

H5N1 Simulated Outbreak

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I. Introduction

Influenza, or 'the flu' as it is commonly referred to, is a virus that was first observed as early as 412 B.C [Wiki-01]. The fact that the flu was caused by a virus was not discovered until 1933, by scientists at the Medical Research Council in Britain [Blak06]. Throughout the centuries, this tiny virus has killed millions of people. Part of it's deadliness is due to its rapidly evolving nature. Two strains of the virus often combine to form a new lethal strain.

The influenza viruses take on a notation of HxNy, where x and y are integers specifying the configuration of the hemagglutinin (H) and neuraminidase (N) proteins in the virus [Wiki-02]. Table 01 shows various outbreaks of particular strains throughout recent years.

Year	Strain	# Ill	# Dead
1889-90	H2N2 – Asiatic (Russian) Flu	-	.75-1 / 1000
1900	H3N8	-	-
1918-20	H1N1 – Spanish Flu	500 million	40 million
1957-58	H2N2 – Asian Flu	-	1-1.5 million
1968-69	H3N2 – Hong Kong Flu	-	.75-1 million

Table 01 [Hill02]

Viruses can be broken into two categories: epidemic (or non-pandemic) and pandemic. In the case of influenza, it can be said that in non-pandemic years, the virus kills hundreds of thousands of people, while in pandemic years, the virus kills millions of people [Wiki-01]. The terms refer to the spread of the disease, with epidemic being more localized and pandemic more global. New strains of influenza are formed every year, but only certain strains prove particularly effective. In Table 01, three of these cases are considered pandemics – the last major pandemic occurring in 1968 with the H3N2 strain.

A reason for the absence of major influenza pandemics in recent years can

be attributed to increased medical technology and vaccination procedures. Each year, various medical organizations come together in an attempt to predict the strain of flu for the next year. A significant amount of money and resources are put into influenza research and prevention, with millions of vaccines being produced each year in the United States.

Although there has been no major outbreak in over 30 years, many medical professionals predict that a current strain, H5N1, of influenza (also known as Avian Influenza, Avian Flu, or Bird Flu) will change all this. "Genetic reassortment ("mixing") of a human flu virus with the current H5N1 avian influenza has been identified as the most likely source of the next pandemic" [Wiki-01]. An outbreak in the 21st century may prove even worse than the 1918 Spanish Flu (which is thought to have killed more people in a matter of weeks than the number of casualties in World War I [Wiki-01]) as the world has become even 'smaller' due to more efficient methods of transportation and globalization.

It is critical to note that a human-to-human spreading strain of Bird Flu has not yet come into existence. The current strain, H5N1, is endemic in many animal populations, especially in Asia. Here it has resulted in the death of hundreds of millions of birds [Wiki-03]. It *has* made the transition from bird-to-human, resulting in 196 reported cases and 110 deaths, or a mortality rate of approximately 56%, as reported by the World Health Organization [WHO-01].

It is suggested that there are two 'natural' (non-engineered) methods that the human strain of H5N1 can come into existence. The first is through humans, and the second is through pigs. These are the only two entities that are susceptible to *both* the avian H5N1 and the human flu virus. If a human or a pig contains both these viruses in their system, it is possible that they will act as a "mixing vessel", allowing the two viruses to swap genes and to produce the new virus [BUPA-01].

Because of these statistics and the opinions of many medical experts, the H5N1 (Avian Flu) virus has been the subject of countless studies and simulations within the past few years, so that if it does mutate and become a major

pandemic, the global community might be prepared for it.

II. Model Design

An objective of computational simulations is to 'model' the real-world with mathematics, as it is often expensive (in terms of influenza, the cost is human life) to test in the real-world. Given facts and rules, one can manipulate the facts using mathematical procedures in order to arrive at new conclusions. These conclusions are merely predictions, however, and cannot be verified completely until they come to pass. Therefore, a key element in all simulations is prediction.

Secondly, as simulations sometimes simulate things that have not yet come into existence, some of the initial variables or 'facts' of the simulation cannot be known.

In terms of Bird Flu, both of these mentioned problems hold true, and so they must be considered in the design and results of the simulation. A strain of Bird Flu has not yet mutated to a form which allows human-to-human spread of the virus in a manner similar to the modern flu (an airborne pathogen). Therefore, we have no real-world results to compare any findings with in order to verify their validity – we must not necessarily take the results of the simulation as absolute. In the same manner, as an airborne strain of Bird Flu that transmits from human-to-human has not yet come into existence, no data on its characteristics can be known (transmission rate, mortality rate, etc). "...It's impossible to make a vaccine for a virus that hasn't been identified, let alone one that doesn't even exist yet" [CBC-01]. Therefore we must estimate and make educated guesses regarding its properties.

