising the duration, magnitude and trigger point of five different NPI scenarios, to minimise the peak prevalence and attack rate of a simulated UK COVID-19 outbreak.

Each intervention scenario differed with regards to the transmission reductions modelled, with each scenario possessing a distinct optimal parameter space. We note that these interventions may be prone to implementation error, with small deviations from the optimal parameter space often resulting in detrimental human health outcomes. However, we also note the potential use of suboptimal interventions, which are more robust to implementation error, but less capable of mitigating peak prevalence and attack rate compared to an optimal intervention. This work provides a simple illustrative example of the concept of intervention optimisation across a wide range of different scenarios and serves as a basis for future in-depth modelling work.

## **INTRODUCTION**

The ongoing COVID-19 pandemic has highlighted the vital role of non-pharmaceutical interventions (NPIs) in mitigating the spread of SARS-COV-2. These interventions break chains in transmission through population and individual-level behavioural changes, which can consequently reduce opportunities for transmission (1). NPIs encompass a large range of potential outbreak control strategies, ranging from simple advice to encourage hand-washing to country-wide, severe “lockdown” measures such as stay-at-home orders, mobility restrictions and closure of businesses (2).

While an effective tool to drive down disease prevalence, these severe NPI measures are considered unsustainable and time-limited, with economical, physical and mental health repercussions during and following the cessation of these interventions (3-5). This has driven calls to retrospectively understand the human health impact of introducing severe NPIs under a different set of circumstances (6-8). This includes insight into how differences in the timing, duration and strength of these interventions could have potentially altered COVID-19 associated mortality and morbidity compared to the actual course of action.

Exploratory mathematical modelling into “optimising” NPIs has arisen from these retrospective analyses (9-15). The concept of intervention optimisation is based on the potential for policy makers to fine-tune the characteristics of an intervention to minimise epidemiologically relevant outcome measures. One such desired outcome includes minimising the peak incidence, analogous to “flattening the curve” of an outbreak. The importance of this was illustrated by the early COVID-19 outbreaks in Lombardy, Veneto and Wuhan, with the overwhelming of health service capacity resulting in significant increases in patient mortality (16, 17).

Optimisation has been explored for a large range of potential COVID-19 NPI strategies, including single time-limited reductions to transmission (9, 10), intermittent pulsing of NPIs (14) and gradual ramping-down of intervention measures following an initial reduction to transmission (11, 12). Despite an optimal parameter space being identified for each of these explored interventions, the ability for policy makers to achieve these results in practice has been questioned (9). This stems from the narrow windows for optimal timing and the severe adverse human health outcomes borne out of intervention implementation error (9, 11). An alternative strategy is to use generalised intervention strategies, including longer-than-optimal or earlier-than-optimal interventions, with the aim to identify a broad and achievable parameter space that may be suboptimal, but still capable of mitigating the detrimental epidemiological and human health effects of COVID-19 (9). While not as obviously beneficial as an optimal intervention, these sub-optimal interventions are more robust to implementation error and offer more practical and flexible guidance to policy makers than specific optimal intervention timings or durations.

This study aims to provide a mathematical modelling framework to explore the concept of optimal and suboptimal interventions across a range of different NPI scenarios. We explore and compare the existence, patterns and optimal parameter spaces for each intervention to minimise the peak prevalence or the attack rate of a simulated outbreak. This was explored for three main parameters: 1) intervention duration, 2) intervention strength and 3) the intervention trigger point. The results from this study are not intended to highlight a best course of action. Rather this analysis provides an illustrative example to describe how optimal and sub-optimal outbreak control can be achieved under different circumstances and intervention strategies.

## **METHODS**

* 1. **SIR Model Structure**

A deterministic SIR model (18) was used to explore the impact of time-limited non-pharmaceutical interventions (NPI) on a simulated UK-based COVID-19 outbreak. *S*, *I* and *R* compartments were used to denote the fraction of susceptible, infected and recovered individuals respectively within the population(eqn 1.1).

eqn 1.1

Susceptible individuals (*S*) are infected at the time-varying rate *β(t)*, which represents the daily per-capita rate of transmission in a randomly-mixing population. Infected individuals (*I*) recover at rate *γ*, representing the daily per-capita rate of recovery. This rate was taken as the inverse of the average duration of infectiousness. A baseline pre-NPI basic reproduction number (*R0*) of 2.8 and doubling time (*Td*) of 3 days were assumed, in line with epidemiological and model-based estimates for COVID-19 transmission in the UK and abroad (19-23). The generation time was calculated as a function of these two quantities (24), with a baseline generation time of 7.79 days and a resulting *γ* of 0.128 day-1 (eqn 1.2).

eqn 1.2

* 1. **Defining the time-varying β(t)**

By setting *β = R0γ*, we define the baseline per-capita transmission rate in the absence of NPIs, *β =* 0.359 day-1. To capture the impact of smaller scale NPIs, *β* was multiplied by a scaling factor of 0.7, *βscale* = 0.252 day-1, with this 30% reduction being roughly in line with estimates of the impact of NPIs, such as school-closures, introduction of social distancing and isolation upon COVID-19 symptoms, and excluding severe NPIs, such as stay-at-home orders and movement restrictions (23, 25, 26). Using the UK as a representative example, these measures were introduced between 12-21st March 2020 with severe intervention measures initiated on the 25th March 2020 (26). We assume that these measures are in place at the initiation of the model simulation. We note that it was not the intention of this study to model the exact timing of the UK outbreak response, rather use the epidemiological characteristics of the UK outbreak as a motivation for this study.

