The interplay between genomic surveillance and public health interventions

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Office of Health Affairs
National Biosurveillance Integration Center

https://biocomplexity.virginia.edu/

Joint work with:

Aniruddha Adiga, Srinivasan Venkatramanan, Andrew Scott Warren, Jiangzhuo Chen, Bryan Leroy Lewis, Anil Vullikanti, Samarth Swarup, Sifat Moon, Christopher Louis Barrett, Siva Athreya, Rajesh Sundaresan, Vijay Chandru, Ramanan Laxminarayan, Benjamin Schaffer, H. Vincent Poor, Simon A. Levin.

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VDH VIRGINIA DEPARTMENT OF HEALTH

NIH National Institutes of Health

NSF

DEPARTMENT OF DEFENSE UNITED STATES OF AMERICA

CDC

Biocomplexity Institute's Approach: TRANSDISCIPLINARY TEAM SCIENCE

Can informatics tools be developed to aid design and analysis of actionable policies pertaining to complex <u>STIO (social, informational, technical and organizational)</u> systems, e.g. sustainable habitats, pandemics, global conflicts?

- Undertake problems that cannot be solved by a single faculty member or within the narrow boundaries of a discipline

- Application-driven science and engineering: work on problems that are motivated by real-life applications

- This paradigm produces fundamental advances

- These problems require *sophisticated tools and diverse intellectual resources*, making them impossible to solve within the narrow confines of a single discipline or by a few individuals

complex system
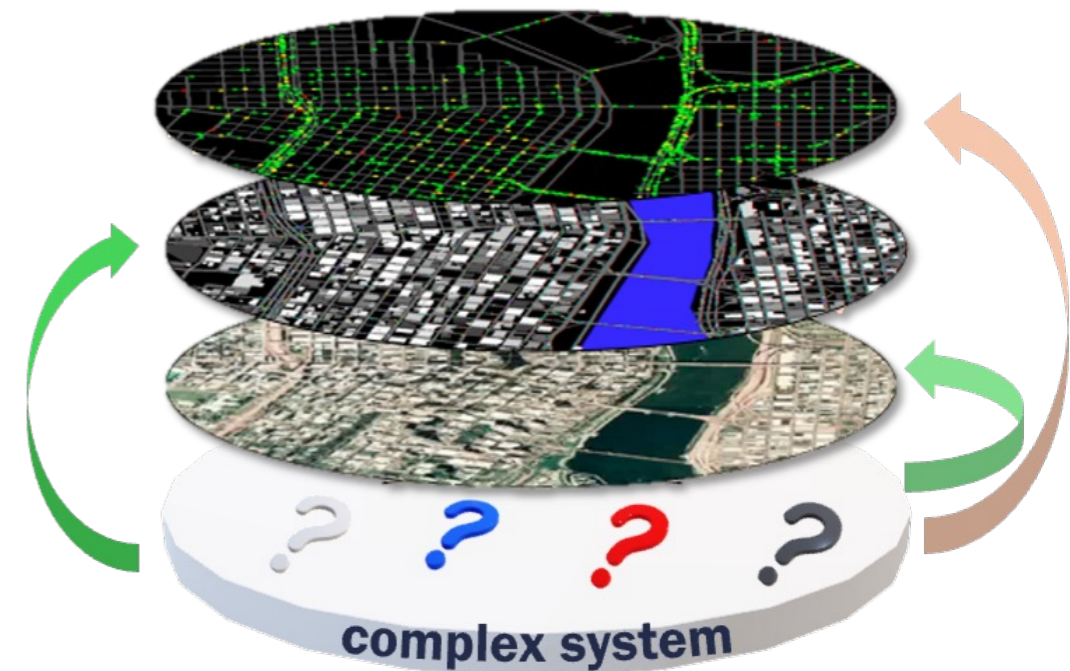
Real-time Comprehensive Analytics For Pandemic Response

FEDERAL LEVEL

STATE & LOCAL LEVEL

Participation in CDC-coordinated hubs for forecasting and scenario-based projections

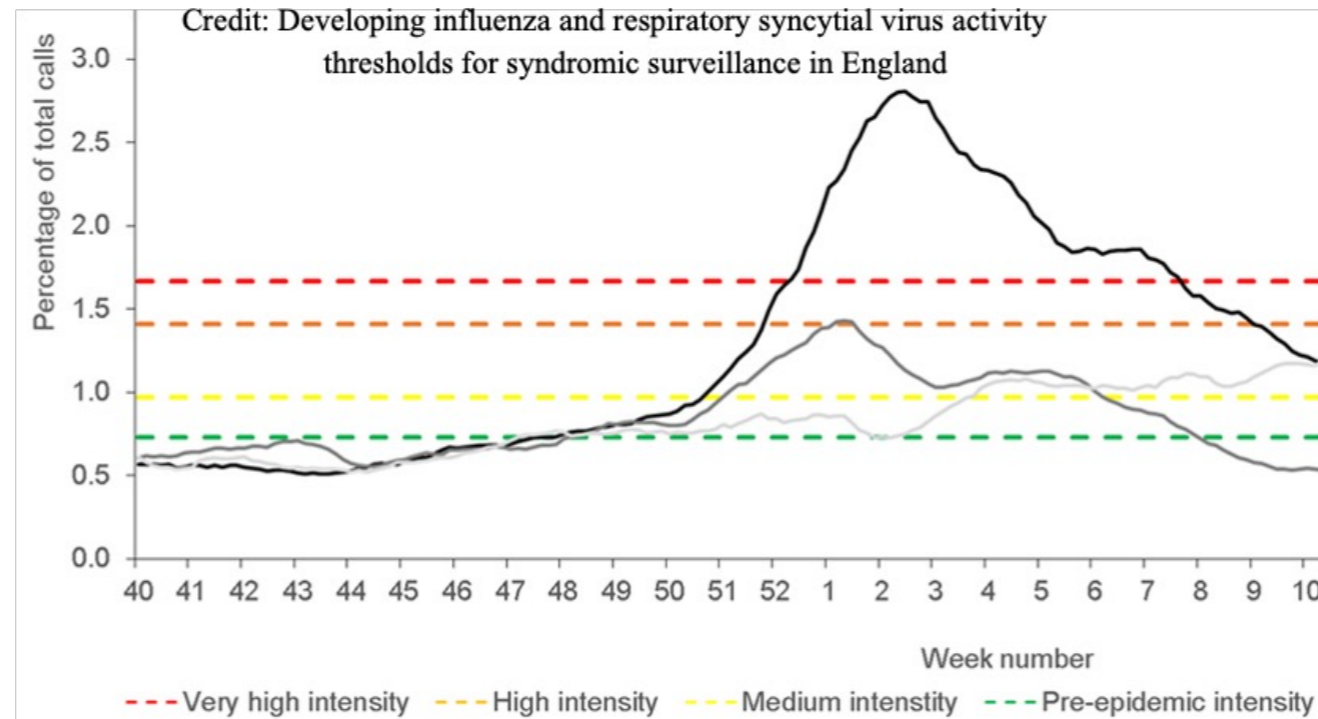**Weekly projections and bespoke modeling for federal partners**

Multiple presentations and data deliveries each week from spring 2020 - present

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Challenges of classic disease surveillance systems

Classic surveillance relies on fixed thresholds - a static problem approach

Disease surveillance and response is a dynamic problem and depends on multiple factors:

- Surveillance effort: number of samples, resource allocation, test accuracy

- The disease ecology: pathogen's infectiousness, host immunity, virus evolution

- Population's structure: size and density, age distribution, activity patterns

G. Shmueli, H. Burkom, Statistical challenges facing early outbreak detection in biosurveillance. *Technometrics* 52, 39–51 (2010).
J. D. Robishaw et al., Genomic surveillance to combat COVID-19: Challenges and opportunities. *Lancet Microbe* 2, e481–e484 (2021).

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Challenges of classic disease surveillance systems

