7 Applications of SIR-family Models

This week, we'll turn to a set of applications of the models and concepts introduced in class so far. To do so, we'll read and discuss a set of important papers in the recent literature, which will be facilitated by these Lecture Notes. Our goal is therefore not to recapitulate each paper in its entirety, but instead prepare you to read the paper and understand its technical content.

7.1 Kissler and Tedijanto et al., 2020

In Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period by Kissler, Tedijanto, Goldstein, Grad, and Lipsitch (and its Supplemental Materials), the authors try to understand what the future of SARS-CoV-2 and COVID-19 might be, from the difficult vantage point of February, 2020. To do so, they introduce two classes of models, each designed to answer a different question.

The first model asks what the possible future scenarios might be for SARS-CoV-2 transmission in the absence of interventions *but* in the presence of other, related circulating coronaviruses. The second model considers COVID-19 hospitalization and critical care needs, compares them to the U.S.'s capacity, and asks what kinds of interventions we need to avoid exceeding our capacity. You might think of the first model as asking "what happens to y if x is such and such" questions, and the second model as "fix y and then solve for x" type questions.

To prepare you to read Kissler and Tedijanto et al., we'll need to introduce a set of key concepts along with how those concepts are modeled.

1. The **effective reproductive number** R_e is the average number of secondary infections caused by a single infected individual in a population where there is some immunity or interventions have been put in place. In other words, if R_0 is the typical number of secondary cases when everyone is susceptible (and immunologically naïve), then R_e is what happens when immunity is involved.[1]

   Importantly, when $R_e < 1$ infections are in decline. If vaccines are used to achieve $R_e < 1$, one might call this point herd immunity through imperfect vaccination. Indeed, we previously described this as $vVE < 1 - \frac{1}{R_0}$, but another way of writing this is to note that $R_e = (1-v)\,R_0 + v\,(1-VE)\,R_0$ and ask that $R_e < 1$.[2] In general, the goal of transmission-reducing interventions is to achieve $R_e < 1$.

2. **Betacoronaviruses**. The family *Coronaviridae* includes many coronaviruses, which are large, enveloped RNA viruses. Figure 1 shows a neighbor-joining tree of 50 coronaviruses from Chan et al 2015, primarily discussing MERS-CoV which is in clade βCoV-C. For reference, SARS-CoV-1 and SARS-CoV-2 lie in the clade βCoV-B. In Kissler and Tedijanto et al., the authors also discuss two

[1] Revisit our derivation of R_0 for the SIR model and consider what would happen if, instead of $s = 1$, you considered a value of $s < 1$. Such a calculation could lead you to derive R_e for the case that not everyone is susceptible, i.e. some folks in the population are already immune.

[2] Notice that R_e is proportional to R_0, and that the proportionality constant depends on v and VE.

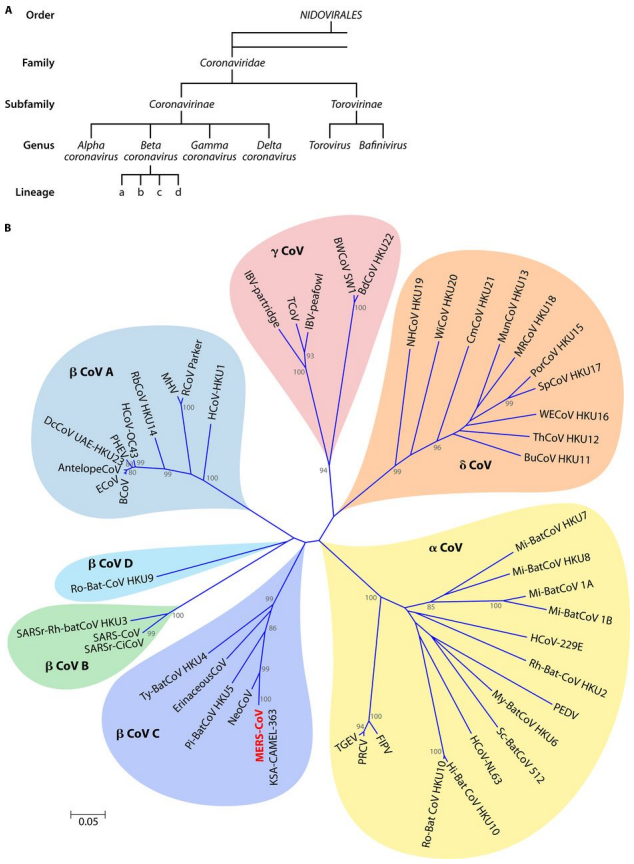

Figure 1: This phylogenetic tree of the subfamily *Coronavirinae*, using the neighbor-joining method, is Figure 1 from Chan et al 2015, in which the focus was MERS-CoV (highlighted in red text). Note that SARS-CoV-2 is now classified with SARS-CoV-1 in clade βCoV-B.

coronaviruses which cause the common cold, both of which lie in clade β CoV-A. Note that there are also α, δ, and γ coronaviruses.