The main goal of this model will be to simulate an outbreak of an airborne strain of Bird Flu that is able to spread human-to-human in a manner similar to current strains of influenza that affect the human population. The simulation will be limited to the population of the United States. The goal of the simulation will be to observe various effects on the population once the outbreak begins, in

hopes of learning new information regarding US preparedness for a pandemic influenza virus.

As with all computational models, various parameters are required. These parameters can be set prior to simulation initialization (and may be modifiable during the simulation). They are essentially the independent variables, and therefore directly affect the outcome and results provided by the model. Also, changing parameters allows the researcher to observe possible characteristics or sensitivities of the model. Table 02 shows a listing of all the parameters used in this simulation, as well as a brief description of each.

Parameter Name	Parameter Description
Days Of Outbreak	The number of days that the outbreak will be simulated for.
Total Population	The total population that the virus is being exposed to. In this simulation, this number will be taken as the current population of the United States of America.
Initial Vaccinated	The initial population that has been vaccinated.
Initial Infected	The number of people who are initially infected with the virus. They are the cause of the outbreak.
Max Contacts Per Day	The number of people per day that an infected person might come in contact with. This number is the <i>maximum</i> number of people; therefore, the actual number will typically be lower.
Mortality Rate	The rate of death once infected with the virus. Again, as the virus does not yet exist, the exact mortality rate cannot be known. It will be estimated near the current mortality rate of the H5N1 strain. However it should be noted that the rate may decline as time increases and the virus is introduced into more urban settings with better health care.
Transmission Rate	The rate of transmission of the virus (the chance that the virus will be spread to another individual). Since the virus being simulated doesn't exist yet, the transmission rate will be estimated at somewhere near current transmission rates of human-to-human strains of influenza.
Birth Rate	This is the <i>crude</i> birth rate – the number of live births for

Parameter Name	Parameter Description
	a year, per 1000 people.
Death Rate	Also known as the Mortality Rate. This is the <i>crude</i> death rate – the number of deaths in a year, per 1000 people.
*Incubation Period	The period from initial infection in an individual until symptoms develop. The individual is not contagious until the very end of this period.
*Symptom Period	The period that symptoms of the virus are visibly noticeable. At the end of this period, the individual is either dead or recovered.

Table 02

** denotes hard-coded parameter in .exe*

After being infected with a strain of Influenza, the individual remains in an incubation period for approximately 7 days [WHO-02]. This is greater than the normal seasonal influenza which is usually around 2 to 3 days. After this period, the individual proceeds to the symptomatic period. Here, the symptoms of the virus are clearly visible. Common symptoms of individuals infected with H5N1 transferred from birds-to-humans (as the human H5N1 does not yet exist) include fever, chills, cough, sore throat, muscle aches, conjunctivitis, breathing problems, pneumonia, diarrhoea, vomiting, abdominal pain, chest pain, encephalitis, and bleeding from the nose and gums [WHO-02]. Another interesting symptom of H5N1 which is not an issue in the more common flu viruses is called a 'cytokine storm'. For a reason that is not completely understood, the immune system will enter an uncontrolled loop (positive feedback loop), where it will produce a large amount of a given protein that is particularly destructive to organ tissue – usually leading to death [Wiki-03]. The symptoms last for an average of 6 days, although the range observed can be anywhere from 4 to 13 days [WHO-02]. With the human strain of influenza, the individual is contagious 1 day before symptoms develop and up to 5 days after becoming sick [CDC-01].

A parameter that was originally considered was “vaccine production rate”.

Along with the initial vaccines available when the outbreak first begins, it was thought that more vaccines could be produced while the outbreak was occurring. These vaccines would not cure those with the virus, but it would prevent new infections from happening. Upon careful consideration, this parameter was removed from the application. Current influenza vaccines are created through a process involving chicken eggs. "All the vaccines commercialized now use egg-based technology. Eggs have to be ordered more than one year before production... This process is long, and each egg needs to be inoculated one by one (despite the fact that this is an automated operation). As a result, there is no possibility of ramping up the production rate very quickly, should it be needed" [Chu05]. This is the limiting factor in vaccine production. The eggs must be ordered many months in advance, and the vaccine must have a chance to incubate inside of the eggs for more months. To produce any reasonable number of vaccines, 6 months to a year will elapse. Due to the high fatality and transmission rate of the H5N1 virus, it spreads much like a wild fire. The simulation will be run for a period of less than 6 months, so any new vaccine production will not be completed in time.