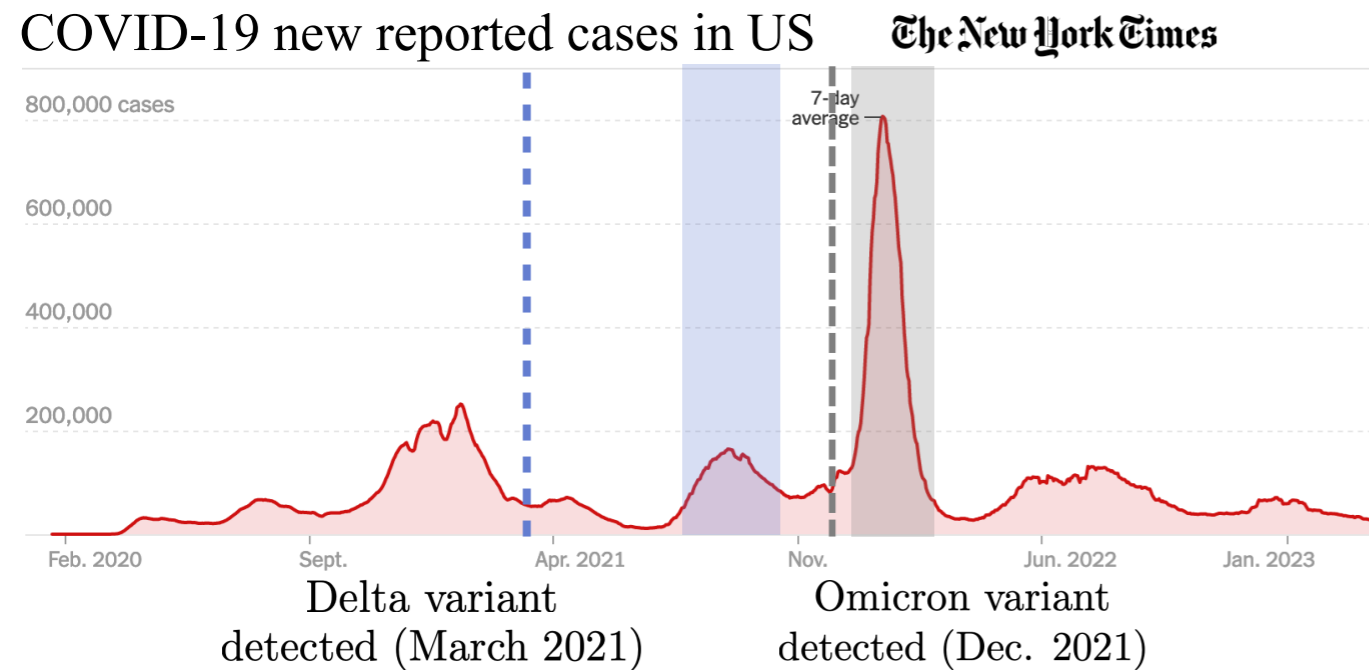## The basic reproductive number

$$\mathcal{R}_0$$ determines the outbreak's propagation speed and intensity

Disease prevalence
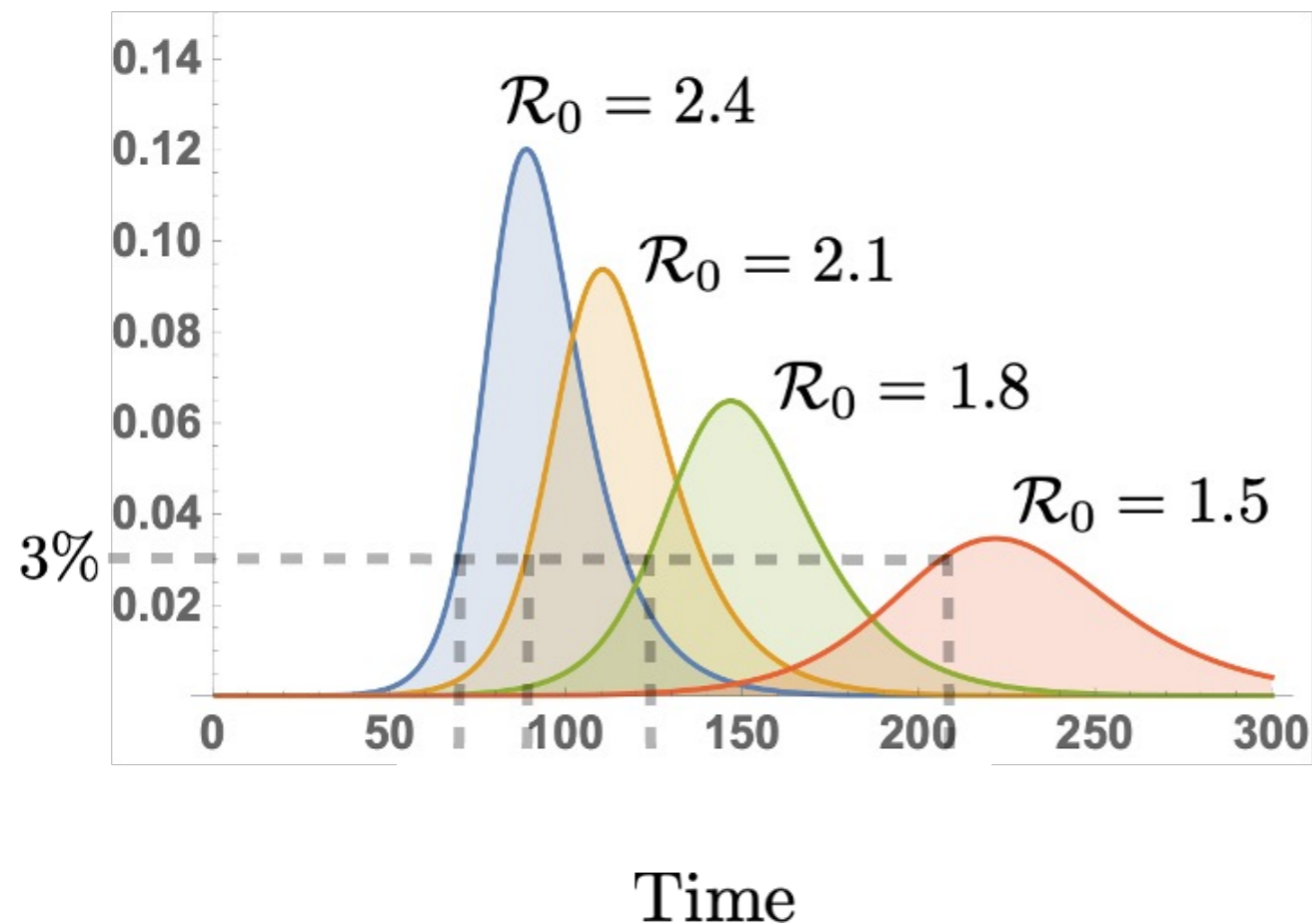
Time

- Diseases with high $\mathcal{R}_0$ are detected earlier but there is less time to respond.

- High $\mathcal{R}_0$ leads to lower marginal benefits of increasing sampling size.
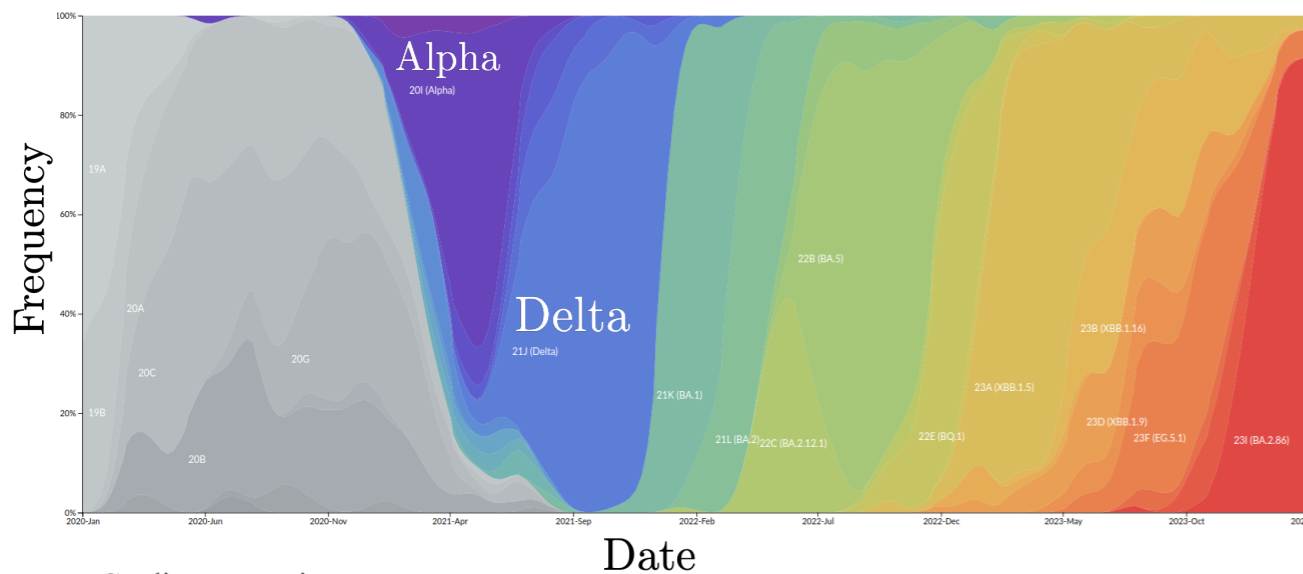
Genomic epidemiology

COVID-19 new reported cases in US   The New York Times

Delta variant detected (March 2021)

Omicron variant detected (Dec. 2021)

COVID-19 variants in North America

Credit: nextstrain.org

Variants' dominance time in the US*

Delta
　　within 7-13 weeks after detection

Omicron
　　within 4-6 weeks after detection

How do different variant's importation conditions shape epi-genomic dynamics?

How fast can we detect:
- an outbreak?
- a novel variant?

How do intervention effects depend on the variant's competing dynamics?

