

## **Infectious Disease Transmission Models to Predict, Evaluate, and Improve Understanding of SARS-COV-2 Trajectory and Interventions**

Andrea G. Buchwald, PhD<sup>1</sup>, Jimi Adams, PhD<sup>2</sup>, David M. Bortz, PhD<sup>3</sup>, Elizabeth J. Carlton, PhD<sup>1</sup>

<sup>1</sup>Department of Environmental and Occupational Health, Colorado School of Public Health, University of Colorado, Anschutz, Aurora, CO, USA

<sup>2</sup>Health & Behavioral Sciences, University of Colorado Denver, Denver, CO, USA

<sup>3</sup>Applied Mathematics, University of Colorado Boulder, Boulder, CO, USA

### **Corresponding Author:**

Andrea G. Buchwald

13001 E. 17<sup>th</sup> Place

Aurora, CO 80045

[andrea.buchwald@cuanschutz.edu](mailto:andrea.buchwald@cuanschutz.edu)

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COVID-19 has spread rapidly around the world with devastating consequences. Large questions loom about how this epidemic will proceed and what interventions can slow the spread. In the face of a global pandemic with a novel infectious agent, policymakers face the difficult task of deciding how and when to adopt measures to control COVID-19 - measures with profound economic and social impacts [1]. They face the extraordinarily difficult challenge of finding balance between a societally tolerable burden of death on one side, and economic activity and returning towards normalcy on the other. Mathematical models of infectious disease transmission serve a key role in guiding government response, they provide a framework for evaluating the potential impact of different policies – from mask wearing to relaxation of social distancing - on the course of the epidemic, on the expected number of lives lost, and whether and when hospital capacity may be exceeded. We are working with the state of Colorado, using transmission models to help policy makers predict the future course of the epidemic, and estimate the potential impact of interventions to slow the spread of SARS-CoV-2. Given the critical role of infectious disease models in this pandemic, it is important to understand their strengths and limitations, as well as why different models may yield conflicting results.

## **Modeling Infectious Disease Epidemics**

Transmission models have been used to predict the duration and magnitude of infectious outbreaks, evaluate the potential impact of interventions, and estimate important biological and clinical parameters. They are particularly well-suited for the early stages of an outbreak as they make lean use of sparse data. The model employed is, ideally, defined by the question of

interest – and tailored to specific pathogens. This approach has proven extraordinarily powerful, providing insights into the drivers of disease dynamics as well as a framework to explore the impact and efficacy of numerous mitigation strategies.

The application of mathematical modeling to infectious diseases is dated to the 1600s. The work of Kermack and McKendrick early in the 20<sup>th</sup> century led to the now standard partitioning of a population into Susceptible, Infectious, and Immune (or Recovered) categories that make up an SIR model [2]. This formulation prioritizes the flux between categories, particularly the transmission rate, i.e., the rate of population transition from Susceptible to Infectious. SIR models can be either deterministic or stochastic, and complexity can be increased to tailor the models to the characteristics of specific pathogens, accounting for variations in incubation periods, symptom severity, and multiple transmission pathways, as seen with the Colorado model (Figure 1). SIR models can be extended further into a meta-population framework [3] and, with modern computing capacity, agent-based models (ABMs) can simulate a population of individuals—rather than compartments – with complex demographic and behavioral profiles interacting to spread pathogens [4].

With any model, estimates and predictions are only as good as their assumptions and are highly dependent on data quality, which may be limited early in an epidemic. In the 2014-2015 Ebola epidemic, most models overestimated the severity of the outbreak due to insufficient data and multiple unknowns [5]. However, mathematical models have shown great utility in predicting influenza outbreaks, particularly in the context of reliable data sources [6]. Additionally, while technology offers the opportunity to create ever more complex models, for every additional element of complexity, an additional set of assumptions is required [7]. These

expanding assumptions create an inherent tension between complexity and parsimony and bolster the need for transparency about model assumptions and data sources among researchers so that results of different models can be compared and interpreted.

## **Transmission Modeling during the COVID-19 Pandemic**

In the early phase of the pandemic, transmission models were used to estimate basic characteristics of SARS-CoV-2, including the proportion of cases detected by surveillance systems and differences in infectiousness among detected and undetected cases [e.g., 8]. For these purposes, researchers have developed transmission models and by comparing model projections to observed data, they infer unknown parameter values.

Transmission models are also being used to estimate the impact of interventions by simulating the future course of the pandemic under different intervention scenarios. Modelers at Imperial College published a set of projections in March that had widespread impact on policy and public opinion. Using an ABM incorporating high-resolution population density and human interactions, they projected dire levels of hospitalizations and deaths under all but the most intense intervention scenarios, and concluded that population-level social-distancing measures, in combination with case containment, would be necessary for months to avoid exceeding hospital capacity [9], and the relaxation of such measures is likely to produce resurgent curves [10].

