



Coupled models of genomic surveillance and evolving pandemics with applications for timely public health interventions

Baltazar Espinoza^{a,1}, Aniruddha Adiga^a, Srinivasan Venkatramanan^a, Andrew Scott Warren^a, Jiangzhuo Chen^a, Bryan Leroy Lewis^a , Anil Vullikanti^{a,b}, Samarth Swarup^a, Sifat Moon^a, Christopher Louis Barrett^{a,b} , Siva Athreya^{c,d}, Rajesh Sundaresan^{e,f,g}, Vijay Chandru^{h,i}, Ramanan Laxminarayan^{j,k} , Benjamin Schaffer^{l,m}, H. Vincent Poor^l , Simon A. Levin^{l,1} , and Madhav V. Marathe^{a,b,1}

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Disease surveillance systems provide early warnings of disease outbreaks before they become public health emergencies. However, pandemics containment would be challenging due to the complex immunity landscape created by multiple variants. Genomic surveillance is critical for detecting novel variants with diverse characteristics and importation/emergence times. Yet, a systematic study incorporating genomic monitoring, situation assessment, and intervention strategies is lacking in the literature. We formulate an integrated computational modeling framework to study a realistic course of action based on sequencing, analysis, and response. We study the effects of the second variant's importation time, its infectiousness advantage and, its cross-infection on the novel variant's detection time, and the resulting intervention scenarios to contain epidemics driven by two-variants dynamics. Our results illustrate the limitation in the intervention's effectiveness due to the variants' competing dynamics and provide the following insights: i) There is a set of importation times that yields the worst detection time for the second variant, which depends on the first variant's basic reproductive number; ii) When the second variant is imported relatively early with respect to the first variant, the cross-infection level does not impact the detection time of the second variant. We found that depending on the target metric, the best outcomes are attained under different interventions' regimes. Our results emphasize the importance of sustained enforcement of Non-Pharmaceutical Interventions on preventing epidemic resurgence due to importation/emergence of novel variants. We also discuss how our methods can be used to study when a novel variant emerges within a population.

biosurveillance | epidemic modeling | pandemics | coupled dynamics | COVID-19 variants

Infectious disease surveillance provides a systematic framework by collecting, analyzing, and interpreting data to monitor disease burden, identifying emergent outbreaks, and detecting new pathogens (1–3). Surveillance systems inform public health strategies aimed to contain outbreaks before they are out of control. Epidemiological monitoring systems that use a systematic collection of incidence trends to study syndromic time series have been the standard disease detection systems for more than a century (4–8). The importance of these systems came to the fore once again during the West African Ebola virus disease epidemic and, more recently, during the COVID-19 pandemic (9). In both cases, the lack of early detection capacity impeded rapid disease prevention, detection, and intervention, leading to a public health crisis (10, 11).

Most disease surveillance frameworks envision disease detection as a static problem based on a threshold condition. Consequently, the interdependence between epidemiological surveillance, disease dynamics, and intervention strategies remains unclear. The 2022 National Biodefense Strategy Plan, released by the White House, comprises five pillars: risk awareness and detection, prevention of bioincidents, reduction of impacts, rapid intervention, and recovery facilitation (12). The plan highlights the need for assessment and preparedness to respond to and recover from any future biological incident. Yet, a systematic study incorporating genomic monitoring, situation assessment, and intervention strategies is lacking in the literature to the best of our knowledge.

Pandemics pose a complex challenge in which epidemiological surveillance is essential but not sufficient to achieve containment. Upon identification of transmission, epidemiological surveillance motivates the front-line of Non-Pharmaceutical Interventions (NPIs) which focus on modifying the population's behavior (13–15). However, it is important to recognize the role of genomic surveillance as a critical component toward the development of precision epidemiology (16, 17); an integrative framework

Significance

We formulate a modeling framework that integrates genomic surveillance, two-variants dynamics, and intervention strategies. We study the impact of the variants' competing dynamics (determined by the second variant's importation/emergence time, relative infectiousness, and cross-infection) on both the variants' detection time and the effectiveness of different intervention scenarios during an evolving pandemic. We found that the novel variant's detection conditions are determined by the competitive dominance, modulated by the population's susceptibility. Our findings show that, depending on the target metric, different intervention scenarios lead to better outcomes and highlight the impact of sustained interventions on suppressing epidemics revival. Finally, we found that the transmission process' characteristics inherently limit detection and the impact of intervention strategies.

The authors declare no competing interest.

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¹To whom correspondence may be addressed. Email: baltazar.espinoza@virginia.edu, slevin@princeton.edu, or marathe@virginia.edu.