*Chan Y, Irvine MA, Prystajecky N, Sbihi H, Taylor M, Joffres Y, et al. Emergence of SARS-CoV-2 Delta Variant and Effect of Nonpharmaceutical Interventions, British Columbia, Canada. Emerg Infect Dis. 2023;29(10):1999-2007. https://doi.org/10.3201/eid2910.230055

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Multi-theory computational modeling framework

- Multi-variant disease dynamics

- Disease and genomic surveillance

- Interventions strategies
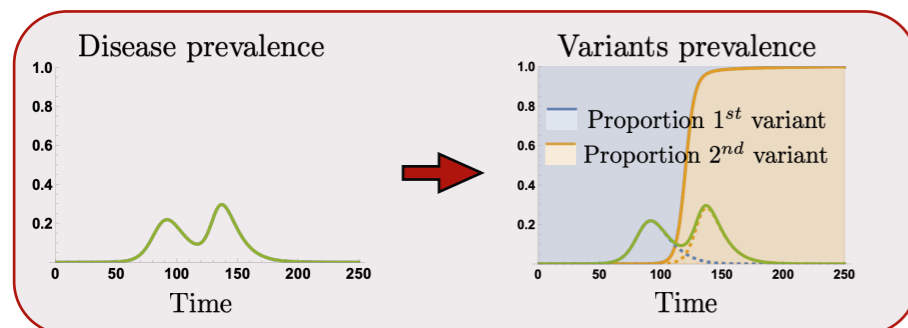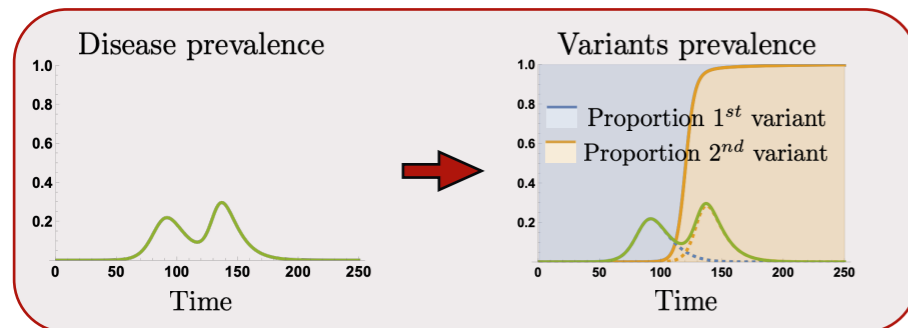
Multi-theory computational modeling framework

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

Baltazar Espinoza ✉, Aniruddha Adiga, Srinivasan Venkatramanan, +14, and Madhav V. Marathe ✉ Authors Info &

A modeling framework integrating:

- multi-variant disease dynamics

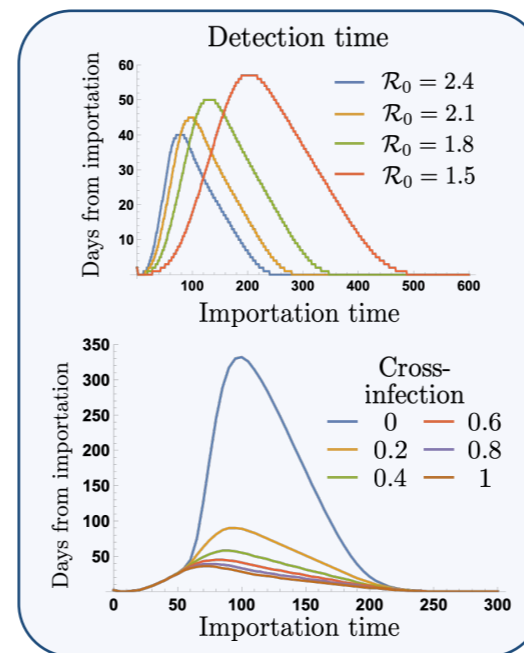- disease and genomic surveillance

- intervention strategies

Outbreak & variant detection

Testing   Sequencing

Multi-theory computational modeling framework

PNAS

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

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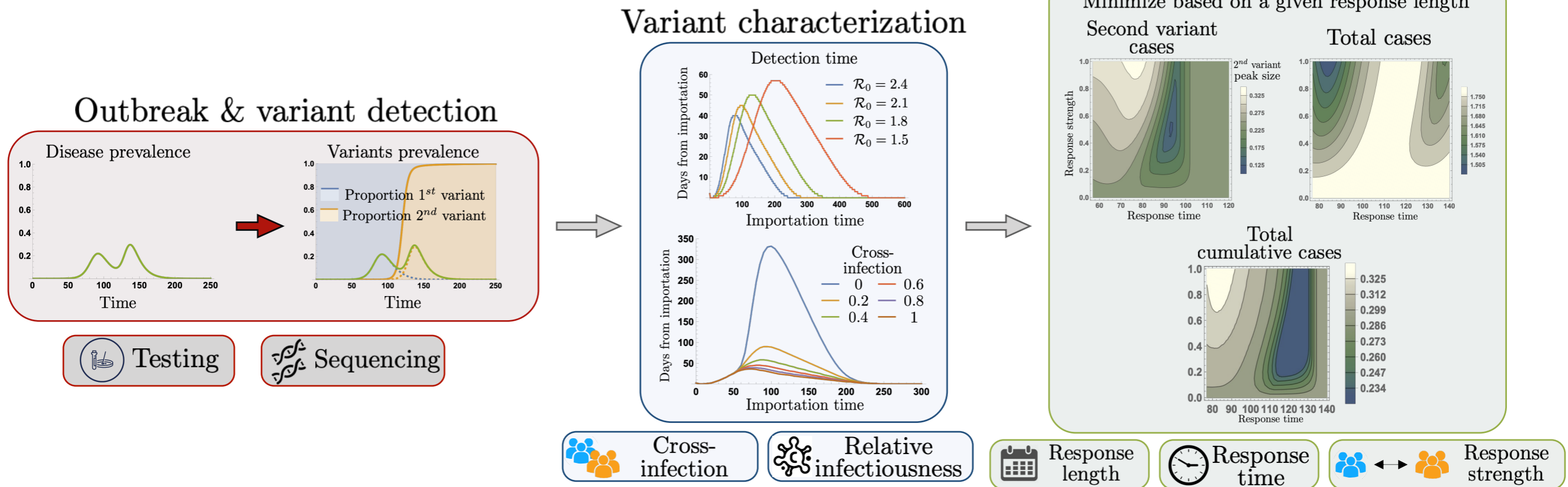
A realistic course of action based on sequencing, analysis, and response

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Key policy insights

- Effective responses requires to characterize the genomic landscape

- Depending on the target metric different intervention scenarios lead to better outcomes

- Robust surveillance systems allow to study multiple intervention scenarios

- Sustained interventions suppress potential epidemic revival

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Key scientific insights

- Multi-variant competing dynamics inherently limit:

    - Novel variant's detection   - Intervention effectiveness

- Novel variant's detection could be delayed by:

    - co-circulating variants   - importation time

- Cross-infection levels do not impact the detection
  time of early imported variants

Multi-variant model

$$S \xrightarrow{\beta} I \xrightarrow{\gamma} R$$

$[t_{start}, t_{imp}]$
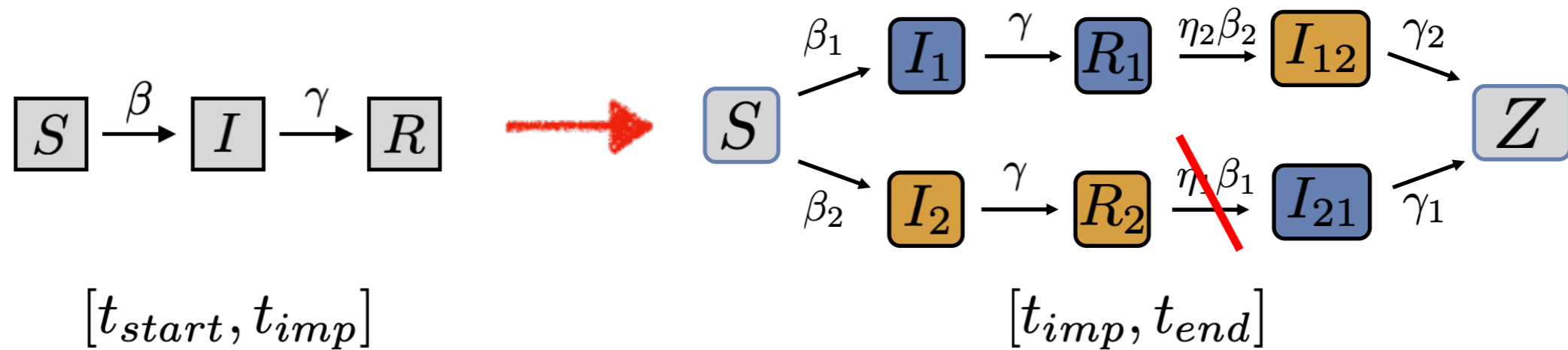
τ_{imp} - novel variant's importation time

