 doi:10.20944/preprints202007.0475.v1

Title: The Silent Partners

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Abstract:

Despite great advances in understanding the dynamics of viral epidemics, the emergence of rapidly spreading, highly pathogenic viruses remains a realistic and catastrophic possibility, which current health systems may not be able to fully contain. An intriguing feature in many recent zoonotic viral outbreaks is the presence of 'superspreaders', which are infected individuals that cause dramatically more new cases than the average. Here I study the effect of superspreaders on the early dynamics of emerging viruses that have not gained the capacity for efficient human-to-human transmission, i.e viruses with R0 < 1. I show that superspreaders have a higher chance of rapid extinction, but under 'crowded' conditions can lead to 'outbreaks', causing far more cases than regular viruses. Hence I suggest that outbreaks of highly pathogenic superspreaders are more likely when they coincide in time and space with an unrelated outbreak leading to increased hospital admission rates. These superspreader outbreaks may be difficult to detect, especially in the context of a different epidemic in progress, and can significantly affect mortality patterns observed in affected areas.

Keywords:

Mathematical model; SARS; COVID-19; Superspreaders; Viral outbreaks; H7N9; Influenza; zoonotic

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Introduction

Mathematical models play an increasingly important role in studying pathogen dynamics and guiding public health policies. In a basic SEIR model for viral spread the host population is divided into 4 compartments: susceptibles (S), exposed (E), Infected (I), and removed (R). Susceptibles become exposed to the pathogen after interacting with infected individuals, and after an incubation period exposed hosts progress to the infected compartment. The infected then transmit the pathogen to susceptible hosts until they recover and develop immunity, or die, and are so 'removed' from the transmission process. The average number of new cases caused by infected individuals is denoted by R0. When R0 is greater than 1 the virus is expected to survive, and when R0 < 1 then each infected individual causes on average less than 1 new case, leading to extinction of the virus. Numerous variations on this model have been developed in efforts to represent the complex biological reality more accurately (1-5).

Data accumulated during the SARS outbreak in 2003 revealed an unusually large variability in the number of new cases caused by SARS-CoV infected individuals, where the majority of patients caused no additional transmissions, but a small fraction of patients, termed 'superspreaders', caused far more transmissions than the overall R0 would suggest (6-8). It is not clear what role, if any, superspreaders play when it comes to 'resident' viral epidemics, however, superspreader phenomenon was observed in several outbreaks of highly pathogenic viruses, including MERS in Saudi Arabia and Korea (9-11), and the recent Ebola virus outbreak in West Africa (12).

To better understand the role superspreaders play during the early stages of outbreaks, I construct a modified SEIR model for a generic virus, Vx, capable of creating 2 compartments/types of infected: IH that can cause a large number of new cases (i.e superspreaders), and IL that cause very few cases if any (13-15).

In agreement with previous results, as the average number of cases caused by IH (denoted rH) grows, Vx survives less frequently but survival can rapidly lead to large outbreaks. In addition, even when the average R0 is set to values < 1, Vx with lower rH values often survive over multiple transmission rounds, although their incidence never reaches outbreak levels. While the survival rate of Vx with very high rH values is lowest, when these Vx survive they are likely to cause large outbreaks. However, the probability of such outbreaks occurring is highly dependent on the number of susceptibles the average infected person can interact with. In healthcare facilities this number is likely to be correlated with the level of serious morbidity in the community.

Consequently, it is possible that *local spikes in the mortality* reported during epidemics of 'known viruses' like influenza, or recently COVID-19 (16-18), are in some cases caused by outbreaks of unidentified, highly pathogenic, and rare viruses that do not survive long under normal conditions, and require unusual levels of crowding to cause local outbreaks. In the context of the COVID-19 pandemic, I argue that some of the policies applied as part of the effort

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to contain the spread of COVID-19 actually increase the probability of Vx outbreaks, and these may account for much of the excess mortality observed in some regions.

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Methods

The dynamics of Vx are described using a modified SEIR model, with a single S population, one Exposed and two Infected populations (IL and IH, as explained below), and two recovered populations, R (recovered) and Rd (died).

