Mathematical Modeling and Analysis of Epidemics

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Global Burden of Some Infectious Diseases

- Smallpox (430 BC-1979): over 300 million deaths in the 19th century
- 1918-1920 H1N1 Influenza Pandemic: four successive waves; 500 million cases over 20-50 million deaths. Other influenza pandemics: 1957-1958 (H2N2); 1968 (H3N2); 2009 (H1N1)
- Black Death (Black plague) 1340-1771: over 75 million deaths
- Malaria (1600-to date): over 500,000 deaths annually (mostly children under five years of age)
- Cholera pandemics and outbreaks (1817-to date): 7 pandemics (hundreds of thousands deaths)
- HIV/AIDS (1981-to date): 38 million PLWHA; 35 million deaths

Global Burden of Some Infectious Diseases Ctd.

- 2002-2003 SARS coronavirus pandemic: 8,000 cases (744 deaths)
- MERS coronavirus pandemic (2012-to date): 2,517 cases (866 deaths)
- Ebola outbreaks in West Africa (2014-2016): 15,261 lab-confirmed (11,325 deaths)
- 2015-2016 Zika outbreaks in the Americas: 707,133 reported cases (175,063 laboratory-confirmed)
- SARS-CoV-2 pandemic (2019-to-date): over 20 million confirmed cases (over 740,000 deaths)

Why do we care? Globalization (we are vulnerable to what's happening in far away places). "We are constantly a short flight away from a serious epidemic" (Canada's Advisory Committee on SARS, 2003)

Role of Mathematical Modeling in Disease Dynamics

- Building and testing theories; assessing quantitative conjectures; providing insights on specific questions; determining sensitivities to changes in parameter values estimating key parameters from data
- Comparing, planning, implementing, evaluating and optimizing various detection, prevention, therapy and control programs
- Identifying trends and making general forecasts
- Early estimate of epidemiological thresholds ($\mathbb{R}_0$) and disease burden

Mathematical epidemiology is inherently interdisciplinary, involving collaborations with other scientists (clinicians, epidemiologists, immunologists, virologists, computer scientists, statisticians, data analysts, social scientists) and public health practitioners and policy makers

Types of Models for Infectious Disease Dynamics

- ◇ Compartmental (deterministic, stochastic, discrete-time)
- ◇ Spatial/patch/metapopulation
- ◇ Agent-based (individual-based)
- ◇ Contact network
- ◇ Machine learning
- ◇ Statistical

Choice of model type depends on:

(a) Type of problem being addressed or question(s) being asked

(b) Nature/type/level/reliability of data available

History of Mathematical Modeling of Infectious Diseases

Framework (mostly) developed by biologists and epidemiologists:

- Daniel Bernoulli (mathematician and physicist): modeling work to assess efficacy of smallpox vaccine in the 1760s
- Sir Ronald Ross (British medical doctor; Nobel prize in Medicine, 1902) and George Macdonald (British malariologist): 1900-1957
- William O. Kermack (Scottish biochemist) and Anderson G. McKendrick (military physician and epidemiologist): 1927-1933

1. Bernoulli, D. Essai d'une nouvelle analyse de la mortalité causée par la petite vérole et des avantages de l'inoculation pour la prévenir. Mém Math. Phys. Acad. Roy. Sci. Paris, 1760: 1-45
2. Kermack, W.O. and McKendrick, A.G. A contribution to the mathematical theory of epidemics. Proc. Roy. Soc. Lond. B. 1927(115): 700-721

Public Health "Wish List" During New Epidemics

- Early estimation of reproduction number ($\mathbb{R}_0$)
- Determining the qualitative nature of disease spread (spreading speed; epidemic peak/decline; multi-wave phenomenon?)
- Estimating disease burden (expected number of infections, hospitalizations, ICU admissions, deaths)
- Assessment of control strategies (targeted strategies; herd immunity; cost of interventions; optimal allocation of limited resources)

Mathematical, Statistical and Computational "Wish List"

Mathematical: characterizing model dynamics (existence and asymptotic stability of steady-state solutions; characterizing bifurcation types; deriving conditions for effective control or persistence of disease; herd thresholds)

Statistical: data-fitting (case, hospitalization, mortality, social media data etc.); parameter estimation; optimization (optimal control); uncertainty quantification; sensitivity analysis

Computational: efficient (high-performance computing), robust, accurate, dynamically-consistent numerical methods for integrating associated continuous-time models for the disease dynamics; simulation of large-scale models (social network, agent-based), design of user-friendly decision support software systems for running scenario analysis in parameter space

Formulating Compartmental Epidemiology Models

- Split the total population at time t ($N(t)$) into mutually-exclusive compartments of susceptible ($S(t)$), infected ($I(t)$) and recovered ($R(t)$) individuals

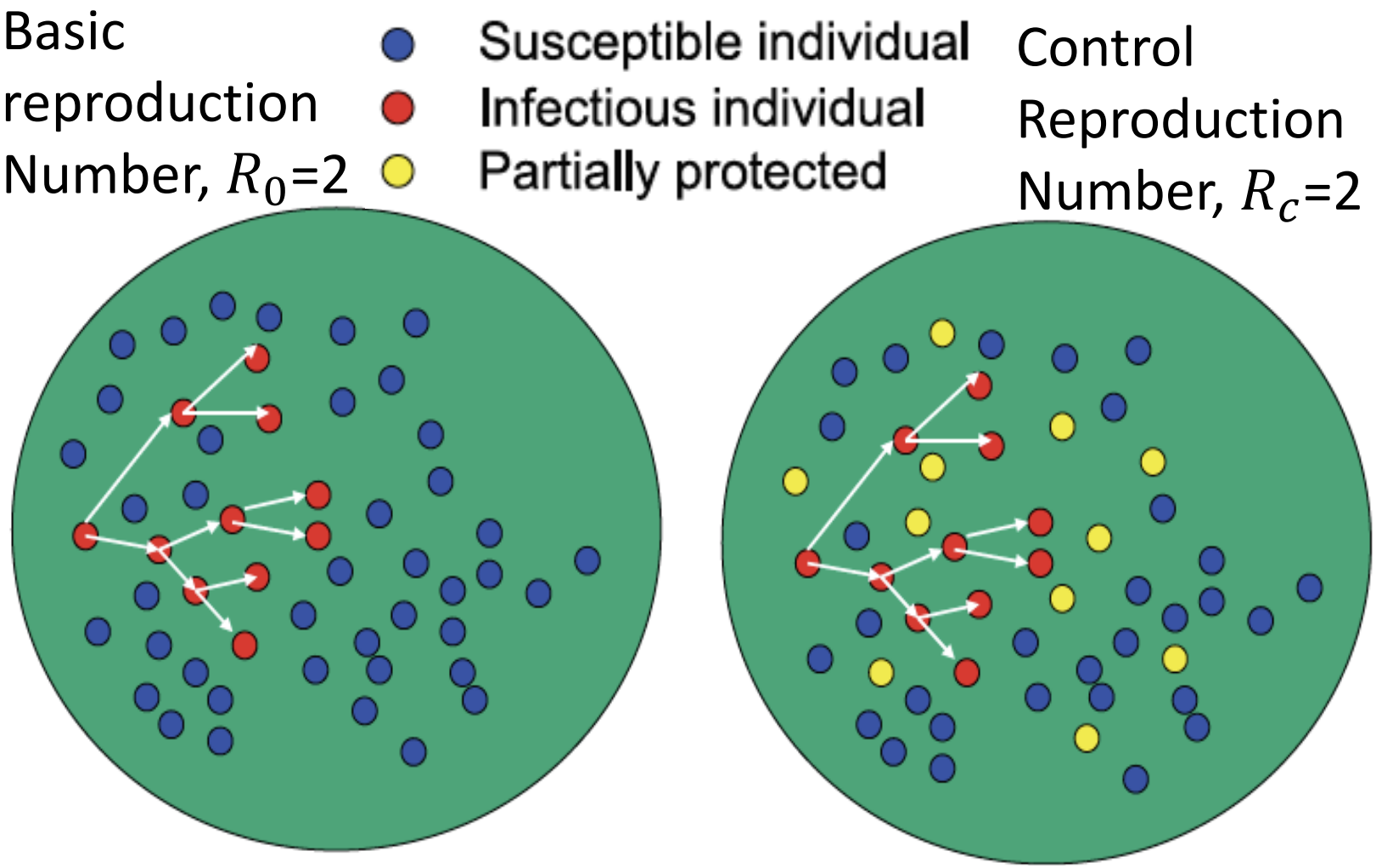
$$N(t) = S(t) + I(t) + R(t)$$

- Let $\beta(N)$ be the effective contact rate *per* person *per* unit time. Then, $\beta(N)I/N$ is the average number of contacts with infectious individuals a susceptible individual makes *per* unit time (disease incidence)
- Consider the disease incidence $g(S, I, N) = \beta(N)SI/N$:
  - (i) Standard incidence if $\beta(N) = \beta$ (a constant)
  - (ii) Mass action incidence if $\beta(N) = \beta N$

Other forms of compartmental models: SIRS, SEIR, SEIRS, SVEIRS etc.
Dynamics typically determined by reproduction number ($\mathbb{R}_0$)

Herbert Hethcote. Mathematics of infectious diseases. SIAM Review, 2000

Basic ($\mathbb{R}_0$) and Control ($\mathbb{R}_c$) Reproduction Numbers



Kermack-McKendrick (KM) SIR Model

$$\frac{dS(t)}{dt} = -\beta S(t)I(t)$$

$$\frac{dI(t)}{dt} = \beta S(t)I(t) - \gamma I(t)$$

$$\frac{dR(t)}{dt} = \gamma I(t)$$

β: mean number of contacts an infective makes *per* unit time
$1/\gamma$: mean duration of infectivity

Model used to explain pattern of epidemics: plague (London 1665-1666, Bombay 1906); cholera (London 1865)

KM Model: Main Assumptions

- Closed population: no births, deaths due to disease or natural causes (no entry into or departure from the population). Time scale of the disease is faster than demographic time scale
- Each infected individual is instantaneously infectious (duration of infectivity= length of disease)
- Homogeneous mixing (no age, spatial or social structure)
- Large population size (stochastic effects for small populations)
- Exponentially-distributed waiting times in compartments
- Recovery induces permanent natural immunity against reinfection

Homogeneous vs. Heterogeneous Mixing Assumptions

Homogeneous mixing: individuals in a population mix randomly and uniformly with each other (i.e., the population is assumed to be homogeneous). Everyone is equally likely to mix with (and infect or acquire infection from) everyone else

Heterogeneous mixing: accounts for heterogeneities in diseases, hosts and their interactions. Incorporates host diversities (such as, risk/age/spatial structure, contact/mixing structure and preferences, compliance to public health interventions)

Homogeneous mixing assumption mostly made for mathematical tractability (although this does not generally affect the predictive power and robustness of the model). Models for heterogeneously-mixed populations are often not amenable to rigorous analyses

KM Model: Basic Reproduction Number ($\mathbb{R}_0$)