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to design and implement informed public health interventions aimed to contain pandemics based on a realistic course of action that accounts for sequencing, analysis, and response (18). Recently, Colijn et al. stressed the need for linking four key data sources (variant sequences, epidemic data, demographic data, and immunization data), to leverage genomics-informed outbreak response and our ability to design early warning systems (3). In conjunction with genomics surveillance, digital epidemiology would extend the capabilities of precision epidemiology with the potential of describing the distribution of health information/misinformation on digital platforms (19). Genomic sequencing can also lead to improved understanding of the geographical spread and the composition of transmission clusters that may be associated with increased infectiousness. For instance, sequencing analyses helped to identify super spreader events as the major threat for COVID-19 spread in the United States (3, 20, 21). The work presented here takes a step in the direction outlined in refs. 3, 18, and 19.

Understanding the genomic composition of ongoing outbreaks helps to characterize the expected disease dynamics and epidemiological outputs, as well as potential vaccination strategies. After the development of vaccines against SARS-CoV-2, immunity waning and the emergence/importation of novel variants producing breakthrough infections represent the major challenges to control the spread of the virus (3, 22, 23). For example, the resurgence of cases in the United Kingdom during November 2021 was associated with the importation (also referred to as introduction), and propagation of the Omicron variant, partially caused due to reduced vaccine effectiveness (24). Moreover, it is known that the available vaccines against COVID-19 were more effective against the Delta variant than for the Omicron variant. Consequently, in the United States, existing vaccines had to be reformulated and provided as boosters to account for the Omicron variant's immune escape (25). Evidence during the COVID-19 pandemic suggests that vaccination not only reduced the severity of cases and the epidemic burden, but also vaccinated individuals shown reduced mutation rates relative to unvaccinated individuals (26, 27).

Epidemiological modeling of infectious diseases is an accepted tool to inform interventions. However, most of the efforts do not often emphasize the role of surveillance and detection in determining the time and ability to respond to a biological threat (28). In a recent work (29), studied the optimal response scenario under single-variant outbreak dynamics. The study showed that the optimal response strategy is difficult to implement and highly sensitive to mistimed implementation, which dramatically reduces the intervention effectiveness, consequently leading to a recommendation of the implementation of more conservative strategies (29). In another study, Eletreby et al., by explicitly incorporating mutation, studied the impact of evolutionary adaptations on both the final epidemic size and the variant-specific infections, as the contagion propagates in complex networks (30, 31). In their study, analytical results for the number of variant-specific cases were derived.

In this work, we focus on aggregate surveillance data, and we consider the number of variant-specific cases detected in a given region and period, without incorporating additional information such as from line lists. We formulate a modeling framework to study the impact of novel variants importation conditions and, potential detection and intervention scenarios to ameliorate the impact of a disease under two-variant dynamics. We show that our framework can address scenarios where the second variant is imported at an arbitrary time or where the

second variant emerges due to a mutation process. Extensions of our framework using epidemic models that incorporate diverse within-host disease progressions and a variety of intervention regimes are also explored in *SI Appendix*. We couple a two-variant mean-field model to study the competing variants' dynamics of disease progression and a probabilistic approach to determine: i) the disease detection time given a specific surveillance level and ii) the new variant's detection time.

The emergence of a novel variant due to evolutionary processes is linked to the local progression of an epidemic and to the nature of interventions that modulate infections; however, an infectious process may be triggered by a novel imported variant and may not be tied to the local disease progression. Importation (also referred to as introduction) events were a major driver for the global spread of SARS-CoV-2 variants (32–35). For example, the coronavirus Alpha variant, originally identified in the United Kingdom, spread to several countries within weeks (36); the Omicron variant was initially identified in South Africa and quickly affected the United Kingdom and the United States (37, 38). To explore the full spectrum of two-variant disease dynamics, our model assumes that the second variant is imported at an arbitrary time after the contagion process starts with cases generated by the first variant. The scenario where the second variant is produced as a consequence of mutation processes due to first variant's infections, and the impact of interventions on delaying or preventing the emergence of a novel variant, is also explored in *SI Appendix*.

We study the feedback loop between disease dynamics and surveillance, which could inform the appropriate intervention time and strength. While the imported variant's detection time is subject to surveillance efforts, the ultimate epidemiological dynamics under intervention depend on the intervention's time, type, and strength. Our results shed light on the intrinsic relationship among disease dynamics, genomic composition, and the impact of aggregated data surveillance systems. Specifically, we show that in the absence of prophylactic interventions, there are scenarios where single-period NPIs (limited-duration interventions applied only once) lead to undesirable epidemiological outcomes, such as an increase in the epidemic burden. The important result here is that, the best response depends on the intervention goal. In particular, the single-period earliest and strongest intervention may not always be the best intervention, a strategy that was followed by many countries during the early COVID-19 pandemic. On the other hand, sustained enforcement of adaptive NPIs (interventions implemented/removed multiple times as the disease prevalence increases/decreases), may ameliorate the epidemic burden and impede its revival, and may delay or even prevent the emergence of a new variant.

