BLOSSOMS MODULE
MATH FLU

L: Dick Larson
S: Sahar
M: Mai
N: Newton

D: Hi, I'm Dick Larson, I'm a faculty member here at MIT in Cambridge, MA, USA, and we're delighted to have you here with us today. I'm also delighted to have with me two student colleagues.

S: Hi I'm Sahar, I'm a physician, I'm also a grad student here at MIT.

M: I'm Mai, I'm a student intern here at MIT as well as a Wellesley College undergraduate. We're all here today to study influenza and how it spreads.

N: Hello everyone. My name is Newton Phillip Isaac and I will back later to help the MIT flu team and Dr. Larson in teaching you all some very important facts about the spread of the flu.

S: How are diseases like common colds and flu spread? Coughing, sneezing, or touching contaminated surfaces. How is this all related to mathematics? What can you do to reduce the spread of infectious disease. Let's explore some options of doing some simple math models of disease spread.

M: If you read in your current newspaper about the spread of the H1N1 influenza, you'll find that every person who gets infected will infect two others. And you can see that on your screen right now.

D: What would happen if each newly infected person infected two others? Think about this. Let's see…. this is a math class, let's think about this. So the first person –call that person Patient 0, we'd now have 1 infected and then he/she infects 2 others; and then each of them infect 2 others, so in the third generation of the flu, we get 4, and then 8, and then 16, and then 32, and 64 and this explodes exponentially. My goodness! that's very scary. So if we did have a situation in which each newly infected person infects 2 others it would exponentially explode like we just saw.

Now, do you think this would happen in your class, if somebody in your class got infected? Would this happen? Is this a realistic depiction mathematically of what would happen with flu progression?

Why don't you take a few minutes, discuss this with your neighbors, discuss this with your teacher, and we'll see you in 3-4 minutes.

D: Welcome back. We hope you had a great discussion with your classmates and with your teacher about this exponential growth right here. We're now going to play a simulation game in your class, which simulates this exponential growth. Since this is mathematical modeling we're dealing with, we need to define the key parameter. The key parameter is called R-0, the basic reproductive number. R-0, as you see on your screen right now, is defined to be the average number of additional people that a newly infected person will infect in a 100% susceptible population. That's a mouthful.

100% susceptible population is the population of people who have not been vaccinated before, or are not immune to the flu, and given an infection event will likely get infected with that flu.

So we're going to play a simulation game right now. If R-0 is great than 1, you have this exponential increase, as we saw here when R-0 is equal to 2. It is a key parameter, it has the power of exponential growth and explosiveness. Sahar, would you give us some more details?

S: OK, Dr. Larson. The idea of our simulation game is that the class members will become infected randomly with a statistical probability determined by our sampling technique.

There are 4 possible disease states of any given student, as you can see on your screen right now

<u>Susceptible</u> is a member of a population who is at risk of becoming infected by a disease.

<u>Infected</u>: when a person in a population gets the infection, he/she is infected.

<u>Infected and infectious</u> is once the infected person passes on the infection to another person

<u>Recovered and now immune</u>, the infected person's body develops immunity.

At any given time during the exercise, we assume that the students are going to have either one—and only one—of these four possibility states.

Susceptible with a GREEN hat.
Infected with NO hat
Infectious with a RED hat
Recovered/Immune with a BLUE hat

M: So I hope you guys all have your props ready in hand. You will all progress through these four stages, in sequence. Stages 2 and 3 last only one day each.

So, if I were to become infected on Day 2, I would remove my hat as an infected person not yet infectious, and on Day 3 I would wear this red hat and be an infected and infectious person. Then on Day 4, I would wear this blue hat and be recovered and immune from now on. Though it is possible that any of you could remain in the green, or susceptible, state.

N: Newton, Phillip Isaac, here again, to help you review. Actually, just call me NPI. Each person must be in one of 4 states. If you are in a green hat, you are susceptible, meaning that you have no immunity to infection of the disease. If you have no hat, you are infected but cannot yet spread the disease. If you are in a red hat, you have been infected and are infectious, meaning that a cough or a sneeze or even a touch may spread the disease. And if you are under a blue hat, you have recovered and are immune to further infection.

In our simulation, we assume that everyone who becomes infected eventually recovers and becomes immune.

D: Thank you Dr. NPI. Now let's play the simulation game.