Suppose at time $t = 0$ all individuals were susceptible (i.e., $S(0) = N$). Hence, at $t = 0$, one infected individual will infect $\beta S(0) = \beta N$ susceptible individuals *per* unit time. Since an infected individual will remain infectious for an average period of $\frac{1}{\gamma}$, then

$$\boxed{\mathbb{R}_0 = \frac{\beta S(0)}{\gamma}}$$

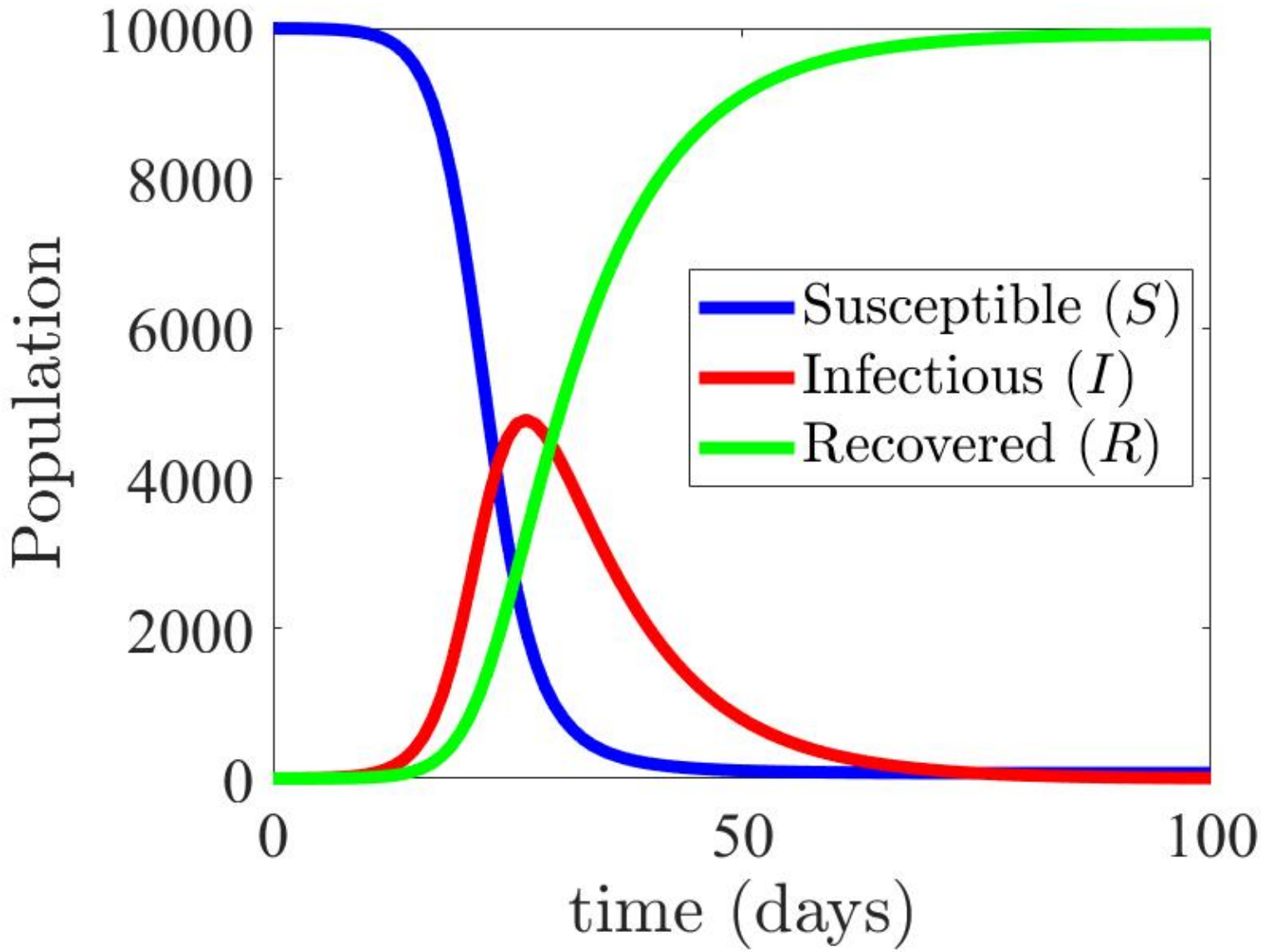
Control and mitigation strategies based on two parameters: decrease β (contact reduction, masks usage) and increase γ (treatment)

(a) $\mathbb{R}_0 < 1$: Epidemic declines to zero

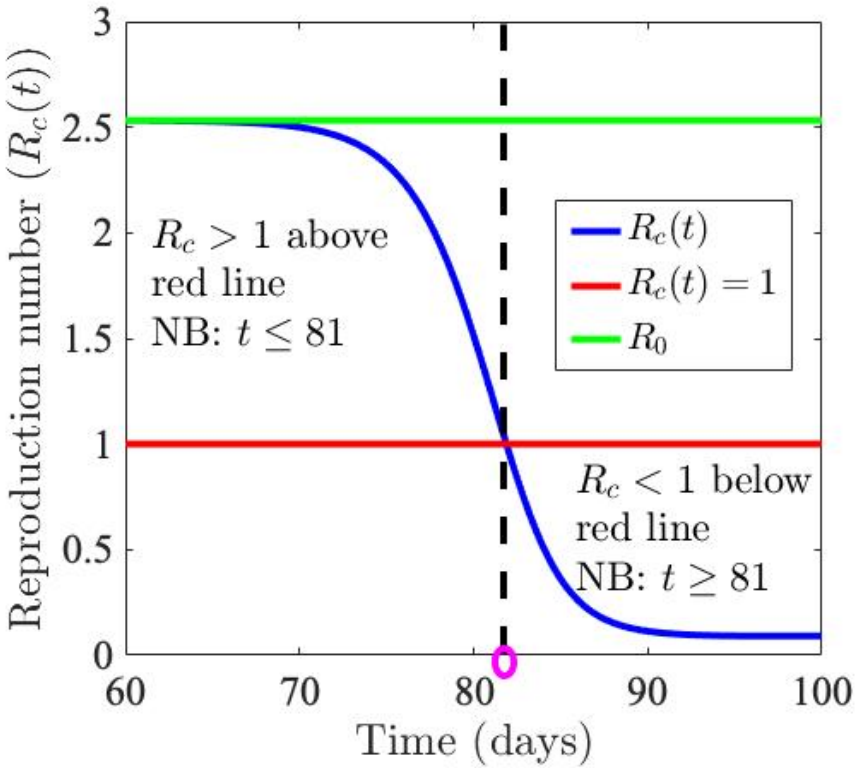
(b) $\mathbb{R}_0 > 1$: Epidemic causes an outbreak (rises to a peak, and then declines to zero)

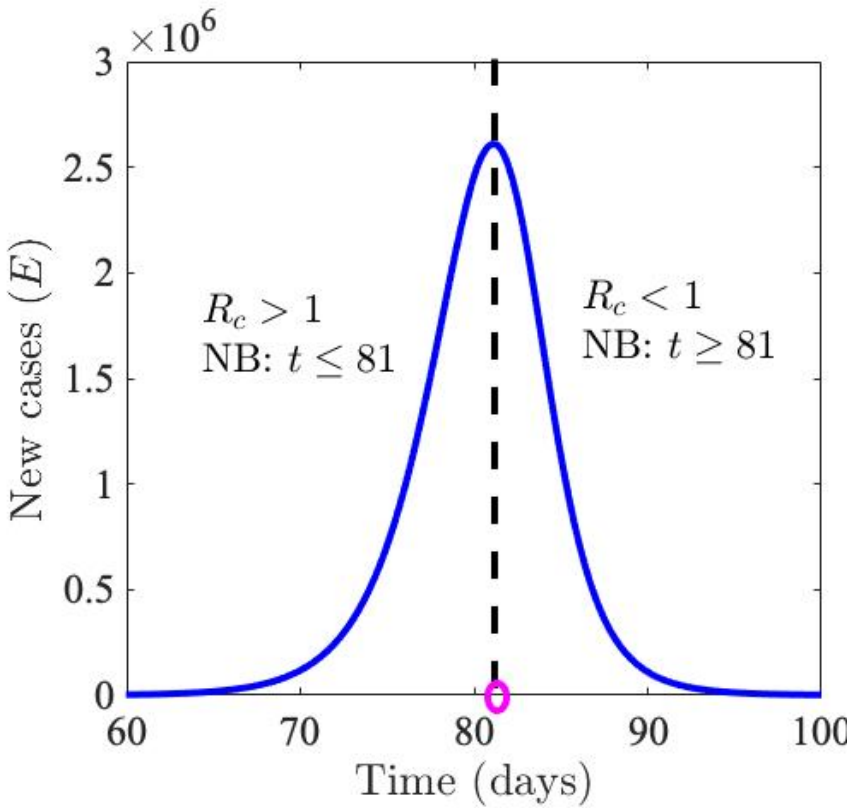
Effective Reproduction Number: $\mathbb{R}_c(t) = \mathbb{R}_0 \frac{S(t)}{N(t)}$

KM Model: Epidemic Curves



Effective (time-varying) Reproduction Number





Agent-based Models (ABMs) for Disease Dynamics

ABMs are a type of computational models for simulating the actions and interactions of autonomous agents (individuals, groups, etc.) with each other and with an environment. The behavior/actions of agents are governed by a set of coded rules. At each time step, an agent decides what it will do

Each agent is unique with different set of characteristic (e.g., age, gender, vaccination status). These characteristics can influence how the agents decide (i.e., they affect the agents' likelihood of acquiring infection)

Disease spread is monitored through each individual. Contacts of each individual with others in the relevant social networks and geographical areas are tracked

ABMs can capture the dynamics of the disease spread combined with the heterogeneous mixing and social networks of the agents, thereby helping to determine where an agent got infected and who infected them

ABMs vs. Equations-based Models

Population type: ABM has heterogeneous agents. Equations-based model generally has homogeneous population (incorporating heterogeneity requires adding more equations)

Mixing type: Heterogeneous for ABM; Homogeneous for Equations-based (mixing patterns across groups may differ, but are same within each group)

Computational costs and data needs: ABMs are "data hungry" and computationally-extensive. ABMs are not amenable to mathematical analysis (generally follow the traditional SEIR formalism, equations ABMs not given explicitly).

Results generated from the two modeling types can sometimes be similar or quite different. ABMs can capture certain complexities that other modeling types may not (Hunter et al., 2018)

1. Perez and Dragicevic. Int. J. Public Health, 2009
2. E. Hunter *et al.* PLoS One, 2018

KM Model: Demographic Effects

$$\frac{dS}{dt} = \Pi - \beta SI - \mu S \equiv f_1(S, I, R)$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I \equiv f_2(S, I, R)$$

$$\frac{dR}{dt} = \gamma I - \mu R \equiv f_3(S, I, R)$$

Feasible region: $\Omega = \{(S, I, R) \in \mathbb{R}^3_+ : S + I + R \leq \Pi/\mu\}$.

Theorem 1

The region Ω is positively-invariant and attracting for the model.

Implication: the model is well-posed mathematically and epidemiologically. Hence, it is sufficient to study its dynamics in Ω.

Linearization

Disease-free equilibrium (DFE): $\mathscr{E}_0 : (S^*, I^*, R^*) = (\Pi/\mu, 0, 0)$

Under what conditions can the system settle at the DFE?