The virus is introduced into a new region through “seeding events”, where infected individuals travel from a region with a Vx outbreak. In the new region Susceptible (S) individuals first become Exposed (E) by interacting with individuals infected with Vx, and after an incubation period become infected (I) as well. As in the 2003 SARS, the infected population can be roughly divided into very low- and very high-transmission potential patients (‘superspreaders’), designated here IL and IH. IL transmit the virus at rate rL and IH at a rate rH, with rH>>rL. For simplicity I assume all those infected develop disease. The parameter ‘L’ describes the proportion of E individuals that become IL, and 1-IL the proportion that become IH (L varies between 0 and 1). The dynamics of these populations are depicted graphically in figure 1.

The transmission probability, p_t, per interaction between I and S is similar for IH and IL, i.e it is independent of rH and RL. Infected recover at rate = gamma*h, and die at rate = gamme*(1-h). I assume there is no difference in recovery rate or fatality between IL and IH cases. The parameter ‘c’ describes the rate of E to I progression.

Equations: single setting/facility

$S(t+1) = S(t)*(1 + Sn - p\_t*rL*IL - p\_t*rH*IH)$
$E(t+1) = E(t)*(1 - c) + p\_t*S*(rL*IL + rH*IH)$
$IL(t+1) = IL(t)*(1 - gamma) + E(t)*c*L$
$IH(t+1) = IH(t)*(1 - gamma) + E(t)*c*(1-L)$
$R(t+1) = R(t)+(IH+IL)*gamma*h$
$Rd(t+1) = Rd(t)+(IH+IL)*gamma*(1-h)$

Transmission from one facility to another, or to/from the community, can be described using an ‘import term’ added to the infected population, e.g.:
$IL(t+1) = IL(t)*(1 - gamma) + E(t)*c*L + imported*IL\_other\_setting(t)$

The parameter *‘imported’* represents connectivity between the two settings (ranging from 0 to 1), and IL_other_setting(t) = number of IL in the ‘other’ setting. In the results below I introduce a single Vx patient into a susceptible population as a “seeding event”.

I assume infection with a different pathogen does not change the probability of becoming infected with Vx (or vice versa), e.g COVID-19 patients have the same probability of becoming infected with Vx as the general population.

Together, the populations (in a given ‘setting’) represented in the model are:
S = susceptible to Vx

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E = exposed to Vx but not showing disease symptoms yet
IL = Infected with Vx but causing low number of transmissions
IH = Infected with Vx and can causing high number of transmissions
R = recovered from Vx
Rd = died due to Vx

In the model I develop here the susceptible population variable S represents the number of individuals an infected person can interact with - the individual ‘network’ of the person - and the extent of this network depends on the setting where the virus is introduced (19).

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Results

The effect of rH on survival and outbreak dynamics

I explore the dynamics of Vx with increasing rH values but a similar overall expected number of progeny per generation, denoted 'fitness', by setting:

rL = 0, and 1-L = 1/rH,

In which case the overall fitness is equal to (while the availability of S is not limiting):

fitness = (1/rH)*p_t*rH = p_t, $1 > p_t > 0$

When rH = 1, all infection cases are IH (1-L = 1), and each infected can cause one additional case at probability p_t. In this trivial case the dynamics of Vx are identical to those of a regular virus with R0 < 1. The probability of Vx at rH = 1 surviving past the seeding event, and then per each transmission round is simply p_t. Since the overall number of infected does not grow beyond 1, probability of extinction, per transmission round, remains constant at 1 - p_t.

For rH values > 1 the situation is slightly more complex after the first seeding event. E.g when rH = 2 only half of imported cases are IH, but these can cause 2 new cases per infection, and each new case that is IH can lead to two more cases and so on.

I define the probability that an imported Vx will lead to an increase in case numbers for over > N transmission cycles as P_N, and the probability of an imported case leading to some threshold number of cases as P_outbreak. I estimate the values of the above for rH values ranging from 2 to 100 by simulating 100k 'seeding events' per rH value (simulation details described in figure 2).

The % of seeding events leading to at least one additional transmission cycle decreases asymptotically with rH (P(1) =~ p_t/rH, blue line in figure 3a), and after the first transmission cycle survival probability at any generation G can be approximated by:

P(G) = p_t*P(G-1) = p_t^(G-1)*p_t/rH = (p_t^G)/rH

The maximal number of cases caused by a seeding event (IH) increases with rH (red line in figure 3a), and so despite occurring less frequently and lasting fewer generations, the average number of cases caused per seeding event, or the fitness of Vx, is similar for all rH values (dashed black line).

