Covariation Effects on Epidemic Size

**Introduction**

Throughout the SARS-CoV-2 pandemic, the importance of super spreading has been imprinted upon our cultural consciousness due to the high visibility of such cases and events; however, in the field of epidemiology the significance of certain individuals being responsible for a disproportionate number of infections is par for the course. One of the earliest and most quintessential examples of super spreading, Typhoid Mary, was documented over a century ago (Brooks 1996). Not only have epidemiologists long known about the existence of super spreaders, but they have shown that a significant number of high-profile outbreaks throughout modern history, including HIV, MERS, Ebola, and SARS, in addition to SARS-CoV-2, have also been driven by super spreaders (Lui et al. 2020, Kain et al. 2021, May and Anderson, 1987, Wong et al. 2015, Gani and Leach 2004). In some well-studied outbreaks, such as SARS, information about identified super spreaders has been recorded in great detail, going so far as to find their respective secondary infection rates, contact rates and other relevant measurements (Stein 2011, Shen et al. 2004). Rudimentary information about specific super spreaders, however, offers limited insight into the epidemiological function of super spreaders on a broader scale. This is because ‘super-spreader’ is a general term for any individual that has a disproportionately high secondary infection rate, but there are multiple paths by which an individual can become a super spreader. For example, Typhoid Mary was a super spreader by way of having low virulence and recovery, while one of the documented SARS super spreaders had a high level virulence and contact rate (Brooks 1996, Shen et al. 2004). This suggests that epidemiological patterns are driven by individual variation in traits that are pertinent to the spread of a disease.

The ways in which individual variation arises are ample; hosts vary in behavior, physiology, and genetics (Vanderwaal and Ezenwa 2016, White et al 2018). The consequences of such variation to an epidemic are equally as diverse. As stated above, individual heterogeneity can lead to the emergence of super spreaders, but that is just one potential outcome since individuals vary at all stages of an epidemic (Keeling and Eames 2005, Oswald 2006, Antonissen et al. 2014, Gou and Jin 2017, Vanderwaal and Ezenwa 2016). These include transmission, which itself depends on many other traits that can vary, such as infectiousness and contact rate (McCallum et al. 2017), virulence, and recovery. For example, hosts can vary in attractiveness to parasites due to individual body odor or body mass (Allan 2010, Takken & Verhulst 2013). In Siberian Chipmunks (*Tamias sibiricu),* disposition (being bold or shy) has been shown to affect contact rates (Boyer et al. 2010). Tasmanian devil’s (*Sarcophilus harrisii)* susceptibilityto facial tumor disease has been linked to genetic makeup (Siddle et al. 2007). Empirical evidence that individuals vary is robust, but a general understanding of how heterogeneity affects population level disease dynamics remains unclear. For instance, it has been assumed that contact rates increase linearly with population density, but in some systems this relationship is sigmoidal due to varying host behavior and social structures (Borremmans et al. 2017). Illustrating how heterogeneity has the potential to upend basic epidemiological assumptions. Similarly, because individual variation and super spreading are so often considered in conjunction, intuition may lead one to assume that heterogeneity will always increase the size of an epidemic, despite this not always being the case.

The effect of individual variation on an epidemic will depend on how the parameter in question is related to the basic reproductive number, R0 (fig 1). R0 defines the expected number of secondary infections when a single infected individual is introduced to a fully susceptible population.

For example, variation in recovery rates in Big Horn Sheep (*Ovis canadensis*) infected with pneumonia is thought to explain population scale persistence despite low overall prevalence (Plowright et al. 2017). Here, individual heterogeneity is not creating a larger epidemic, but increasing the duration of the epidemic. These results are a confirmation of the importance of including individual heterogeneity when exploring epidemiological patterns, either in nature or in theoretical models. Unfortunately, this is an onerous task in practice due to the complexity of having to consider within host and between host dynamics, as well as environmental conditions potentially. The general difference in infection prevalence and intensity between males and females is an apt illustration of this complexity. This disparity is often attributed to male’s elevated testosterone levels, but research has shown that their larger body size and home range size may also be an important factor (Klein et al. 2000, Luis et al. 2012, Muehlenbein & Bribiescas 2005). Furthermore, Ruiz et al (2010) have shown that food supplementation in Sagebrush lizards (*Sceloporus graciosus)* can counteract the immunosuppressant effect of testosterone resulting in increased immunity compared to those who did not have food supplementation.

