

# *The Mathematics of Flu, Explained*

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Thank you for doing this exercise in your class. Here we discuss some of the math behind the simulation games. We are aware that most high school students have not been exposed formally to probability modeling, so even here we tread likely in this subject area. Please consider this an introduction. Much more detail, for advanced students, is contained in the references at the end of this addendum.

To a large extent, the material in each section stands on its own. Thus, you need not read and study each section in sequence to understand a later section. Please feel free to pick and chose whatever topics interest you and your students.

## **1. $R_0$ , the basic reproductive number.**

The parameter  $R_0$  plays a basic, fundamental role in most epidemiology models.  $R_0$  is the basic reproductive number. It is defined as *the average number of new infections caused by a newly infected person in a fully susceptible population*. In the class exercises we model  $R_0$  as 2.0 and 1.5. The value of 2.0 is motivated by the recent news story that we cite in the BLOSSOMS video that “each person newly infected will infect 2 others.” This story does not relate the full complexity, as the current novel H1N1 virus has been estimated to have an  $R_0$  value of somewhere between 1.3 and 2.0. In the deadly 1918 “Spanish Flu,” a typical estimated value for  $R_0$  was 2.0.

In the first exercise we show how a geometric progression  $\{1, 2, 4, 8, 16, 32, 64, \dots\}$  grows so quickly. This is what would happen if indeed each newly infected person were to infect 2 additional people. First, we see that such behavior is mathematically impossible due to the finite size of any given population, even everyone on Earth! Second, such unrestricted exponential growth does not seem intuitively plausible. You might engage the class in a discussion about this. We ask for this at the end of BLOSSOMS video segment 3.

Simulation exercises 2, 3 and 4 show that any predicted exponential growth in the number of newly infected is reduced below exponential growth. This is due to the fact that over time, a growing percentage of the circulating population is recovered and now immune to the flu. Any ‘infection events’ involving such people will produce no new infection. In the BLOSSOMS video, we play out an infection event as Sahar sneezes into her hand and then shakes the hand of Mai. But since Mai is wearing a **Blue Hat** and is

now recovered and immune, this infection event does not cause a new infection. This author (Professor Larson) wearing a **Green Hat** in the skit is not so lucky!

Mathematically, it is convenient to define a time-dependent generalization to  $R_0$ : As the population of susceptibles is depleted, the **generation-specific reproductive number**,  $R(t)$ , is called the **effective reproductive number**.  $R(t)$  is the mean number of secondary infections that will result from each newly infected individual in generation  $t$  of the epidemic.

## **2. Predicting What Happens in Later Exercises.**

Simulation exercises 2, 3 and 4 all rely on probability. The outcomes are uncertain since the evolution of the ‘disease’ depends on the numbers drawn randomly from a hat or basket. So, it is not possible to predict with certainty the outcomes of any of these exercises. To obtain good intuition, one would have to repeat each exercise several, perhaps many times to obtain limiting averages. That is beyond the scope of the in-class exercise, but we do point to a simulation game available on the Internet (from the web site of this BLOSSOMS learning video) that helps out in this regard.

But we can do some calculations here. For instance, let’s step through the first few generations of the flu in exercise 2. Let’s calculate the average or expected number of newly infected people at each generation. Suppose it is your class with  $N = 30$  students. At generation #1, we have one person infected. At generation # 2, we have 2 additional people infected. But at generation #3, we have 27 susceptibles and 1 recovered and immune (patient zero is now wearing a **Blue Hat**). Each time one of the two **Red Hat** infected and infectious students pulls a number from the basket, there is a  $27/28$  probability that the number is that of a susceptible. There is a  $1/28$  probability that the number pulled is that of the student who was patient zero, now happily recovered and immune (wearing the **Blue Hat**). Thus, at generation #3, the mean number of newly infected students is not 4.0, but rather  $4 \cdot (27/28) = 3.857$ . At generation #4, we now have 3 recovered and immune (**Blue Hat**) students in a circulating population averaging  $(30 - 3.857)$  in size. We subtract out 3.857 as the mean number of students who will now wear **Red Hats**. Each draw from the basket of numbers in the basket will offer three possibilities of drawing immune and recovered (**Blue Hat**) students. So, roughly speaking, the mean number of new infections at generation #4 is approximately  $3.857 \cdot 2 \cdot (30 - 3.857 - 3) / (30 - 3.857) = 6.829$ . This contrasts to 8 infections that we observed in simulation exercise #1, sampling without replacement. So, one can already see how the re-introduction of now recovered and immune (**Blue Hat**) people back into the population slows the exponential growth of the disease.