3. **Cross-immunity** refers to the phenomenon that infection with one pathogen may confer immunity to that pathogen as well as those that are antigenically similar. Kissler and Tedijanto et al. discuss how the future of SARS-CoV-2 circulation may depend on the levels (and duration) of cross immunity from HCoV-OC43 and HCoV-HKU1 to each other and to SARS-CoV-2. Another example of cross immunity is that recovery from a ZIKV infection appears to confer protection against DENV infection.[3]

[3] See Ribeiro and Kikuti et al., 2018.

How might one model cross-immunity? For a two-strain model, one way to do this is for those who remain in the R compartment for disease 1 to be less susceptible to disease 2, and vice versa. To draw a comparison, we have previously modeled the effect of a leaky vaccine as making vaccinated individuals less susceptible to infection by decreasing the force of infection by a factor $1 - VE$. Similarly, one can model the effect of cross immunity as decreasing the force of infection of one disease for those who have recovered from the other.

4. The **case fatality rate (CFR)** is the proportion of people who die from a disease (numerator) among all individuals *diagnosed* over a certain period of time (denominator). Note that the CFR is not the same as the **infection fatality rate (IFR)** which is the proportion of people who die from a disease among all individuals *infected* over a certain period of time. Typically, if symptoms and severe disease are involved in the diagnosis of infection, then CFR $>$ IFR.

5. **Influenza-like illness (ILI)** is a medical diagnosis, not a particular disease. ILI symptoms include fever, chills, cough, aches, and nausea. You might think of ILI as "the flu and other things that present like the flu." In fact, as you may know from your own post-vaccination experiences, many of these symptoms are caused by the body's immune response. Most typically, ILI is associated with the flu and common colds.

   Why monitor ILI instead of separately monitoring influenza and common colds (e.g. coronavirus or rhinovirus, separately)? Here, consider resource constraints in global health, and the value of global or national surveillance programs which do not rely on RT-PCR reagents and laboratories.

6. **The SEIR and SEIRS models** are variations on the SIR model. The E compartment stands for Exposed, and allows the model to account for the fact that for some infectious diseases (including COVID-19) there exists a time early during an infection when an individual is exposed and infected, yet not yet infectious to others. Most typically, newly infected individuals enter the E compartment and then flow to the I compartment at a rate ν.[4]

   The second S compartment refers to Susceptible, and is written after R to remind us that, in this model, those who are recovered eventually return to susceptibility. Thus, the SEIR model does not include a loss of immunity following recovery, while the SEIRS model does. Note that the rate at which individuals move from $R \to S$ dictates the typical amount of time that one spends in the R compartment (with its concomitant immunity). As a consequence, if one specifies an SEIRS model, one must specify a typical duration of immunity.

7. **Seasonal and geographic variation** may affect both R_0 and the extent to which R_0 is reduced (or enhanced) seasonally. To understand this important point, consider a respiratory virus whose transmission is facilitated by (1) population density, (2) a propensity to gather indoors (vs outdoors), and

[4] While β and γ are almost always used in SIR-family models for infectiousness and recovery, respectively, the flow from $E \to I$ takes on many letters, typically Greek, and often ν, σ, or α. Kissler and Tedijanto et al. use ν.

(3) lower absolute humidity.[5] Now consider the difference between Toronto and El Paso. Not only should we expect that R_0 will be higher in Toronto vs El Paso, but we should also expect that the difference between winter and summer R_0 should also be larger in Toronto vs El Paso.