After dividing the number of cases/seeding into bins, starting from under 10 cases, under 100, 200 etc, it is clear the distribution of the number of cases shifts strongly to higher rH values for

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higher outbreak numbers (figure 3b). In fact, although seeding success rate was highest at rH = 2, over 96% of these led to fewer than 10 total infected, < 4% led to 11 to 60, and in no case was the total greater than that. In contrast, in cases where seeding is successful at higher rH values the number of infected is almost always higher than the maximal number observed for rH = 2; I plot in figure 3c the % of successful seeding events leading to > 60 cases, denoted as 'outbreak' in the figure.

Superspreader fragility: limited availability of susceptibles

Realistically the number of susceptibles an infected interacts with, denoted here as *S_effective*, is finite. Even in a crowded hospital, the total number of susceptibles an IH encounters, i.e *S_effective*, can usually be limited to a number smaller than the higher rH values.

I denote the difference between rH and S_effective deltaS:

deltaS = rH - S_effective,

Using Eq. 1 the new fitness is:

fitness_new = *(1/rH)*p_t**S_effective

Rearranging terms I get the following relationship between the original and new fitness:

fitness_new = *(1/rH)*p_t**(rH - deltaS) = fitness*(1 - deltaS/*rH*), deltaS < rH

The reduced fitness, i.e fewer average number of new cases per IH leads to reduced survival probability and far lower probability of 'outbreaks', as can be seen in **figure** 4 (starting from top left with an 'unlimited' pool of susceptible, 'outbreak' defined as seeding events leading to > 60 infected).

P'(G) = fitness*P'(G-1) = fitness^(G-1)*pt/rH = p_t^G*(1-deltaS/rH)^(G-1)/rH = P(G)*(S_effective/rH)^(G-1)

Hence when S_effective is limiting, rH > S_effective, survival probability decreases as the exponent of the ratio of S_effective to rH. Furthermore, as long as the average S_effective < r_threshold, larger outbreaks are extremely rare.

Vx to the power of COVID-19

Since the causing agent behind the pneumonia cases in Wuhan was not known initially, samples were sent to the WIV (Wuhan Institute of Virology) for investigation, and COVID-19 was determined to be the probable causing agent (20-22).

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As a matter of a thought experiment, let us assume this conclusion is not entirely correct, and that some of the patients, specifically those with more severe symptoms and higher fatality rate, had a second pathogen present, Vx, which was not identified by the WIV team for any reason.

Normally, in the absence of a known pathogen patients are quarantined based on their symptoms (figure 5 top), and that is likely what happened in Wuhan until mid-January (23-24). During this time both Vx and COVID-19 kept spreading, each at a different pace: COVID-19 spread in substantial numbers in the community, and Vx still at low rH and causing few new cases among the patients.

After COVID-19 was determined to be the causing agent and test kits became widely available, Wuhan patients were quarantined based on both symptoms and COVID-19 results (25), leading to a massive increase in the number of people put in quarantine facilities. Since at that time it was believed that it was still possible to eliminate the outbreak, Wuhan citizens were put in quarantine even with mild or no symptoms, based entirely on their COVID-19 test results (25).

It is possible that such large supplies of COVID-19 patients, susceptible to Vx (figure 5 bottom), essentially guaranteed S_effective was not a limiting factor to the spread of Vx within the quarantine facilities, allowing Vx variants with high rH to infect > r_threshold susceptibles, leading to a full outbreak.

A Vx outbreak in a quarantine facility carries risks beyond increased mortality. First, transferring patients between facilities based on their COVID status carries the risk of introducing Vx into additional facilities and even the community. Second, there is the danger of Vx developing mutations that allow more efficient human-to-human transmission.

Empirical evidence for *a potential* Vx in the Wuhan outbreak

There is data to suggest some of the early cases in Wuhan could have been caused by something other than only COVID-19 infection. It was recently pointed out (26) that traces of fluA H7N9, a variant of avian flu, were present in specimens from 3 out of the 5 “original patients” in Wuhan.