Compute Jacobian of the system (standard linearization):

$$J(S,I,R) = \begin{pmatrix} \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial R} \\ \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial R} \\ \frac{\partial f_3}{\partial S} & \frac{\partial f_3}{\partial I} & \frac{\partial f_3}{\partial R} \end{pmatrix} = \begin{pmatrix} -\beta I - \mu & -\beta S & 0 \\ \beta I & \beta S - (\gamma + \mu) & 0 \\ 0 & \gamma & -\mu \end{pmatrix}$$

Hartman-Grobman Theorem: topological equivalence of phase portraits

Linearization Ctd.

Negative eigenvalues if $\mathbb{R}_0 = \dfrac{\beta\Pi/\mu}{\mu+\gamma} < 1$. $\mathbb{R}_0 < 1$ is necessary for disease elimination

Theorem 2

The DFE is locally-asymptotically stable if $\mathbb{R}_0 < 1$, and unstable if $\mathbb{R}_0 > 1$.

Theorem 3

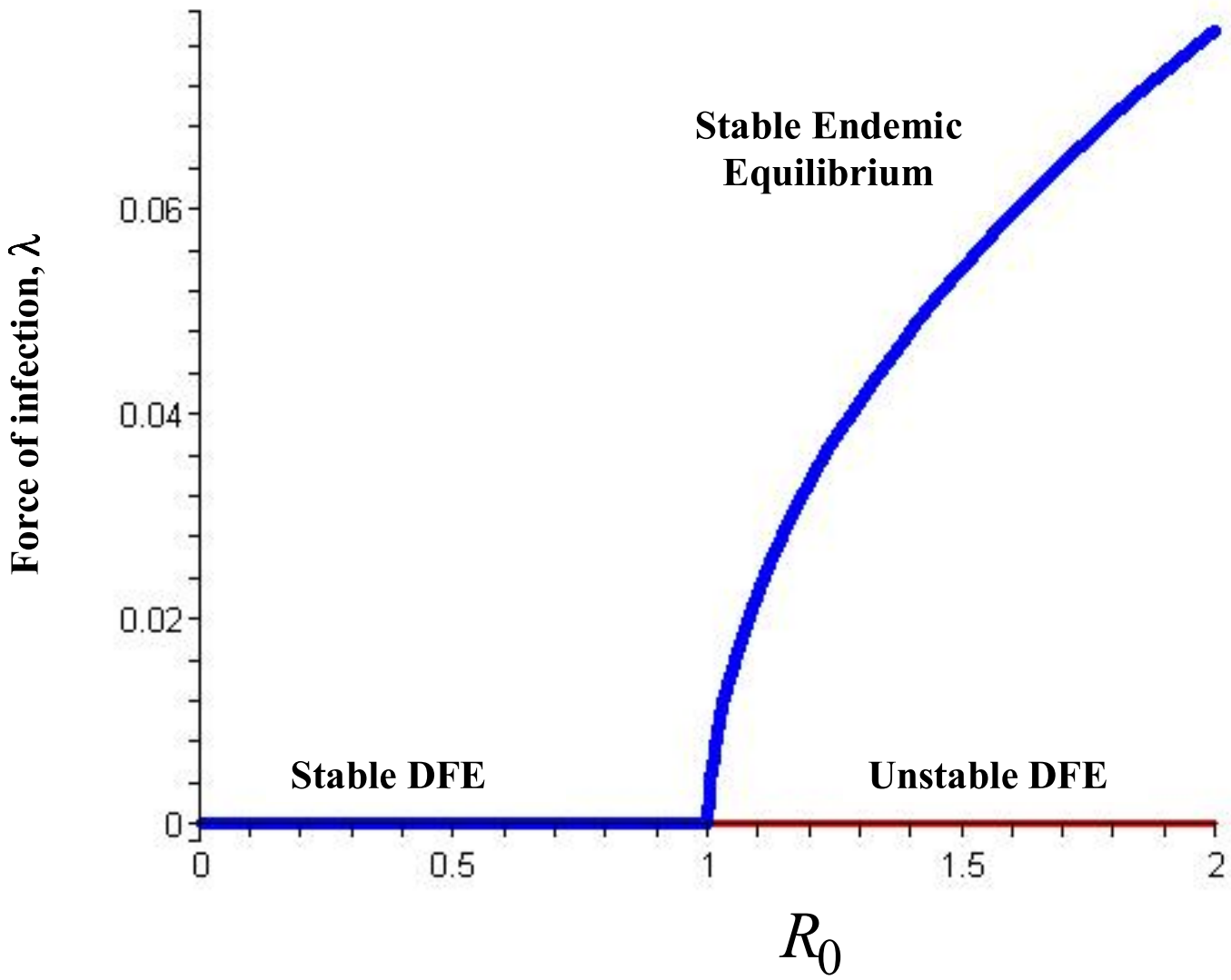
The DFE is globally-asymptotically stable in Ω whenever $\mathbb{R}_0 \leq 1$

Theorem 4

The model has a unique endemic equilibrium point (EEP), given by $(S^{**}, I^{**}) = \left(\dfrac{\gamma+\mu}{\beta}, \mu(\mathbb{R}_0 - 1)\right)$, which exists only if $\mathbb{R}_0 > 1$. This equilibrium is globally-asymptotically stable in $\Omega \setminus \mathscr{E}_0$ whenever $\mathbb{R}_0 > 1$.

Proofs of G.A.S. based on using Lyapunov function theory. Transcritical/forward bifurcation at $\mathbb{R}_0 = 1$

Forward Bifurcation Diagram



Computation of Reproduction Number Using Other Methods: Inspection & NGM

$\mathbb{R}_0$ measures the average number of new cases a typical infected person will generate during his/her duration of infectiousness if introduced in a completely susceptible population

Let F represents the nonnegative matrix of new infection terms. Let V represents the $M-$matrix of linear transition terms in the infected compartments of the model.

Intuitively, $\mathbb{R}_0$ is defined (First Principle) as:

$$\begin{aligned} \mathbb{R}_0 &= (\text{infection rate near the DFE}) \times (\text{average duration of infectiousness}) \\ &= \rho\left(FV^{-1}\right) \end{aligned}$$

Computation of $\mathbb{R}_0$ Ctd.

For the KM model with demographics,

$$\begin{aligned}\mathbb{R}_0 &= (\beta S^*) \times \left(\frac{1}{\gamma+\mu}\right) \\ &= (\beta \Pi/\mu) \times \left(\frac{1}{\gamma+\mu}\right)\end{aligned}$$

Thus, the disease will be effectively–controlled (or eliminated) if $\mathbb{R}_0 < 1$.

$\mathbb{R}_0$ for SEIARS Model

$$\begin{aligned}
\frac{dS}{dt} &= \Pi + \psi R - \beta\left(\frac{I+\eta A}{N}\right)S - \mu S,\\
\frac{dE}{dt} &= \beta\left(\frac{I+\eta A}{N}\right)S - \sigma E - \mu E,\\
\frac{dI}{dt} &= r\sigma E - \gamma_I I - \mu I - \delta_I I,\\
\frac{dA}{dt} &= (1-r)\sigma E - \gamma_A A - \mu A - \delta_A A,\\
\frac{dR}{dt} &= \gamma_I I + \gamma_A A - \psi R - \mu R;\ \ N(t) = S(t) + E(t) + I(t) + R(t).
\end{aligned}$$

DFE: $(S^*, E^*, I^*, A^*, R^*) = (\Pi/\mu, 0, 0, 0, 0)$

$\mathbb{R}_0$ for SEIARS Model Ctd.: First Principle

Two sources of infection (I and A). Let $\mathscr{R}_{0I}$ and $\mathscr{R}_{0A}$ represent the average number of new cases generated by individuals in the I and A class, resp.

$$
\begin{aligned}
\mathscr{R}_{0I} &= (\text{infection rate near the DFE}) \\
&\times (\text{probability of surviving E and moving to the I class}) \\
&\times (\text{average duration in the I class}) \\
&= (\beta S^*/N^*) \times \left(\frac{r\sigma}{\sigma+\mu}\right) \times \left(\frac{1}{\gamma_I+\mu+\delta_I}\right)
\end{aligned}
$$

$$
\begin{aligned}
\mathscr{R}_{0A} &= (\text{infection rate near the DFE}) \\
&\times (\text{probability of surviving E and moving to the A class}) \\
&\times (\text{average duration in the A class}) \\
&= (\beta\eta S^*/N^*) \times \left[\frac{(1-r)\sigma}{\sigma+\mu}\right] \times \left(\frac{1}{\gamma_A+\mu+\delta_A}\right)
\end{aligned}
$$

$$\mathbb{R}_0 = \mathscr{R}_{0I} + \mathscr{R}_{0A}$$

SEIARS Model Ctd.: Next Generation Operator Method

$$F = \begin{pmatrix} 0 & \beta & \beta\eta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \sigma+\mu & 0 & 0 \\ -r\sigma & \gamma_I+\mu+\delta_I & 0 \\ -(1-r)\sigma & 0 & \gamma_A+\mu+\delta_A \end{pmatrix}.$$

$$\mathbb{R}_0 = \rho(FV^{-1})$$

Challenge: Proof of G.A.S. of endemic equilibrium of SEIARS model?

1. Diekmann *et al.* On the definition and computation of the basic reproduction ratio $\mathscr{R}_0$ in models for infectious disease in heterogeneous population. *J. Math. Biol.*, 1990
2. van den Driessche and Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math. Biosci.*, 2002

Vaccine-induced Herd Immunity

A population is at herd immunity if a large enough fraction has been immunized to ensure that the disease cannot become endemic.

That is, herd immunity is the "indirect protection from infection conferred to susceptible individuals when a sufficiently large proportion of immune individuals exist in a population" (Randolph and Barreiro, 2020).

Often considered in the context of vaccination programs. Once attained, those that cannot be vaccinated (e.g., infants, immunocompromised, anti-vaxxers etc.) are still protected against acquiring infection.

Herd Immunity Ctd.

Let p be the proportion of successfully immunized individuals

$$\begin{aligned}
\frac{dS}{dt} &= \Pi(1-p) + \psi R - \beta\left(\frac{I}{N}\right)S - \mu S \\
\frac{dV}{dt} &= \Pi p - \mu V \\
\frac{dI}{dt} &= \beta\left(\frac{I}{N}\right)S - \gamma I - \mu I \\
\frac{dR}{dt} &= \gamma I - \psi R - \mu R
\end{aligned}$$

Main assumptions: homogenous mixing; perfect vaccine protection; no waning or therapeutic benefits

Feasible region: $\mathscr{D} = \left\{(S,V,I,R) \in \mathbb{R}^4_+ : S+V+I+R \leq \Pi/\mu\right\}$

Herd Immunity Ctd.