How can one trust a model whose key parameters not only vary over space and time, but whose parameters' magnitudes of variation, themselves, vary? In Kissler and Tedijanto et al. the authors employ a common approach called a **sensitivity analysis**, in which parameters are varied over a range of plausible values in order to answer two questions. First, when measuring a quantitative outcome (e.g. total epidemic size, or total mortality), how much does the outcome vary over the range of plausible parameters? Second, when measuring a qualitative outcome (e.g. SARS-CoV-2 transmission settles into a seasonal pattern), does the category of outcome change over the range of plausible parameters? Critically, a sensitivity analysis is typically interesting no matter whether the answer is "yes, things change" or "no, nothing changes." We learn something in either case.

8. **Non-pharmaceutical interventions (NPIs)**, which contrast pharmaceutical interventions such as medicines and vaccines, represent a broad category of transmission countermeasures that rely on behavioral changes, voluntary or involuntary. In this light, masking and handwashing, but so too are travel restrictions, border closings, and forced quarantine and isolation. The term **social distancing** refers to the general set of NPIs whose goal is to prevent infectious people from coming into contact with susceptible people.

   NPIs are important because they can be implemented in practice in a variety of ways. For instance, education around handwashing has helped to deploy this powerful NPI against past outbreaks of *Shigella* bacteria[6] in Chasidic Jewish communities in New York City. Interestingly, those communities wash their hands frequently but ritualistically—a religious practice that need not involve soap and scrubbing. The NPI in this case was well-designed education, creating habits of soap-and-water handwashing in conjunction with prayer (Fig. 2).

   How do we model NPIs? The answer depends on the particular way in which the NPI affects transmission. If the effect of the NPI is to decrease the rate at which people come into contact, or to decrease the probability that a contact results in an infection, both effects may be captured by multiplying the term β by a constant less than one. For NPIs that affect transmission in other ways, including bednets for mosquito-borne diseases, models can be modified in other ways with the goal of including parameters that attenuate or exacerbate the problematic or valuable mechanism in question.

9. **Critical care capacity** describes the total number of available hospital beds for critical care that are available in a particular area (city, state, region, or country). In the event that an epidemic or pandemic leads to a critical care need that exceeds this capacity, individuals who might otherwise survive an

[5] See e.g., Shaman & Kohn.

[6] Shigella bacteria causeshigellosis, a diarrheal disease. Typically, transmission is fecal-oral, making handwashing a valuable NPI. Not also that there are types of *E. coli* that produce something called shiga toxin (Stx) that also leads to diarrhea. In spite of their phonetic similarity, Shigella and shiga toxin are unrelated.

Figure 2: These posters exemplify a simple NPI (handwashing) and a campaign to deploy it (educational posters). The posters show the same content, in both English and Yiddish, and here are made to carry the message to adults (left) and children (right). The final step is prayer, specifically the prayer spoken after using the toilet. These posters were created through NYC Health Department in 2008.

illness may instead die.

10. Though not a commonly used term, the authors of Kissler and Tedijanto et al. refer to the **pandemic establishment time** as a parameter that they investigated in their model. From the perspective of this course, we might think of this parameter as the initial conditions of the model: *when*, during the course of a year with typical betacoronavirus infections, does the pandemic SARS-CoV-2 arrive? Might it matter if the pandemic establishment time is in the winter vs the summer?

11. **Exponential vs Gamma wait times.** As we learned in homework 1, a flow from one compartment to another at a given rate (e.g. from $I \to R$ at per-capita rate γ) results, mathematically, in an exponential distribution of wait times. It turns out that this distribution is not particularly realistic: the most common (modal) wait time is zero, the mean is γ^{-1} and the median is $\gamma^{-1} \ln 2$, in fact! However, it also turns out that it is possible to use a clever trick[7] to switch from exponential wait times to Gamma wait times, which are more realistic, without a considerable increase in computational cost. How?

    Here is the trick: instead of a single compartment from which individuals leave at rate σ, create n compartments in sequence from which individuals leave at rate $n\sigma$. Why does this work? Here are some helpful facts:

    - The sum of n independent Gamma random variables with shape k and scale θ is a single Gamma

[7] Here we use the term "trick" loosely. In fact, an important adage of mathematics states: *if it works once it's a trick; if it works twice, it's a method.*

random variable with shape nk and scale θ.

- An exponential random variable is a special case of the Gamma random variable with shape $k = 1$ and scale θ.[8]
- The scale θ is related to the rate σ by $\theta = \sigma^{-1}$.
- Therefore the sum of n independent exponentials with the same rates σ is a Gamma with rate σ and shape $k = n$.
- Bonus: when a Gamma distribution has an integer shape, it is also called an Erlang distribution.[9]

If this is a topic that interests you, I would recommend further reading beginning with the brief but wonderful paper Appropriate Models for the Management of Infectious Diseases by Wearing, Rohani, and Keeling, 2005.