With all these explanations in mind, we must come up with appropriate parameters to model the outbreak. For the number of days of the outbreak, this was taken as 90 days, or 3 months. The reader should note, that this is not entirely accurate. On day 1, a host is introduced into the population. The host will not be contagious for some period after this. Therefore, no spread of the virus (or outbreak) occurs until a week or more after the initial host becomes contagious. It is also possible, although highly improbable, that the host never comes into contact with another individual and/or never spreads the virus during the period he/she is contagious.

The population was taken as approximately 300 million – the current population of the United States in 2006.

The initial number vaccinated was 2 million. This was the most recent figure found concerning the United State's number of avian flu vaccines. "The US

government has ordered 2 million doses from Sanofi Pasteur, despite the fact that the vaccine is still in clinical trials... However the question of exactly how 2 million doses will treat the 250 million inhabitants in the country is one that still remains unanswered" [Chu05].

The initial infected is simply one individual. This is perhaps the most realistic situation. It is unlikely that a human-to-human H5N1 strain will originate in the United States, as we still have no reported cases of *any* strain of bird flu within our borders or neighboring countries¹. If an outbreak begins in Asia, it is likely that a single individual visiting Asia will become infected and not know it. The individual will then return to their home country (the USA), and the outbreak will then occur once the contagious period is reached.

The maximum number of contacts per day was taken from personal experience. This parameter is used to reflect the number of people, on average, an individual may come into close contact with on any given day. Close contact is defined as any sort of direct physical contact, or any prolonged proximity (i.e. the people sitting in a one seat radius of the individual in a movie theater). This number represents a maximum, so the actual number will typically be lower.

The mortality rate is taken as .55, or 55% of the people die who have this virus. It should be noted, that this number is most likely an *absolute worst-case scenario of the mortality rate*. This mortality rate is the recorded rate of those infected with the bird-to-human H5N1 in the past 4 years, when the virus first emerged. These cases were mostly in poorer nations and rural areas: Azerbaijan, Cambodia, China, Egypt, Indonesia, Iraq, Thailand, Turkey, and Vietnam [Wiki-03]. It is most probable that this mortality rate will drop considerably when the virus is introduced into a wealthy and urbanized nation such as the United States. There is no real accurate way of predicting the new rate, so this high rate of .55 was maintained.

Like many of the other parameters, the transmission rate cannot be exactly

¹ On 01 May 2006, it was reported that a mild form of avian flu has been found in a live bird market in New Jersey.
Source: Reuters

known. It has been reported [DeLo05] that the normal seasonal flu virus has a transmission rate of between 5 to 20 percent. The pandemic flu strains of the past, however, have a much larger transmission rate of between 25 and 35 percent – this is one of the reasons they become a pandemic. With this data in mind, a transmission rate of 30% was used for this simulation. This seems to paint the most accurate picture of what a true pandemic virus can do.

The birth and death rates, as mentioned, represent the *crude* birth and death rates of the United States (see Table 02 for definition of crude). These variables were included in the simulation, as with such a large initial population, the net births in a single day is a fairly large number. It is interesting to see how these parameters will affect the simulation as time progresses.

The last two parameters are the incubation period and the symptomatic period. These parameters are 'hard-coded' into the application. The incubation period represents the time that the virus is multiplying within the host. The host is not contagious until the end of the incubation period (the last day of it). The symptomatic period represents the time in which the host begins showing symptoms of the virus. Assuming the 7 day incubation period and 6 day symptomatic period, the host is contagious from day 7 until day 12. These numbers are a combination of seasonal flu statistics, and individuals with the bird-to-human H5N1 strain who have been observed in medical facilities. They are the best representation of the virus, at the present time, according to the CDC.

III. Development and Implementation of Model

In every simulation, certain assumptions must be made. These assumptions are necessary for various reasons – to lessen computation time, to simplify the simulation, or to hold some parameters constant so that other relationships can be studied. Some of the assumptions made in this simulation follow.

This assumption can be referred as 'integer days'. Days are broken into integer time intervals – no one gets infected or dies half way through a day. Everyone infected either dies or lives on the last day (the last day of the symptomatic period). This was done in order to simplify the model. The period of 13 days is the average, as reported by the CDC. It is possible that individuals live longer, or shorter. Tied to this, the incubation and symptomatic periods are constant for the entire simulation. In the 'real-world', these periods are not so distinctive, and there may be some overlap and variation.