Such transmission models are useful for guiding national policies, but the course of the epidemic varies widely across localities and therefore models must be tailored to local

conditions. In Colorado, our group developed an SIR-based model in collaboration with state officials to evaluate the impacts of state-level policy measures retrospectively and to project the impacts of future measures on hospital demand and deaths [11]. Our model extends the basic SIR framework to account for the viral incubation period, asymptomatic infections, and to incorporate the impact of age structure on disease progression (Figure 1). The model is fit to local COVID-19 data and uses statewide hospital and ICU capacity estimates specific to Colorado. We have responded to direct requests from state government and designed the model specifically to answer policy-based questions about the outbreak trajectory and hospital and ICU needs (Figure 2). We've additionally been asked to quantify the impact of policy on the epidemic shortly after implementation. Other models have been developed to provide estimates of healthcare needs, most notably the COVID-19 Hospital Impact Model for Epidemics (<https://penn-chime.phl.io/>). The CHIME model allowed hospitals to generate estimates of hospital demand early in the epidemic but suffers in its simplification of locality-specific data fitting.

One consequential outlier in public prediction models has been the model developed by the Institute for Health Metrics and Evaluation [12]. It began, not as a mechanistic transmission model that explicitly models infection spread, instead, it used deaths as an indicator variable, back-calculating expected hospitalization and ICU usage via curve-fitting techniques. Despite recent updates that now add the implications of relaxing social distancing, IHME's estimated epidemic trajectory still diverges from those of other transmission models, particularly by not predicting a second wave of infections [13].

## Models and Decision-Making

Modeling teams must be transparent about their model's assumptions and update these assumptions as understanding of COVID-19 evolves, which will unquestionably lead to changes in projections with time and experience.

How should decision-makers decide which model to believe and use in decision-making? As scientists, we look for consistency [14]: Ideally, multiple models executed by different teams converge on similar conclusions, strengthening our confidence in these findings [15]. When projections from different groups do not converge, policymakers face the difficult task of incorporating seemingly conflicting information from these models. Ideally, policy and practice decisions should be based on a range of models employing different structures and assumptions, rather than depending on a single approach. As of this writing in May 2020, there is near consensus that complete relaxation of social distancing could lead to a catastrophic second wave of infections.

Infectious disease transmission models initially developed more than a century ago will continue to play an important role in informing response to COVID-19. The optimal use of such models requires clear communication about their underlying assumptions, ongoing refinement to reflect the current state of the science, and policymaking informed by the conclusions of multiple models.

**Figure Legends:**

**Figure 1.** The structure of the SEIR model used to model the SARS-CoV-2 outbreak in Colorado. Infected individuals are separated into asymptomatic and symptomatic compartments. The asymptomatic individuals are assumed to be less infectious but circulate in society whereas the symptomatic individuals are assumed to be more infectious but some proportion of them self-isolate following onset of symptoms.

**Figure 2.** Projected Covid-19 hospitalizations (left) and ICU need (right) in Colorado under varying intervention scenarios using and SEIR model. Bold lines show projected policies for promoting social distancing at different intensities, and dotted lines shows combined interventions including both social distancing as well as mask wearing by the general public. Social distancing is modeled as a percent reduction in the contact rate where, for example, 65% social distancing is a 65% reduction in close contacts between individuals. Grey horizontal line indicates ICU capacity of 1,800 beds. Full modeling details are provided in (Buchwald et al 2020).

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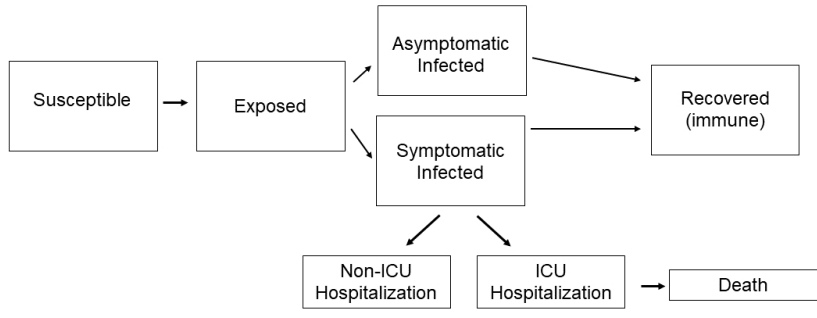


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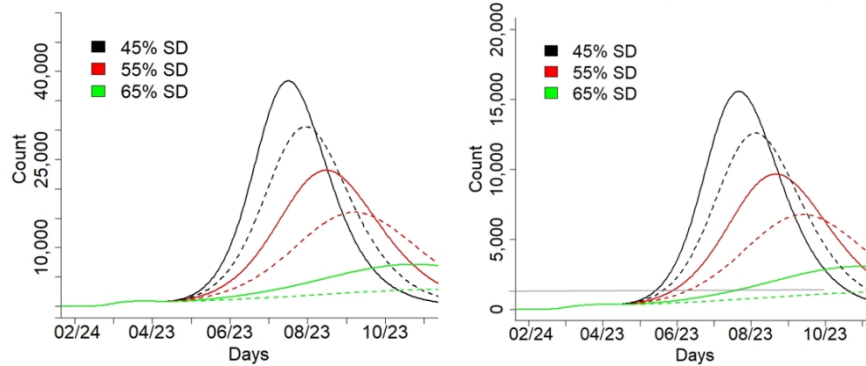


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