Positive feedback loops exacerbate the influence of superspreaders in disease transmission

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Positive feedback loops exacerbate the influence of superspreaders in disease transmission

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Abstract

Superspreaders are recognised as being important drivers of disease spread, most recently having played a major role in the ongoing COVID-19 pandemic. However, models to date have assumed random occurrence of superspreaders, irrespective of whom they were infected by. Evidence suggests though that this may not be the case, and that those individuals infected by superspreaders may be more likely to become superspreaders themselves, hence creating a positive feedback loop. This could happen, for example, through superspreaders releasing high infective doses that cause high infection intensities in newly-infected individuals, which increases the likelihood that they, in turn, will become superspreaders. Here, we examine the effects of such a positive feedback loop on (1) the final epidemic size, (2) the basic reproductive number, R_0 , and (3) the peak prevalence of superspreaders. We show that positive feedback loops can have a profound effect on the outcome of an epidemic, even when the transmission advantage of superspreaders is moderate, and despite peak prevalence of superspreaders remaining low. We argue that positive superspreader feedback loops in different infectious diseases, including SARS-CoV-2, should be investigated further.

Keywords

Epidemic models, supershedders, supercontactors, COVID-19, R_0 , final epidemic size

Introduction

Pathogen transmission requires an appropriate contact between a susceptible and infected individual, such that the susceptible individual is exposed to pathogens shed by the infected individual. For example, for the respiratory pathogen, SARS-CoV-2, this may include both direct and indirect contact: either physical contact or close proximity, which increases the risk of exposure to infective respiratory droplets, or indirect contact via infective aerosols suspended in the air or on objects contaminated with the pathogen by an infected person (Zhou et al., 2021). Most traditional compartmental models of infectious disease dynamics, for example SIR (Susceptible – Infected – Recovered) models, assume that, on average, all individuals behave in the same way (Anderson & May, 1981). However, it has long been known that some individuals, termed “superspreaders”, contribute far more to pathogen transmission, and epidemic spread, than others (Anderson & May, 1987, 1991; Woolhouse et al., 1997). Superspreaders may be defined as those individuals who are in the upper 1% tail of the distribution of pathogen transmission (Lloyd-Smith et al., 2005), but the term has been more widely applied to those with a strongly disproportionate contribution. The importance of accounting for this individual variation in epidemiological models has more recently been recognised, not least because it has played a major role in the ongoing COVID-19 pandemic (Adam et al., 2020; Correa-Martínez et al., 2020; Gómez-Carballa et al., 2020; Liu et al., 2020; Miller et al., 2020; Zhang et al., 2020).

Superspreaders exist for most diseases, whether in human, livestock or wildlife populations (Stein, 2011), and may originate in two ways. First, supercontactors are those who transmit infection to more individuals because they have a larger number of

contacts than the average. There are clear examples of this in the transmission of HIV and other sexually-transmitted diseases in humans, through those who are more sexually active (Aral, 2004); while for non-humans, the transmission of a hantavirus (Sin Nombre virus) in deer mice, for example, has been shown to be driven by animals with larger home ranges who engage in more territorial defence (Clay et al., 2009). Second, supershedders are individuals who shed more infectious particles than average and so increase the probability of infection once an appropriate contact has been made. In the case of HIV in humans, for example, individuals co-infected with other sexually-transmitted diseases have been shown to shed more HIV (Cohen et al., 1996). In cattle, heterogeneity in shedding of *Escherichia coli* 0157 has also been described (Omisakin et al., 2003). Mathematically, both mechanisms for superspreading (supercontacting and supershedding) result in an increase in the transmission term in standard compartmental models, and an increase in the basic reproductive number (R_0) of the pathogen (Lloyd-Smith et al., 2005), leading to an increased probability of establishment and rate of spread of the epidemic. However, Ma & Earn (2006) showed that for a closed, fixed sized population, the formula for the final epidemic size is unchanged by the presence of superspreaders.