There are no 'high-risk' individuals or regions. Anyone is equally likely to get sick as anyone else. In actuality, the virus may not have a chance to infect certain people due to their isolation. Also, some individuals such as the elderly, infants, or those with weak immune systems, may be very susceptible to infection and death. There is no notion of that in this simulation.

It is assumed that those initially vaccinated are actually immune (i.e. the vaccines work). All viruses are constantly mutating. A slight change in the protein structure of the virus may make the vaccinations completely useless. Also, the two million vaccines purchased by the US government that are used to inoculate these individuals were only trial vaccines against the H5N1 strain of bird-to-human transmission. There is no guarantee that these vaccines will have any effect on a human-to-human H5N1 strain.

In a similar assumption, it is assumed that the virus does not mutate during the course of the outbreak. Because of this, those individuals who have survived the virus and are now resistant (immune) cannot become reinfected. In actuality, the virus may change slightly, and these people are still susceptible. Or, the

individuals may not develop complete immunity after the first infection, and therefore may still be vulnerable.

The birth and death rates are constant additions to the population. These don't change for any reason. As such, we are not taking into account mothers that die and hence don't give birth. We also assume that infected people don't die due to natural cause – the death rate only affects non-infected people. This was done to simplify the model. The birth and death rates are not very large in relation to the deaths due to the virus, therefore they are fairly inconsequential.

Related to the birth rate, all newly born individuals are given no immunity to the virus in this simulation. It is possible that a mother who gets infected with the virus, survives, and becomes immune while pregnant, will pass this immunity to her child. This would greatly complicate the model, so it was ignored.

Perhaps one of the largest assumptions, is that we are assuming the infected person does not seek medical attention. A viable change in the simulation would be to essentially (randomly) shorten the contagious period. Once an individual begins to show clear signs of infection (after the first couple days of being in the symptomatic period), most individuals will look for medical attention. The medical community, well aware of the symptoms and risk of Avian Influenza, will likely place the individual in isolation, thus preventing any further infections due to that individual.

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The logic of the simulation program is fairly straightforward. There is a central loop that takes us through each of the days of the outbreak. For each day, we must check the individuals contagious on that day, and determine how many individuals they infect. This number is determined by first randomly calculating how many individuals the host comes into contact with on that day. Using the number of contacted individuals, we randomly determine whether they become

infected. This based entirely on the transmission rate. A transmission rate of zero indicates no individuals become infected, while a transmission rate of one indicates every individual becomes infected.

Next, we calculate the number of individuals who die on the current day. According the the above assumptions, the only individuals capable of dieing on the current day are those on the last day of the symptomatic period. To determine if the individual lives or dies, we generate another random number. Based on the mortality rate, the individual is granted life and resistance to the virus, or death.

The last step is to essentially 'move' all infected individuals to the next day of their 13 cycle. This will move some into the infected period, some into the symptomatic period, and some into the newly infected (incubation) period. Now the simulation can continue to the next day, and the process repeats.

As can be noted by the above algorithmic description, the implementation of this simulation is based heavily on stochastic methods. The number of people a contagious individual comes into contact with, the transmission of the virus, and the survival of the infected individual are all based on random numbers. This is the most straightforward way of simulating an outbreak of this type, as there are much too many factors to be accounted for in an actual viral outbreak.

IV. Interpretation of Results

The data is split into four sets: population, deaths, resistances, and infected. The population data is simply the *current population* at the given time, t . The 'deaths' data shows the number of deaths *on the given day*, t . Note that each entry is not cumulative. To get the total deaths up to that point, the previous entries in the list must be summed. The 'resistances' data shows the number of people who have evaded death and have become resistant to the virus (they cannot be reinfected) on that given day, t . Again, summation is necessary to get the total values. Last is the 'infected' data. This data represents the number of *newly infected* individuals on the given day, t .

Analyzing the data, there are some interesting features to be extracted from it. Starting with the population data, it can be seen that the population is actually rising before the virus begins spreading. This is due to the birth and death rates, and sum of the two, which results in a net growth in population. Once the virus begins killing people, this natural growth is made completely inconsequential. The population falls off *very* drastically until it reaches some minimum value. This minimum value is when there are no more people left to transmit the virus to – everyone is either dead or resistant to the virus.