New variant's characteristics
similar to Delta importation

$$\mathcal{R}_0 = 2.4 \qquad \beta_2/\beta_1 = 1.6$$

Linear cross-immunity scheme
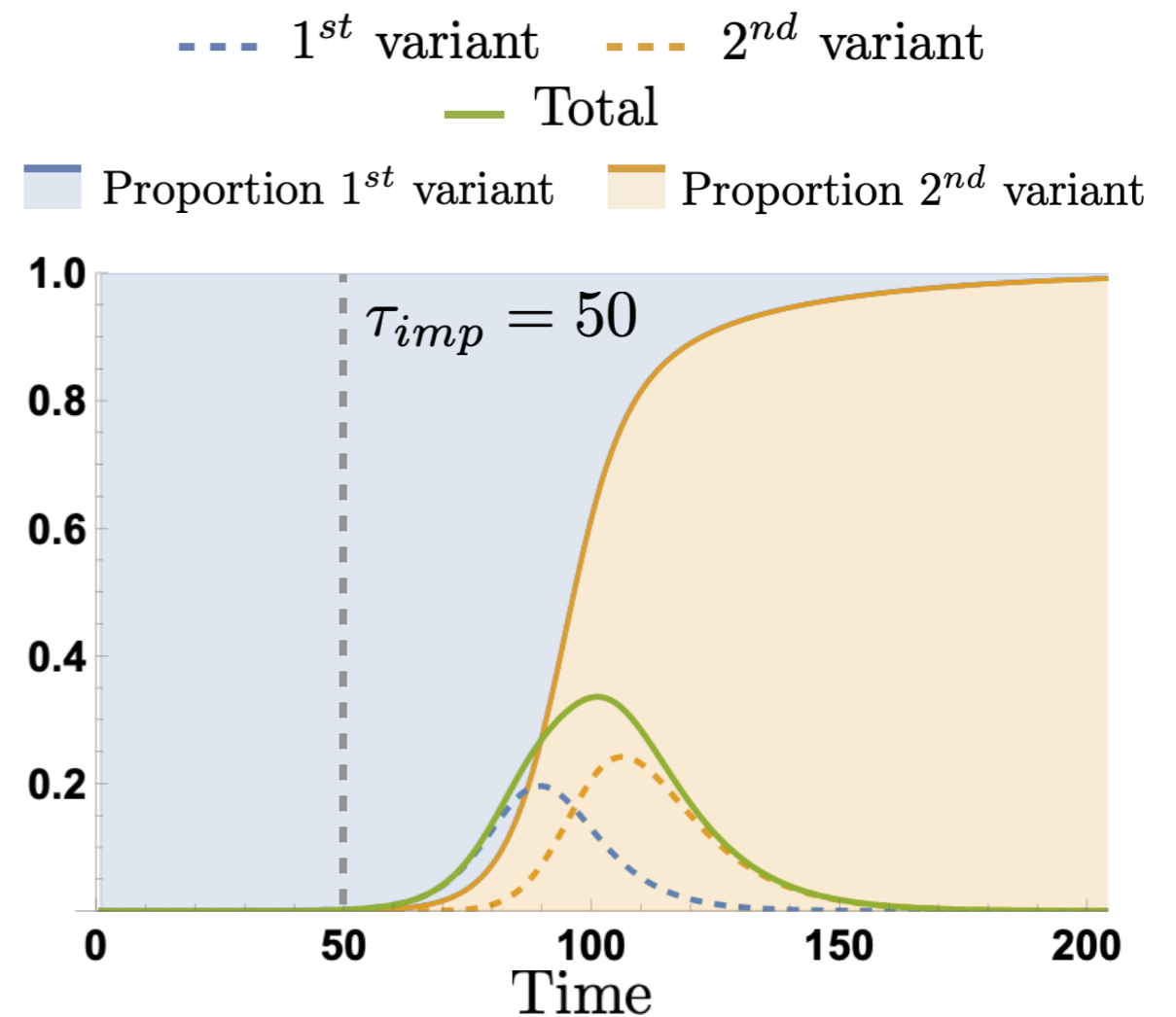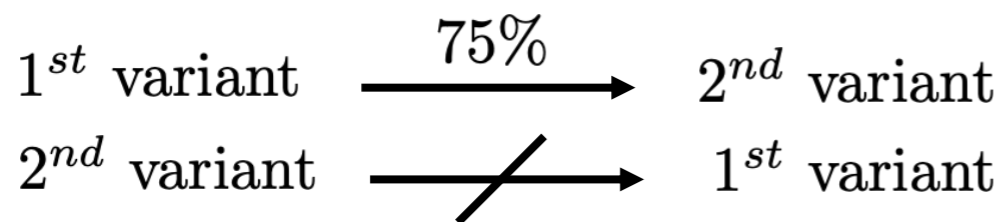
1st variant $\xrightarrow{75\%}$ 2nd variant

2nd variant $\xrightarrow{\quad\quad}$ 1st variant

$\tau_{imp} = 50$

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Variant's competing dynamics
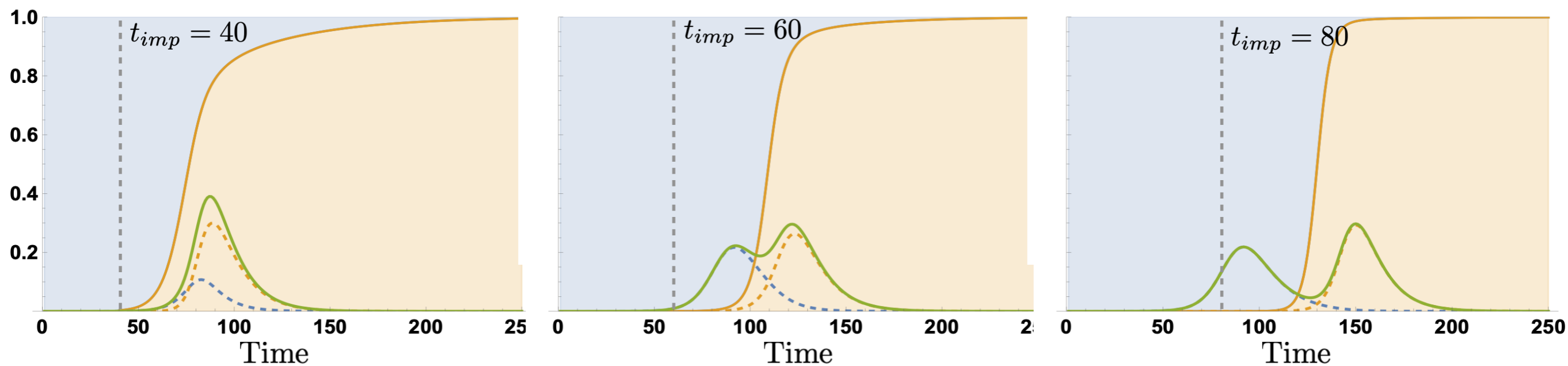
Disease and variants dynamics are highly sensitive to importation conditions:

- Importation time
- Relative infectiousness
- Cross-immunity

Novel variant's detection

- Imported variants: population mobility

- Emerging variants: evolutionary processes
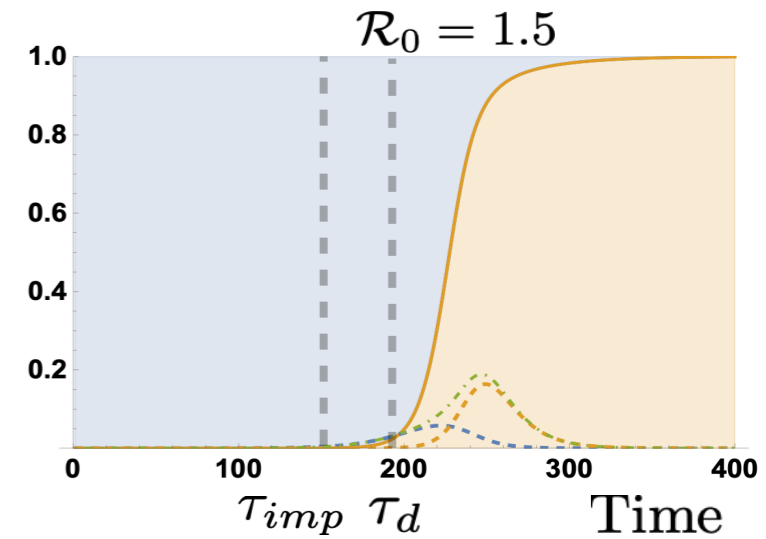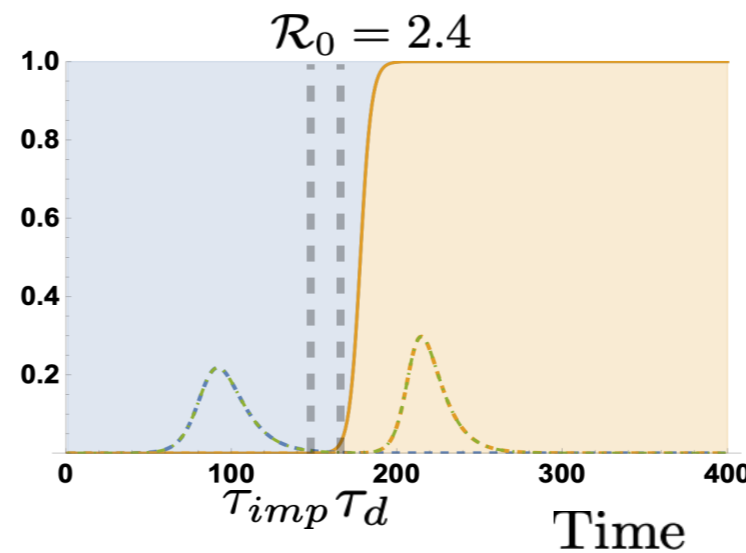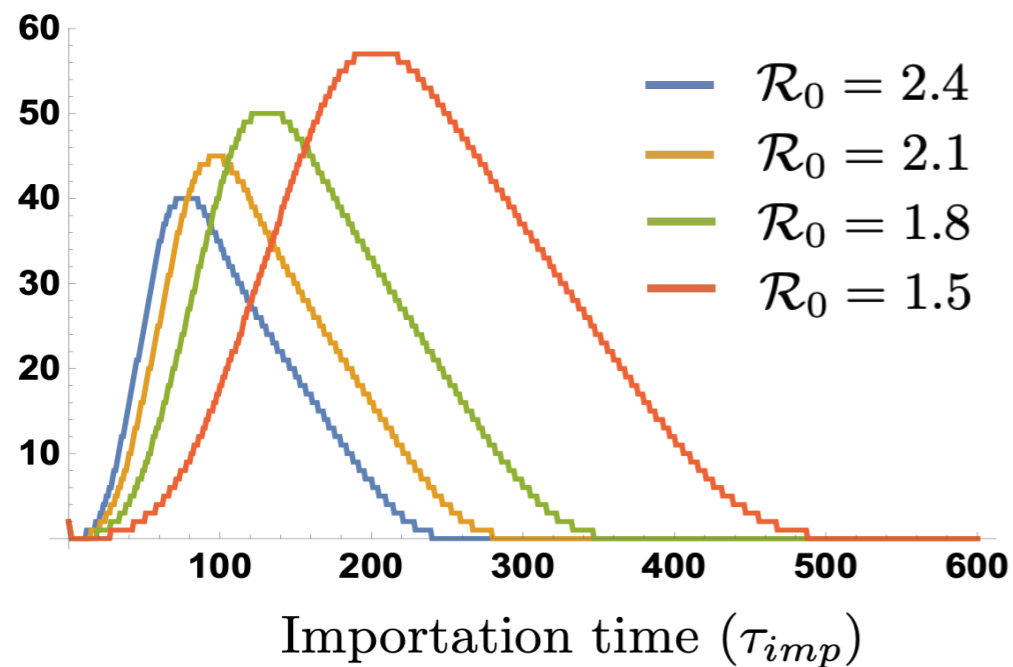
Novel variant's detection trade-offs