- Vaccination reproduction number: $\mathbb{R}_V = (1-p)\mathbb{R}_0$
- Basic reproduction number: $\mathbb{R}_0 = \dfrac{\beta\Pi}{\mu(\gamma+\mu)}$
- Herd immunity threshold (solve for p from $\mathbb{R}_V = 1$): $p_c = 1 - \frac{1}{\mathbb{R}_0}$

Theorem 5

DFE is globally-asymptotically stable (G.A.S.) in the region $\mathscr{D}$ if $\mathbb{R}_V < 1$ (i.e., $p > p_c$), and unstable if $\mathbb{R}_V > 1$ (i.e., $p < p_c$). The model has a unique and G.A.S. endemic equilibrium (in $\mathscr{D} \setminus \mathscr{D}_0$), where $\mathscr{D}_0 = \{(S, V, I, R) \in \mathscr{D} : I = 0\}$, whenever $\mathbb{R}_V > 1$.

Proof based on using a Lyapunov function of Goh-Volterra type

Community-wide vaccine-derived herd immunity achieved if $p > p_c$

Herd Immunity Thresholds for some Diseases

Disease	$\mathbb{R}_0$	Herd Immunity Threshold (p_c)
Diphtheria	6-7	$83\% - 86\%$
Ebola (2014 outbreaks)	1.5-2.5	33%-60%
Influenza (pandemics)	1.5-1.8	33%-44%
Measles	**12-18**	**92%-95%**
Mumps	4-7	75%-86%
Pertussis	**12-17**	**92%-94%**
Polio	5-7	80%-86%
Smallpox	5-7	80%-86% (**eradicated**)
SARS	2-3	50%-67%

SIR Model with Imperfect Vaccine

$$
\begin{aligned}
\frac{dS}{dt} &= \Pi + \omega V - \beta \frac{I}{N} S - \xi S - \mu S \\
\frac{dV}{dt} &= \xi S - \beta(1-\varepsilon_v)\frac{I}{N} V - \omega V - \mu V \\
\frac{dI}{dt} &= \beta \frac{I}{N} S + \beta(1-\varepsilon_v)\frac{I}{N} V - \gamma I - \mu I - \delta I \\
\frac{dR}{dt} &= \gamma I - \mu R
\end{aligned}
$$

Π (recruitment rate), ω (vaccine waning rate), β (infection rate), ξ (vaccination rate), μ (natural death rate), $0 < \varepsilon_v \leq 1$ (vaccine efficacy to prevent infection), γ (recovery rate), δ (disease-induced death rate)

SIR Model with Imperfect Vaccine Ctd.

Disease-free equilibrium:

$$((S^*, V^*, I^*, R^*) = \left(\frac{\Pi(\omega+\mu)}{\mu(\omega+\xi+\mu)}, \frac{\xi\Pi}{\mu(\omega+\xi+\mu)}, 0, 0 \right)$$

Reproduction number: $\mathscr{R}_v = \left[\beta \frac{S^*}{N^*} + \beta(1-\varepsilon_v)\frac{V^*}{N^*} \right] \left(\frac{1}{\gamma+\mu+\delta} \right)$

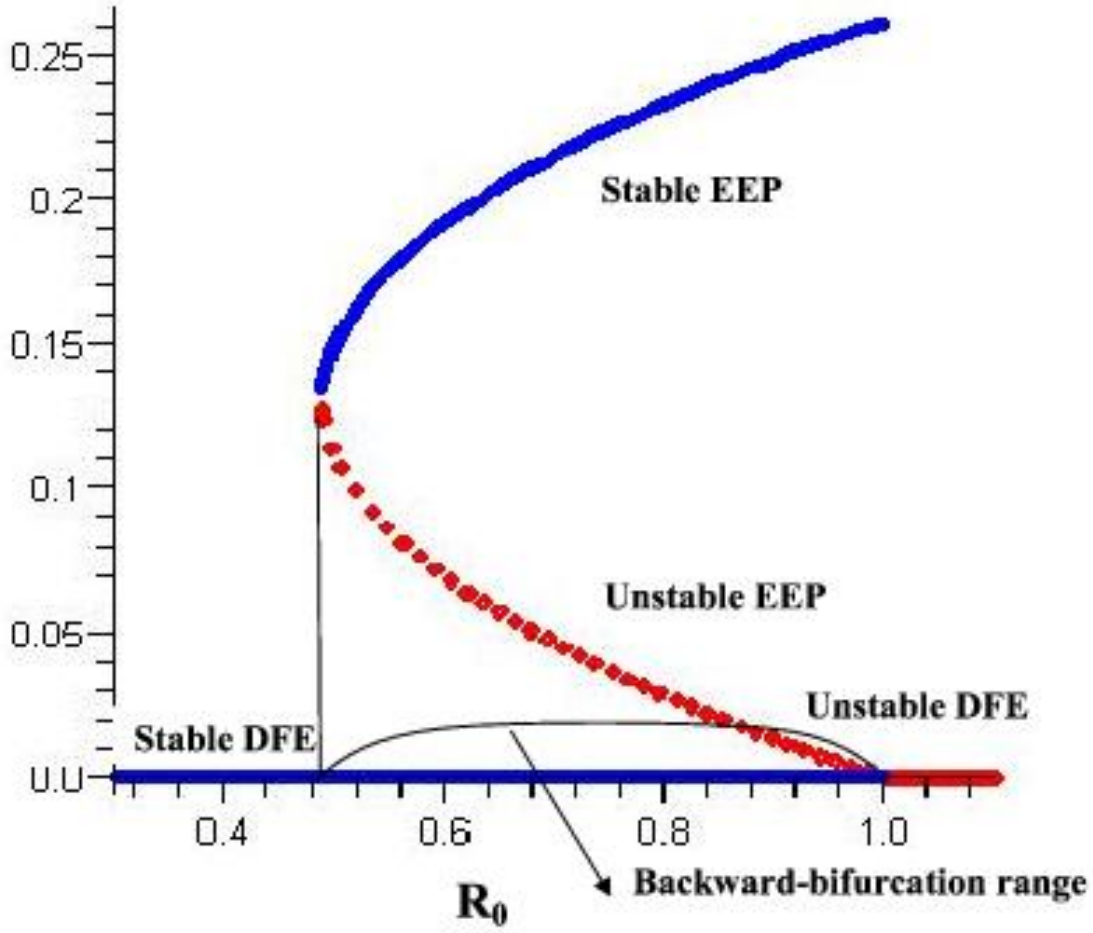
Herd immunity threshold: $\frac{1}{\varepsilon_v}\left(1 - \frac{1}{\mathbb{R}_0}\right)$

Theorem 6

Model undergoes a vaccine-induced backward bifurcation at $\mathscr{R}_v = 1$

Proof based on using center manifold theory

Backward Bifurcation Diagram



Modeling Dynamics of 2019 Novel Coronavirus

Timeline:

- Wuhan city public health officials informed the W.H.O. of a pneumonia of an unknown etiology on December 31, 2019
- Disease rapidly spread globally (index case in US on January 20, 2020). W.H.O. declared COVID-19 to be a global pandemic on March 11, 2020

Coronaviruses are a group of related RNA viruses that cause diseases in mammals and birds (they cause respiratory track infections in humans). There are numerous coronaviruses in the wild (about 2 million)

No safe and effective vaccine or antiviral for use in humans. Control measures limited to basic public health measures using NPIs (community lockdown, face masks, social/physical-distancing, closure of large gatherings, quarantine, isolation, testing, contact tracing etc.)

Comparing the three recent coronavirus cousins

	SARS-CoV	MERS-CoV	COVID-19 (SARS-CoV-2)
Origin	Guangdong, China	Saudi Arabia	Wuhan, China
Duration	2002-2003	2012-to date	Dec. 2019-to date
Reservoir	Bats and civet cats	Bats/camels	Bats (Pangolin?)
Countries	29	27	220
Incubation period	2-7 days	5 days	2-14 days
Confirmed cases	8,000	2,519	$>$ 20 million
Global deaths	744	866	$>$ 740, 000
Case fatality ratio	9.5%	34.4%	2.3%-4%

Symptoms:

(a) SARS: Flu-like; coughing; fever

(b) MERS: Flu-like; coughing; fever

(c) COVID-19: Shortness of breath; coughing; fever

Main lesson from SARS and MERS: coronaviruses are controllable using basic public health measures!

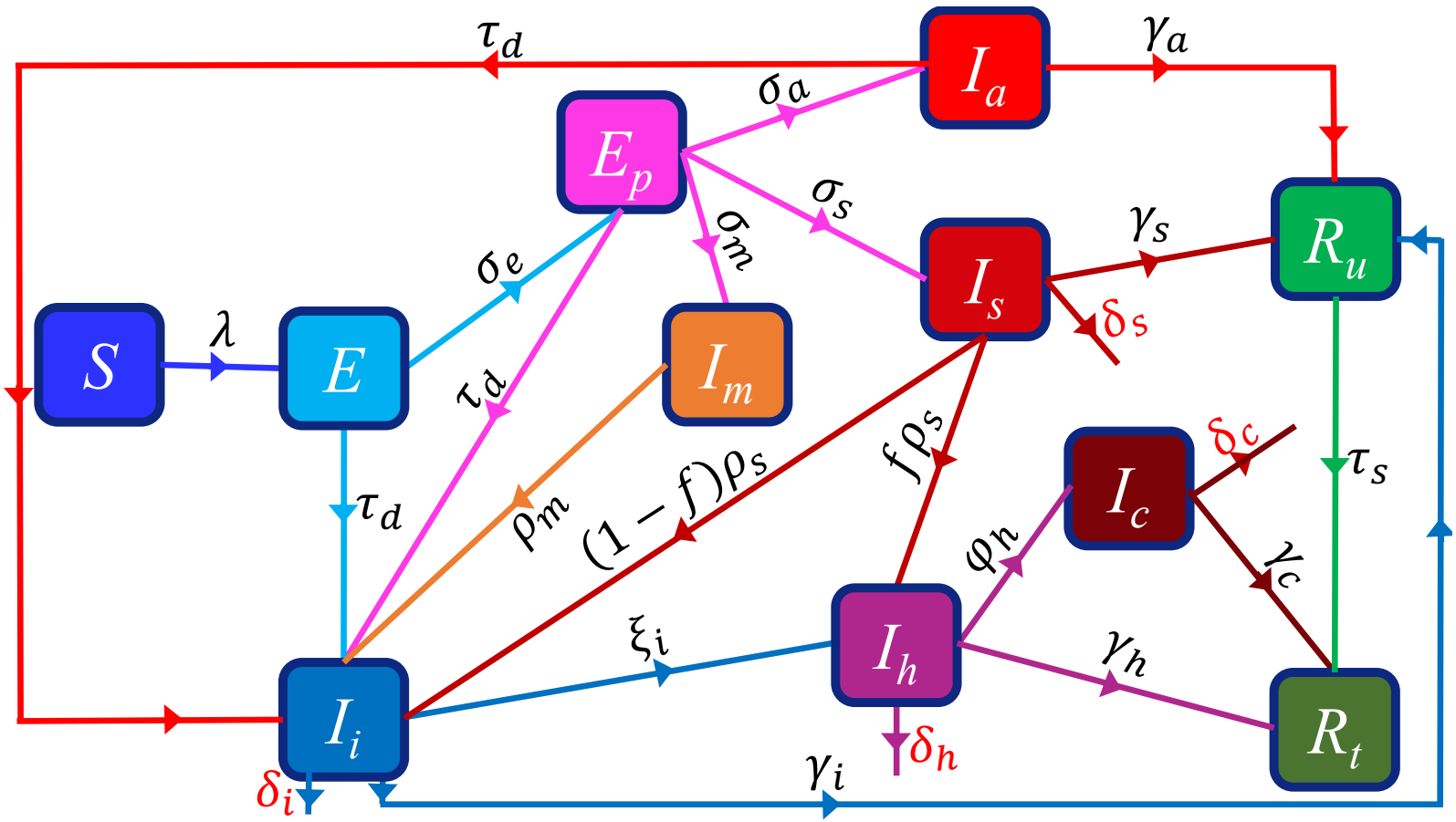
Modeling COVID-19 Dynamics in U.S.