Our results show that the transmission process characteristics (the first variant's basic reproductive number, the second variant's relative infectiousness with respect to the first variant, cross-infection, and importation time) determines the best response strategy. Moreover, we show that the impact of NPIs is inherently limited by the competing variants' dynamics, see Fig. 1.

Genomic Surveillance for Disease Detection

Detecting an Outbreak. First, we study how the detection time of positive cases depends on both the disease transmission dynamics and the surveillance effort. For a given sampling size and a uniformly random sampling strategy, power calculations determine the minimum disease prevalence for identification of at least one positive case with a target probability, e.g. 95%.

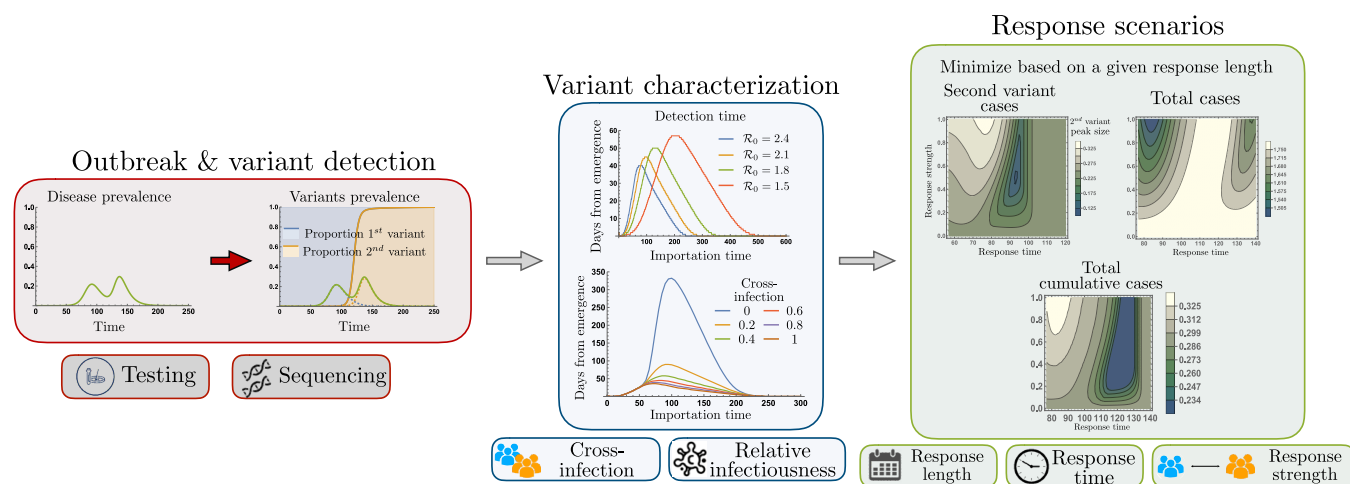


Fig. 1. A schematic of our detection and response framework. The proposed framework captures the impact of disease dynamics on the detection time of an emergent/imported variant, which in turn limits the fastest intervention time against the novel variant. The detection time and, consequently, the response time are dependent on the variants' competing dynamics, whose dynamics are determined by the relative infectiousness and the cross-infection levels. Finally, the goal-specific best intervention scenario is given by the intervention length, the intervention time, and the intervention strength.

Our findings highlight that i) the detection time increases as the disease's basic reproductive number (R_0) decreases, and ii) the marginal benefit of increasing surveillance efforts decreases as the R_0 increases. The detailed formulation of the detection framework and the numerical analysis are provided in [SI Appendix](#).

Detecting a Novel Variant. We study the time required to detect at least a single case of an emerging/imported variant by randomly sequencing positive cases. We assume the epidemic progression is driven by two-variant dynamics in a scenario similar to the importation of the COVID-19 Delta variant (39). We assume that the novel variant is 60% more infectious than the first variant (i.e., the ratio of the infection likelihoods of the second variant to the first variant is $\beta_2/\beta_1 = 1.6$) and further assume that individuals recovered from the first variant infection exhibit a 75% chance of getting infected with the second variant, but not vice versa (i.e., variant 1 to variant 2 cross-infection $\eta_2 = 0.75$ and, variant 2 to variant 1 cross-infection $\eta_1 = 0$; see [SI Appendix](#) for details). As for the single-variant case, for a given sampling size, a uniform random sampling strategy, and genomic surveillance sequencing a fixed number of positive tests, we determine the minimum prevalence of the imported variant for identification of at least one positive variant-specific case with a target probability. We explore the impact of varying the surveillance and the disease parameters in [SI Appendix](#).