$$\beta_2/\beta_1 = 1.6 \qquad \tau_{imp} = 150$$

1st variant $\xrightarrow{75\%}$ 2nd variant

2nd variant $\xrightarrow{\quad\not\quad}$ 1st variant
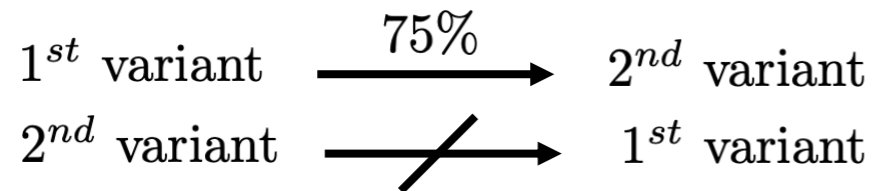
τ_{imp} - novel variant's importation time

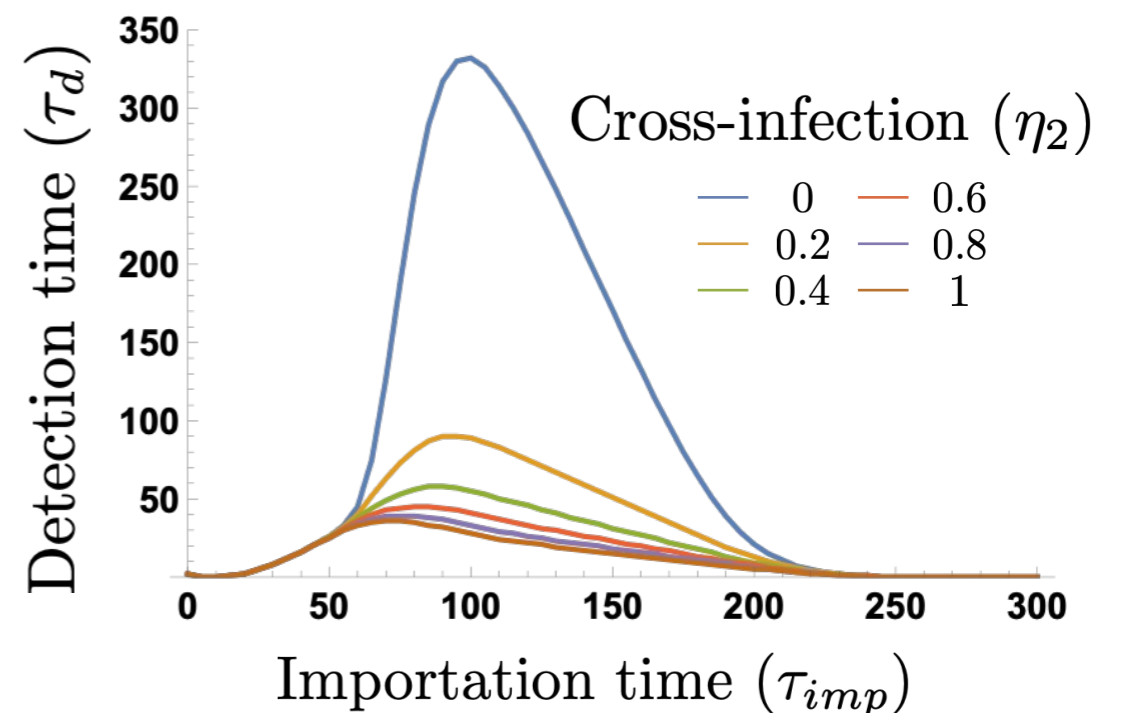τ_d - novel variant's detection time

Time from importation to detection

$\mathcal{R}_0 = 2.4$
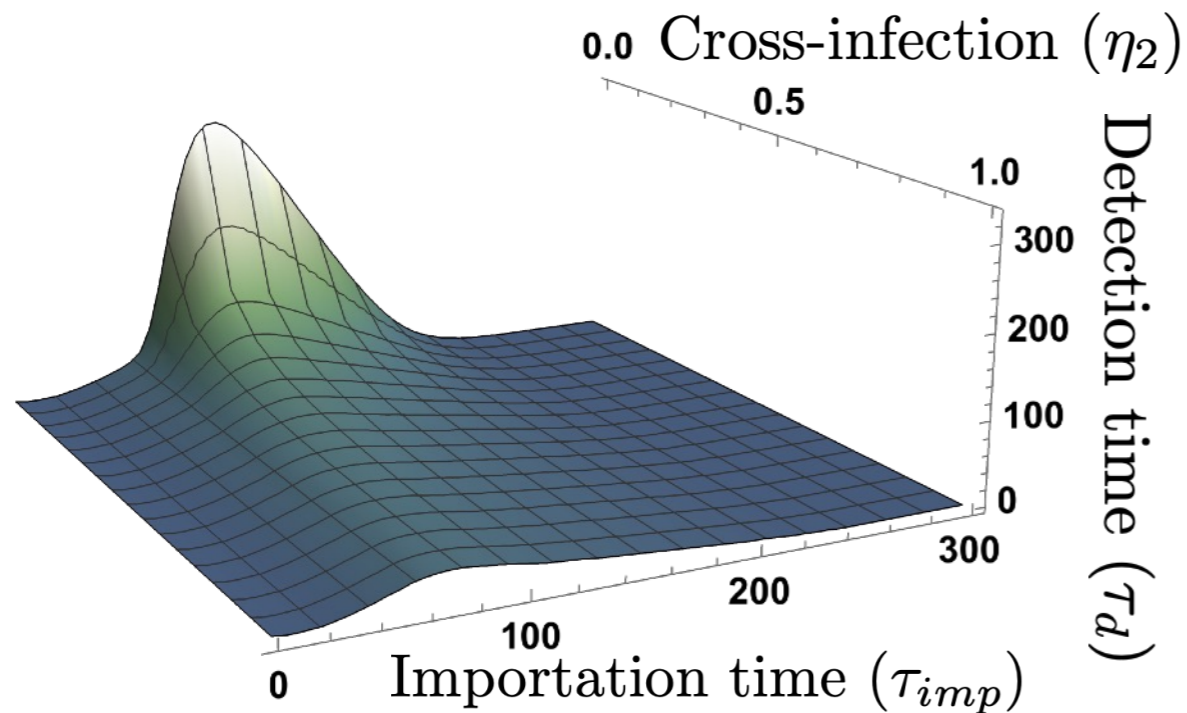$\mathcal{R}_0 = 2.1$
$\mathcal{R}_0 = 1.8$
$\mathcal{R}_0 = 1.5$

Importation time (τ_{imp})

$\mathcal{R}_0 = 2.4$

$\tau_{imp}\tau_d$ Time

$\mathcal{R}_0 = 1.5$

τ_{imp} τ_d Time

A trade-off between

- the disease's propagation speed (Ro)

- the novel variant's importation time

Novel variant's detection sensitivity

The detection time depends on the varying cross-infection and importation times

- **Detection times are not sensitive to cross-infection for 'early' importation times.**

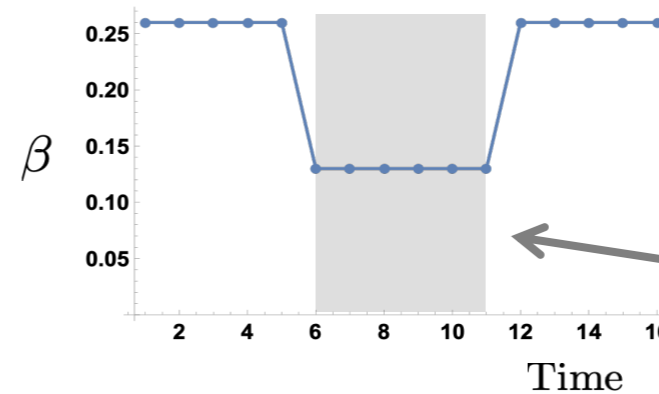- **Low cross-infection values delay detection times.**