Recently, authors have suggested that the processes that result in variation in host susceptibility, infectiousness, recovery, and virulence also produce covariation between these traits (REFS?). This was first suggested in the evolution of virulence literature which presupposes a mechanistic link between disease parameters via within-host parasite replication. For example, a trade-off (negative covariation) between virulence and transmission results when increasing within-host replication increases transmission by increased infectiousness or shedding but comes with a cost of increased virulence (Anderson and May 1982, Ewald 1983). There may also be a trade-off between virulence and recovery if high within-host replication reduces the ability of the immune system to clear the infection (Anderson and May 1982). Conversely, the parasite can experience a trade-off between transmission and recovery if high within-host replication increases both transmission and recovery, due to the immune system responding in a density dependent manner (Alizon 2008). Lastly, a trade-off between contact rates and infectiousness can arise if high within-host replication increases infectiousness but also leads to increased sickness behavior that decreases host contact rates (Ewald 1994).

These trade-offs make a strong case for covariation being possible in nature but are examples of negative covariation exclusively; there are equally plausible reasons to suspect that these correlations may be positive in some cases. For example, Johne’s Disease (JD), or paratuberculosis, in cattle may be an example of positive correlation between recovery and virulence (shedding?). The incubation period for JD is extensive, ranging from 2 years to 14 years, during which infected individuals shed only intermittently (Whittington and Sergeant 2001). Infected individuals are able to transmit paratuberculosis for years without ever showing symptoms, indicating very low virulence but also low recovery since individuals do not clear the infection after being exposed. A potential example of positive covariation between contact rates and shedding can be found in canine rabies. Brookes and Ward (2019) show that infected canines have increased bite rates due to behavioral changes induced by infection demonstrating that the more a host sheds the more likely they will be to have elevated contact rates.

The population-level consequences that positive or negative covariation could have on epidemic dynamics have begun to be investigated. Susceptibility and recovery are predicted to make a population more, or less, vulnerable to an epidemic depending on if they are positively or negatively correlated, respectively (Gou and Jin 2017). Covariation between susceptibility and contact rates has also been explored. White et al (2018) found that negative covariation could slow the spread of an epidemic, even with high transmission rates, and potentially lead to extinction; although, their results were most robust when testing a theoretical pathogen with low transmission and high contact rates.

Outside of this handful of studies, theory showing what to expect, epidemiologically, if covariation between disease parameters is present is scant. The objective of this paper is to develop a more generalized quantification of how covariation between contacts, shedding, virulence, and recovery changes the trajectory of an epidemic. Furthermore, we aim to identify which cases of covariation are the most ecologically impactful in hopes of directing future empirical inquiries of covariation. We show that the effect of covariation is dependent on what traits are covarying and the variation in trait values. At low levels of variation, there is almost no effect of covariation in any case, but as variation increases the effect of covariation becomes more pronounced. If covariation increases or decreases the size of the epidemic is largely dependent on direction of covariation. For example, we show that at moderate rates of variation negative covariation between contact rates and shedding causes a decrease in epidemic size while positive covariation increases epidemic size. However, this is not a constant rule; we show that when virulence and recovery covary, the only detectable effect on epidemic size is amount of variation, with increasing amounts of variation leading to progressively larger epidemics.

**Methods**

**Model Description and Assumptions**

We used an SIR model where movement between classes is determined by contact rate, shedding rate, which we assume determines infectiousness, virulence and recovery rate (fig. 1). We included density dependent births and density independent deaths.

Diagram

Description automatically generated

**Figure 1.** Flow diagram of SIR model. Contact and shedding determine movement from susceptible to infected, recovery determines movement from infected to recovered, and virulence determines infected individuals that do not recover. Births and deaths are not included in this diagram but are included in the SIR model used.