We study the dynamics of the second variant's detection time (τ_d) and dominance time (i.e., the time at which there are more infected by the second variant than by the first variant), by varying the second variant's importation time (τ_{imp}), the first variant's basic reproductive number (R_0), and its cross infection level (η_2). Furthermore, we do not explicitly model the stochastic extinction of the second variant's contagion process, i.e., we assume the necessary conditions to sustain it around (τ_{imp}). Fig. 2A shows the time from importation to detection (*Left*) and the time from detection to dominance (*Right*), as a function of τ_{imp} . Our simulations show that, for a given surveillance effort, both the detection and the dominance times show maxima as functions of τ_{imp} . In other words, the time from importation to detection is largest (i.e., takes most time to detect) when the

importation of the second variant is camouflaged around the peak of the first variant.

In contrast, lower detection times for the second variant are produced either: During early importation times, producing disease dynamics dominated by the second variant, or, during importation times after the first variant's peak time, producing decoupled infectious processes for each variant.

Fig. 2B, *Left* depicts the detection time (τ_d) as a function of both the importation time (τ_{imp}) and the second variant's cross-infection (η_2). Our results show that low cross-infection levels lead to longer detection times (and vice versa), due to the impact of the partially susceptible pool on the progression of the second variant. Fig. 2B, *Right* shows that, for low values of importation times (when the epidemic is mainly driven by the totally susceptible population), the detection time is unaffected by changes in the cross-infection level. For larger importation times, the detection times increase significantly as the cross-infection levels become smaller. Thus, the detection of the second variant is tied to the variants' competing dynamics, specifically to the second variant cross-infection level. In [SI Appendix](#), we explored different values of the first variant's R_0 and observed similar qualitative features.

Response after Novel Variant's Detection

NPIs constitute a suite of front-line responses aimed to reduce individuals' likelihood of infection. However, their deployment depends on the identification of an imminent threat. We study the impact of two intervention regimes, single-period and adaptive NPIs. For single-period NPIs, we focus on three parameters: i) strength given by the reduction of the β_i to a lower constant value (29), ii) duration, and iii) starting time of the intervention, also called the intervention time. We then study the detection-response tradeoff by tying the intervention time to the detection of the imported variant. We focus on three intervention goals: i) minimizing the second variant peak size, ii) minimizing the total prevalence (both variants) peak, and iii) minimizing the overall cumulative cases; our simulations show that the best intervention, defined in terms of starting time and strength, depends on the specific goal.

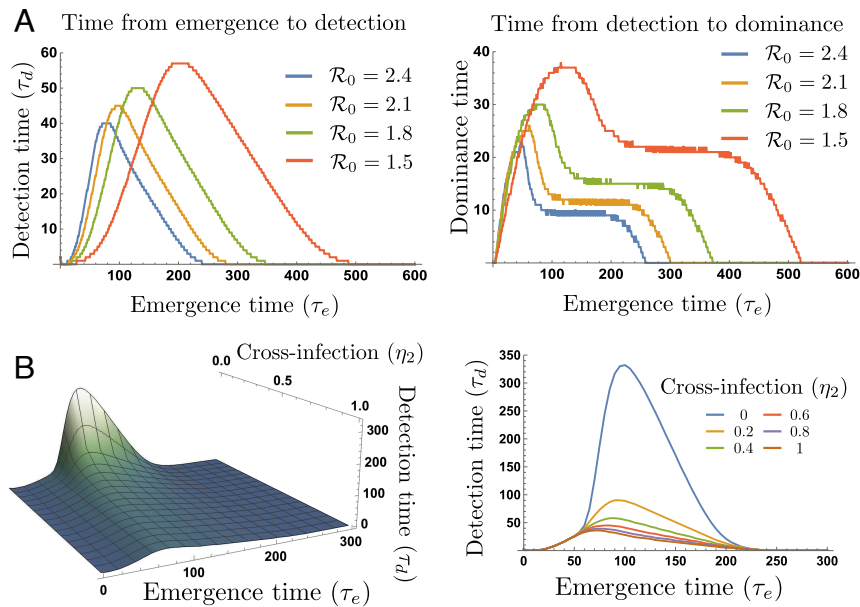


Fig. 2. The impact of the importation time on the second variant detection and dominance times. The second variant's detection and dominance times show a maximum as a function of the importation time (τ_{imp}), panel A. Cross-infection (η_2), impacts the second variant's detection time for intermediate and delayed importation times, but not for early importation times, panel B. We assume 60% infectiousness advantage for the second variant, one-way cross-immunity ($\eta_2 = 0.75$ and $\eta_1 = 0$), 90 sequences per week, and first variant's basic reproductive number $\mathcal{R}_0 = 2.4$.