Response after novel variant's detection

Response after novel variant's detection

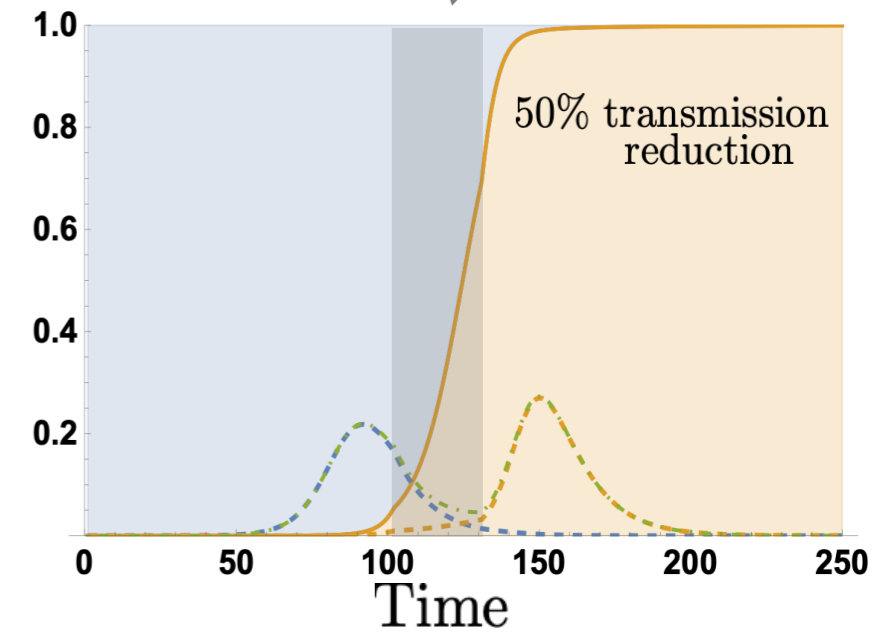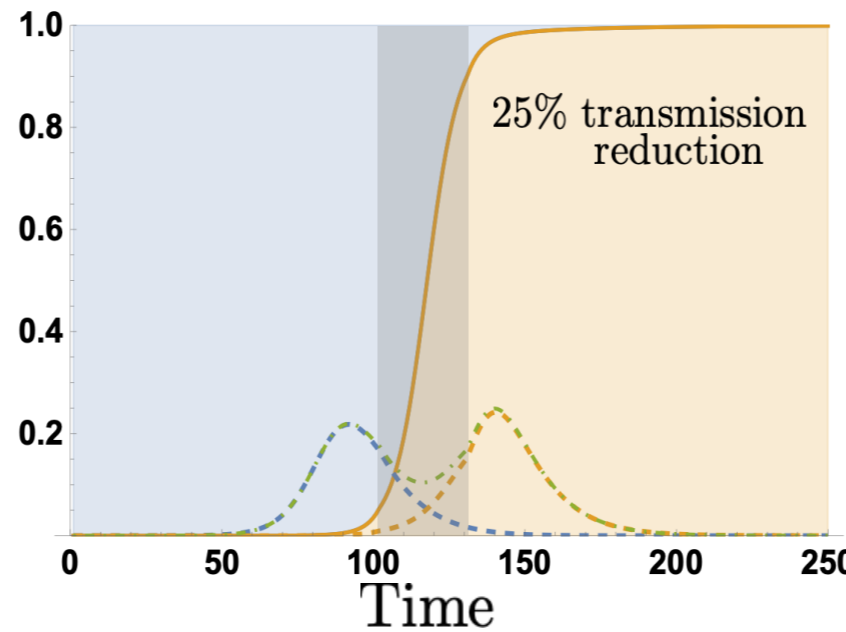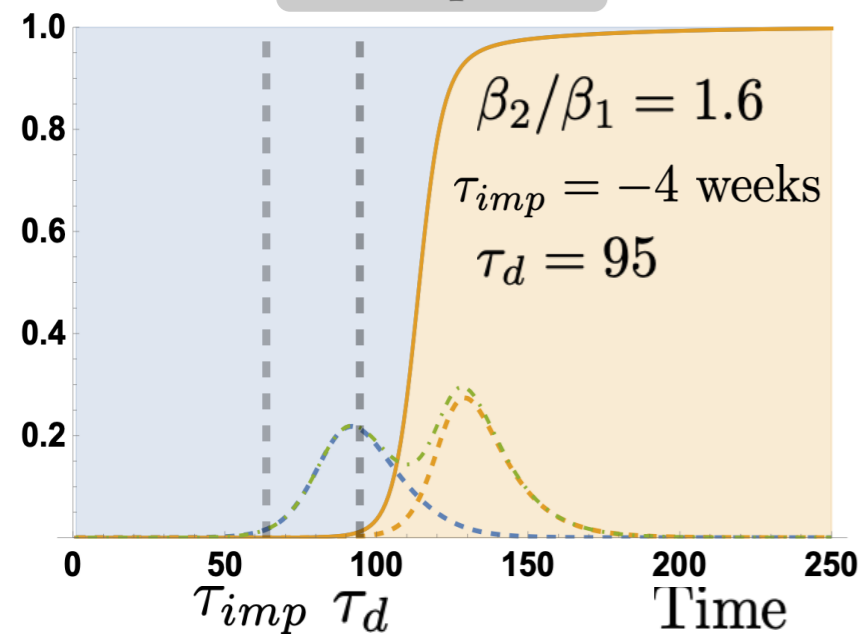Interventions temporarily reduce the infection likelihood

Intervention period

τ_{imp} - novel variant's importation time

τ_d - novel variant's detection time

Response delay = 1 week
Response duration = 4 weeks

No response

$\beta_2/\beta_1 = 1.6$

$\tau_{imp} = -4$ weeks

$\tau_d = 95$

τ_{imp} τ_d

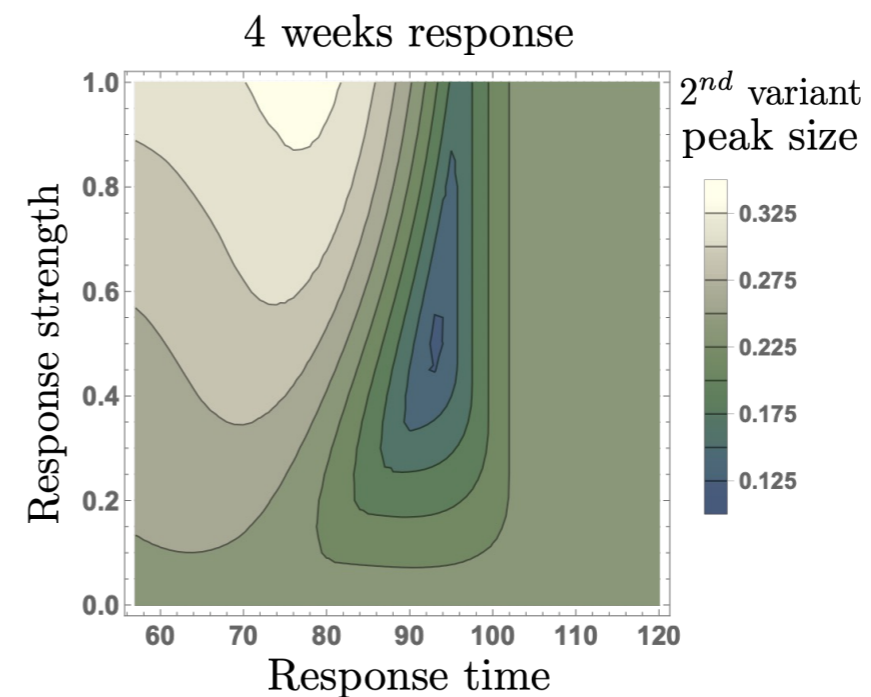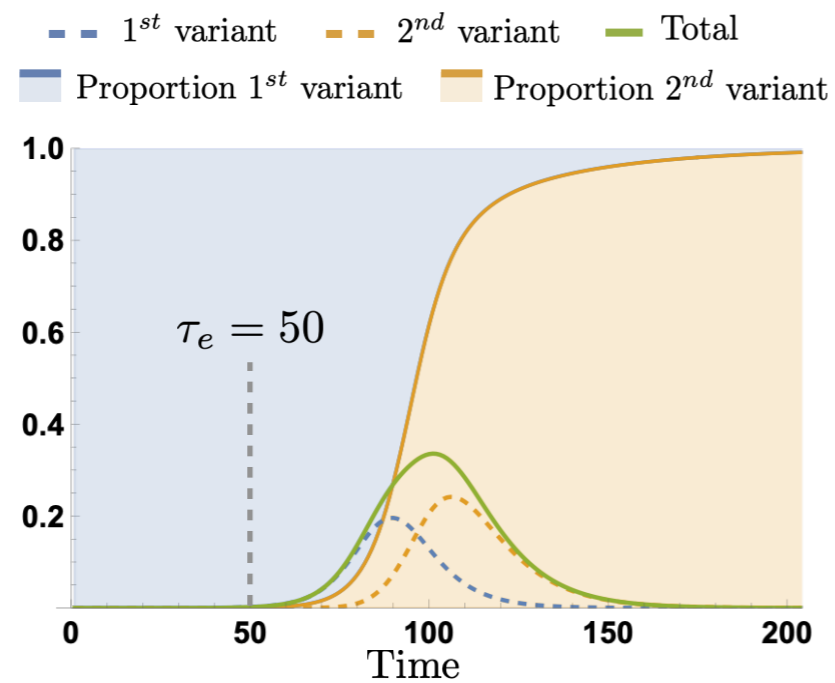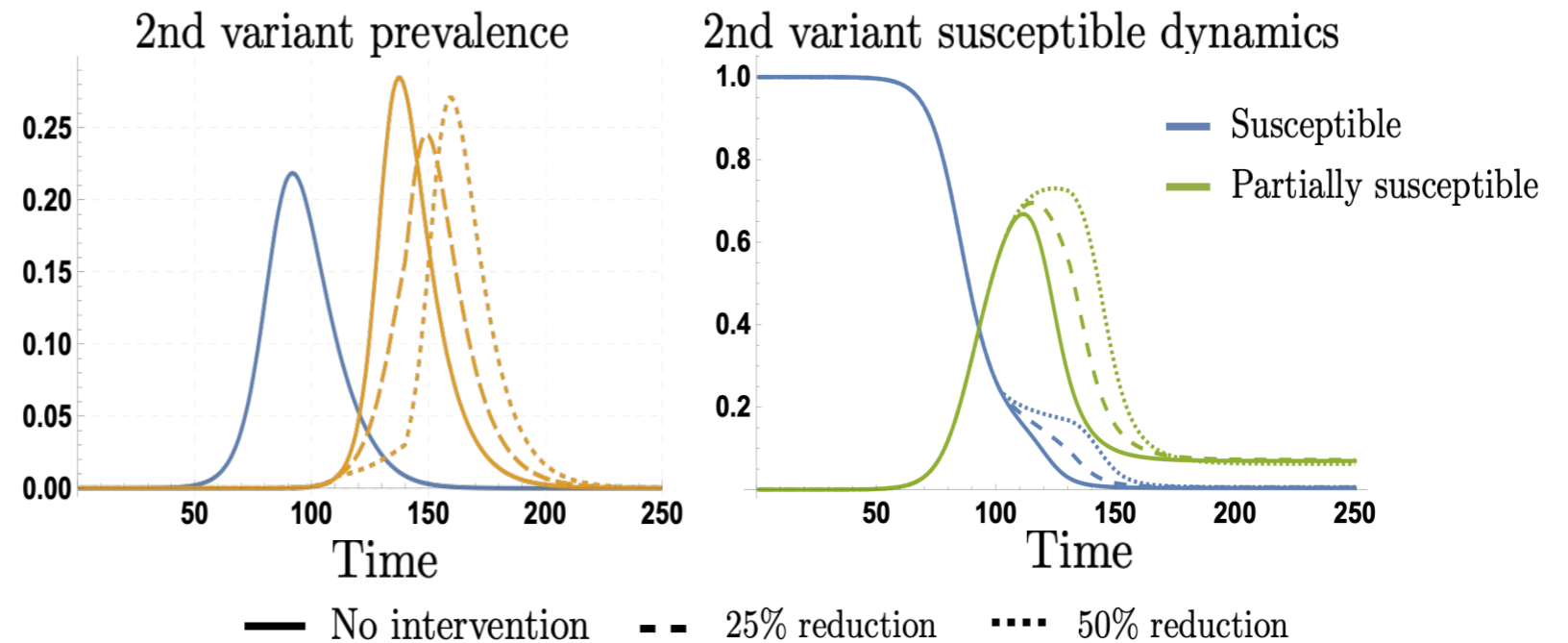25% transmission reduction