Of note, H7N9 infections in humans are described as indistinguishable from the 2003 definition of SARS (27-29), causing fever, hypenia, long-term damage to lung and cardiac tissue in recovered patients, and high mortality rate. Moreover, H7N9 viruses can be antigenically and genetically very different from common fluA strains (e.g H1N1), making them undetectable by standard flu tests and likely to go undiagnosed in hospital settings (30-31).

There have been 5 documented H7N9 outbreaks in China from 2013 to 2017, but human-to-human transmission was only evident to some extent in the last outbreak (32-34), consistent with a Vx that is not yet humanized and likely to cause far fewer cases than other respiratory pathogens. However, considering the estimated CFR for H7N9 patients is ~30% (30, 34), even if only 10% of the COVID-19 patients in Wuhan also had H7N9 it would explain the high CFR initially reported in China.

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Discussion

I show that survival probability of superspreader viruses with R0 < 1, referred to here as Vx, is maximal at low rH values, but Vx can cause a large number of cases only at high rH values, and these can be averted. Under normal conditions, medical staff tries to isolate patients with symptoms of a severe respiratory disease, even if no pathogen is identified. Hence patients with Vx are likely to be separated from the general patient population based on a set of symptoms typical to Vx patients. During the 2003 SARS outbreak for example, detection of the causing agent, SARS-CoV, did not play a role in early quarantine decisions, as the causing agent was unknown at the time (20-21). Patients were quarantined based on their symptoms, and on their recent contacts and travel history.

The danger in quarantining based on symptoms is that several pathogens can initially lead to similar symptoms such as respiratory distress, cough, fever etc. If e.g. Vx causes fever and cough on the first few days, and severe pneumonia and death after 7 days on average, then based only on symptoms patients with 'regular' flu-like disease could be put together with Vx patients. These regular patients quarantined with Vx patients can become infected themselves, and worse, if the number of Vx patients is much smaller than that of the regular patients, S_effective may exceed r_threshold, allowing Vx to shift from survival at low rH and case numbers to high rH and increased probability of outbreaks, as shown in figure 4.

Hence the combination of increased hospitalizations due to COVID-19, and more critically erroneously grouping large numbers of patients with positive covid-19 test results, and patients with SARS-like undiagnosed Vx infection, could have dramatically increased the probability of additional transmission cycles and higher mortality rates. If authorities in e.g Italy quarantined large numbers of pneumonia patients, even milder cases if they had positive COVID-19 test results (35), they may have helped create the necessary breeding grounds for local Vx outbreaks, travelling silently alongside COVID-19, and greatly increasing CFR where present.

There are several unusual simplifications in the model. First, I kept the number of susceptibles constant. In the context of a single Vx patient sent to a quarantine facility with thousands of susceptible people this may be less unrealistic. Second, I assume Vx to have a set R0 value and therefore a fixed ratio between the probability of IH (1-L) and the average number of transmissions it causes, rH. There is no reason to presume mutations dont change this ratio, decreasing/increasing fitness.

The model presented here differs from previous models in 2 important ways: 1. It assumes the possibility of a parallel outbreak of an as of yet unverified pathogen, and 2. Model predictions may be refuted/verified with already existing patient samples. For example, the results suggest that Vx incidence will be low in most facilities, but high in facilities where patient fatality rate rose sharply for short periods (1-4 weeks). If no traces of an unusual pathogen, other than COVID-19, can be found in patient specimens from such facilities, then the 'silent partner' hypothesis

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should be dismissed. If on the other hand some pathogen is found at a high frequency in regions with high CFR, but in low frequency when/where CFR was low, then it must be considered as a possibility and an effort must be made to identify a potential Vx.

Considering the cost in human lives and resources already associated with the COVID-19 pandemic, and the growing uncertainty regarding the symptoms and outcome associated with infection, it is beyond amazing no effort was made to independently verify that COVID-19 is the only responsible pathogen.

The only data to back the model I propose is the NGS data from the first few patients in Wuhan (Bioproject: PRJNA605983), which may have been infected with some fluA strain related to avian fluA H7N9. Sadly there is no raw NGS data from patients from NYC or Italy, and very few labs have the capacity or authority to carry out such tests on large numbers of patient samples from various areas. I believe it is important for the CDC to confirm independently, using data collected in the US over recent months, that COVID-19 is the sole responsible pathogen in severe/fatal cases, and that no other suspicious pathogens are present.