Finally, with those 11 points of background established, let us examine the structure of the two models used by the authors. The first model (Figure 3) is a two-strain model SEIRS model (extended in practice, but not in diagram, to a three-strain model). Its goal was to understand how the future dynamics of pandemic SARS-CoV-2 might develop over the years 2020-2025, in the context of the two other major betacoronaviruses.

The second model (Figure 4) shows an SEIR model that includes hospitalization and critical care. Its goal was to understand how NPIs in the form of social distancing might be used to avoid exceeding critical care capacity.

7.2 Medlock and Galvani, 2009

In Optimizing Influenza Vaccine Distribution by Medlock and Galvani (and its Supplemental Materials), the authors use models to explore optimal vaccine allocation. To do so, they draw on five different lenses through which one might argue optimality. They also use the age-structured contact patterns introduced by Mossong et al (see previous week's Lecture Notes). You will also see broad use of sensitivity analyses, which the authors use to explore a variety of conditions.

The paper contains one general model, which is an age-structured SEIR model of a leaky vaccine (and later, a two-factor vaccine with reductions in susceptibility and mortality). As is common, the flow diagram avoids showing the age-contact structure, and instead shows the single-age flow (Fig. 5). To this model structure, the authors consider a variety of influenza strains (i.e. sets of age-specific mortality estimates) and a continuum of vaccination strategies. As before, we will now introduce and discuss a set of key concepts that will help you read this paper.

[8] And, a χ^2 distribution with m degrees of freedom is a special case of the Gamma distribution with shape $m/2$ and scale 2.

[9] The Erlang distribution is named after Agner Krarup Erlang who had a remarkable beard and made foundational contributions in the early 1900s to traffic engineering, queuing theory, and telecommunications. The international unit of telephone traffic is, today, called an *erlang*. Now, why is a Gamma distribution called a Gamma distribution? I have no idea.