To simulate continuous individual variation in all parameter values, we simulated the above SIR model with a Gillespie Eco-Evolutionary model (GEM) (DeLong 2016). GEMs draw an event from a “wheel of fortune” of probabilities at every time step. In our model, the possible events were births, deaths, infection, and recovery. The probabilities for each possible event were determined by relative rates of each process. The rates (eq. 1-5) of each event are calculated from the ordinary differential equations derived from the SIR model (eq. 6-8). Because GEMs are individual-based models they track unique fates of each individual in the population. The allows population dynamics to emerge out of the stochastic processes of birth, death, infection and recovery.

Parameters

|  |  |
| --- | --- |
| α = disease induce mortality | b = birth rate |
| γ = recovery rate | d = death rate |
| σ = shedding rate | bs = density dependence of birth rates |
| c = contact rate | Nt = St + It + Rt |

GEM Rates

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| |  |  |  | | --- | --- | --- | |  |  |  | | Infection |  | *Eq. 1* | | Recovery |  | *Eq. 2* | | Birth |  | *Eq. 3* | | DeathS |  | *Eq. 4* | | DeathR |  | *Eq. 5* | | DeathI |  | *Eq. 6* | |  |  |  | |
|  |

SIR Model

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| |  |  |  |  | | --- | --- | --- | --- | |  | |  |  | |  |  | | *Eq. 7* | |  |  | | *Eq. 8* | |  |  | | *Eq. 9* | |  | |  |  | |

To simulate individual variation, each individual in the population is assigned a unique trait value drawn from a log-normal distribution. In our model, transmission rate is split into a contact rate term (*c),* and an infectiousness term (), which we call shedding rate. We assume a linear relationship between contact rates and R0 (fig. 2a) and a saturating relationship between shedding and R0 (fig. 2b). This assumption seems reasonable because shedding is essentially the probability of infection given contact and at a certain level of shedding this probability will be one meaning that every contact will result in an infection despite an increase in shedding. We chose to separate transmission rate into these two terms to allow for variation and covariation between contact rate and infectiousness to impact overall transmission rate. We assume the opposite relationship between virulence/recovery and R0 (fig. 2c).

**Chart, line chart

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**B**

**C**

**A**

**Figure 2a-c.** Assumed relationship between each parameter and R0.

Covariation was simulated by drawing trait values from a multi-variate log-normal distribution. No correlation, positive correlation and negative correlations were tested all with a moderate, 0.5, correlation strength.

We ran our GEM SIR model allowing for variation in one parameter 20 times and compared the mean equilibrium number of susceptible individuals of all runs to the equilibrium number of susceptibles in a deterministic model. Allowing for variation in contact rates did not change the equilibrium number of susceptibles, while variation in shedding caused a higher equilibrium and variation in virulence and recovery had lower equilibriums. These results are consistent with our expectations based on how each parameter is assumed to be related to R0 (fig. 2a-c) and confirm that the model runs in the way we intended.

**Model Analyses**

We ran our model with all possible parameter combinations while allowing for covariation between two parameters and all directions of covariation (none, positive, and negative), resulting in 18 different model variants. The parameter set we used resulted in an R0 of 3.8. We then ran each of those variations with low, medium, and high levels of variation. We simulated each model variant at each level of variation 50 times. Again, we compared the mean epidemic size, or mean equilibrium number of susceptibles from the 50 runs to epidemic size of a deterministic version of the model. Due to the nature of GEMs, our model output the trait of each individual and the number of secondary infections. With these values we looked at the distribution of each individuals’ trait values, number of secondary infections, and individual R0. We also calculated the proportion of individuals that had zero secondary infections.

We looked at variation within the 50 stochastic simulations of each model variant as well. We calculated the ending number of susceptibles, mean and median secondary infection rates, and the fraction of zero secondary infections for each stochastic run. (I actually haven’t done this yet, but I was thinking that if you wanted to put in the analytical part it would probably kick out this extra. Or I suppose it could be more just for the discussion and not a formal result??)