COVID burden in U.S.: over 5 million confirmed cases; over 164,000 deaths

Objective: could face masks curtail post-lockdown resurgence of COVID-19 in the U.S.?

State variable	Description
S	Population of susceptible individuals
E	Population of exposed (newly-infected but not infectious) i
E_p	Population of pre-symptomatic (infectious) individuals
I_a	Population of asymptomatically-Infectious individuals
I_m	Population of infectious individuals with mild symptoms
I_s	Population of infectious individuals with severe symptoms
I_i	Population of infectious individuals in self-isolation
I_h	Population of hospitalized individuals
I_c	Population of individuals in ICU
$R_u(R_t)$	Population of untested (tested) recovered individuals

Flow Diagram of the Model



Notation: $\sigma_a = r\sigma_p, \sigma_m = (1-r)g\sigma_p, \sigma_s = (1-r)(1-g)\sigma_p$

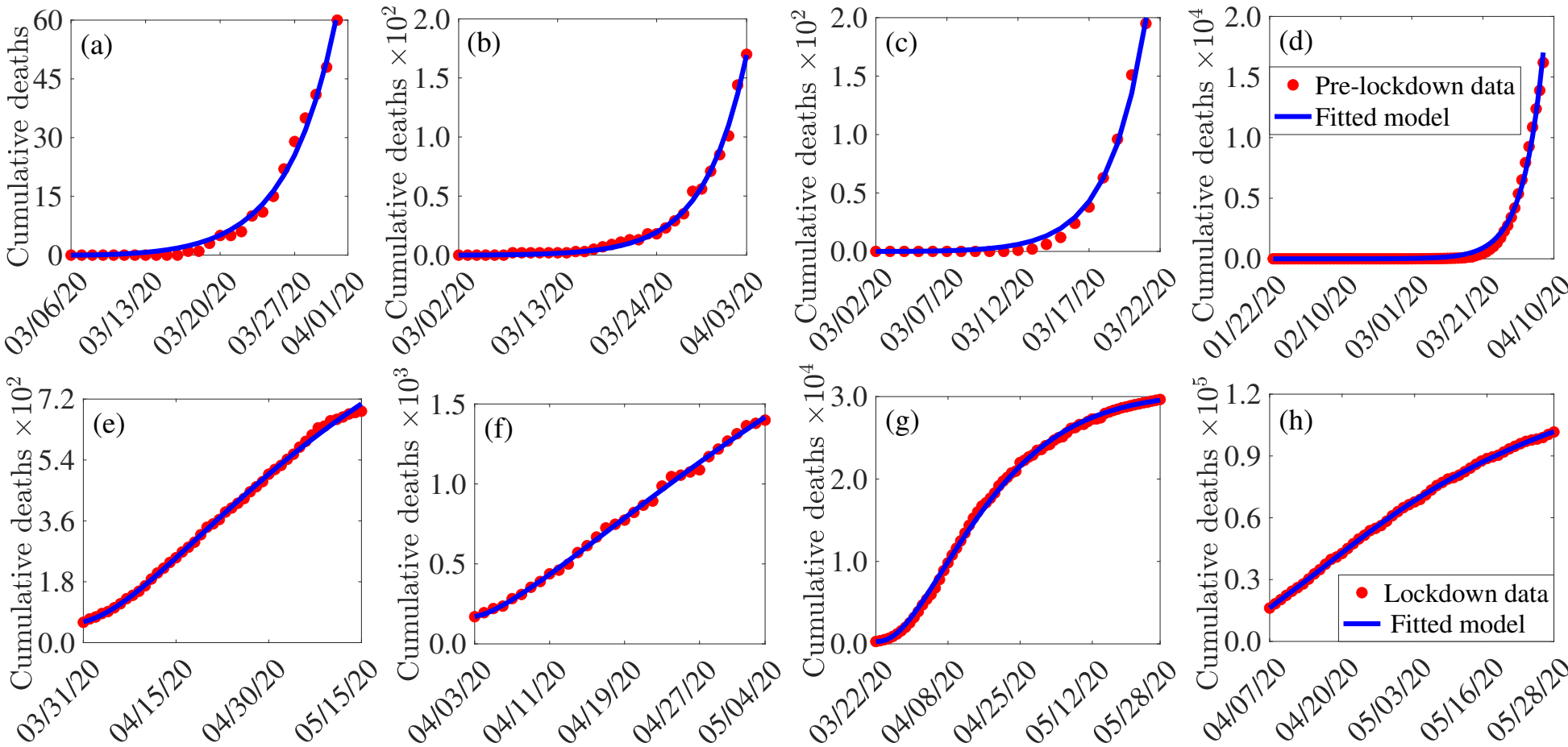
Equations of Mathematical Model

$$
\begin{aligned}
\dot{S} &= -\lambda S,\ \ \dot{E} = \lambda S - (\sigma_e + \tau_d)E,\ \ \dot{E}_p = \sigma_e E - (\sigma_p + \tau_d)E_p,\\
\dot{I}_a &= r\sigma_p E_p - (\gamma_a + \tau_d)I_a,\ \ \dot{I}_m = (1-r)g\sigma_p E_p - \rho_m I_m,\\
\dot{I}_s &= (1-r)(1-g)\sigma_p E_p - (\delta_s + \gamma_s + \rho_s)I_s,\\
\dot{I}_i &= \tau_d(E + E_p + I_a) + \rho_m I_m + (1-f)\rho_s I_s - (\gamma_i + \xi_i + \delta_i)I_i,\\
\dot{I}_h &= f\rho_s I_s + \xi_i I_i - (\gamma_h + \psi_h + \delta_h)I_h,\ \ \dot{I}_c = \psi_h I_h - (\gamma_c + \delta_c)I_c,\\
\dot{R}_u &= \gamma_a I_a + \gamma_s I_s + \gamma_i I_i - \tau_s R_u,\ \ \dot{R}_t = \gamma_h I_h + \gamma_c I_c + \tau_s R_u.
\end{aligned}
$$

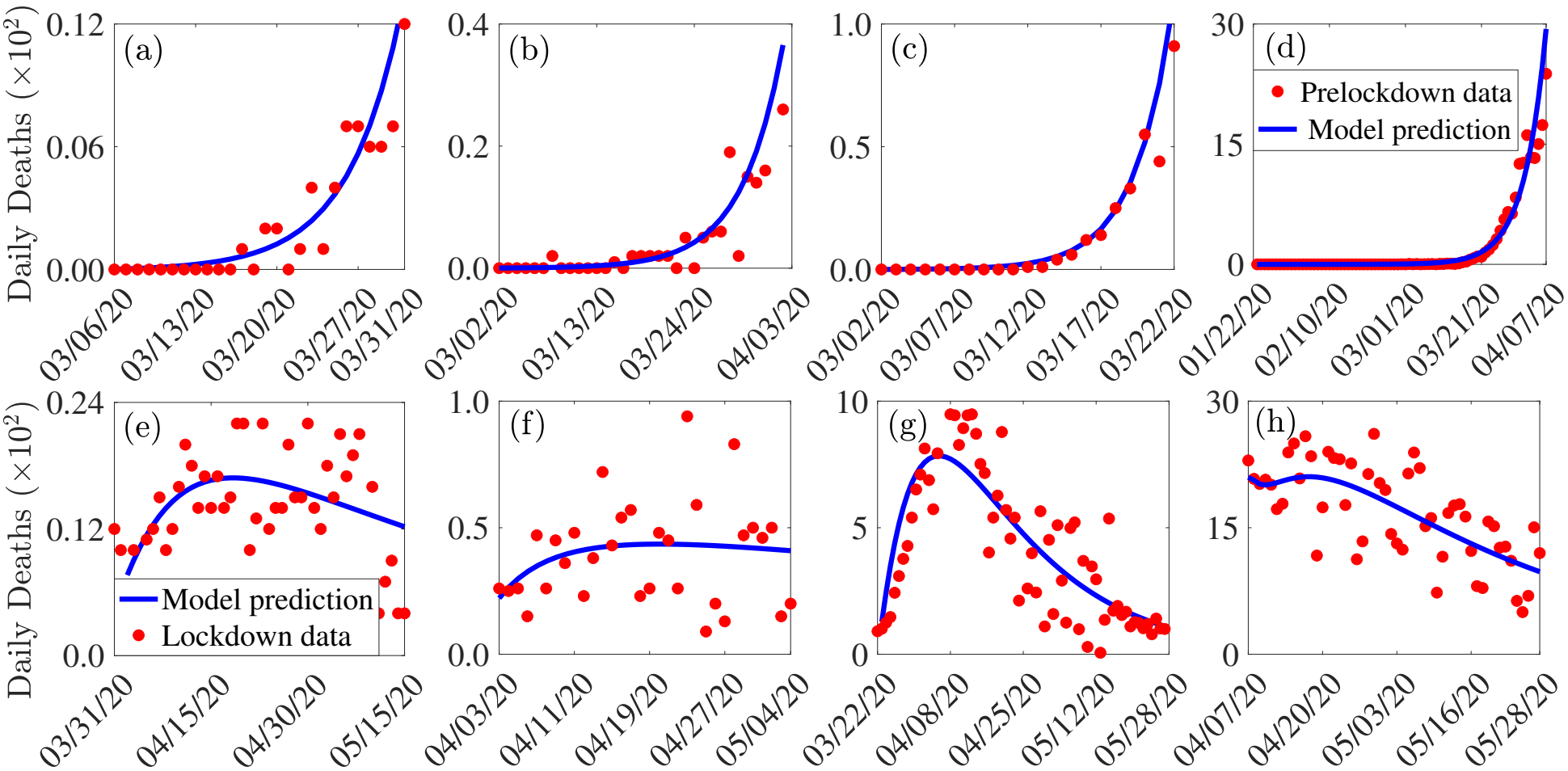
$$
\boxed{\lambda = (1 - \varepsilon_m c_m)\left[\frac{\beta_p E_p + \beta_a I_a + \beta_m I_m + \beta_s I_s}{N - \theta(I_i + I_h + I_c)}\right].}
$$

Ngonghala *et al.* Could masks curtail the post-lockdown resurgence of COVID-19 in the US? Mathematical Biosciences, 2020. Mask types: cloths, surgical/medical, N95 respirators

Fitting Cumulative Deaths Data for AZ, FL, NY and U.S.



Daily Deaths Data



Aim 1: Main drivers of the pandemic in the U.S.

Objective: who (among the four infectious classes) are responsible for most of the infections during the pre-lockdown and lockdown periods?