*β(t)* is defined as the product of *βscale* and a time-varying scaling factor *c(t)*, which reduces *βscale* over the course of the simulation to model the impact of severe NPI measures, with 0 ≤ *c(t)* ≤ 1 (eqn 1.3). Reductions associated with this scaling factor are introduced on the trigger day, *tp* and with *dt* describing the duration of the intervention.

eqn 1.3

The shape of the *c(t)* factor varies with the different intervention scenarios explored, with parameter *cmin* describing the minimum value of *c(t)* during the intervention. This can be considered a proxy measure of the magnitude of the intervention. This parameter ensures that for each considered intervention scenario, the same minimum value of *c(t)* and therefore *β(t)* is obtained.

For baseline reductions to *β(t)* we define *cmin* = 0.4, resulting in *β*(t)= 0.101when the NPI measures are at their greatest magnitude*.* Baseline *cmin* was chosen to roughly achieve an effective reproduction number (*Re*) of 0.7 ≤ *Re* ≤ 1 during the intervention, similar to that observed in COVID-19 literature (23, 25, 26), with *Re* defined as *R0S*. All interventions were initiated at baseline *tp* = 52 days, equivalent to a attack rate at the initiation of the severe NPI measures, *Ic*(52)= 0.02, in line with model-based UK COVID-19 estimates (26). The model was seeded with an initial infectious fraction, *I*(0) = 0.00001.

* 1. **Single period of strict NPI measures**

A time-limited, single period of severe NPI measures was the primary intervention explored in this model, with optimisation occurring in relation to this intervention. We explored five different intervention scenarios, with each scenario differing with regards to the shape of *c(t)* and the subsequent *β(t)* reductions over the duration of the intervention, (*dt*) (Table 1). The total duration of the simulation, *tmax*, was set at 400 days and 1000 days for all other sensitivity analyses. We provide the rationale and real-world parallels for each of these scenarios in the supplementary material.

**Table 1** – Description of the five intervention scenarios.

|  |  |  |
| --- | --- | --- |
| Scenario | *c(t)* during the simulation | Definition of *c(t)* scaling parameter |
| 1 | Immediate and constant reduction to *cmin*. |  |
| 2 | Immediate reduction to *cmin* followed by a linear increase back to *c(t)* = 1. |  |
| 3 | Linear decrease to *cmin* followed by an immediate return to *c(t)* = 1. |  |
| 4 | Linear decrease to *cmin* at *dt*/2, followed by a linear increase back to *c(t)* = 1. |  |
| 5 | A “pulsing” intervention occurring with immediate reductions to *cmin* between intervention intervals 0-21, 35-49 and 63-77 days (for an example total intervention duration, *dt* = 84 days). |  |

For a total length of intervention duration, *dt*, the magnitude of *c(t)* scaling reductions over the intervention period is half for scenario 2, 3, 4 and 5 relative to scenario 1. To maintain comparable *β(t)* reductions over the intervention period, *dt* was doubled for scenario 2, 3, 4 and 5 relative to scenario 1 for baseline analyses. This corresponds to *dt* = 84 days for scenario 1 (12 weeks) and *dt* = 168 days (24 weeks) for all other scenarios.

An alternative approach was considered by keeping *dt* constant and doubling *cmin* in scenario 2, 3, 4 and 5 relative to scenario 1 (Figure S1 + 2). Either method is plausible when considering potential intervention scenarios, but we argue that in practice it is more plausible to alter *dt* than it is to alter *cmin* in a public health context. This can be attributed to the limited control of policy-makers to determine the exact strength of an intervention (25).

* 1. **Multiple NPI measures**

To explore the transmission dynamics resulting from multiple, time-limited periods of severe NPI measures, two interventions for each scenario were modelled sequentially over the course of the simulation. We define the minimum value of the *c(t)* scaling factor, intervention trigger point and duration of the intervention as *cmin1* and *cmin2*, *tp1* and *tp2*, and *dt1* and *dt2* respectively for intervention 1 and 2. We note that *tp2* is defined relative to the end of intervention 1, with the start of intervention 2 defined as *t* = *tp1* + *dt1* + *tp2*.