**Results**

**Effects on Epidemic Size**

**Contact Rate and Shedding Rate**

When contact rate and shedding vary at low levels, there is no effect on epidemic size as it remains the same as the deterministic model. With moderate variation, we see a smaller epidemic if these parameters covary negatively and larger epidemic if they covary positively. With large amounts of variation in trait values, we see high rates of extinction in all directions of covariation. There were the most extinctions when the parameters negatively covaried; no simulations made it to our designated maximum time. After running a linear model with the trait values of the negative covariation model and epidemic duration, we found a strong positive relationship between maximum shedding rates and epidemic duration, but not between maximum contact rates and epidemic duration.

**Chart, line chart, histogram

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(I think we need to remake these graphs with ggplot so they match the other plots (?) but including them just for reference now)

**Contact Rate and Virulence/Recovery**

**Diagram

Description automatically generated with medium confidence**

We see the same results when contact rates covary with virulence and recovery. When there is no covariation but both traits are allowed to vary, epidemic size is the same as the deterministic model. When contact rates covary negatively with virulence or recovery, however, the epidemic gets progressively larger with increasing amounts of variation. When there is positive covariation this pattern is not as systematic; large amounts of variation caused a marginally larger epidemic and moderate amounts of variation lead to an even smaller increase in epidemic size.

**Shedding Rate and Virulence/Recovery**

**Graphical user interface

Description automatically generated with medium confidence**

Again, the results of covariation between shedding rate and virulence are the same as covariation between shedding rate and recovery. With no covariation, only large amounts of variation influence epidemic size, making it smaller. With negative covariation, the effect of large and moderate amounts of variation has a similar influence leading to slightly larger epidemic sizes. With positive covariation, again, moderate and large amounts of variation lead to smaller epidemic with about the same magnitude of effect.

**Virulence and Recovery**

**Chart, line chart, histogram

Description automatically generated**

When virulence and recovery covary, there is no difference in epidemic size between any of the directions of covariation. The only effect on epidemic size is amount of variation. We see that as variation increases epidemic size increases. The magnitude of increase is the same across all directions of covariation.

**Trait Analyses**

**Calendar

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**Secondary Infections**

Figure above shows the proportion of infected individuals that had no secondary infections. Across almost all the variants, we see a pattern of increasing proportion of no secondary infections with increasing variation in trait values. Additionally, the variation in proportions also increases, though in general they are much higher. When moderate variation is allowed, there are lower proportions of no infections, and at low variation there are the lowest with most simulations falling around 50% of infected individuals having no secondary infections. The standout case here is covariation between virulence and recovery. In all levels of variation, the proportions remain at around 50% generally.

**Table 1.** Proportion of infected individuals that had no secondary infections for each model variant and level of variation.

|  |  |  |  |
| --- | --- | --- | --- |
| Proportion of no secondary infections |  |  |  |
| **No Covariation** | **Low Variation** | **Moderate Variation** | **High Variation** |
| Contact - Shedding | 0.513 | 0.623 | 0.827 |
| Contact - Virulence | 0.505 | 0.578 | 0.733 |
| Contact – Recovery | 0.508 | 0.579 | 0.74 |
| Shedding - Virulence | 0.505 | 0.570 | 0.704 |
| Shedding - Recovery | 0.505 | 0.568 | 0.705 |
| Virulence - Recovery | 0.502 | 0.513 | 0.530 |
| **Positive Covariation** |  |  |  |
| Contact - Shedding | 0.514 | 0.670 | 0.861 |
| Contact - Virulence | 0.504 | 0.579 | 0.746 |
| Contact – Recovery | 0.507 | 0.578 | 0.751 |
| Shedding - Virulence | 0.506 | 0.569 | 0.7025 |
| Shedding - Recovery | 0.504 | 0.570 | 0.705 |
| Virulence - Recovery | 0.502 | 0.517 | 0.527 |
| **Negative Covariation** |  |  |  |
| Contact - Shedding | 0.507 | 0.582 | 0.795 |
| Contact - Virulence | 0.509 | 0.602 | 0.768 |
| Contact – Recovery | 0.511 | 0.602 | 0.769 |
| Shedding - Virulence | 0.507 | 0.589 | 0.726 |
| Shedding - Recovery | 0.509 | 0.591 | 0.726 |
| Virulence - Recovery | 0.502 | 0.512 | 0.523 |