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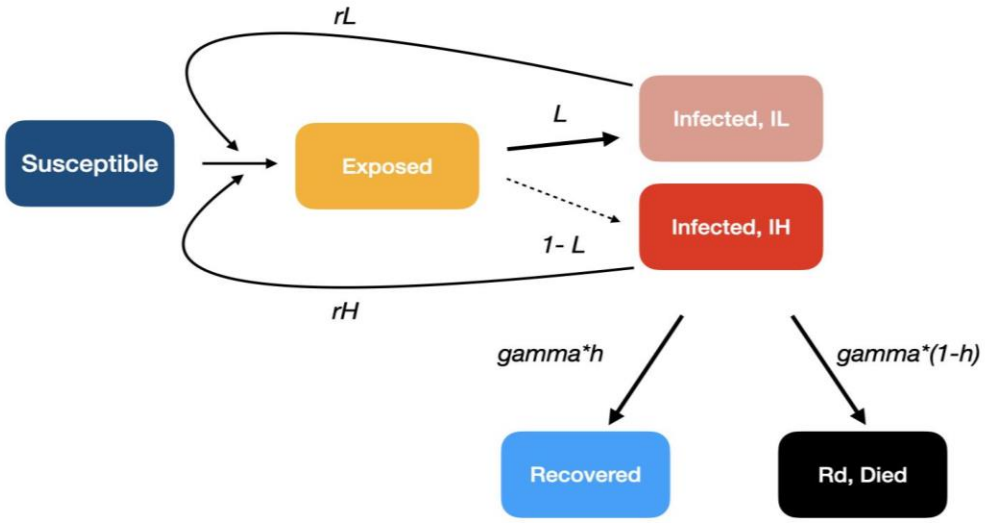
Figures

Figure 1: SEIR model



Legend: susceptibles become exposed after contact with infected individuals. Exposed individuals create Infected of type IL at rate L and IH at rate 1-L. IH can cause rH new cases, and IL cause rL new cases, with rL << rH. After transmitting the infection, IH and IL recover/die at rate gamma.

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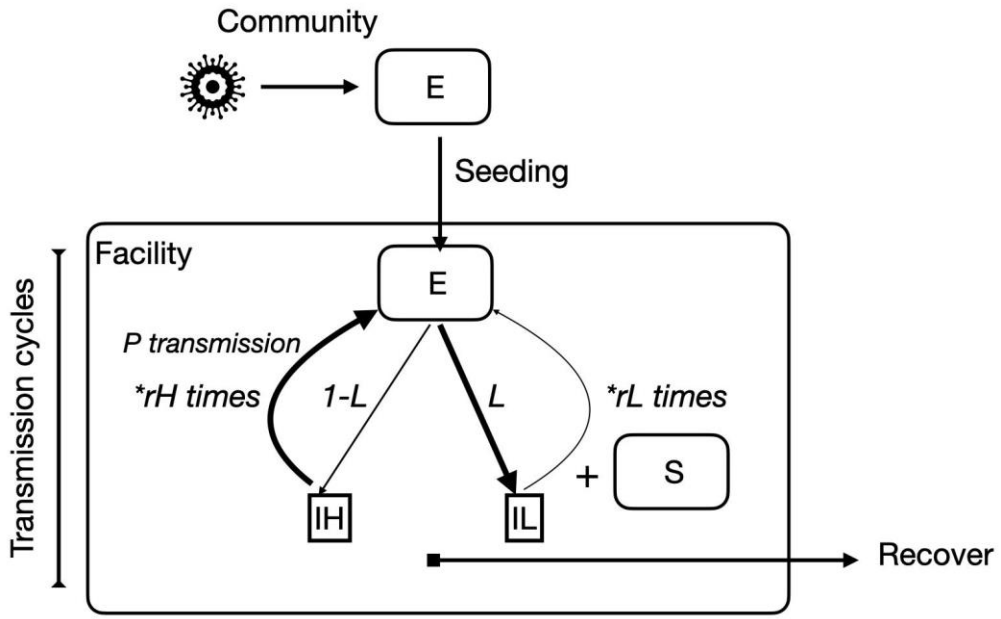
Figure 2: experimental procedure per seeding event



Legend: a person infected by Vx becomes ‘exposed’ and is admitted to the facility in a ‘seeding event’. The patient may become IL or IH with probabilities L and 1-L. Once Infected, patients can transmit the virus to susceptible patients at some probability P_transmission. IH patients can infect more patients than IL patients as long as the number of nearby S is not limiting. IH and IL ‘recover’ after transmitting the virus, and exit the transmission cycle. When no new transmissions take place (extinction) or when the total number of infected exceeds a set threshold (outbreak) the experiment/simulation ends.