Baseline parameter values for the multiple intervention scenario were set at *dt1* = *dt2* = 42 days (6 weeks) for scenario 1 and *dt1* = *dt2* = 84 days (12 weeks) for scenarios 2, 3, 4 and 5. This was halved relative to the single intervention scenarios to allow for the two interventions to occur within the timeframe of the simulated outbreak. The baseline minimum value of the scaling factor *c(t)* was kept constant at *cmin1* = *cmin2* = 0.4.

* 1. **Outcome Measures of Interest**

The primary objective of all analyses in this study was to identify the optimal parameter space for the intervention trigger point (*tp*), duration (*dt*) and magnitude (cmin) to minimise two outcome measures:

1. Peak prevalence *I(t): Imax*
2. Attack Rate:

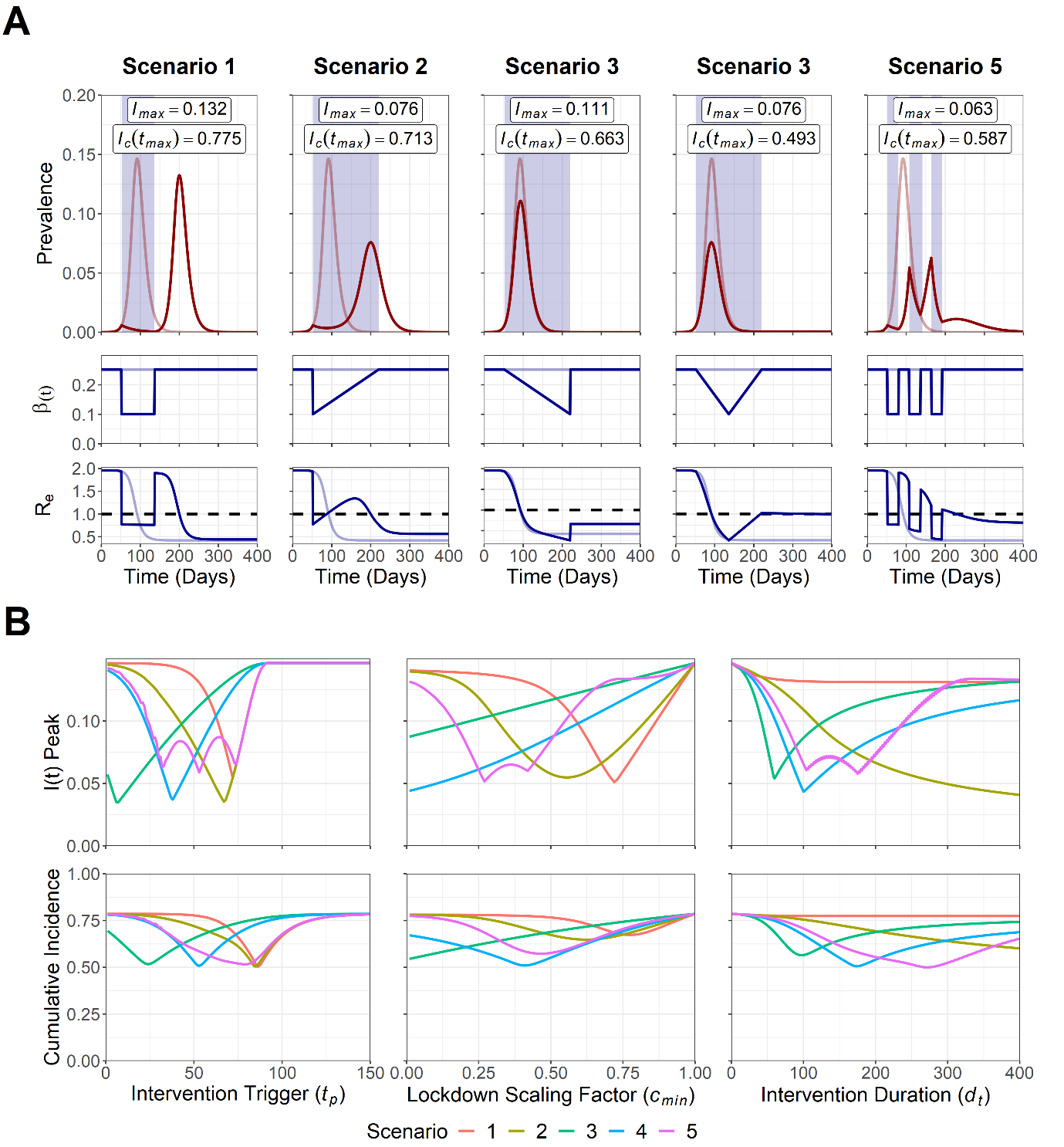
We define *Imax* as the global maximum of the function describing the trajectory of the fraction infectious during the simulated epidemic, with subsequent references to “epidemic peaks” describing the local maxima where *I(t)* > 0 and *I’(t)* = 0. The attack rate, *Ic(tmax)*, is defined as total proportion of cases that develop over the model simulation. The optimal parameter space is defined as the combination of parameter values that result in the lowest possible value of *Imax* or *Ic(tmax)*.