Minimizing the Second Variant's Peak Size. One of the critical public health intervention goals is to avoid health-care system collapse, for example, by "flattening the curve" which helps lower the mortality. First, we study single-period interventions aimed to minimize exclusively the second variant's peak size. Our simulations yield the following insights: i) early and strong single-period interventions are not always the best, since these

may increase the second variant's peak size, relative to the no-intervention scenario (Fig. 3A); ii) delayed and intermediate strong interventions minimize the second variant's peak size (*SI Appendix, Figs. S23 and S25*); iii) for intermediate and late importation times (i.e., large τ_{imp} relative to the first variant's peak time), the best intervention strength depends on the second variant's cross-infection, while there is not much variation in the

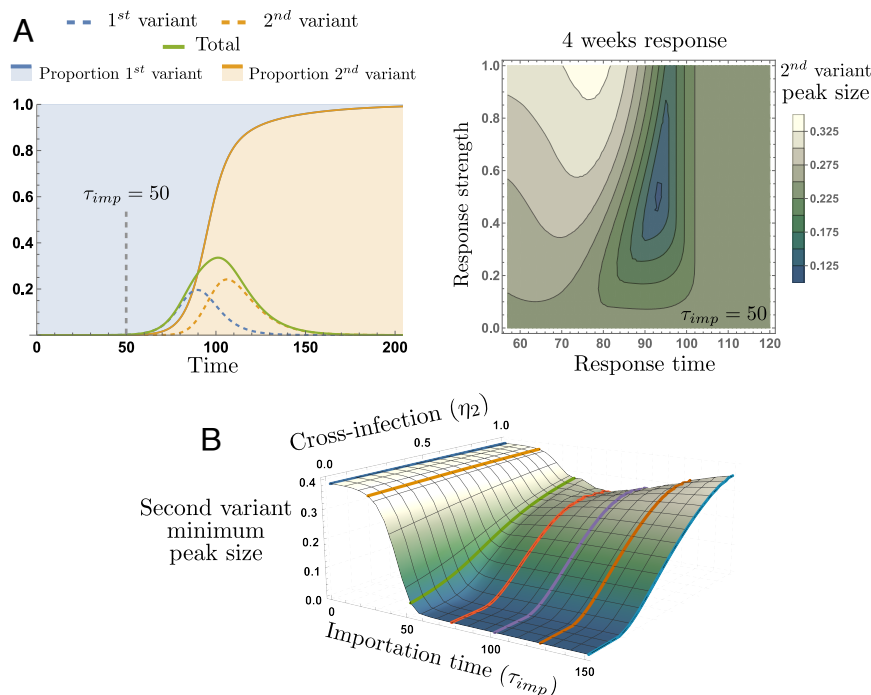


Fig. 3. Second variant's peak size as a function of the response time, the response strength, and the cross-infection level. Early and strong single-period responses increase the second variant peak size; in counterpart, delayed and intermediate response strengths are best (panel A). The biggest reduction of the second variant's peak size is attained for importation times near the first variant's peak time (panel B). We assume the second variant's importation times $\tau_{imp} = 50$ and $\tau_{imp} = 70$, first variant's $\mathcal{R}_0 = 2.4$, one-way cross-infection, where $\eta_1 = 0$ and $\eta_2 = 0.75$, and 4 wks' intervention length.

second variant's peak at early importation times as the cross-infection values change (Fig. 3B).

We explore the intervention landscape by assuming the earliest intervention can be deployed a week after the importation of the second variant. Note that, this would require extremely high surveillance and sequencing levels. Specifically, we study the single-period best intervention strategy in terms of intervention times and strengths, for a 4-wk intervention duration. We explore the effect of changes in the interventions' length in [SI Appendix](#). Fig. 3A, Right shows that for $\tau_{imp} = 50$, the best intervention time and strength are approximately (92 d and 0.5, respectively). Moreover, Fig. 3B shows that, for any fixed cross-infection value, importation times close to the first variant's peak time yield the biggest reduction in the second variant's peak size.