An enterprising student may want to generalize this argument in a spreadsheet model and predict the mean or average outcome – by generation -- for the entire exercise. But remember, we are dealing with probabilities, and the mean outcome is usually not very likely to be the outcome actually experienced on any given execution of the simulation game. This is especially important in simulation exercise #3, with super-spreaders, were

the mean is likely to be far from the actual observed – due to the rapid die out of over half of the started epidemics.

### **3. Dealing with Super Spreaders.**

In the third simulation game, we retain a value for  $R_0$  at 2.0, but we assume that each newly infected person will infect either zero or 4 other people, with equal likelihood of each outcome. Each ‘newly infected student’ in your class should flip a fair coin (Heads: infect 4 others; Tails: infect zero others) to see what he or she should do. The average or expected number of susceptibles infected under this scenario is  $(1/2)*4 + (1/2)*0 = 2.0$ , indicating that  $R_0$  is still equal to 2.

An infection can grow in a fully susceptible population if and only if  $R_0 > 1$ . This well-established statement can be somewhat misleading because an  $R_0 > 1$  does not guarantee that a disease will take off. Usually, a value of 2 for  $R_0$  is thought to result in a doubling of the number newly infected with each generation of the flu. But in this third exercise we consider a population where half of the population – group 1 (“Heads” on the coin flip) – because of behavioral and immunological reasons, will spread the virus to 4 people if infected, while the other half – group 2 (“Tails” on the coin flip) – never spreads the virus. By most definitions of the reproductive number, we have an  $R_0$  of 2. If the first person to get infected is a member of group 2 the virus dies out right away. This is an example of a case where  $R_0 > 1$ , but the disease dies out after the index case more than half of the time. We can write an equation from which we can compute the exact value for the self-extinction probability, which we will call  $P_E$ . For our class exercise, we can write

$$P_E = (1/2) + (1/2)P_E^4 .$$

The logic is this:  $P_E$  is equal to 1/2, due to the 50% chance that patient zero will infect no others, plus (1/2) times the probability that each of the four people infected under the second possibility for patient zero will themselves spawn an infection process that dies out – each independently and each with probability  $P_E$ . The numerical solution to this equation is  $P_E = 0.543$ . (You might ask the students to derive and solve this equation.) So, we have a feasible situation in which  $R_0$  is 2.0 and yet 54.3% of the ‘epidemics’ die out very quickly on their own. There is no exponential growth, obviously, for such cases.

**This is important:** To see such variability on epidemic outcomes in your class, it is important that you run this third simulation game several times, to show the two distinctly different outcomes: sometimes the disease dies out right away, and sometimes it takes off and becomes a true epidemic. Just one execution of this exercise of the simulation game will not show the students such variability.

#### 4. Deconstructing $R_0$

The consensus definition of  $R_0$  states that it is the mean value of a random variable, namely the mean number of susceptible people to be infected by the newly infected person, assuming a population where all others are susceptible. As in all probabilistic situations, the mean of a random variable conveys some useful information. But expressing the mean in terms of other more fundamental quantities can yield additional insights. Here we deconstruct  $R_0$  into two constituent parts, each somewhat controllable by our individual and collective behaviors.

Suppose I come face to face with  $\lambda$  people on a day that I am infectious but asymptomatic. I am a **Red Hat** student in the simulation game. We select the Greek letter lambda ( $\lambda$ ) since in modeling analyses it often refers to frequency of occurrence, such as the daily frequency of interacting with other people. Many people who become infected with the flu have one such day before they feel and appear sick, and not being able to identify these people is what makes eradication of the flu so difficult. Define an ‘indicator variable’ as follows:

$$X_i = \begin{cases} 1 & \text{if person } i \text{ becomes sick as a result of exposure to me} \\ 0 & \text{if person } i \text{ does not become sick as a result of exposure to me} \end{cases}$$