Standard models assume that the generation of superspreaders is random, irrespective of whom they were infected by (Ma & Earn, 2006). Yet there is evidence from some systems of a positive feedback loop whereby those individuals infected by superspreaders are more likely to be superspreaders themselves. For example, supershedders could generate further supershedders if an individual exposed to a higher infection load is itself more likely to develop a higher infection load, because higher inoculum doses may be more likely to overwhelm the mechanisms of resistance,

resulting in poor control of viral replication. Evidence for this comes from experiments in various virus-host systems showing that the outcome of infection is dose dependent, with animals receiving a higher dose developing more severe disease and more pronounced viral replication and shedding than those receiving lower doses (Gaskell & Povey, 1979; Mumford et al., 1990; Strong et al., 2015; Zarkov & Bochev, 2008). At the individual level, infections arising from exposure to high doses of virus are more likely to be symptomatic and to have higher intensity (Bjorkman et al., 2021; Dabisch et al., 2021); whereas two independent studies found that asymptomatic, likely low viral load cases pose a lower risk of transmission, with their infected contacts themselves more likely to be asymptomatic (Ge et al., 2021; Wu et al., 2021). Such positive superspreader feedback loops have recently been proposed as an explanation for the heterogeneous propagation pattern of COVID-19 (Beldomenico, 2020; van Damme et al., 2021). SARS-CoV-2 viral loads have been found to drive the size and duration of COVID-19 clusters (Hay et al., 2021; Jones et al., 2021; Ladoy et al., 2021); while in a cohort study in Spain, the viral load of index cases was a leading driver of SARS-CoV-2 transmission (Marks et al., 2021). Moreover, the only empirical study that has so far explored the positive feedback loop hypothesis, while controlling for number of secondary infections, found that the ratio of observed to expected superspreader-superspreader dyads was greater than that expected by chance in 13 of 18 infection trees (Taube et al., 2021).

Hence, despite the recognition that superspreaders may generate superspreaders, and the suggestion that this may be important for diseases like COVID-19, the role it plays in driving the epidemiology of such diseases remains unknown. In this study, therefore, we develop a generic model to understand how such positive feedback loops affect (1) the

final epidemic size, (2) the basic reproductive number, R_0 , and (3) the peak prevalence of superspreaders, of an emerging epidemic.

Methods

In order to understand the role of the positive feedback loop between superspreaders we formulated the following model:

$$\frac{dS}{dt} = -S\beta_L(L + pH)$$

$$\frac{dL}{dt} = S\beta_L((1 - \sigma_L)L + p(1 - \sigma_H)H) - (\alpha + \gamma)L$$

$$\frac{dH}{dt} = S\beta_L(\sigma_L L + \sigma_H pH) - (\alpha + \gamma)H$$

$$\frac{dR}{dt} = \gamma(H + L)$$

where S refers to the number of susceptible hosts, L to low-titre infected hosts (non-superspreaders), H to high-titre infecteds (superspreaders) and R to recovered. β_L represents the baseline transmission rate arising from L-infected hosts. This baseline rate is then increased through transmission by superspreaders (H-infected hosts) by a magnitude p (we assume $p \geq 1$) representing the factor by which the transmission rate from a superspreader is greater than the transmission rate from a non-superspreader (i.e., the transmission advantage of superspreaders); p has no upper bound.

σ_L is the proportion of infections from a non-superspreader that result in a superspreader, and so represents background, spontaneous generation of superspreaders that we might expect in the absence of positive feedback. σ_H is the

proportion of infections from a superspreader that result in another superspreader. σ_H and σ_L both vary between 0 and 1, but if $\sigma_H > \sigma_L$ then superspreaders are more likely to generate new superspreaders, and hence σ_H/σ_L represents the strength of the positive feedback loop of superspreader infections.

α is the death rate due to the disease, and γ is the recovery rate from the disease, both assumed here to be the same for superspreaders and non-superspreaders. For this model, there are no natural births or deaths, so the population only changes in size due to deaths resulting from the disease. So, if $\alpha = 0$ then the population remains constant, size $N = S + L + H + R$.