1. **Software Used**

All simulations were carried out using R (27) and RStudio (28). The following R packages were used: “desolve” (29), “ggplot2” (30) and “reshape2” (31). Reproducible code can be found at: <https://github.com/alexmorgan1995/SDM_Analysis>.

**RESULTS**

The impact of the five intervention scenarios on the trajectory of a simulated COVID-19 outbreak was explored (Figure 1A). Scenario 4 was identified as the most effective scenario at mitigating peak prevalence and total cumulative incidence under baseline parameters (*Imax* = 0.076, *Ic(tmax)* = 0.493) relative to an unmitigated outbreak (*Imax* = 0.146, *Ic(tmax)* = 0.786). Scenario 1 and 2 resulted in the suppression of the initial outbreak and delay in the peak prevalence following the initiation of lockdown measures. In contrast, a single mitigated epidemic peak was observed for scenario 3 and 4, with the steady ramping up of *β(t)* reductions and the protective effects of population immunity resulting in a more gradual, sustained reduction to *Re* below 1, preventing peak resurgence. The pulsed nature of scenario 5 allowed for brief opportunities for the build-up of population immunity (*Re* > 1) and subsequent epidemic control (*Re* < 1).



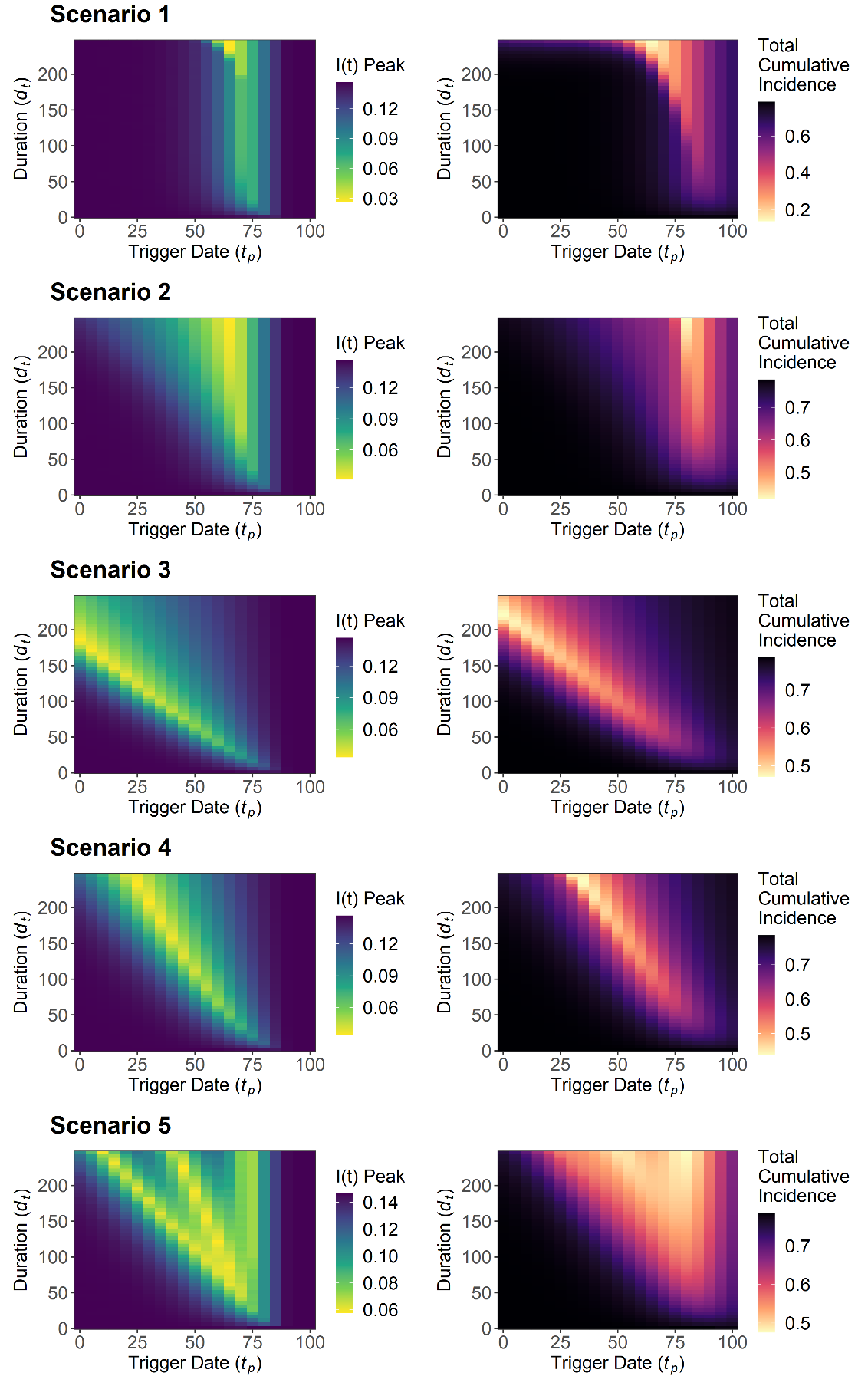
**Figure 1. A) Trajectory plots for the epidemic curve, *β(t)* reductions and *Re* for the five intervention scenarios. B)** **Sensitivity analysis for Intervention trigger day (*tp*), magnitude of lockdown measures (*cmin*) and intervention duration (*dt*) to minimise maximum *I(t)* peak, *Imax*, and total cumulative incidence, *Ic(tmax)*.** For A) opaque red and blue lines depict unmitigated epidemic curve dynamics,blue shading indicates the intervention duration and the dotted line depicts the *Re* = 1 threshold for sustained epidemic growth. *Imax* and *Ic(tmax)* values are annotated for each scenario.Note that for B) aside from the *dt* sensitivity analysis, all scenarios are comparable for a specific explored parameter value, with an inability to model *dt* compensations to ensure similar magnitude of interventions across all scenarios, as *dt* is an explored value.