Based on fitted values of the community contact rates (β_p, β_a, β_s, β_m)

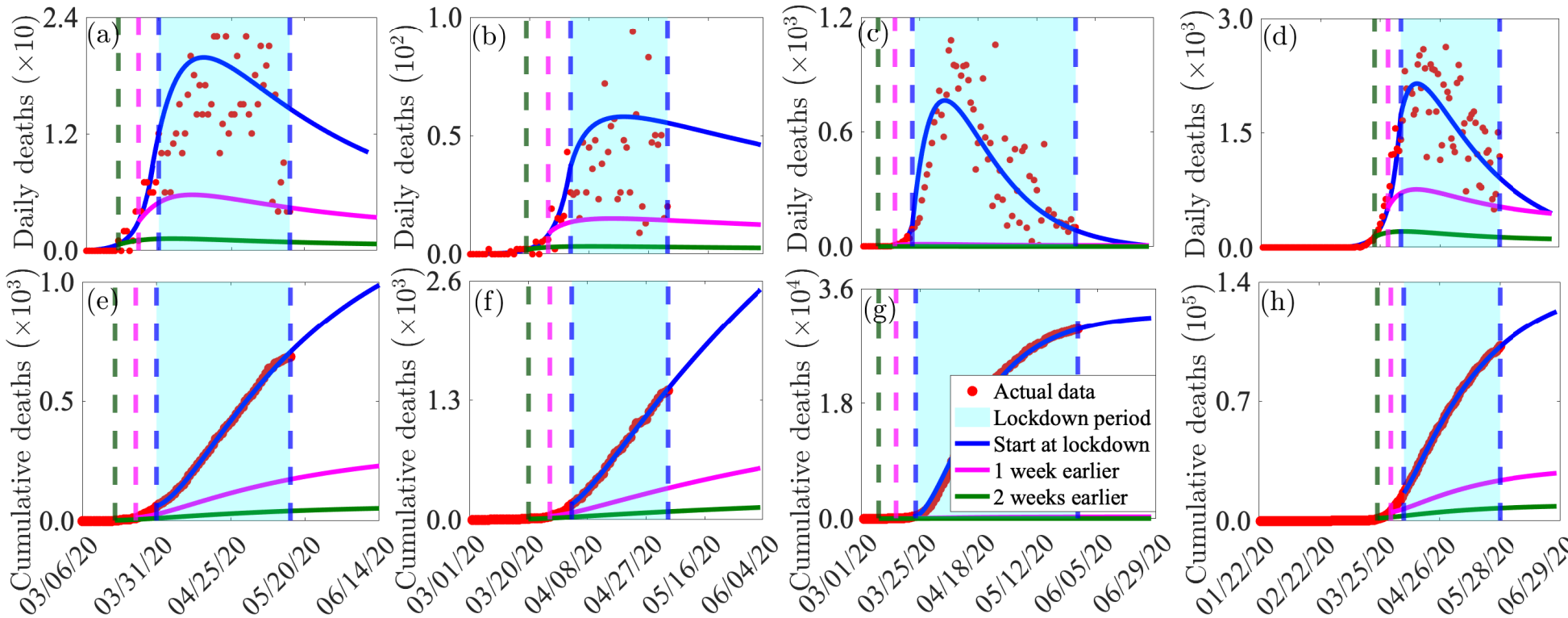
Period	**Transmission source**	**AZ**	**FL**	**NY**	**US**
Pre-lockdown	Pre- & asymptomatic ($E_p + I_a$)	65%	72%	87%	57%
	Symptomatic ($I_m + I_s$)	35%	28%	13%	43%
Lockdown	Pre- & asymptomatic ($E_p + I_a$)	70%	76%	66%	63%
	Symptomatic ($I_m + I_s$)	30%	24%	34%	37%

Majority of cases generated by asymptomatic people (i.e., people who do not even know they had the disease). This emphasize the urgent need for widescale random testing (and tracing and isolation)

Aim 2: Impact of Early Lockdown on Pandemic Trajectory

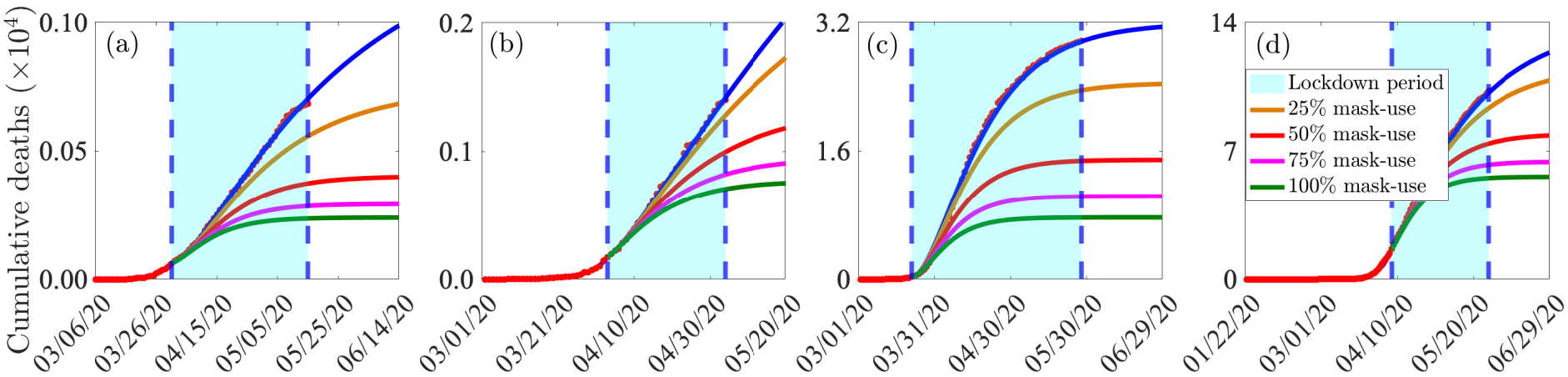
A week before lockdown, NY state had 740 cases and 10 deaths. A week later, number of cases and deaths rose to 15, 885 and 740, resp. Exponential spread phase. "Hit hard, hit early strategy"

Jurisdiction	Pre-lockdown period	Lockdown period
AZ	March 6-31, 2020	March 31-May 15, 2020
FL	March 1- April 3, 2020	April 3-May 4, 2020
NY	March 1-22, 2020	March 22-May 28, 2020
US	January 22-April 7, 2020	April 7-May 28, 2020



Aim 3: Impact of Increased Masking During Lockdown

Mask compliance during lockdown period (obtained from fitting): AZ (14%-17%), FL (16%-21%), NY (15%-21%) and U.S. (18%-23%)



Aim 3: Impact of Increased Masking During Lockdown Ctd.

Actual cumulative mortality on the day lockdown was lifted (Row 2), and cumulative mortality as a function of mask use compliance that would have been recorded on the day lockdown was lifted

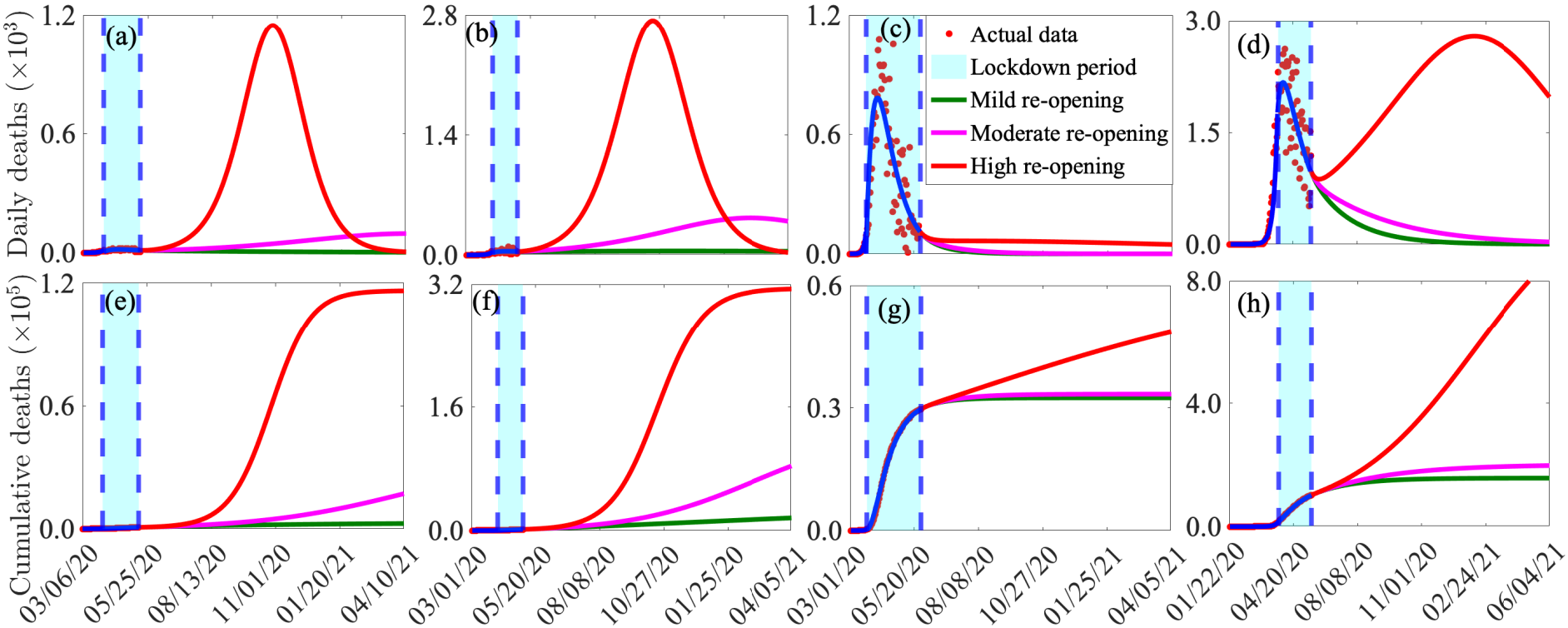
Mask compliance level (c_m)	**AZ**	**FL**	**NY**	**USA**
Baseline mask compliance during lockdown	651	1,399	30,140	105,896
25% mask compliance	558	1,282	23,540	93,410
50% mask compliance	374	996	1,4780	74,030
75% mask compliance	285	819	10,320	62,540
100% mask compliance	236	705	7,682	55,300

Deaths averted on the day of lockdown lifting if certain percentage consistently wore masks during lockdown:

- 50% masks usage during lockdown: up to 30,000 deaths averted
- 100% masks usage during lockdown: up to 50,000 deaths averted

Aim 4: Impact of Increased Masking After Lockdown Lifting

Three levels of lifting of community lockdown measures (mild, moderate, high)



High lifting of lockdown: devastating second waves for AZ and FL in October 2020 and entire U.S. in Feb. 2021 (if control measures are maintained at their lockdown baselines). No second wave for NY state