50% transmission reduction

Three epidemiological metrics for interventions:

- Minimize the second variant's peak size

- Minimize the total peak size (both variants)

- Minimize the final epidemic size

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Minimizing the second variant's peak size

The second variant's peak size shows non-linear dynamics

2nd variant prevalence

2nd variant susceptible dynamics

— No intervention   - - 25% reduction   ···· 50% reduction

$\tau_e = 50$

4 weeks response

- **Effective responses requires to characterize the genomic landscape**

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Minimizing the total disease prevalence
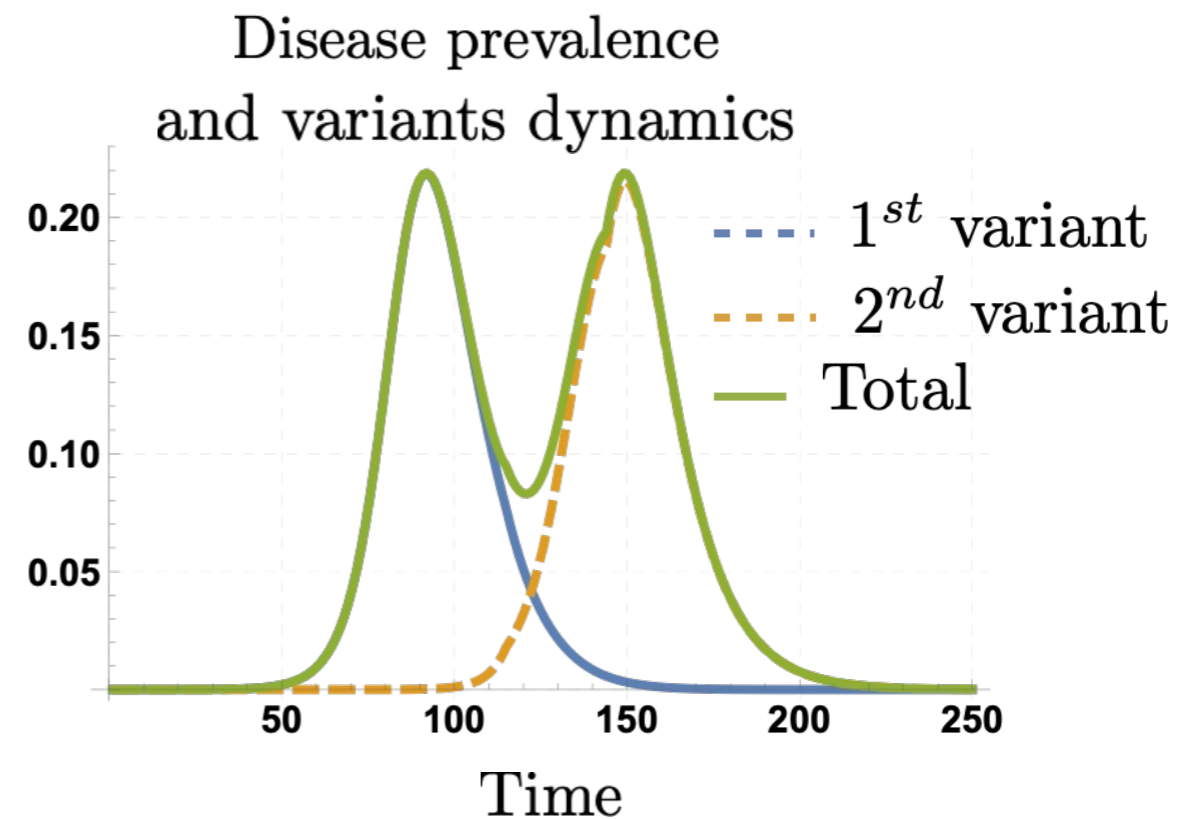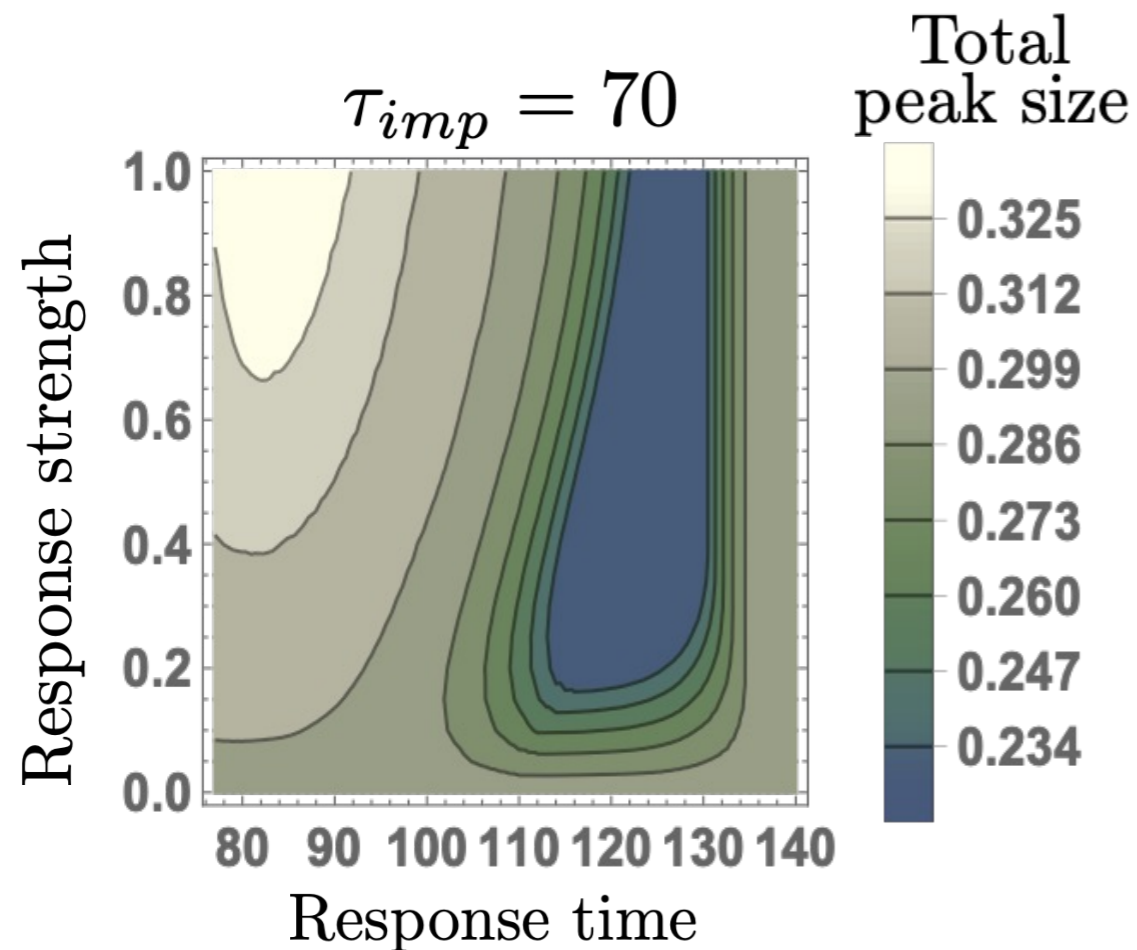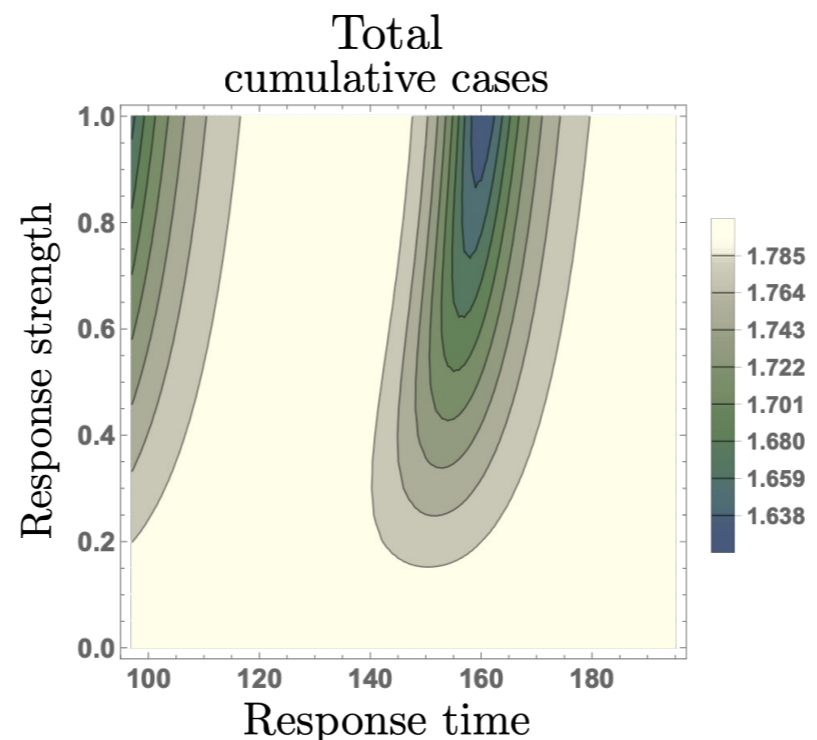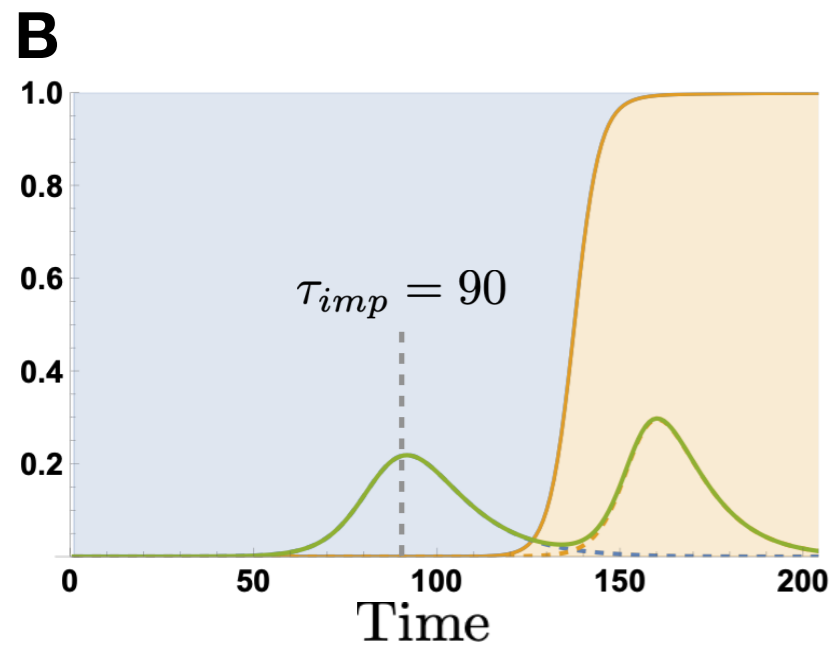