Sensitivity analyses were conducted to observe the sensitivity of the maximum *I(t)* peak, *Imax*, and the total cumulative incidence, *Ic(tmax)*, to the intervention trigger day (*tp*), magnitude of lockdown measures (*cmin*) and intervention duration (*dt*) (Figure 1B). Optimal parameter values for all scenarios can be found in the supplementary material (Table S3). A specific optimal trigger point was observed for all scenarios to minimise both *Imax* and *Ic(tmax)*, with these optimal values found within an early-intermediate trigger point range (7 ≤ *tp* ≤ 74). Interestingly, three relatively similar optimal trigger points were identified in scenario 5 to minimise *Imax* (*tp* = 32/53/74 days). Scenarios 1, 3 and 4 were found to be highly sensitive to deviations from the optimal *tp* value, with steep increases in *Imax* and *Ic(tmax)* either side of the optimum. However, we note that if a suboptimal trigger point is chosen, an earlier-than-optimal trigger point is preferable in scenario 2, with a milder increase in *Imax* relative to later-than-optimal values of *tp*. The opposite phenomenon was observed in scenario 4, with a later-than-optimal trigger point being somewhat more favourable.

Stronger interventions were more optimal to minimise *Imax* and *Ic(tmax)* for scenario 3 and 4 (*cmin* → 0). In contrast, intermediate strength interventions were found to be more optimal in scenario 1, 2 and 5 (*cmin* = 0.72/0.77, 0.56/0.62, 0.27/0.47) for *Imax*/*Ic(tmax)* respectively. We note that despite the optimums observed for these three scenarios, it was more beneficial to intervene too strongly than insufficiently if a suboptimal *cmin* value was chosen. This was observed with lower-than-optimal *cmin* values resulting in gentler increases in *Imax* and *Ic(tmax)* compared to *cmin* values which were greater-than-optimal.

Longer intervention durations were found to be optimal to reduce *Imax* for scenario 2 (*dt* → 400). Interestingly, increasing the intervention duration was found to have minimal impact on *Imax* and *Ic(tmax)* in scenario 1, attributable to the delaying action of the intervention, with the strictness and constant nature of *β(t)* reductions simply delaying an identically sized peak until after the cessation of the intervention, regardless of the intervention length. In contrast, intermediate length interventions were found to be optimal for scenario 3 and 4 (*dt* = 60/97, 100/174) for *Imax*/*Ic(tmax)* respectively, with scenario 5 displaying two relatively similar optimal points to minimise *Imax* (*dt* = 104/175). We note that if a suboptimal intervention duration is introduced for these scenarios, it was more beneficial to intervene for too long, with increases in *Imax* and *Ic(tmax)* being less severe in an intervention that was longer-than-optimal, compared to an intervention that was shorter-than-optimal.

To explore the interplay between multiple model parameters, a sensitivity analysis was next conducted to identify the optimal parameter space to minimise *Imax* and *Ic(tmax)* for a multi-dimensional parameter space: 1) Intervention trigger day (*tp*) and 2) Intervention duration (*dt*) (Figure 2). The optimal parameter space for all scenarios can be found in the supplementary material (Table S3).



**Figure 2. Sensitivity analysis for maximum *I(t)* peak, *Imax*, and total cumulative incidence, *Ic(tmax)*, for intervention trigger day, *tp*, and the intervention duration, *dt*.** This was explored for the five intervention scenarios.Note that for a specific value of *dt*, scenario 1 is not comparable with scenario 2, 3, 4 and 5, as *dt* remains an explored parameter, and therefore *dt* compensations to ensure a comparable intervention magnitude over the intervention duration were not possible.