Now, we let  $NI$  be defined to be the number of people I will infect on this day.  $NI$  can be written as simply counting the indicator variables,

$$NI = X_1 + X_2 + X_3 + \dots = \sum_{i=1}^{\lambda} X_i$$

Suppose for example  $\lambda = 50$  and that all  $X_i$ 's are 0 except for  $X_9$ ,  $X_{18}$  and  $X_{45}$ , each being equal to one. In that case, I have infected 3 of the 50 individuals that I have come face to face with on this day. Now, at any given level of intensity of face-to-face contact, there is a probability  $p$  that I will pass the infection on to the person I am facing. Sometimes  $p$  is called the “transmission probability.” We can now write an expression for the mean number of people I will infect on this day. It is simply the mean of

$$NI = X_1 + X_2 + X_3 + \dots = \sum_{i=1}^{\lambda} X_i, \text{ which equals } \lambda p.$$

We thus have a simple expression for  $R_0$ , and that is

$$R_0 = \lambda p.$$

**This is a fundamental relationship that you may want to derive and discuss with your students, especially for advanced classes.**

Flu is an infectious respiratory disease, spread by human contacts. Reduce human contacts, and reduce prevalence of the flu. By writing  $R_0 = \lambda p$ , we have expressed  $R_0$  in terms of two other parameters, each of which we can control to some extent. We have a fighting chance of reducing  $R_0$ , perhaps a little, perhaps even to below 1.0, the critical value to assure that the disease dies away rather than grows exponentially. In the sense of this discussion,  $R_0$  indeed does not exist as a separate quantity. It is a function of both the inherent properties of the given virus *and* the population's behavioral responses to it.

How do we control  $\lambda$  and  $p$ ? One reduces  $\lambda$  simply by reducing the number of face-to-face contacts we have each day. If a parent is shopping for groceries, rather than following the European tradition of daily shopping, perhaps one switches to weekly shopping, or, better yet, to groceries delivered to one's door. If you manage a team of employees, rather than have face-to-face meetings during a flu emergency, have conference calls instead, with many workers telecommuting. Many companies have already created comprehensive pandemic flu plans that include telecommuting, reduced face-to-face encounters and even minimum desk spacing between workers. The desk spacing idea relates more to the parameter  $p$ , the probability that any given face-to-face contact will result in a new infection. How else can we reduce  $p$ ? Wash hands with hot water and soap several times daily. Do not shake hands during greetings with colleagues. Cough or sneeze into your elbow, not into the open air or your bare hand. Be careful not to touch surfaces that might have recently been contaminated with flu virus. Encourage your city's large employers to stagger work hours, so that public transportation subways and busses are less crowded during now-stretched-out rush hours. Even run the subways and busses with windows opened. The key here is that  $R_0$  is a direct function of social context and human behavior, behavior that can be altered to reduce the numerical value of  $R_0$ . That is why we can reduce the value of  $R_0$  from 2.0 to 1.5 in the fourth and final class simulation exercise.

Reducing the number and intensity of human-to-human contacts has been called "social distancing." It is a key control parameter in any engineered response to the flu. Social distancing has roots over centuries, often as a type of group evolutionary survival mechanism. In rural India in the 19<sup>th</sup> and early 20<sup>th</sup> Centuries, subsistence farm families who lived closely together in villages but who worked separate land plots outside of the villages, left the villages and lived separately on their land whenever they heard from a trusted messenger that 'a plague' was 'in the vicinity.' They returned to their village homes once the signal was given that the risk of plague had subsided, the duration of the distancing typically being about two weeks.

While this isolation policy seemed to work well for rural subsistence farmers, we may well ask, "What is the analogue to the movement to the land in our highly-networked interconnected Western style of life?" We are not self sufficient and we rely on others to provide virtually all essential services and products for living. Given all the interconnected networks upon which we rely, is social distancing itself, in the simple ways in which we can do it, sufficient to control the evolution and penetration of a flu pandemic? This question is a major challenge when addressing response to pandemic flu. You may want to discuss this with your class.

## **5. Herd Immunity.**

All else being equal, herd immunity occurs in a population when the infectious disease no longer grows exponentially, and starts to die out from generation to generation. Herd immunity occurs when the *effective reproductive number* drops to  $R(t) = 1$ , signifying that each newly infected person infects – on average -- only one additional person. At this point in the evolution of the pandemic, no further exponential increase occurs. Usually herd immunity is achieved because a significant fraction of the population has become immune to the disease, either by vaccination or by having had the disease and being recovered and immune to further infection. Let us call  $R(0) = R_0 > 1$ . Recall from Section 4 that  $R_0 = \lambda p$ , where  $\lambda$  is the pre-intervention mean number of daily face-to-face contacts by a random member of the population, and  $p$  is the initial conditional probability of passing on the infection to the person in a random face-to-face contact. Define the “critical time”  $t_c$  such that  $R(t_c) = 1$ . The critical time is the time at which herd immunity is achieved.