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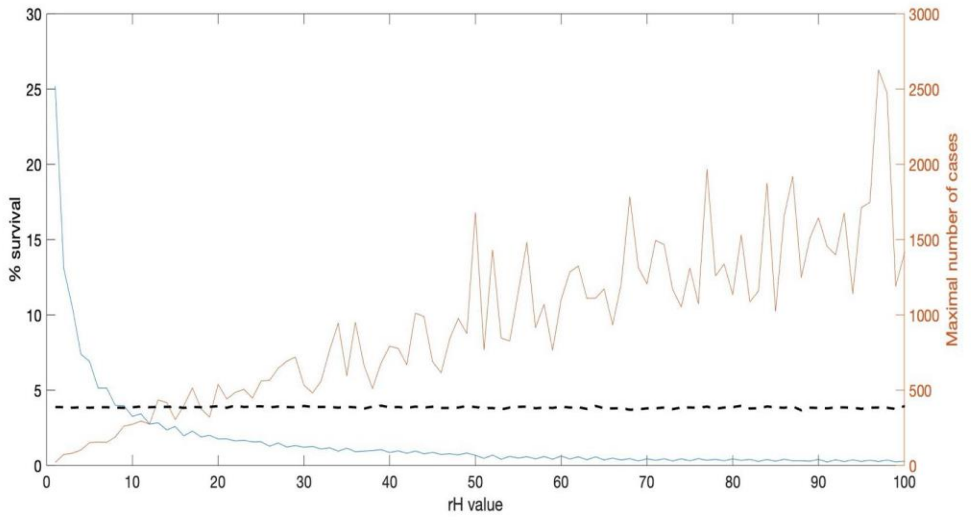
Figure 3a: Survival probability and maximal size vs. rH



Legend: survival % (left y-axis) and maximal number of cases (right y-axis) vs rH values from 1 to 100. Maximal survival % (blue) at rH = 2 and lowest at rH = 100. Average number of cases per 100k seeding events is represented by the dashed black line.

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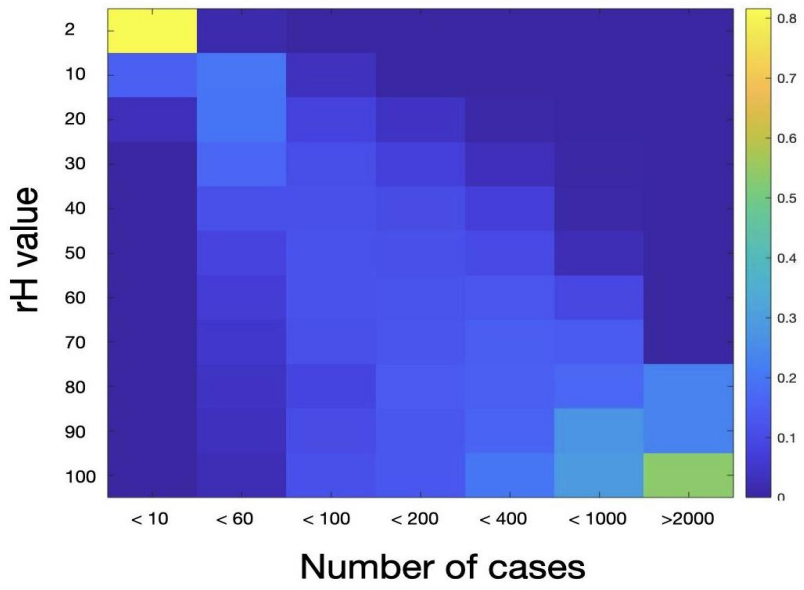
Figure 3b:



Legend: rows on the y-axis represent rH values from rH = 2 to 100. Columns on the x-axis represent the number of cases caused by a seeding event, from 1 to 10 cases on the left, to over 2000 cases on the right end. Color of element [x,y] represents the fraction of seeding events by rH = y leading to x or less cases, over the total number of cases <= x. E.g, over 0.8 of seeding events leading to 10 or less cases were caused by rH = 2 (upper left corner, yellow), whereas 60% of all events leading to > 2000 cases were caused by rH = 100 (bottom right, green)

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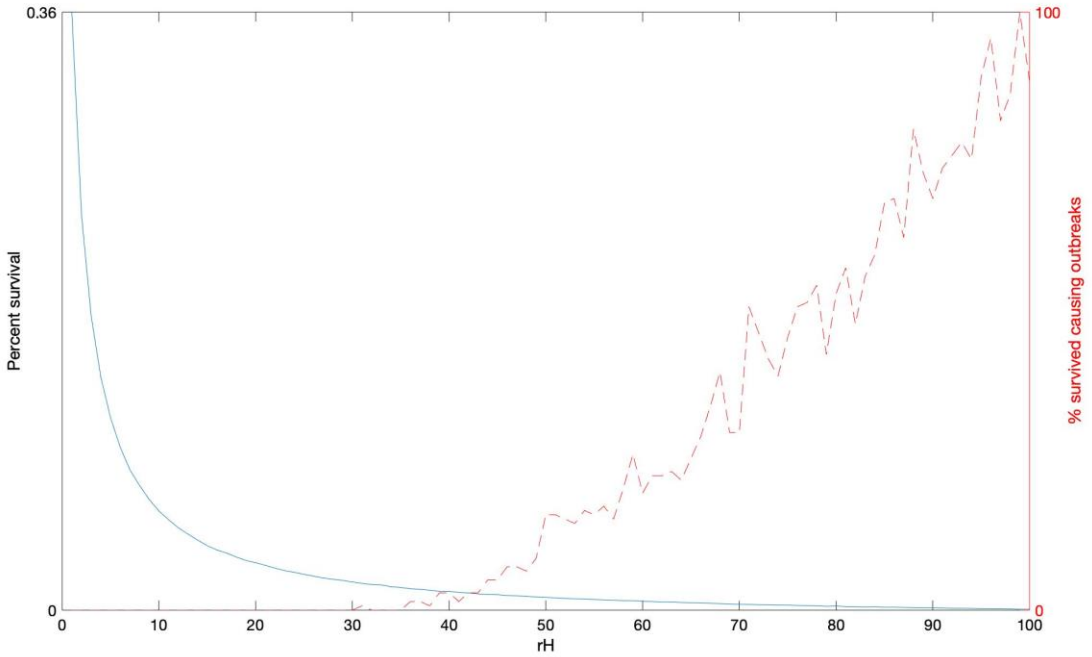
Figure 3c



Legend: survival % (left y-axis) and % of cases that survived that caused > 60 cases (right y-axis) vs rH values from 1 to 100.

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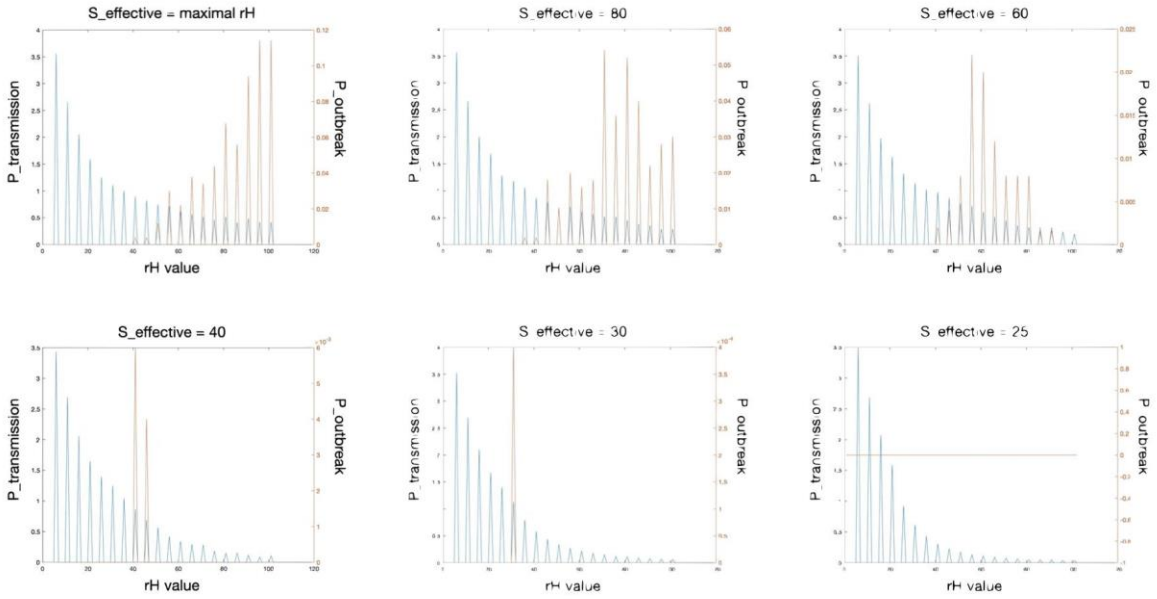
Figure 4: The sensitivity of Vx P_transmission and P_outbreak to the availability of S per I, as a function of rH