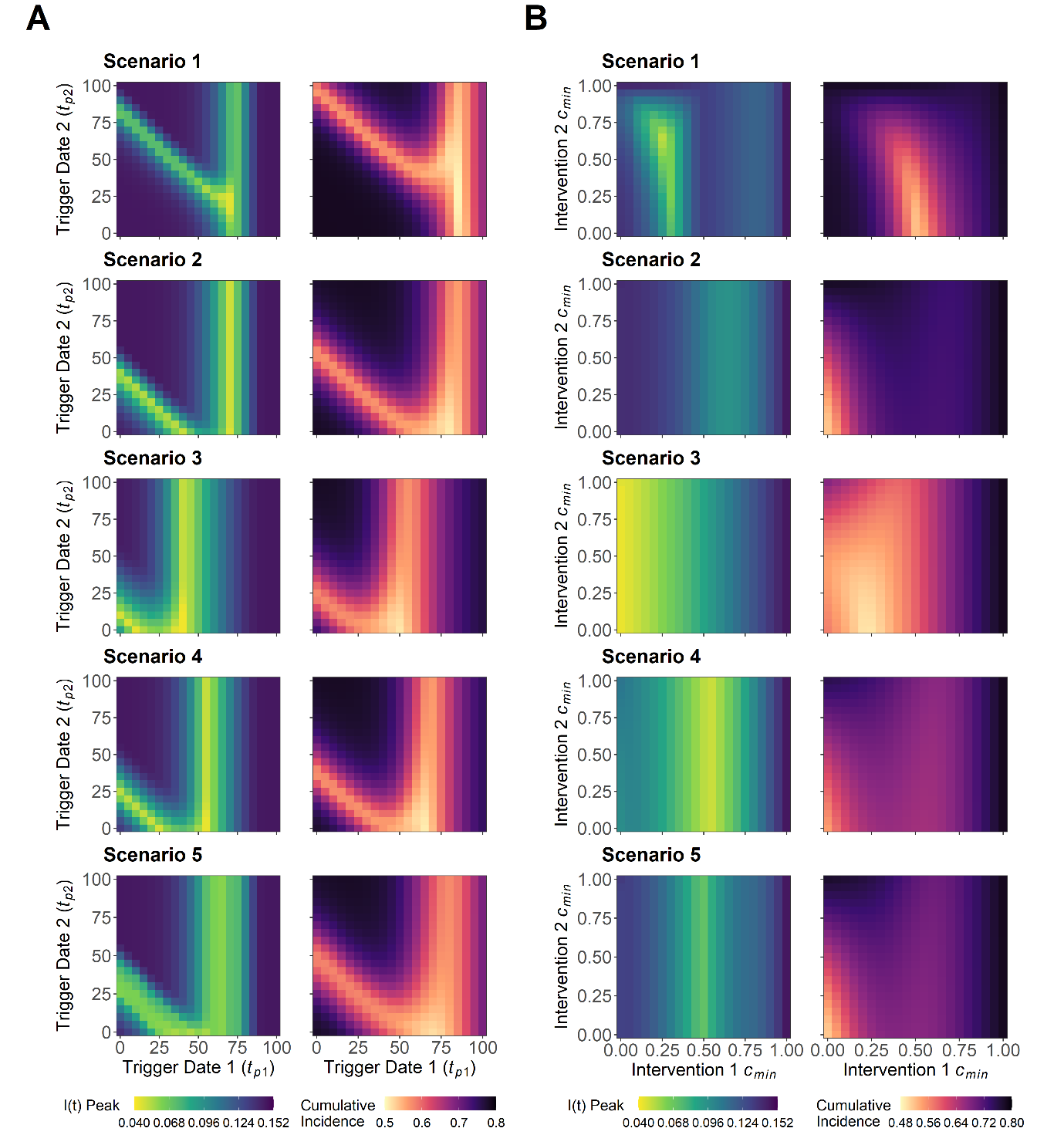
A longer intervention duration (*dt* → 250) and intermediate trigger point (*tp* = 65) was optimal for scenario 1 and 2 to minimise *Imax* and *Ic(tmax)*. A different qualitative pattern was observed in scenario 3 and 4, with decreases to the intervention duration found to maintain the optimal parameter space with a later intervention trigger. We also note the existence of suboptimal trigger point “gaps” in scenario 5, with increases and decreases in *Imax* as the trigger point was varied. This resulted from the fixed periods between pulsed interventions, with these “gaps” increasing as the duration of the overall intervention increased. These “gaps” were found to be less pronounced for *Ic(tmax)* relative to *Imax*.

Increasing the length of the intervention had interesting compensatory effects for scenario 2, 3, 4 and 5, with both *Imax* and *Ic(tmax)* being less sensitive to deviations from the optimal intervention trigger point as the duration of the intervention was increased. This suggests that increasing the duration of can make the intervention more robust to optimal trigger date implementation error.

The sensitivity analysis was repeated with *cmin* = 0.25/0.5/0.75 to assess the sensitivity of the *dt*/*tp* relationship to alterations to the magnitude of the intervention (Figure S3 + 4). Low-intermediate *cmin* values of 0.25 (scenario 1, 2 and 3) and 0.5 (scenario 3 and 4) were found to be more optimal to minimise *Imax*, with the lowest explored value of *cmin* being optimal to minimise *Ic(tmax)* for all scenarios.