A Two-group Face Masks Usage Model

Subscript notation: consistently wear face masks (M), no masks (U)

$$
\begin{aligned}
\frac{dS_U}{dt} &= -\beta(I_U+\eta A_U)\frac{S_U}{N}-\beta\left[(1-\varepsilon_o)I_M+(1-\varepsilon_o)\eta A_M\right]\frac{S_U}{N}\\
\frac{dE_U}{dt} &= \beta(I_U+\eta A_U)\frac{S_U}{N}+\beta\left[(1-\varepsilon_o)I_M+(1-\varepsilon_o)\eta A_M\right]\frac{S_U}{N}-\sigma E_U\\
\frac{dI_U}{dt} &= \alpha\sigma E_U-\phi I_U-\gamma_I I_U,\ \frac{dA_U}{dt}=(1-\alpha)\sigma E_U-\gamma_A A_U\\
\frac{dH_U}{dt} &= \phi I_U-\gamma_H H_U-\delta H_U,\ \frac{dR_U}{dt}=\gamma_I I_U+\gamma_A A_U+\gamma_H H_U.
\end{aligned}
$$

$$
\boxed{\frac{dD_U}{dt}=\delta H_U;\ \ \frac{dD_M}{dt}=\delta H_M.}
$$

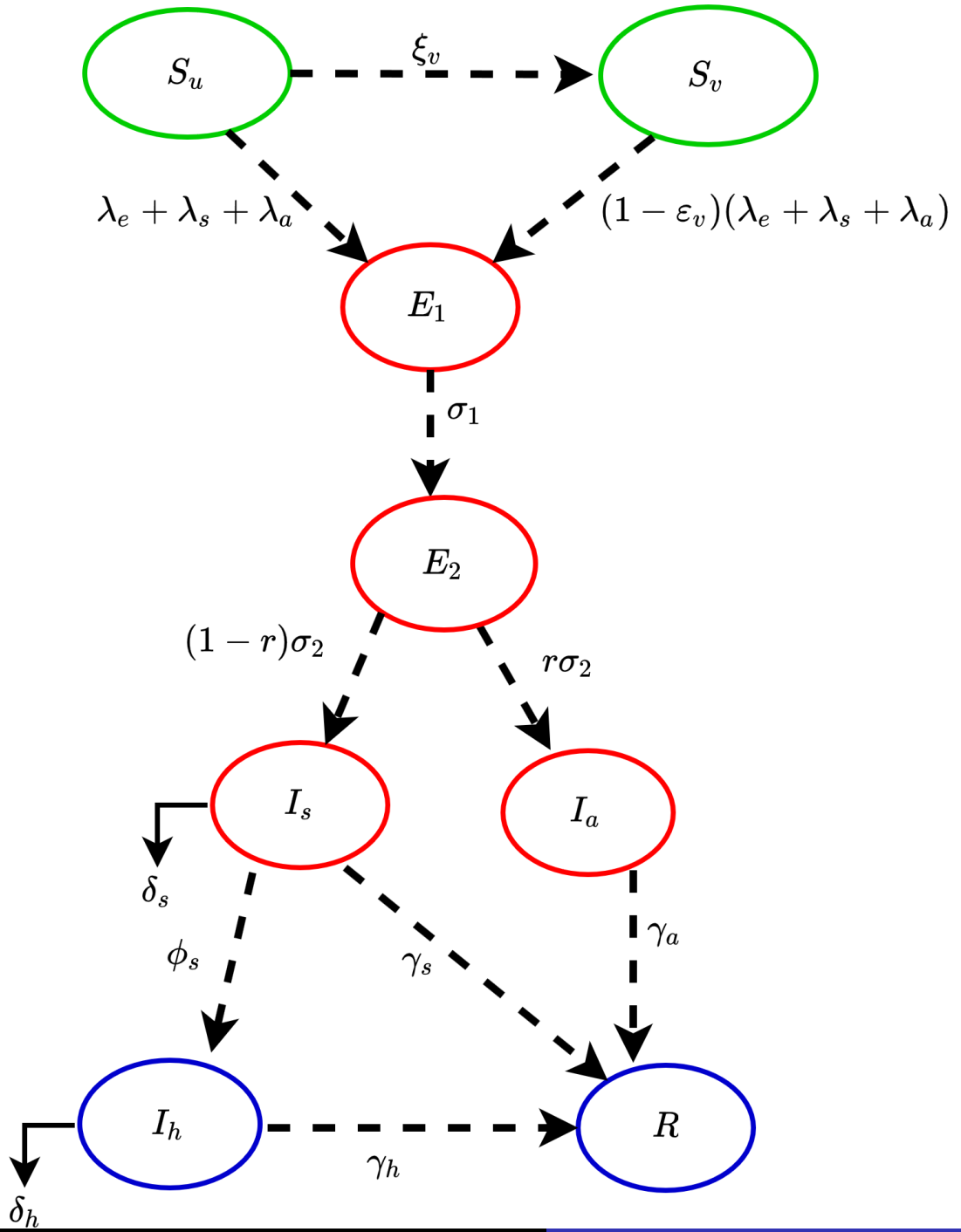
$$
\begin{aligned}
\frac{dS_M}{dt} &= -\beta(1-\varepsilon_i)(I_U+\eta A_U)\frac{S_M}{N} \\
&- \beta(1-\varepsilon_i)\left[(1-\varepsilon_o)I_M+(1-\varepsilon_o)\eta A_M\right]\frac{S_M}{N} \\
\frac{dE_M}{dt} &= \beta(1-\varepsilon_i)(I_U+\eta A_U)\frac{S_M}{N} \\
&+ \beta(1-\varepsilon_i)\left[(1-\varepsilon_o)I_M+(1-\varepsilon_o)\eta A_M\right]\frac{S_M}{N} - \sigma E_M \\
\frac{dI_M}{dt} &= \alpha\sigma E_M - \phi I_M - \gamma_I I_M, \quad \frac{dA_M}{dt} = (1-\alpha)\sigma E_M - \gamma_A A_M \\
\frac{dH_M}{dt} &= \phi I_M - \gamma_H H_M - \delta H_M \quad \frac{dR_M}{dt} = \gamma_I I_M + \gamma_A A_M + \gamma_H H_M.
\end{aligned}
$$

Eikenberry *et al.*. To mask or not to mask: Modeling the potential for face mask use by the general public to curtail the COVID-19 pandemic. Infectious Disease Modeling, 2020

$$
\boxed{\mathbb{R}_0 = \beta_0\left[1+(1-\varepsilon_o)(1-\varepsilon_i)\right]\left[\frac{\alpha\sigma}{\sigma(\phi+\gamma_I)}+\frac{\eta(1-\alpha)}{\gamma_A}\right]}
$$

Could a transmission-blocking vaccine eliminate COVID-19?

State variable	Description
S_u	Population of unvaccinated susceptible individuals
S_v	Population of vaccinated susceptible individuals
E_1	Population of early-exposed individuals
E_2	Population of pre-symptomatic infectious individuals
I_s	Population of symptomatically-infectious individuals
I_a	Population of asymptomatically-infectious individuals
I_h	Population of hospitalized individuals
R	Population of recovered individuals


S_u
ξ_v
S_v
$\lambda_e + \lambda_s + \lambda_a$
$(1-\varepsilon_v)(\lambda_e + \lambda_s + \lambda_a)$
E_1
σ_1
E_2
$(1-r)\sigma_2$
$r\sigma_2$
I_s
I_a
δ_s
ϕ_s
γ_s
γ_a
I_h
R
γ_h
δ_h

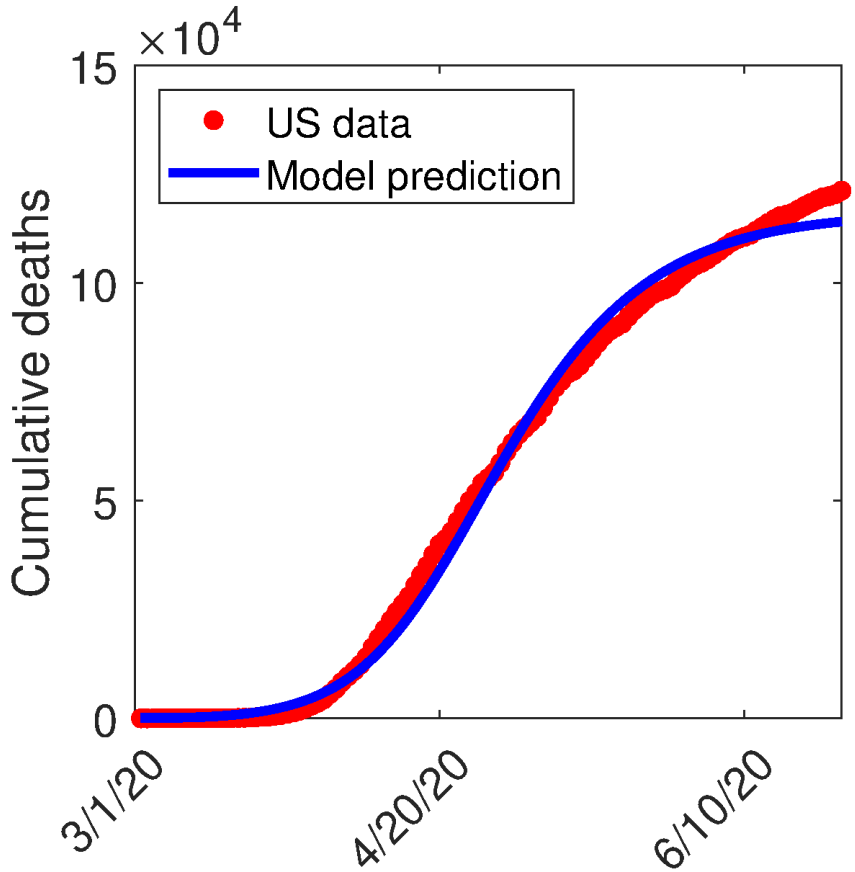
Equations for COVID-19 Vaccination Model