Let’s first do this without NPI’s. At  $R(t_c) = 1 = \lambda_{t_c} p_{t_c}$ , we assume that the frequency of day-to-day contacts  $\lambda_{t_c} = \lambda$  is unchanged during the pandemic<sup>1</sup>. Thus, for this equation to work, we need a reduction in  $p$  so that  $p_{t_c} < p$ . We get this because some face-to-face contacts are recovered or vaccinated and now immune to further infection. The “infection event” fails. Suppose at time  $t_c$ , the time of herd immunity, we have a fraction  $f$  of the population in state **R**, immune to re-infection, and the residual  $(1-f)$  still susceptible. For those who are still susceptible, the conditional probability of infection given exposure from a face-to-face contact remains unchanged at  $p$ . Thus  $p_{t_c} = p(1-f)$ . Then we must have  $\lambda p_{t_c} = \lambda p(1-f) = 1$  or  $f = (\lambda p - 1)/\lambda p = 1 - 1/R_0 > 0$ . To see if this makes sense, we try  $R_0 = \lambda p = 2$  and obtain  $f = 1 - 1/2 = 1/2$ . This makes sense: with  $R_0 = 2$ , one half of the population needs to be immune for herd immunity to occur. This is what your class experienced in simulation exercise #2. Other numerical examples are similarly intuitively appealing.

This equation for  $f$ , the fraction of the population that is immune (due to recovery or vaccination), for herd immunity to occur, is fundamental and may be derived and discussed in advanced classes:

$$f = 1 - 1/R_0 > 0$$

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<sup>1</sup> This may be corrected in a more sophisticated analysis, as we adjust for the reduced population because some are either sick in bed or may have died. With a reduced population, we may wish to model the number of face-to-face daily contacts as reduced in accordance with the reduced circulating population.

Now, let's redo this exercise initially having  $R_0 = \lambda p = 2$ , but reducing it with NPI's. Suppose we alter daily behavior to reduce  $l$  by a factor of  $1/\sqrt{2}$ , that is we have a new  $\lambda$ , call it  $\lambda'$ , such that  $\lambda' = \lambda/\sqrt{2}$ , roughly a 30% reduction in daily contacts. Suppose by social distancing and hygienic steps we also reduce  $p$  by a factor of  $1/\sqrt{2}$ , defining a new  $p$ , call it  $p'$ , such that  $p' = p/\sqrt{2}$ , which is roughly a 30% reduction in infection probability, given face to face contact. If we can all do that by invoking NPI's, then the new  $R_0$ , call it  $R'_0$ , becomes  $R'_0 = \lambda' p' = (\lambda/\sqrt{2})(p/\sqrt{2}) = \lambda p/2 = 2/2 = 1$ . That is, we can start the pandemic at herd immunity level by invoking NPI's at the beginning. If we could do that, the pandemic would never grow exponentially and would die off instead. This is most likely impossible in practice, since time is required for officials to observe and recognize a new and novel flu virus, one that could grow to epidemic and then pandemic levels. But the point remains: We individually and collectively have the power through self-selected behavioral changes to alter dramatically the course of the flu. To avoid a dangerous re-emergence, perhaps a 'second wave' after NPI's have squelched the first wave, these behavioral changes must be held in place until the threat of the flu is passed.

## **6. Complexities**

In a new disease such as the novel H1N1 flu currently going around the globe, most people are susceptible at the start of the pandemic. This is how we model the population in your classroom. At the beginning, everyone is equally susceptible. But it is a simplification. But not all are equally susceptible, as there is evidence that older people may have antibodies from an earlier influenza that partially protect them from the current H1N1 virus. Thus, you their teacher, may be less likely to get the flu from any given person-to-person 'infection event' than your students are! The class exercises and the assumptions therein provide a rich background to discuss with the class simplifying assumptions and how they may be made more realistic with more sophisticated mathematical modules. The sophistication need not be represented by fancy mathematics, either deterministic or probabilistic, but by more complex rules in the simulation game. These ideas, plus the many public web sites that we list, provide much food for thought and for further class discussion, even take-home projects.

**Acknowledgement:**

Material in sections 3, 4 and 5 is adapted from Larson and Nigmatulina, 2009.

**References.**

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