- Early importation leads to minimize the second variant's peak size
- Delayed importation leads to equalize both variant's peak size

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Minimizing the final epidemic size

A
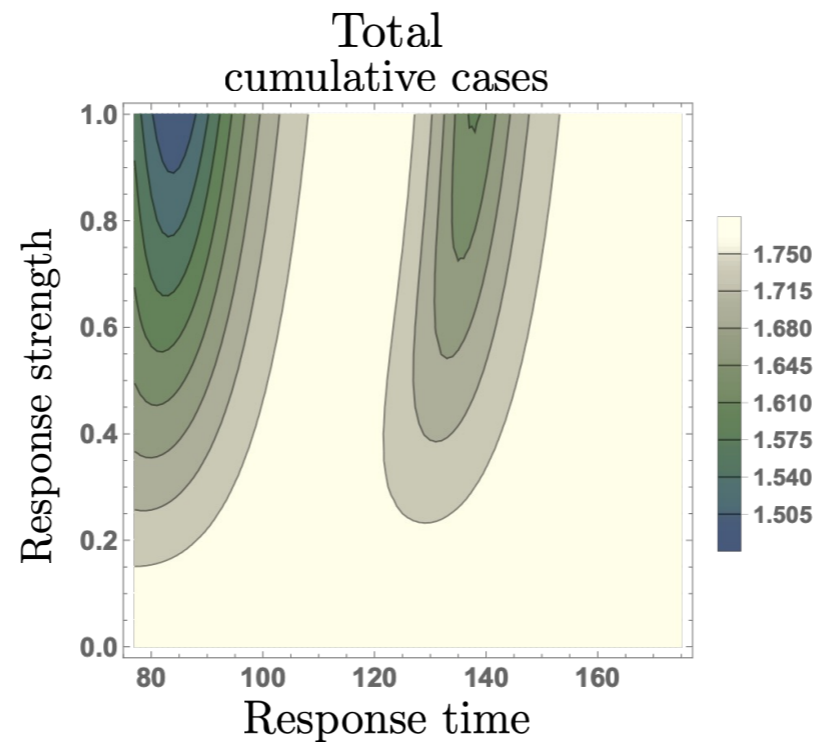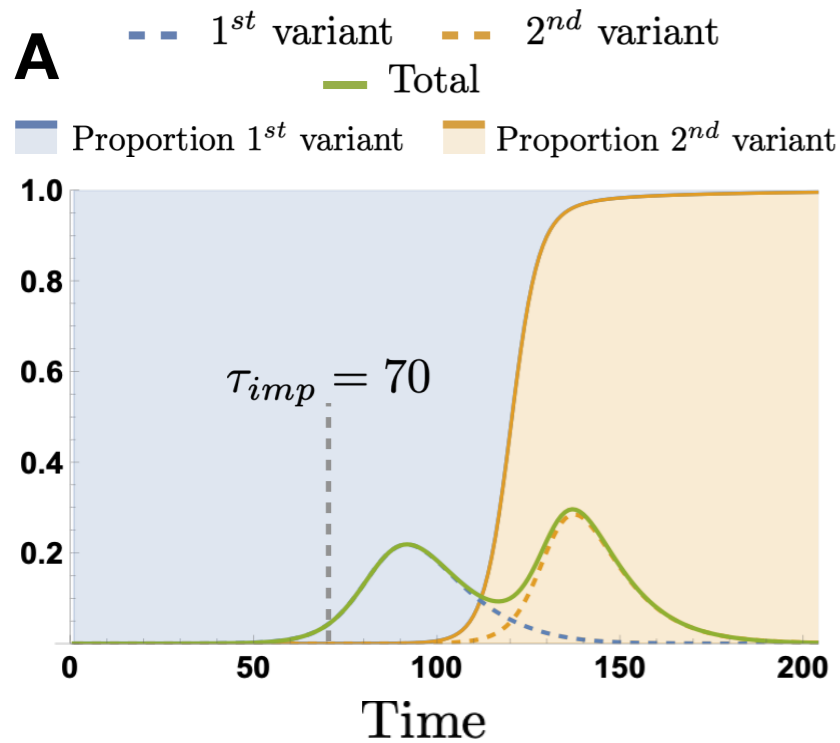
- Early importation:
  early and strong interventions are best

B

- Delayed importation:
  delayed and strong interventions are best

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Limitations of the work

- Homogeneous mixing Susceptible-Infected-Recovered model

  - Complex within host dynamics

  - Spatial disease distribution

- Surveillance is exclusively driven by infectious cases

  - Geographical and temporal surveillance effort distribution and costs

  - Hospitalization and mortality rates must be incorporated

- Centralized simple interventions reducing the effective transmission

  - Pulsated and pharmaceutical interventions

  - Adaptive interventions

- Potential viral evolution

Key insights

- Tracking infection counts alone is not sufficient to assess public health interventions

- Characterization of the genomic landscape is critical to study complex disease dynamics

- Robust surveillance systems provide critical time for planning timely interventions

Ongoing work

- Incorporate adaptive human behavior

- Pathogen's mutation framework

- Multi-variant dynamics

- Complex intervention strategies

Thanks!

Comments and questions

- Model extensions to incorporate zoonotic and vector borne diseases

- Model extension to study potential trade-offs between surveillance and responses across different regions

- How could machine learning leverage the proposed framework?