Our simulations show that early single-period interventions ameliorate the impact of the first variant and delay the growth of the second variant; however, the replenishment of the partially susceptible population boosts the second variant's peak size. Consequently, for single-period interventions, the minimum second variant's peak sizes are attained in scenarios of delayed interventions of intermediate strength. Moreover, we found that adaptive NPIs also minimize the second variant's peak size at intermediate strength ([SI Appendix](#)). Our results are consistent with the recent work by Bjornstad, who coined the so-called S^* theory of strains dominance and suggested that the competing dynamics between an established variant and an invading one follow analogous dynamics than those of Tilman's R^* theory of resource-based competition of free-living organisms (40, 41). The underlying idea of this theory relies on the impact of a variant to deplete the susceptible pool, consequently modulating the invasion (persistence) conditions of novel (established) variants. In summary, the benefit of early detection attained with high surveillance levels is that it provides time for planning the starting time and identifying the strength of the best intervention.

Minimizing the Total Disease Prevalence (Both Variants). We now focus on the impact of single-period interventions on minimizing the overall disease prevalence. Fig. 4A shows that for early importation times, the second variant dominates, thereby reducing the problem to minimizing the second variant's peak size, where delayed responses of intermediate strength are best. In counterpart, Fig. 4B shows that for delayed importation times, the variants' dynamics decouple, thereby reducing the problem to timing the intervention and choosing its strength to equalize the two variants' peak sizes. Interestingly, as the second variant's importation is delayed, the required intervention's strength decreases. For the parameters chosen, the second variant's peak is larger than the first variant's peak for all importation times; it follows that the best intervention time is close to the second variant's peak time (see [SI Appendix](#), Fig. S28 for scenarios of different importation times and varying intervention's duration).

Further simulations in [SI Appendix](#) show that for adaptive NPIs, also intermediate strong interventions minimize the total prevalence, ([SI Appendix](#), Fig. S32). Our results on the impact of adaptive NPIs stress the importance of continuous surveillance and interventions that restrain high prevalence levels and effectively prevent epidemic's revival.

Minimizing the Total Cumulative Cases (Regardless of the Variant). Despite the genomic composition of an epidemic, reducing the total number of cases or the final epidemic size is another important objective which we study in this section. Similar to our previous analysis, we assume the earliest intervention is deployed a week after the novel variant is imported. Fig. 5A shows the scenario where the second variant is imported at time $\tau_{imp} = 70$. Our simulations show that, for early importation, quick and strong interventions produce a higher reduction of the first variant's cases relative to the reduction of the second variant's cases, ([SI Appendix](#), Fig. S24). Consequently, for importation times before the first variant's peak time, the minimum of

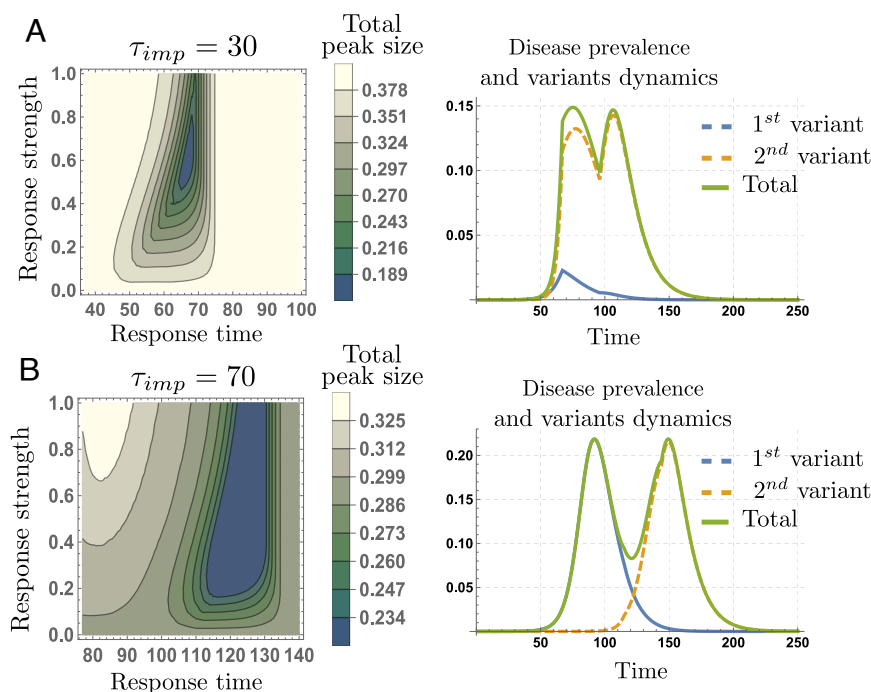


Fig. 4. Total disease prevalence as a function of the response time and response strength. Early importation produces coupled dynamics and, the best response time is delayed until the second variant overcomes the first variant (A). Delayed importation produces decoupled dynamics, and the best response time is delayed until the second variant exponentially grows (B).