We note that NPIs and population lockdown measures are often not considered in isolation, and are often introduced as package of measures, or with the expectance that strong NPIs may be introduced at a later date to tackle epidemic resurgence. To model this, two sequentially implemented lockdown measures were introduced for each of the five scenarios. Descriptive baseline trajectory plots for each of the five multi-intervention scenarios can be found in the supplementary material (Figure S5). Similar dynamics were observed relative to the single-intervention scenario, although we note a higher value of *Imax* for scenarios 2 and 5 relative to the single-intervention scenarios, attributable to the shorter intervention duration used for the multi-intervention scenarios.

A sensitivity analysis was conducted with the multi-intervention model to explore the optimal parameter space to minimise *Imax* and *Ic(tmax)* for two sets of parameters: 1) Intervention 1 trigger date, *tp1*, and Intervention 2 trigger date, *tp2,* and 2) Intervention 1, *cmin1*, and Intervention 2, *cmin2* (Figure 3). The optimal parameter space for all scenarios can be found in the supplementary material (Table S3).



**Figure 3. A) Sensitivity analysis for maximum I(t) peak, *Imax*, and total cumulative incidence, *Ic*(*tmax*), for intervention 1 trigger date, *tp1*, and intervention 2 trigger date, *tp2*. B) Sensitivity analysis for the** **minimum value of lockdown-related scaling factor *c(t)* for intervention 1, *cmin1*, and intervention 2, *cmin2*.** This was explored for the five intervention scenarios. Due to *dt* compensations, all scenarios are comparable for a given parameter value combination, with heat map scales remaining constant for each set of explored parameters.

A large range of trigger points for intervention 2 (1 ≤ *tp2* ≤100) were optimal to minimise *Imax* and *Ic(tmax)*, on the condition that the optimal trigger point for intervention 1 was achieved (50 ≤ *tp1* ≤ 65) (Figure 3A). This was found to differ if a suboptimal *earlier* intervention 1 trigger point was chosen, with only a narrow selection of optimal intervention 2 trigger points able to compensate for a suboptimal *tp1* value. The choice of a *later* than optimal intervention 1 trigger was found to completely negate the ability for an intervention 2 trigger to prevent increases in *Imax* and *Ic(tmax)*, suggesting that it is better to introduce the initial intervention earlier, rather than later, if the optimal intervention 1 trigger point is unknown. Extending the duration of intervention 1 and 2 did little to alter the optimal trigger points for either scenario (Figure S6-15).

Optimising the magnitude of intervention 1 was found to be more critical to minimise *Imax* and *Ic(tmax)*, with a large range of optimal magnitudes possible for intervention 2 (0 ≤ *cmin2* ≤ 1) if the magnitude of intervention 1 is sufficiently optimised for scenario 2, 4 and 5, these optimums were found within the range 0.25 ≤ *cmin1* ≤ 0.65 (Figure 3B). Scenario 1 and 3 displayed subtly different dynamics, with an optimal intervention 1 ideally being as strong as possible (*cmin1* → 0) in scenario 3 and a specific optimal parameter space being observed for scenario 1 (*cmin1* = 0.26/0.62, *cmin2* = 0.52/0, for *Imax* and *Ic(tmax)*). Increases in the duration of intervention 1 allowed for greater reductions to *Imax* and *Ic(tmax)* for a given *cmin1*/*cmin2* parameter space, relative to baseline parameters (Figure S16-25). The exception was scenario 3, with increases in the intervention 1 duration resulting in detrimental increases to possible *Imax* and *Ic(tmax)* values for a given combination of *cmin1*/*cmin2*.

## **DISCUSSION**

This work builds on previous epidemiological modelling (9-15) to explore the optimal parameter space to minimise maximum peak prevalence (*Imax*) and total cumulative incidence (*Ic(tmax)*) across five different NPI scenarios. We identified an optimal parameter space for all considered intervention scenarios, with each scenario capable of minimizing both *Imax* and *Ic(tmax)* for a given set of unique, optimal parameter values. However, we note that the exact position of the parameter optimums are often highly nuanced and unintuitive, with the optimal parameter space shifting throughout the sensitivity analyses.

The optimal parameter space was found to be strongly influenced by 1) the intervention peak timing and 2) Intervention *cmin* balance. Matching the timing of an intervention to the epidemic peak is not a novel concept, with this being explored previously (9, 10). However, we demonstrate that it is also necessary to match the timing of the epidemic peak with the greatest extent of the intervention (*cmin*/*cmin1*/*cmin2*) if reductions to *β(t)* are allowed to vary. This can be intuitively observed by comparing scenario 2 (*cmin* at *tp*) and scenario 3 (*cmin* at *tp* + *dt*) (Figure 2), with scenario 2 being optimal at a later trigger day to coincide with the early *cmin* reduction and scenario 3 optimal with an earlier intervention trigger to coincide with the later *cmin* reduction. We also note the existence of optimal intermediate *cmin* values facilitating the build-up of infection-induced, protective immunity during the intervention. This phenomenon is well reported in epidemiological literature, with time-limited interventions found to be optimal when *Re* is maintained near the threshold for sustained transmission (*Re* ≈ 1) (32).