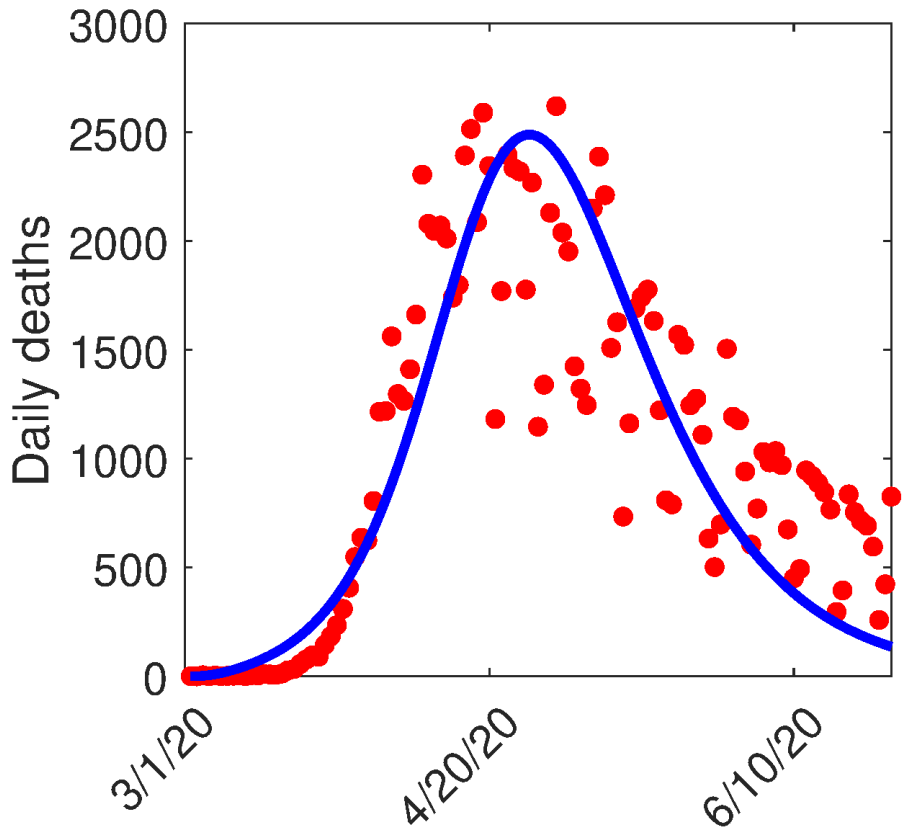
$$
\begin{aligned}
\dot{S}_u &= -(\lambda_e+\lambda_s+\lambda_a)\,S_u-\xi_v S_u,\\
\dot{S}_v &= \xi_v S_u\ -(1-\varepsilon_v)(\lambda_e+\lambda_s+\lambda_a)\,S_v,\\
\dot{E}_1 &= (\lambda_e+\lambda_s+\lambda_a)\,[S_u+(1-\varepsilon_v)S_v]-\sigma_1 E_1,\\
\dot{E}_2 &= \sigma_1 E_1-\sigma_2 E_2,\ \ \dot{I}_s=(1-r)\,\sigma_2\,E_2-(\phi_s+\gamma_s+\delta_s)I_s,\\
\dot{I}_a &= r\,\sigma_2\,E_2-\gamma_a I_a,\ \ \dot{I}_h=\phi_s I_s-(\gamma_h+\delta_h)I_h,\\
\dot{R} &= \gamma_s I_s+\gamma_a I_a+\gamma_h I_h.
\end{aligned}
$$

$$
\lambda_e=\beta_e(1-\varepsilon_M c_M)\frac{E_2}{N},\ \lambda_s=\beta_s(1-\varepsilon_M c_M)\frac{I_s}{N},\ \lambda_a=\beta_a(1-\varepsilon_M c_M)\frac{I_a}{N}
$$

Enahoro *et al.* Will an imperfect vaccine curtail the COVID-19 pandemic in the U.S.? Infectious Disease Modeling, 2020

Data Fitting for Vaccination Model





Herd Immunity Threshold: Impact of increased masking

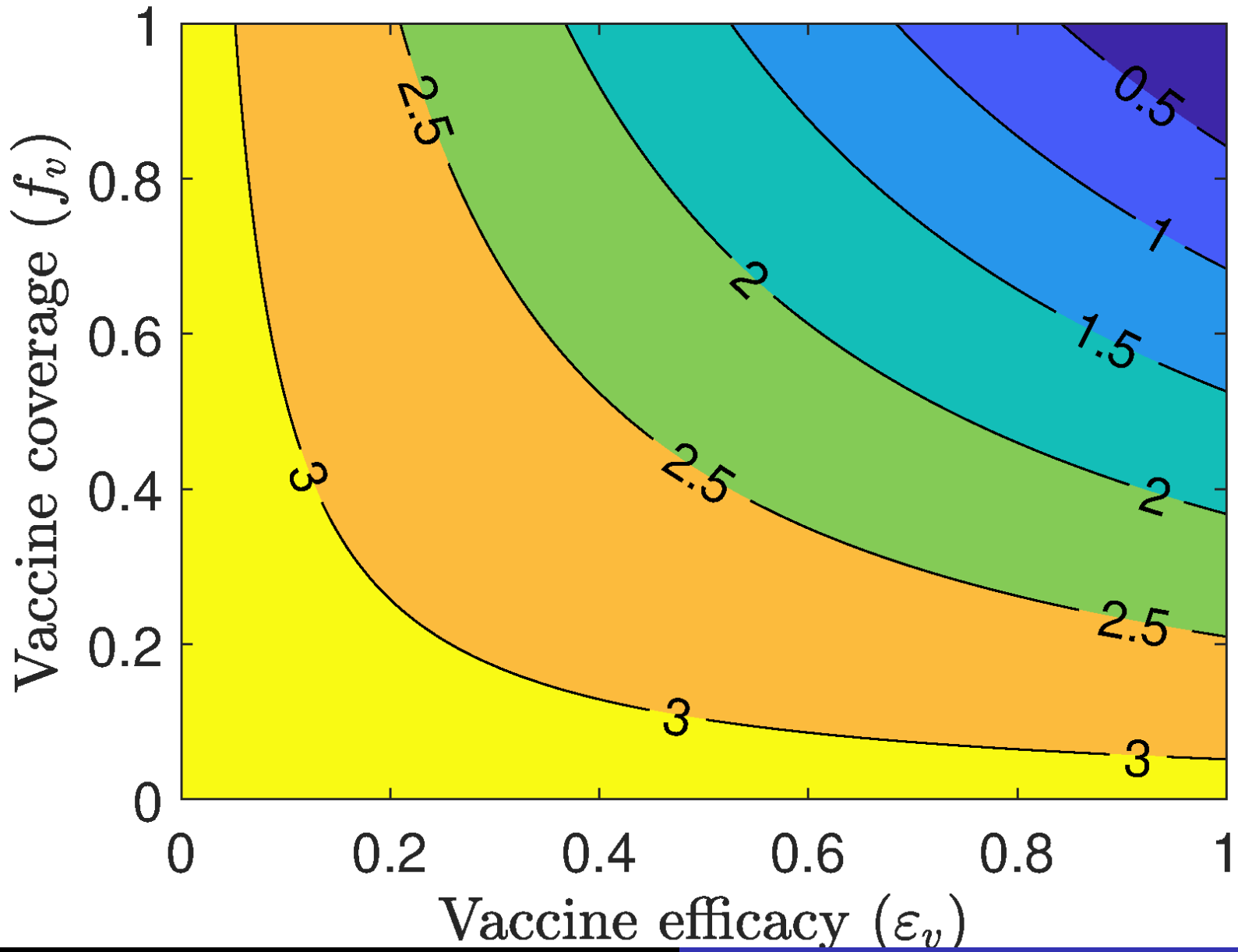
Herd immunity threshold: $f_v = \frac{1}{\varepsilon_v}\left[1 - \frac{1}{\mathscr{R}_0(1-\varepsilon_M c_M)}\right]; \quad \varepsilon_M c_M \neq 1$

c_M	0%	10%	17.04% (baseline)	30%	50%	100%
f_v	85.4%	83.4%	81.8%	78.5%	72.3%	45.9%

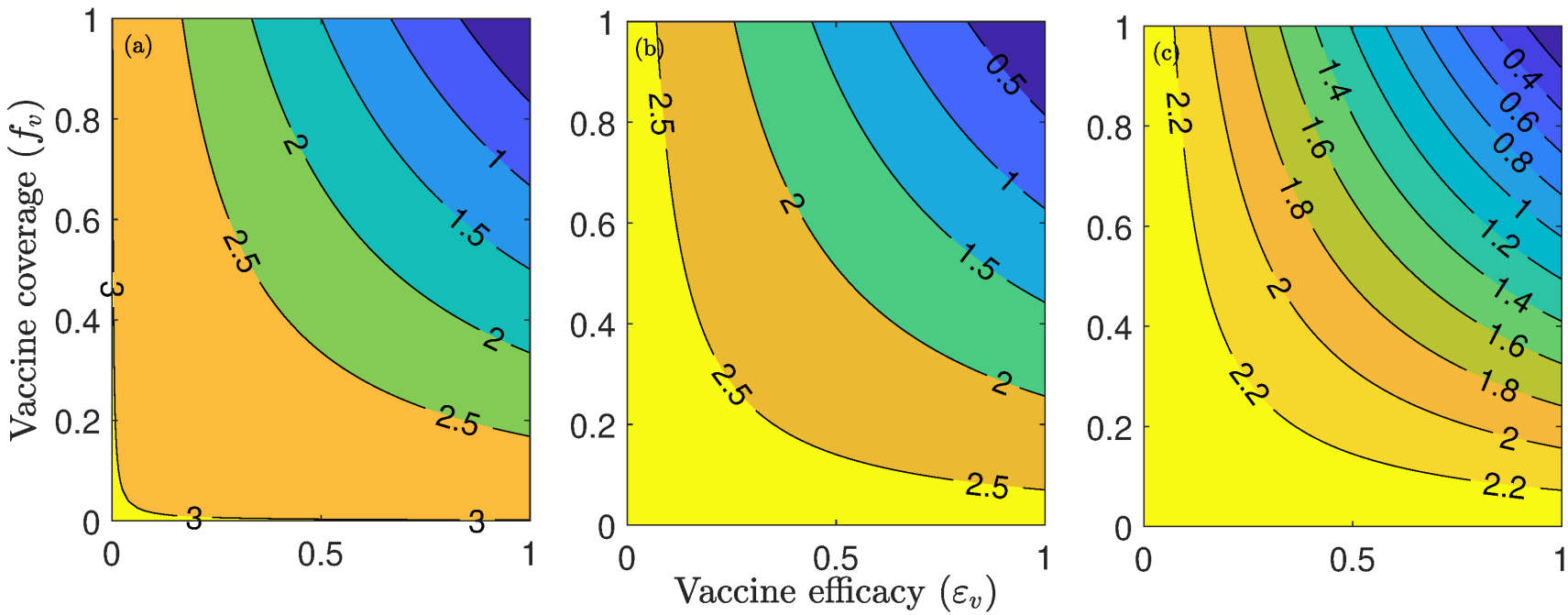
Size of herd immunity threshold may depend on the level of heterogeneity incorporated into the model (Britton *et al.*, 2020)

Britton *et al.* A mathematical model reveals the influence of population heterogeneity on herd immunity to SARS-CoV-2. Science, 2020

Effect of Vaccine Efficacy and Coverage on Disease Burden



Effect of Mask Compliance



Mask compliance (C_M): (a) 10%, (b) 30%, (c) 50%

My Top 10 Mathematical Challenges

- Mathematical analysis of non-autonomous COVID-19 model associated with implementing gradual refinement of control and mitigation interventions and/or seasonality: persistence and bifurcations (Hopf?) assuming endemicity conditions
- Mathematical analysis of a COVID-19 model in a heterogeneously-mixed population (preferential mixing): existence and stability of solutions; bifurcation types
- Dynamics of COVID-19 and seasonal influenza
- Mathematics of risk-structured COVID-19 vaccination model
- Mathematics of a metapopulation model for the U.S.: does the effective suppression of community transmission in one or few states absolve those states from future outbreaks? We are ALL in this together

My Top 10 Mathematical Challenges Ctd.

- Statistical and machine learning tools and theories for integrating social media data to parametrize COVID-19 model
- Statistical tools for avoiding identifiability challenges in fitting COVID-19 models (multiple local minima)
- Uncertainty quantification and sensitivity analysis of COVID-19 models (model reduction?)
- Using zoonotic data for dynamics of coronaviruses in the wild (epidemic intelligence) to effectively predict the probability of a spillover that could trigger human pandemics
- Designing numerical methods that capture the correct asymptotic stability and bifurcations of COVID-19 model