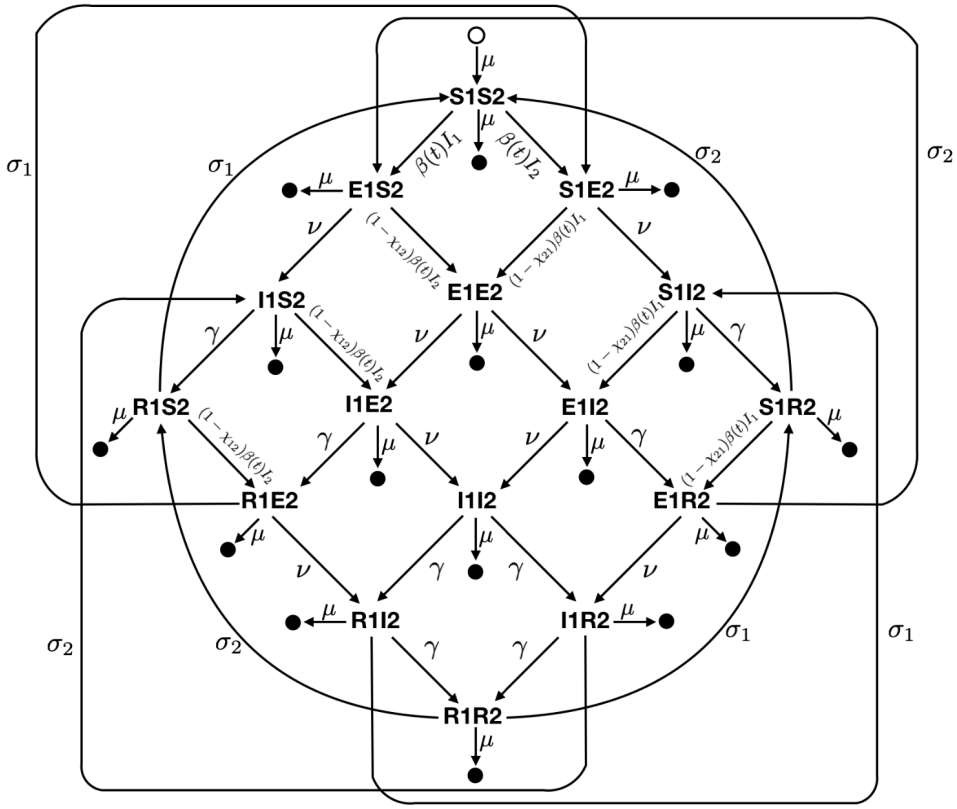

Figure S4. Schematic diagram of the two-strain SEIRS transmission model. Diagram of the two-strain compartmental SEIRS model used to describe the transmission of HCoV-OC43 and HCoV-HKU1 in the United States. Epidemiological compartments are represented by the bold letter-number pairs, such that an individual in compartment S1S2 is susceptible to both strains, while a person in compartment I1E2 is infectious with strain 1 and has been exposed to strain 2. Filled circles represent death and the open circle represents births. Transition rates are given next to the arrows between compartments. Estimated parameter values are listed in **Table S8**.

Figure 3: Figure from Kissler and Tedijanto et al. with original caption included.

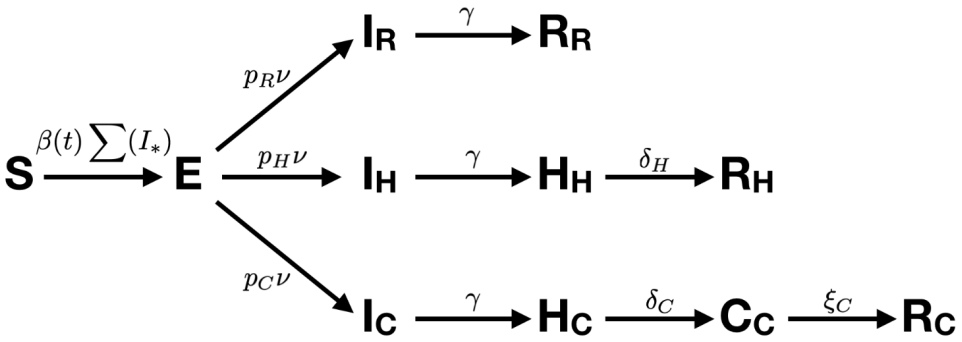

Figure S9. Schematic diagram of the SARS-CoV-2 transmission model accounting for hospitalizations and critical care. The population begins as susceptible (S). Infection is introduced through a half-week pulse in the force of infection of 0.01/week starting on 11 Mar 2020. The transmission rate $\beta(t)$ is a cosine with 52-week period parametrized by a phase shift (ϕ), a maximum value (max(R_0)), and a seasonal forcing factor (f), with values given in **Table S8**. Infected individuals then proceed to an exposed (E) state, after which a proportion $p_R = 0.956$ enters the 'recovery' arm, $p_H = 0.0308$ enters the 'hospitalization' arm, and $p_C = 0.0132$ enters the 'critical care' arm. Exposed individuals become infectious (I) at rate $\nu = 1/4.6$ days. Individuals in the recovery arm then recover (R) at rate $\gamma = 1/5$ days, but individuals in the hospitalization arm must pass through the hospitalization state (H) and individuals in the critical care arm must pass through both the hospitalization (H) and critical care (C) states. The average duration of hospitalization was $1/d_H = 8$ days in the hospitalization arm and $1/d_C = 6$ days in the critical care arm (*26*). The average duration of critical care was $1/\xi_C = 10$ days (*26*).

Figure 4: Figure from Kissler and Tedijanto et al. with original caption included.

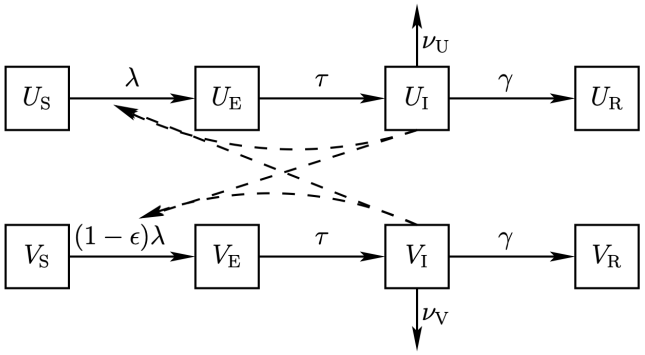

Figure S1: Model diagram without age structure. The solid lines indicate transitions of individuals to different infection states. The dotted lines represent transmission routes.

Figure 5: Figure from Medlock and Galvani with original caption included.