As suggested by previous research, attainment of these optimums in practice is likely to be difficult (9). The ongoing COVID-19 outbreak has highlighted the limited capacity of policy-makers to effectively micromanage the course of an outbreak, with the introduction of policy often only slightly modifying the course of an outbreak (33). Factors such as varying public compliance, imperfect disease surveillance, policy miscommunication, confounding parallel interventions and an implementation lag between the introduced interventions and observable changes in disease prevalence, will contribute to large levels of intervention implementation error (8, 34, 35). If placed in the context of the narrow parameter optimums observed throughout this study, these errors will likely result in serious human health consequences.

A more viable approach could involve the use of sub-optimal interventions. Parallels of these interventions can be observed in the ongoing COVID-19 outbreak, with recurring themes of “hit it hard and fast” providing simple, yet robust advice to policy makers (36, 37). We note that for a single time limited intervention, the most effective suboptimal strategy to reduce *Imax* and *Ic(tmax)* can be achieved by intervening stronger and for longer than what is considered optimal (Figure 1 + 2). Similarly, for the multi-intervention scenario, an earlier and stronger intervention can provide reductions to *Imax* and *Ic(tmax)* under suboptimal circumstances (Figure 3). However, we note that this only holds true in the context of the initial intervention, with this acting as a delaying action, allowing for successive interventions to compensate and further reduce *Imax* and *Ic(tmax)*. This is corroborated in literature, with suggestions that uncertain policy makers could use an earlier intervention to delay the peak if the optimal intervention is unknown, providing time for the build-up of healthcare capacity and the opportunity for later interventions to “course-correct” (9).

We also note that NPIs such as population lockdown measures are often considered an integral part of a package of wider measures, often used to drive down the level of infection and “buy” time for the introduction of more sustainable measures, such as contact tracing or vaccination (38, 39). We note that in this context, it is universally more optimal to introduce the initial lockdown measures earlier, more strongly and for as long as necessary, until more sustainable intervention measures can be introduced indefinitely (Figure S26). This corroborates the results obtained from the sub-optimal analysis of the time-limited single/multi intervention scenario (Figure 2 + 3), and provides support for the current rationale of “hard and fast” introduction of intervention measures. However, this highlights the importance of prioritising the development of these sustainable measures, with the harsh consequences of long lockdown measures making indefinite delaying actions unsustainable.

In contrast to the SIR model structure used by this study, we note that an SEIR framework could be considered more accurate to describe the epidemiological characteristics of SARS-COV-2, with this resulting in a delay between the intervention and observed effects in *I(t)* (Figure S27). However, this was considered unnecessary, with the aim of this study to describe the existence and patterns of intervention optimums, and not forecast or describe the exact timing of said optimums.

An assumption of life-long immunity was also made following SARS-COV-2 infection. This choice was made due to the large amount of uncertainty regarding the immunological characteristics of the virus (40). Particular avenues for future research could include modelling impact of waning immunity or serological cross-reactivity and how this could impact the optimal and sub-optimal parameter spaces highlighted in this study (41).A relatively simple disease metric was also used for this study, with an optimal intervention able to reduce maximum peak prevalence, *Imax*, and total cumulative incidence, *Ic(tmax)*. While outside of the scope of this study, the use of other epidemiologically relevant outcome measures such as occupied ICU capacity or deaths per 100,000 population may be of interest when investigating optimal COVID-19 interventions in a more policy-relevant context. This could also be complemented by an exploration into the impact of individual or population level variation of risk on intervention optimisation (42-44).

NPI optimisation has been highlighted in this study as a powerful tool to greatly mitigate the human health impacts of a COVID-19 outbreak. This can be considered of significant relevance, with the recent reinstitution of NPIs and local lockdowns being used to combat resurgent outbreaks. However, the results described in this study are highly nuanced, with narrow intervention optimums and a number of other factors likely preventing the trajectory of an epidemic conforming uniformly to the dynamics observed in this study. We highlight suboptimal interventions as an alternative policy option, with these less efficacious interventions being less prone to implementation error and having the additional benefit of being a risk-averse approach. This is often favourable during the initial stages of the outbreak, where the potential impact of risky public health policy can lead to disastrous consequences. Finally, we highly stress that it was not the intention of this study to propose any one strategy as a singular policy option for COVID-19 control. The evidence from this study should be taken into context with the work tirelessly undertaken by the wider epidemiological and modelling community. It is only through this collaboration and synthesis that effective and altruistic public health policy can be generated to combat the COVID-19 pandemic.

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