We're going to assume, for the sake of argument, that there are 30 students in your class, but you can adjust it up/down to maybe 25, 35, 40, whatever number. We're going to go through certain steps, and these are the same steps you're going to do in your class.

So, in Step 1, you should have a basket or a hat or something that has in it numbers from 1 to N, where N = the number in your class. Here we have 30. So we reach down and we pull out a number. Aha! This is the first number, Student #3, who is going to be Patient 0, the first one infected in your class. Here on Day 1, oh my goodness, it's Mai who is #3, so she takes off her hat and she's now infected but not yet infectious. That's the end of Step 1.

Now, in Day 2, now she's going to be wearing a red hat because she's infected AND infectious, and she's going to select the next 2 of you who are going to get infected. To do this, she selects two numbers out of the hat. Notice I'm still having 3. You can't select yourself. And these two numbers are: #19 and 20. Ahhh, probably sitting right next to each other, somewhere in your class, 19 and 20. So you will have to take your hats off. You are infected but not yet infectious on Day 2.

Now we're going to the next step, which is Day 3, and all of a sudden Mai is cured, she's now recovered from the flu, she's now immune, and forever more in Day 3, and Day 4, and Day 5, she always wears that magnificent blue color. OK?

So that's basically the game you're going to play right now. Have fun with this and your teacher will answer any questions you have. This should be fast. We'll see you in a few minutes.

D: Welcome back! You can take your hats off now.

With R-0 = 2, did everyone in your class get infected by our sampling technique of sampling without replacement? I think they did, right?

S: Is this the way you expect the common cold or flu to behave? Is this the way it would work in an actual town or city? Think about it. Your simulation suggests that with an R-0 of 2, fully 100% of the population would become infected. Even if the R-0 is 1.1, that would eventually be the case. Why don't you discuss it in your class and great ready for your next exercise.

D: Welcome back! You see I'm now part of your class. I'm susceptible, wearing the green hat.

We'd like you to re-do the exercise you did before but with one major difference. This time you're going to do sampling with replacement. Mai is going to show you what that means. So she's working from day to day here, and ooops, she's now in Day 3 and she's now infectious and infected. OK? There she is, infectious and infected. Now she's going to go to Day 4 and she's going to be a very happy smiley face on Day 4 because she puts on the blue hat, and she's going to wear blue forevermore. She's now immune from this infectious disease called the flu/common cold, whatever it is.

Now, the moment she becomes a blue hat person, she takes her number 3 and puts it in the basket so that future infected students in the class can draw on #3.

Ohhh, I see another student coming along right now [S sneezes politely in the background] coughing and sneezing, wearing the red hat. I think Sahar might be infected and infectious. Oh my goodness, look what she just did. She shook hands with Mai and that would be an infecting event. However, since Mai is wearing the blue hat, she doesn't get infected, she's immune from further infections.

But hmmmm, yours truly is wearing a green hat. I think Sahar is coming toward me. Hello, Sahar, I just shook her hand, a hand that she just sneezed in. Off goes my hat, I've just been infected, I'm not yet infectious.

We'd like you to play this version of the game in your class. It will take a few minutes. See you in a few minutes.

D: Welcome back, we hope you enjoyed that exercise. I'll bet you noticed, a lot of you stayed green the whole time, never got infected. A lot of your are still wearing the green hat, like this. Now why is that? Because R-0 is equal to 2, which suggests this exponential increase. Why did the exponential increase not take over and infect all of your class? Well, if you think about it, people who eventually wear the blue hat are circulated around. There are infectious events like we saw Sahar with Mai, shaking hands after she'd sneezed into her hand, but those infectious events no longer cause a new infection because somebody is immune. And as the disease progresses over the generations, a larger and larger fraction of the population becomes immune, so a smaller fraction of those infecting events actually cause new infections. That's why the sampling with replacement is a much more accurate model of what goes on in real life than the thing we did in the first exercise.

M: Thanks Don. For instance, say we're at Day 5 now, and that half of you are recovered and immune. Say that I am newly infected and I draw two numbers from the basket: 16 and 12. To close the approximation, each of these numbers has a 50/50 chance of being the number of a blue person, and my human interaction with them would, if he/she were susceptible, cause a new infection. BUT, since they are blue and recovered and immune, they can no longer be infected. So maybe I infect 2 people, maybe I only infect 1 person, or maybe I infect none. In this way, the number of newly infected people in subsequent generations no longer grows exponentially. And then the growth stops, and eventually it stops altogether.