1. A **vaccine distribution strategy** is a strategy for administering limited doses across a population. Two other terms of art are common in the literature and sound the same but are not: **vaccine allocation strategy** typically refers to strategy for vaccine distribution between countries or other geographies, while **vaccine prioritization strategy** typically refers to strategy for vaccine distribution within a country. You might gain some intuition from thinking about allocation as *where* the doses go, while prioritization is about *to whom* the doses go. Note that these terms of art may be poorly translated to popular press.

   Mathematically, we have only previously introduced vaccination as a fraction of the population vaccinated, v. Here, the authors divide the population into age groups which they index by a, which means that a vaccination strategy is given by the proportion of each age group to be vaccinated, v_a, with the natural constraint that $0 \leq v_a \leq 1$. The total number of vaccines is thus $X = \sum_a N_a v_a$, and the goal of the paper is to ask: what should $\mathbf{v}$ be, given a fixed X?

2. **Age-specific vaccine efficacy** is exactly what it sounds like, and recognizes that the same vaccine may provide different levels of protection based on age. The authors use ϵ_a to indicate VE for age group a. An important term in this area is **immunosenescence** which refers to the decrease in immune response among older adults, typically over 65. For this reason, vaccine doses are often higher for older age groups in an attempt to counteract the effects of immunosenescence.

   Vaccine efficacy and/or effectiveness may also depend on other factors. One key factor is the amount of time elapsed between vaccination and exposure. Another key factor is the interval between vaccine doses. A third class of key factors includes the body's state at the time of vaccination, including concurrent other infections, malnutrition and micronutrient deficiencies, and maternal antibodies and breastfeeding.[10]

3. **Age-specific mortality** is also exactly what it sounds like, and recognizes that the same illness may lead to different outcomes depending on age. Two diseases that represent opposite ends of the age-specific mortality skew spectrum are COVID-19 (increasing mortality with age) and *P. falciparum* malaria (decreasing mortality with age). Of course, mortality may also depend on other factors, and indeed, many of the factors that affect vaccine efficacy also affect mortality due to the fact that both are related to the immune response.

4. **Virus-specific mortality** is included in Medlock and Galvani by analysis of the 1918 and 1957 influenza pandemics. While both were influenza pandemics, the mortality rates were $10\times$ higher in 1918 than in 1957. Critically, the authors use the fact that their vaccine distribution recommendations do not depend heavily on strain to argue their point of optimality.

5. **Deaths, infections, years of life lost, contingent valuation, and economic costs** are five ways that the authors measure the impacts of influenza. Deaths and infections are straightforward outputs of models, and years of life lost (YLL) are typically calculated by weighting each death by the difference

[10] To read more about this topic, see the introduction of Hoest et al., 2014.

between the life expectancy and the age of the individual. These views of impact come from a public health perspective.

Contingent valuation comes from an ethicist's perspective. **Contingent valuation** refers to the practice of surveying people to determine the value of something that has no market and thus no market value. For instance, you can estimate the value of eggs by going to the grocery store, but it's difficult to estimate the value of these gorgeous Flatiron views we've got in Boulder.

Economic costs come from a health economist's perspective. **Economic costs** in Medlock and Galvani include the cost of vaccination (e.g. $37.26), the cost of infection to an unvaccinated person (e.g. $275.30 to a 0-19yo, but $492.56 to someone 65+), the cost of infection to a vaccinated person, and the cost of medical care prior to illness-caused death (e.g. $8309 for someone 65+). See Table S2 in Medlock and Galvani's Supplementary Materials for details and references.

With those preliminaries, this paper shows clearly how one can use a mathematical model to evaluate different policies. In fact, the authors use an (approximate) optimization approach to determine the optimal policy for a particular vaccine supply.

As you read, take note of the stark differences in recommendations as vaccine supplies increase. For low vaccine supplies, you will notice an emphasis on **direct protection** in which the biggest impact of the vaccine is to protect the individual. For high vaccine supplies, you will notice an emphasis on **indirect protection** in which the biggest impact of the vaccine is to curtail transmission and protect everyone through an approach to herd immunity.

Finally, as you read, consider the differences between the authors' studied scenarios and your experience of the COVID-19 pandemic and vaccine rollout. How might you adjust a model to consider not just vaccination prior to the epidemic wave, but vaccine rollout simultaneous with transmission? For further consideration of this topic, consider reading Model-informed COVID-19 vaccine prioritization strategies by age and serostatus from Bubar et al., 2021.