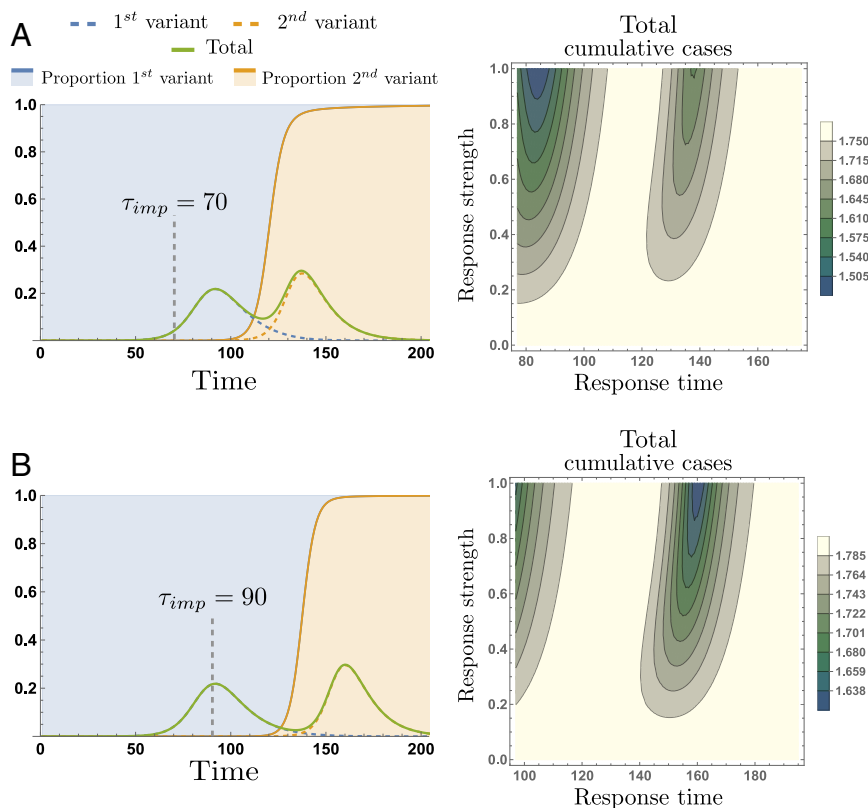


Fig. 5. Total cumulative cases as a function of the response time and response strength. For the scenarios of the second variant being imported before the peak time of the first variant, interventions targeting the cumulative cases of the first variant minimize the total number of cases (A). For these scenarios, quick and strong single-period responses are best. In counterpart, for scenarios of the second variant importation during or after the first variant's peak time, interventions targeting the cumulative cases of the second variant minimize the total number of cases (B). For these scenarios, delayed and strong single-period responses are best.

cumulative cases is attained by early and strong interventions, which aim to control the propagation of the first variant.

In contrast, Fig. 5B shows the scenario where the second variant is imported during the first variant's peak time, i.e., $\tau_{imp} = 90$. In this scenario, the major reduction of cases is attained by delayed and strong single-period interventions, targeting the cases generated by the second variant, (*SI Appendix, Fig. S24*).

In summary, the best single-period interventions that minimize the cumulative cases depend on the second variant's importation time: i) Early interventions are best for early importation times of the second variant, and ii) delayed interventions are best for delayed importation times of the second variant. The intuition of implementing early interventions for early importation scenarios is that, even when the second variant is more infectious than the first variant, preventing first variant's cases reduces reinfections, which are counted twice in the cumulative case count.

Conclusions

The COVID-19 pandemic highlighted the role of early detection of novel variants and appropriately designed public-health interventions. Real-world intervention scenarios also depend on potential delays that may arise from implementation logistics. While we have assumed a one 2-wk delay between the detection time and the intervention time, our framework models a realistic course of action that leads to different best intervention scenarios in terms of the intervention's type, timing, and strength.

In our proposed framework, we have studied the interplay between the competing dynamics of two simultaneously circulating variants (based on their relative infectiousness, the second variant's importation time, cross-infection levels), the dynamics of detection times, and potential interventions. We found that early and strong single-period public health interventions are not the best to minimize uniformly all the fundamental objectives such as the second variant's peak size, the total prevalence of the disease, and the cumulative cases. From a public health perspective, if minimizing the peak size of the second variant or the total prevalence is of importance, then our results recommend delayed interventions, i.e., the intervention time should be calibrated to the beginning of the second variant's exponential phase (Table 1 and *SI Appendix, Figs. S27 and S28*). On the contrary, if control of the total cumulative cases is of importance, then the best intervention depends on the second variant's importation time. If this is around the first variant's peak, then early and strong interventions are recommended. Alternatively, if it is before or after the first variant's peak, then a strong intervention starting at the beginning of the second variant's exponential phase is recommended (Table 1 and *SI Appendix, Fig. S29*). The diverse best intervention scenarios emphasize the benefit of early detection attained with high surveillance levels, which provides time for planning the starting time and identifying the strength of the best intervention.