It's kind of like what happened with SARS in 2003.

D: In epidemiology, the mathematical study of epidemics, there's a concept called "herd immunity", like this herd of buffalo you see on your screen right now. The original thing was assigned to animals, herds of animals, but the same concept applies to infectious disease in humans.

Herd immunity – how is it defined? It is defined to be the fraction of the population that must be recovered and now immune such that no further exponential growth in the number of newly infected occurs from that point on.

So even though R-0 could be 2, and you think you get exponential growth, because there is such a large fraction who are now recovered and immune, there is no further exponential growth.

So I want you to discuss with your neighbors, with your classmates, and with your teacher – for the exercise you just did, what fraction of your class has to be recovered and immune so that you have herd immunity now in your class.

See you in a few minutes.

S: How did you do with herd immunity? You're right! When 50% of your class had recovered and become immune, your class enjoyed herd immunity. Chances are, the total fraction of your class that will eventually become infected exceeded the herd immunity 50% mark, perhaps reaching up to 70-75%. But it is very unlikely that 100% of you became infected.

Being immune due to your own body's antibodies is the same as having a vaccination. Sometimes it's even better.

D: OK, we want you to do two more exercises. Both of these are learning experiences beyond what you've done before.

In the first one, we're going to keep R-0 at 2, but we're going to have a certain wrinkle here. Let me go to the blackboard.

Each newly infected person will have a 50% chance of infecting 4 other people, OR a 50% chance of infecting 0 other people. 4 or 0. The average number of newly infected people in a fully susceptible population, from this person, will be 2. So we still have R-0 = 2. And this is much more realistic depiction of what happens in real life. Because no known infectious disease is such that each newly infected person infects exactly 2 people. Sometimes they infect 0, sometimes the average, sometimes above average, sometimes WAY above average. WAY above average are the so-called "super spreaders". And there are cases where one person might infect 50 other people and still R-0 could be 2.

So we might call this example "moderate super spreaders." The people who infect 4 people are moderate super spreaders.

So we want you to do exercise #3 here. I want you to do this the same way you did exercise #2, sampling with replacement, OK? But your key is going to be to figure out how you figure out whether each new person who is red (infectious and infected) infects 4 or 0? Hmmmmm…. I wonder what Mai is doing here. Think about this. Think about how to figure out a 50/50 chance here. Do this exercise, and we'll see you in a few minutes.

D; Welcome back! You might have noticed something strange in that most recent simulation exercise, that game you just played – especially if you played it several times.

At least half the time, the pandemic stopped dead in its tracks. No further people got infected after Patient 0, or maybe a very small number, and then the pandemic stopped.

S: 50% of such pandemics stopped? Why? Do super spreaders occur in real life? Later, check out the references we have attached here, at your library.

So you see, adding uncertainty to our model certainly makes it more complex and less easy to forecast outcomes. Welcome to the real world of modeling and disease progression.

D: Now we have one exercise left for you. Sahar, who is an MD, is going to enter pretty soon and show you how by behavioral changes you can reduce R-0 from 2 to a lower number. Bear with us right now and you will find out exactly how to do this.

S: Here's the good news. You and your family can do something to reduce the chance of getting infected, within yourselves or within the community. You can't reduce the chance to 0, but you can reduce it substantially.

These things are called behavioral changes, or non-pharmaceutical interventions (NPIs). That's why we had Dr. NPI assisting us today. You don't need to have medicines for that. No medicines, no pills, and no shots. Here's a list of all of them.

First of all: Wash your hands frequently with very warm water, lots of soap and for at least 30 seconds each time.

Second: sneeze or cough into your elbow or into a handkerchief.

Third: avoid shaking hands with people, especially when you're sick, or otherwise touch them in a way that would encourage virus transmission from one person to another. Avoid crowds and crowded places when you have the flu.

If you must have meetings with colleagues, try and arrange for these to be done by phone or internet.

Last but not least, there is a website where you can read up on it. It's called the Home Flu Kit to Empower Individuals and Families for Pandemic Flu, which you see on our website right now.