**Distribution of R0 Values**

**Contact and Shedding**

Graphical user interface, application, histogram

Description automatically generated

Overall, there is a clear pattern in distributions. As variation increases, the distribution shifts further left and the tail length increases. The main difference between the model variants is the mean R0 values with each level of variation. In the no covariation case, the mean values all fall close to one another. In the positive covariation case, the moderate variation mean is slightly higher than the low variation mean and the high variation model is much higher. The mean in the high variation model is being inflated by the surplus of extreme (50+) R0 values in the tail end of the distribution. In the negative covariation case, the order is opposite that of positive covariation. The low variation mean is the largest, the moderate variation is slightly smaller, and the high variation case is the lowest mean. In the negative covariation case, there are very few extreme R0 values when allowing for high variation. In the no covariation case, we see a number of extreme values that act to increase the mean R0 just enough to be about the same as the low and moderate variation means.

Graphical user interface, chart, box and whisker chart

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Looking at boxplots of R-effective values, we see a similar pattern. High levels of variation result in most individuals with an R-effective value of zero, but also the potential to have extremely high R-effective values as well. In the negative covariation case, we see that a moderate level of variation leads to a higher maximum R-effective value than high variation, though only by a small margin.

**Shedding and Virulence/Recovery**

Graphical user interface

Description automatically generated

The general pattern of R0 distributions of shedding and virulence and shedding and recovery are similar to when contact rate and shedding covary, with increasing variation leading to a shift left and increasing tail length. With no covariation, the mean R0 values all fall near the expected value, likewise with positive covariation. When these traits negatively covary, however, we see that the mean R0 values increase with increasing levels of variation. In conjunction, we see increasing numbers of individuals with extreme R0 values, which acts to inflate the means.

Graphical user interface, application

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Graphical user interface, chart

Description automatically generated

Unlike with covariation between contact and shedding, in these variants the box plots of R-effective are virtually identical aside from their outliers. In all directions of covariation, high levels of variation lead to higher maximum R-effective values.

**Virulence and Recovery**

Graphical user interface, chart

Description automatically generated

As with epidemic size, we see no effect of covariation direction on R0 distributions. The only effect is from level of variation. At low variation levels, we see a normal distribution centered around the expected R0 value of about 3.8. With moderate variation, this distribution flattens out and we see a larger diversity of R0 values, but still a generally normal shape. With high variation, the distribution is very flattened with very similar frequency of R0 values from about five to ten. In these model variants, increasing variation always increases the mean R0 value. We do not see as extreme of values in these simulations as all other parameter pairings.

**Discussion**

From our results, two clear patterns emerged. One, sans covariation between virulence and recovery, increasing the level of variation increases the proportion of infected individuals that cause no secondary infections, irrespective of direction of covariation. Secondly, again barring covariation between virulence and recovery, as variation increases, the distribution of R0 shifts towards zero while the tail of the distribution is elongated, indicating an increase in maximum R0 values despite the shift of R0 values towards zero. Despite these patterns, we do not see a clear-cut pattern in effect of covariation and amount of variation on epidemic size. For example, when contact rate and shedding covary, positive covariation at moderate level of variation leads to a larger epidemic, while negative covariation leads to a smaller epidemic.

This result follows from the findings of White et al (2018) where they show that negative covariation between contact rates and susceptibility has the potential to slow the spread of an epidemic, even with high transmission rates. In our model, we see R0 values as high as 50, but still an overall smaller epidemic as they predict. (I don’t actually know if this is true…im thinking its somehow related but im a little confused on how susceptibility compares to our parameters. If an individual is shedding a lot, those who come into contact with them would seemingly have an increased chance of getting sick so like a pseudo increase in susceptibility as a function of the infected individual?? I could be totally off here but was trying to relate the result from White to ours!)