For an infection spreading through a closed, fixed sized population, it is possible to calculate the final epidemic size – the total number of individuals infected throughout the epidemic (Kermack & McKendrick, 1927). Ma and Earn (2006) showed that the formula for the final epidemic size, Z , is unchanged by the presence of a fixed proportion of superspreaders:

$$Z = S[0] \left(1 - \text{Exp} \left(-Z \frac{\beta_L}{\alpha + \gamma} (1 - \sigma_H + p \sigma_L) - \left(\frac{\beta_L}{\gamma + \alpha} \right) (L[0] + p H[0]) \right) \right)$$

For a fixed population size of 1 and in the limit $I(0) \rightarrow 0, S(0) \rightarrow 1$ the final epidemic size, Z , for all of the models they considered, is given by $Z = 1 - e^{-R_0 Z}$ (Ma and Earn 2006).

For the current model, when $\sigma_H = \sigma_L$ (i.e., when there is no positive feedback loop) the final epidemic size, Z , is also given by the same formula (see Supplementary Materials). However, when $\sigma_H > \sigma_L$, and so the positive feedback loop does exist, it is not possible to use the methods of Ma and Earn to calculate the final epidemic size, since additional non-linearities in this model disqualify the simplifications they use. However, in the Supplementary Materials we show that in the presence of a transmission feedback loop (i.e., when $\sigma_H > \sigma_L$), the final epidemic size will be larger than in the absence of any such feedback loop, and this difference increases as the difference between σ_H and σ_L increases. In the results that follow, we quantify the final epidemic size numerically by running models in R (R Core Team, 2020) using the deSolve package (Soetaert et al., 2010) and calculating the final epidemic size and the peak prevalence of superspreaders, while varying the ratio σ_H / σ_L (the strength of positive feedback loop, assuming $\sigma_H / \sigma_L \geq 1$) and p (the transmission advantage of superspreaders, assuming $p \geq 1$). Other parameter values were kept constant and were chosen for illustrative purposes (Table 1). The initial number of non-superspreader infecteds, L , was kept constant at 10% of the total population size, N , as was the initial number of recovered, R , at 0%. We varied the initial number of superspreaders, S , between 0-10%. All models were run for sufficient periods of time to ensure that the epidemic had completed in all cases.

Furthermore, we calculated the basic reproductive number (R_0), i.e. the number of new infections generated by one infectious individual in a completely susceptible population for each of these scenarios. Using the next generation method of Diekmann et al. (2010; see the Supplementary Materials), R_0 for this model is given by:

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$$R_0 = \frac{N\beta_L(1 + p\sigma_H - \sigma_L + \sqrt{(\sigma_L - 1 - p\sigma_H)^2 - 4p(\sigma_H - \sigma_L)})}{2(\alpha + \gamma)}$$

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198 **Table 1** Model parameters and their values.

Parameter	Symbol	Per capita rate	Comment
Death rate due to disease	α	0	For simplicity assumed no excess death due to infection.
Recovery rate	γ	0.1	Assumed an average infectious period of one week.
Baseline transmission rate arising from non-superspreaders (L-infected hosts)	β_L	8×10^{-6}	Used an arbitrary β_L that put the baseline R_0 in the absence of superspreading (i.e., when $p = 1, \sigma_H = \sigma_L$) below 1 (see Supplementary Materials; for the values used here, $R_0^L = 0.8$). From this basis we can explore whether superspreading and/or a positive feedback loop has the potential to drive an epidemic that would not otherwise occur.
Proportion of infections from a non-superspreader (L-infected host) that result in a superspreader (H-infected host)	σ_L	0.05	Assumed that 5% of infections from a non-superspreader result in a superspreader.
The number of times more superspreaders (H-infected hosts) generated by a superspreader (H-infected host) than a non-superspreader (L-infected host) i.e. the strength of the positive feedback loop	σ_H / σ_L	1-20	Varied from 1 (equal generation of superspreaders by superspreaders and non-superspreaders) to the maximum feasible value of 20 (20 times more superspreaders generated by a superspreader than a non-superspreader). This maximum feasible value arises since σ_H cannot exceed 1; given the default value of $\sigma_L = 0.05$, σ_H / σ_L cannot exceed 20.
The number of times by which the transmission rate from a superspreader (H-infected host) is greater than the transmission rate from a non-superspreader (L-infected host; the transmission advantage of superspreaders)	p	1-20	Varied from 1 (equal transmission rate from a superspreader and a non-superspreader) to 20 (20 times higher transmission rate from a superspreader than from a non-superspreader).