N: One of the most important ways to slow down the spread of flu is to keep sick people away from people who aren't sick. In this type of situation, it's best to stay at home until you get better. Rest up in the comfort of your own home. Don't go to school, don't play hooky at the mall, and please avoid crowded places so as not to get others sick. This should be good news for those of you who enjoy a nice day or so in bed.

Actually, this goes for you teachers out there too. You all need to be cautious. If you are sick on a school day, don't worry about staying home in bed for a few days. I'm sure your students will appreciate the distance, and if you need any extra help trying to do in the event that you get the flu, I suggest you read the Flu Kit paper by Dr. Larson and his team. If you read that, you'll be sure to be in the clear blue sky in no time.

D: OK. Suppose with NPIs we can reduce R-0 from 2 to 1.5, a 25% reduction. That seems very reasonable.

How do we do this? I want you to play the game the fourth and last time, sampling with replacement like we did in 2 and 3. OK?

So let's look at this example here. We're not going to have super spreaders, so we want a 1.5. And suppose we put each newly infected person with have 2 infection events, or 1 infection event, with a 50/50 chance, OK? In that case, we reduce R-0 to 1.5. I think you know how to do this in terms of either 2 or 1.

Why don't you talk to your neighbor for a few seconds.

OK? You remember how to do this. If you have a 50/50 chance, either 2 or 1 for a newly infected person who is now wearing the red hat.

So I want you to do this exercise. This is the last one, but it's the most important because it shows that you have some control over the prevalence of the flu.

At the end I want you to count two things: one, the number of generations of the flu in your class until you were done; and two, the number in your class who got infected, and compare that to Exercise #2.

See you soon.

D: Well, we hope you're really enjoyed your learning exercise today. Your first entry into mathematics and the study of flu progression or just infectious diseases in general.

The flu simulation games you played were obviously simplifications of the way the real flu or real infectious diseases progress.

For instance, with the real flu, after somebody has an infectious event that infects them, it usually takes 1-3 days until they show symptoms. It's variable. And usually the last 24 hours before they show symptoms – before they have a fever, before they start coughing and sneezing – they can walk around and interact with other people and infect them just by breathing and touching them, and there are no symptoms. So these people are called asymptomatic infectious individuals. And that's what makes it so difficult to control the flu because a lot of time people who are infecting folks don't show any outward symptoms.

Another thing is, we talked about people who were susceptible as if everyone was equally susceptible. Well, for instance, with the current H1N1 flu which is going around the world, it's been discovered that people 65 and older are much less likely to get it, primarily because they have probably been exposed to some previous flu in their past which has given them some antibodies that tend to fend off the new H1N1 flu, whereas younger people are more prone to get it.

So there are many approximations and many complexities in reality. Our simulation game was just to show you the essence, the core of the way infections spread.

Now, you might say "This is a math class, where's the math?"

Well, we have some of the math in probability and other things on our website if you want to delve into that, please do. I hope you enjoy that.

S: So that's Phase 4. Hopefully you saw in your class that NPIs can reduce, perhaps substantially, the total number of people infected in your class.

If the flu hits, from these exercises now you've learned that there are these behavioral changes that can help you and your family to reduce infection in the community.

This is a lesson you can tell your parents, your friends, even your siblings or colleagues, that NPIs do work.

N: Goodbye everyone. it's been wonderful, and I hope you remember to share your newfound knowledge of NPIs and everything else you've learned today with your friends and family.

M: Goodbye for now, and may all your colors be that of the clear sky – BLUE!

D: So long everyone. Thanks for staying with us.

S: Bye.

TEACHER MODULE

D: Hi. I want to thank you, the math teacher, for considering this module in your high school math class.

The prerequisites the way we did it, are not large. This could be any level of mathematics in high school, perhaps even middle school.

There are more mathematics developed, particularly applied probability, simple modeling, that are in the handouts in .pdf files on the website of this Blossoms learning module.

We decided that the focus of this particular class exercise should be experiential learning. We want the students to learn the power of exponential growth, and we want them to learn that different models and different behavioral assumptions, implemented here by sampling without replacement, and sampling with replacement, give distinctly different answers in terms of the simulation games that the students play.

So we couldn't do a lot of math AND do four simulation exercises in one high school math class. So you may decide that you want to assign them some reading of the mathematics of this before, or maybe (preferably) afterwards. Or maybe just some subset of the students are interested in some of the math behind.