Legend: % of seeding events leading to Vx multiple transmission generations (blue) and % of cases leading to outbreaks (red). When S is not limiting (top left) survival % is highest for minimal rH (3%), and outbreak % is highest for maximal rH (0.1%). As the number of S becomes increasingly limited (going left to right) survival % (blue) while rH < S_effective is unaffected, and moderately reduced at higher rH values. As S is reduced the maximal outbreak % (red) is reduced and shifts to lower rH values (= ~ S_effective). Outbreak % is halved at S_effective = 80, cut to 0.02% at 60, 0.005% at 40, sharply drops to < 0.0005 at S_effective = 30 and essentially vanishes when S is reduced further (bottom right, flat red line).

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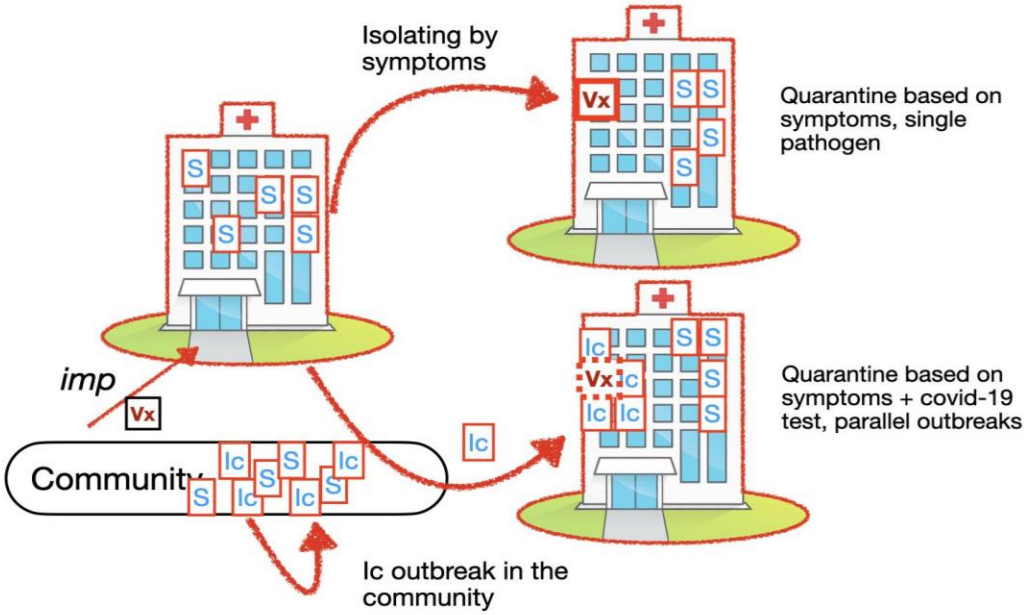
Figure 5: facility “seeding event”



Legend: rare Vx cases are imported from the community into a healthcare facility at some low rate *imp*. The number of other patients potentially exposed to Vx is minimal when the patient is isolated (upper right). When the presence of Vx, and some of the symptoms caused by Vx overlap with an outbreak of a second pathogen, e.g COVID-19, denoted ‘Ic’,the relatively small number of Vx patients may be quarantined alongside a large pool of susceptibles (Ic), creating conditions conducive for a Vx outbreak.