Interestingly, the positive covariation model with moderate variation has a noticeably larger proportion of infected individuals that caused no secondary infections than the negative covariation model with the same level of variation. This indicates that positive covariation between contact rates and shedding may play a role in the emergence of super spreading individuals. At high levels of variation, rates of extinction were very high which allowed us to investigate the relationship between epidemic duration and trait values. We found that there is positive relationship between maximum shedding rate and epidemic duration, but not between maximum contact rates and epidemic duration. This relationship points to infectiousness being more important for disease persistence than contact rates when contact rates covary with shedding rates; this has important disease management implications. For example, the predicted efficacy of management strategies that target contact rates, such as lock downs or social distancing, may be lower if there is covariation between these traits (Barnett-Howell et al. 2021, Zhang et al. 2021 (not published yet, but maybe once I am finally done with this thing), Nyabadza et al. 2020). Alternatively, negative covariation seems to be more important if there is covariation between contact rates and virulence/recovery and shedding rates and virulence/recovery. In both cases, we see that negative covariation leads to larger epidemics, though with covariation cases involving contact rates the increase in epidemic size is larger. The case of covariation between virulence and recovery stands out from all other covariation combinations. When these traits covary, we see no effect of direction of covariation but an effect of increasing amounts of variation. As variation increases, mean epidemic size also increases, however, unlike other cases, we do not see an increase in proportion of infected individuals with no secondary infections. Instead of seeing more individuals with more extreme trait values, we see the R0 distribution become less normal and more uniform resulting in most individuals having moderate R0 values and not many with zero and some with extreme values as we saw with other parameter combinations. The behavior of this model variant may indicate that covariation between virulence and recovery is not common given the empirical evidence that the distribution of transmission for a number of diseases tends to follow the pareto principle, or 80/20 rule (Cooper et al. 2019; Stein 2011; Woolhouse et al. 1997). This principle is a way to describe heterogeneity by positing that approximately 20% of individuals are responsible for 80% of transmission (Anderson and May 1991). Furthermore, this empirical evidence points towards our moderate or high variation models being the closest to what may be found in nature as the proportion of infected individuals with no secondary infections comes out to approximately 80% in all our model variants besides covariation between virulence and recovery. This is an important understanding as changes in variation was one exceedingly influential in all of our measures of epidemic dynamics.

Above, we speculated that there may be positive covariation between contact rates and shedding in individuals infected with rabies, if this is the case, our model predicts that the epidemic size would be larger when covariation is included versus a deterministic model. In contrast, Hamilton et al. 2020, have shown a negative relationship between contact rates and tumor load in Tasmanian devils (*Sarcophilus harrisii*) infected with Devil Facial Tumor Disease (DFTD). This is a departure from the accepted assumption that probability of transmission increases as DFTD progresses, however, it is supported further by our model. We show that if contact rates and shedding are negatively correlated, there should be a decrease in epidemic size. Our theoretical framework outlines what to expect when these traits covary negatively and a departure from such expectations can help signal when investigation is necessary, aiding management decisions. For example, a sudden uptick in DFTF transmission would indicate an important change in the epidemiological dynamics and identifying the source of this change is further supported by the understanding that our framework offers. Due to the nature of negative covariation, it would likely be a change in the early stages of the disease when transmission is most likely to occur or an adaptation, such as with Rabies, to overcome the subsequent decrease in contact rates with disease progression. Our findings offer a general framework for understanding the effects of individual covariation on population level epidemiological dynamics; however, the utility of our work is dependent on knowing when and between what traits covariation occurs. The virulence evolution theory literature hinges on negative covariation of disease traits, and empirically, there is evidence that other directions of covariation are possible and already identified (Hamilton et al. 2020, Vanderwaal and Ezenwa 2016, Anderson and May 1982, Ewald 1983). Our work should help direct future research on between which parameters and what directions of covariation to investigate as we identified which cases will be most important for transmission and management.

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