Tracking infection counts alone might not be sufficient to assess public health interventions and one must take into account hospitalization rates and mortality as well. Moreover, the epidemiological and operational uncertainties posed by different

Table 1. Intervention scenarios and policy insights

Intervention goal	Best intervention time & strength	Policy insights
Minimizing the second variant peak size	Delayed interventions with intermediate strength are best Quick strong interventions lead to worst-case scenarios	Early detection allows longer planning periods Delayed and intermediate strong interventions are best
Minimizing the total peak size	Delayed interventions with intermediate strength are best The later the importation time, the lower the intervention's strength required	Intermediate interventions are always best Delayed interventions are best for importation before the first variant's peak time Very delayed interventions are best for importation around the first variant's peak time
Minimizing the total cumulative cases	For importation times before the first variant peak time, early and strong interventions are best For importation times during or after the first variant peak time, delayed and strong interventions are best	Strong interventions are always best Depending on the second variant's importation time, early or very delayed interventions are best

intervention types and the decision-making process should also be considered (42, 43). In our framework, the single-period interventions focus solely on lowering the effective transmission and have fixed duration. Other pulsed interventions as well as informed pharmaceutical interventions should be considered. Our analysis of the best intervention targeting the fundamental objectives is extended in *SI Appendix* by incorporating adaptive NPIs. Our results for adaptive NPIs stress the impact of continuously enforced interventions on preventing high disease burden and avoiding epidemic revival due to the importation or emergence of novel variants.

Furthermore, we extend our modeling framework in *SI Appendix* by incorporating a simple model of evolution. We aim to study the interplay between the disease dynamics, the evolution model, and the impact of adaptive NPIs on the fundamental goals. Preliminary results show that the role of interventions goes beyond the reduction of infections, since the reduction of first variant's cases may delay or prevent the emergence of a novel variant, thus impacting the subsequent detection and intervention scenarios. In this work, we do not consider the costs of different surveillance levels, sequencing capacities, response implementations, severity of the disease, or its variability across variants. In reality, the relative emergence or importation time of a novel variant is not known. Perhaps, known mutation rates and mobility data can be used to estimate the emergence or importation time of a novel variant. Characterization of the competing variant's dynamics in the absence/presence of different types of interventions is critical as the epidemiological consequences of different emergence/importation times vary. Studying epidemic dynamics given an ongoing epidemic state and a novel variant's characterization may help elucidate potential intervention scenarios, their associated efficacy, and potential evolutionary consequences. We plan to explore some of these aspects in future work.

Data, Materials, and Software Availability. All study data are included in the article and/or *SI Appendix*.

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Author affiliations: ^aNetwork Systems Science and Advanced Computing Division, Biocomplexity Institute, University of Virginia, Charlottesville, VA 22904; ^bDepartment of Computer Science, University of Virginia, Charlottesville, VA 22904; ^cIndian Statistical Institute, Bengaluru, Karnataka 560059, India; ^dInternational Centre for Theoretical Sciences, Bengaluru, Karnataka 560089, India; ^eDepartment of Electrical and Communication Engineering, Indian Institute of Science, Bengaluru, Karnataka 560012, India; ^fRobert Bosch Centre for Cyber-Physical Systems, Indian Institute of Science, Bengaluru, Karnataka 560012, India; ^gCentre for Networked Intelligence, Indian Institute of Science, Bengaluru, Karnataka 560012, India; ^hStrand Life Sciences, Bengaluru, Karnataka 560024, India; ⁱBioSystems Science and Engineering, Indian Institute of Science, Bengaluru, Karnataka 560012, India; ^jPrinceton University, Princeton, NJ 08542; ^kOne Health Trust, Washington, DC 20015; ^lDepartment of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544; and ^mDepartment of Electrical and Computer Engineering, Princeton University, Princeton, NJ 08544

Author contributions: B.E. designed research, developed and implemented the mathematical models; A.A., A.S.W., H.V.P., S.A.L., and M.V.M. designed the study, developed the models and analyzed the results; S.V., J.C., B.L.L., A.V., S.S., S.M., C.L.B., S.A., R.S., V.C., R.L., and B.S. contributed new analytic tools; and all authors wrote the paper.

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