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Results

The final epidemic size (Fig. 1) and the basic reproductive number, R_0 (Fig. 2), both increase with increases in the transmission advantage of superspreaders, p , and with the strength of the positive feedback loop whereby superspreaders generate further superspreaders, σ_H / σ_L . Hence both epidemic outcomes reach their highest values when both p and σ_H / σ_L are high.

Fig. 1 Final epidemic size (where the maximum is 1, reflecting everyone in the population becoming infected) as the strength of the positive feedback loop (σ_H / σ_L ; y-axis), the transmission advantage of superspreaders (p ; x-axis) and the initial number of superspreaders (a: 0%; b: 5%; c: 10%) are varied. See Table 1 for other parameter values.

Fig. 2 The basic reproductive number (R_0) as the strength of the positive feedback loop (σ_H/σ_L ; y-axis) and the transmission advantage of superspreaders (p ; x-axis) are varied. See Table 1 for other parameter values.

Of course, in the absence of superspreading ($p = 1$), R_0 and the final epidemic size are insensitive to σ_H/σ_L since there is no superspreader advantage on which a feedback loop might act (along the vertical axes of the figures). Indeed, as shown in the Supplementary Materials, there is a lower threshold value of p , given by $\frac{(\alpha+\gamma)}{N\beta_L}$, below which no viable amount of positive feedback can drive $R_0 > 1$ (for our baseline parameter values, this lower threshold value of p is 1.25, suggesting superspreaders need at least a 25% transmission advantage for an epidemic to occur, regardless of the extent of positive feedback). Even marginally above this value, R_0 and the final epidemic size are relatively insensitive to increases in the strength of the positive feedback loop when the transmission advantage of superspreaders is low. Thus, for our baseline

parameter values, feedback loop strength has little effect on outcome when superspreaders are, say, only twice as effective in transmission as non-superspreaders ($p = 2$), but the effect is profound as p approaches 10.

Conversely, in the absence of a feedback loop as assumed in previous studies ($\sigma_H / \sigma_L = 1$, along the horizontal axis in the figures) outcomes, especially R_0 , may change little with superspreader advantage. For example, in the absence of feedback, and using the baseline parameter values to generate Fig. 2, R_0 is less than 1 (the pathogen fails to cause an epidemic) unless p exceeds 6 (see Supplementary Materials), and only reaches 1.6 as p approaches 20 (the maximum illustrative value used here). But when there is feedback, and especially when the feedback loop is strong (e.g. $\sigma_H / \sigma_L = 20$ in Fig. 2) R_0 rises rapidly, reaching 16 in Fig. 2 as p approaches 20, and causing an epidemic ($R_0 > 1$) with only very moderate levels of superspreader advantage ($p \geq 1.25$; Supplementary Materials).

It is also noteworthy that this newly identified effect of the feedback loop on epidemic outcome can be profound even when the proportion of superspreaders in the population remains low. For example, at intermediate levels of superspreader advantage ($p = 5$), increasing feedback loop strength from 1 to 5, an intermediate level of feedback, has a powerful effect on both final epidemic size (Fig. 1) and R_0 (Fig. 2), with R_0 , for example, increasing from less than 1 (pathogen failing to cause an epidemic), to more than 1 (pathogen causing an epidemic). This is despite the peak prevalence of superspreaders not exceeding $\sim 0.5 - 10\%$, depending on the initial number of superspreaders (Fig. 3).

Fig. 3 Peak prevalence of superspreaders (as a proportion of total population size, N) as the strength of the positive feedback loop (σ_H/σ_L ; y-axis), the transmission advantage of superspreaders (p ; x-axis) and the initial number of superspreaders (a: 0%; b: 5%; c: 10%) are varied. See Table 1 for other parameter values.