We don't go into a lot of math because we don't assume that the students have been exposed formally to applied probability. One could have a whole course on epidemiology and applied probability, and that's not our focus here.

So in Segment 1, basically we just talk about exponential growth at a rate of 2 per generation. We talk about does that make sense? Is that the way a disease would actually work in practice? Some class discussion.

Then after that they're actually going to do, after Segment 2, they're actually going to experience this as an exercise by pulling numbers out of a hat.
(takes off blue hat)

It's important that the students understand the different states they can be in: susceptible state which is green; infected but not yet infectious, which is no hat on; the infectious state, which is red; and then recovered and immune, which is blue. And that students progress through these things, one at a time. You may have some questions from the students about exactly what all this means, and I'm sure you can answer them.

Once we start sampling with replacement, not all students will become infected. So just like in a regular population, even when a flu like the current H1N1 goes through the population, less than half—sometimes far less than half of the total population—becomes infected. So even though you might have an R-0 of 2 for something like H1N1, you don't have everyone get infected. So the simulation we play in Simulations 2, 3, and 4 are much more like reality.

OK, when you do the sampling with replacement, it is important that each person who was infected, then infectious, and now recovered, that they put their numbers back into the hat or basket, whatever you are using to generate random numbers for your class, OK? Because that will show that the exponential growth eventually stops and the disease is over.

But since we are doing a probabilistic simulation, I can't tell you ahead of time whether 70% of your class will become infected, 55%, or 95%. It's all a probability of distribution. We will have on our website soon (if we don't have it already) an animated simulation game that's in the computer, and you can simulate this 100 times or 1000 times and see what the distribution would be if you could simulate that many times. Obviously, in your one hour of 50-minute class, you can only simulate it once, so you're going to get some number out, like 72% of the students became infected with the Herd Immunity of 50% and R-0 = 2.

The herd immunity concept is interesting, and we developed a little bit more of the math about that in the .pdf downloadable file about mathematics, which actually is an equation you can solve that predicts exactly what the herd immunity fraction is for this particular situation. We have those details in there.

It's important that the students understand the basic concept of herd immunity, but again, the issue of the details of the mathematics are not so important.

About super spreaders. If any of the students are interested in this, they can go back and see that in the spread of typhoid, the spread of SARS in Hong Kong in 2003, even HIV spreads, often there were super spreaders who really accelerated the spread of these diseases at the very beginning and there's evidence also in flu that there are super spreaders.

So an interesting question is: How can R-0 be 2 and you can have some super spreaders who can even be at 10. If they are infected, they might on average infect 10 other people.

So these are questions that the class might ask, or you might ask the class.

Then you get the issue of average here. So that would be an average that would be highly skewed. There would be a lot of zeroes in the distribution, and then it would be a 10 out here with a small probability, and the average still could be 2.

So they should know about super spreaders and be comfortable with that concept.

When we just do 0 or 4, with a 50/50 chance, obviously what they are supposed to do is flip a coin ahead of time. If they flip heads, then they are going to infect 4 people; if they get tails, they will infect 0 people.

Now, the NPIs. One of the real reasons we had this Blossoms module here at this particular time is that we have a pandemic flu in the world, this new, novel H1N1 sometimes but incorrectly called the swine flu. That causes a lot of concern. What we want to show the students is that by certain behavioral changes, which we articulate in the Blossoms module, you can reduce the chance of becoming infected. And again, in our mathematical download, we actually develop this into an equation where we can actually separate out R-0 into two components: the frequency of daily contacts with other human beings, and the likelihood if one of the two of you is infected, that you will infect the other. You can reduce the frequency, as an example, by having meetings over the internet or by phone rather than face to face. And you can reduce that probability if two people meet by doing these behavioral changes: coughing or sneezing into the elbow, washing hands several times a day for 30 seconds, etc. etc.

So we want the students to understand that human behavior can be modeled mathematically and brought rigorously into these mathematical models and to show, hopefully dramatically, the results of that. If a byproduct of this math class is that they go home and they talk to their siblings, their parents, their friends, uncles and aunts, and they explain the benefits of these NPIs, these behavioral changes, that would be great. Because that could reduce for them and their communities the extent or prevalence of the flu currently in those communities.

So thank you for considering this module.

My email address is now shown on the screen. If you have any questions please email me directly and I'll try to get back to you within 24 hours.

Thank you.

END OF MODULE