Discussion

Superspreaders are recognised as being important drivers of disease spread. However, models to date have assumed random generation of superspreaders, irrespective of whom they were infected by. Here, by contrast, and supported by a range of studies, we explore the importance of positive superspreader feedback loops, whereby those individuals infected by superspreaders are more likely to be superspreaders themselves. We show that superspreaders in their own right may have little effect on the outcome of an epidemic, but when positive superspreader feedback is included, the effect may be profound, even when the transmission advantage of superspreaders is moderate, and despite peak prevalence of superspreaders remaining low. Thus, our theoretical framework explores the ideas proposed by Beldomenico (2020), whereby

positive feedback loops have the potential to drive the heterogeneous propagation pattern of a range of infectious diseases, potentially including SARS-CoV-2.

Positive feedback loops in superspreading could arise through both physiological and behavioural mechanisms. There is evidence, elaborated above, that high infective doses cause high infection intensity, which in turn expose new contacts to larger inoculum sizes. By this means, supershedders may generate new supershedders (Beldomenico, 2020). Behaviourally, there is also some evidence that highly-connected individuals tend to contact other highly-connected individuals. In network theory, individuals (nodes) like this are described as having high eigenvalue centrality and have been shown to be important in epidemic spreading (Canright & Engø-Monsen, 2006). In this case, the contact-status of those newly-infected individuals would not change upon transmission, so we cannot say that supercontactors generate new supercontactors. However, a disproportionate number of supercontactor-supercontactor dyads would still be observed. For example, in HIV transmission in humans, those who are more sexually active tend to infect others who are also more sexually active (Kelly et al., 2010); and for COVID-19, it has been suggested that those who are less likely to wear masks may be more likely to come into contact with, and so infect, others who equally do not wear masks and disregard public health recommendations generally (Taube et al., 2021). As such we would expect the overall consequences for the epidemiology of those systems to broadly follow those we present for our model.

In the context of COVID-19, and in addition to the supershedder and supercontactor processes described above, our model could also describe other scenarios. For example, individuals infected by a new, highly-transmissible strain may represent

superspreaders, who infect others with the same strain, therefore only generating more superspreaders ($\sigma_H = 1$); while the non-superspreaders are individuals infected by a less transmissible strain, infecting others with the same strain and only generating more non-superspreaders ($\sigma_L = 0$). In a second scenario, if we assume that vaccines against SARS-CoV-2 are not entirely sterilising but reduce transmission potential (Gier et al., 2021; Singanayagam et al., 2021), then we can think of non-vaccinated individuals infected with the virus as being (relative) superspreaders, and the vaccinated as non-superspreaders. Behaviourally (culturally), there is likely to be some clustering, with the non-vaccinated superspreaders mostly interacting with other non-vaccinated individuals, thereby generating more superspreaders. Our model predictions suggest that such a scenario is likely to result in the non-vaccinated contributing more than previously recognised to the amplification of the epidemic.

It is noteworthy, too, that by introducing a positive feedback loop between superspreaders, we inevitably introduce a positive feedback loop between non-superspreaders. Some positive feedback loops may therefore cause cascades of superspreading, while others favour slow endemic circulation. This may help explain why infectious diseases sometimes circulate at lower levels, while at other times there are explosive uncontrollable outbreaks. The first year and a half of the COVID-19 pandemic in Vietnam, Thailand and Laos may be an example of the former, whereas the months that followed in those countries could be an example of the latter (Chookajorn et al., 2021).

Given the results from this initial study, we contend that the existence of positive feedback loops in different host-pathogen systems should be investigated further.

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Author contributions

P.M.B. conceived the analysis. M.B., K.M.W., A.F. and R.A.N. designed the model. K.M.W., A.F. and R.A.N. analysed the data. K.M.W. led the writing of the manuscript. All authors contributed critically to analysis discussion and manuscript drafts and approved a final version for publication.

Competing interests

The authors declare no competing interests.

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