The 'deaths' data shows that initially, there will be no deaths. This is because the simulation begins on day one. A single individual on the very first day of infection is being introduced into the population. This initial individual will not have a chance to die until day 13, at which point, if he/she does die, they will have most probably transmitted the virus to numerous other individuals. Expectedly, the large spike the deaths plot corresponds with the large dip in the population plot. Looking at the first 35 days, it can be seen that the number of deaths is relatively low. The majority of the deaths occur from around day 50 to day 80. There are still fairly substantial amounts of deaths in the first 50 days, however. From this, one can conclude that both the government and medical institutions will begin some emergency procedure after the first few deaths occur

(definitely within the first month). Medical personnel will be watchful for signs of bird flu. Quarantine zones will be put into place, and the spread of the virus will be limited. Therefore, it is safe to assume, as this simulation takes none of that into account, that the results presented here are the absolute worst case scenario.

The largest amount of deaths (the global maximum of the death plot) occurs on day 78, where there are over 41 million deaths. This is approximately 14% of the initial population that dies on a single day. It is unlikely that the deaths would peak at this high of a number due to some of the aforementioned reasons. Even with government prevention, however, it is likely that there will still exist some peak and falloff once the virus has been contained.

The large peak, in general, is a result of the nature of a virus: the infection spreads at an exponential rate. One person almost always infects more than one other person (i.e. if $\text{maxContactsPerDay} = 20$, there is a $\sim 10\%$ chance the individual infects 0 or 1 person, and 90% chance they infect more than one person). This is the vicious chain that causes an outbreak.

Next is the 'resistance' data. This is almost a mirror image of the 'deaths' data, except with lower values. The death curve will be higher (statistically speaking) at every point, as the mortality rate is .55. With a .50 mortality, one would expect equal number of deaths as resistances. With a number greater than .50, it is expected that there will be more deaths than resistances. This is clearly validated by the data.

The last set of data is the 'infected'. This data seems to mirror the deaths and resistance data, but is shifted to the left. This is understandable, since individuals will become infected 13 days prior to either dieing or becoming resistant to the virus. Clearly the infected global maximum is greater than either the deaths or the resistance data, as it should represent the sum of these two data sets, but at an earlier time.

One thing that all the data sets have in common, is that their values after the 'peak' days suddenly become constant. Constant values would tend to signify

a 'controlled' virus (the situation is not getting any worse). This is perhaps a slight misrepresentation in the model. The 'infected' data best illustrates this point. From day 67 until the end of the simulation, the infected data has the value of 11566. This number is the net birth rate (birth rate – death rate). Since an individual will infect more than one other person 90% of the time, once the vulnerable population (the population still alive and who has never had the virus) reaches a certain value, the only people who can become infected are the newly born. Intuitively, this makes sense – when the number of people who should be infected is greater than X , but only X people exist, then all X people will become infected. This will repeat till infinity, unless for some nearly impossible probabilistic outcome, none of the 11566 infected people transmit the virus to anyone.

With this in mind, the question arises: what should be done with the results after the largest peak? As the simulation is modeling a worst-case scenario, it is showing the results as if no containment procedure was implemented. If this is the case, then the data is accurate – the virus will most likely live forever as there are new people being born each day. This is allowed, because as mentioned in the assumptions, immunity is not being passed on to a baby from a mother who has survived the virus. If this assumption were eliminated, it would make the simulation more complex, but the virus 'infected' rate would go to 0 instead of remaining constant at some non-zero value. Translating this to the real-world, a possible conclusion is that even with full quarantine, there will still be a peak value. After this value, the 'infected' data will become 0 when the virus is completely contained. It must reach 0, or else the virus was not contained, and another outbreak will begin.

After the simulation is complete, final statistics can be calculated through manipulation of the various data arrays. For a simulation of approximately 300 million people, for 90 days, with 2 million people initially vaccinated, a mortality rate of .55 and a transmission rate of .30, approximately 163 million people will die. This is over half of the initial population of the United States. The actually

mortality rate turns out to be slightly less than the real mortality rate of .55.

V. Conclusion

As mentioned, the Spanish Flu of 1918 killed between 40 and 50 million people worldwide. With the large population explosion of the past couple decades, the next pandemic has the potential to kill many more.

While the results concluded in this simulation are certainly plausible, they represent an absolute worst-case scenario in the United States. It is a guarantee that the government and medical institutions will do all they can in order to limit the outbreak of the virus, so one can expect the deaths calculated by this model to be much less. Also, the urbanized United States population will drive the utilized mortality rate down substantially. Lastly, it must be kept in mind that the virus being modeled does not exist yet, therefore all of its' characteristics are predictions themselves.

According to a World Health Organization spokesman: "We're not going to know how lethal the next pandemic is going to be until the pandemic begins". [DeLo05]. Scientists have made predictions ranging from 2 million to 360 million deaths. A simulation cannot state anything with certainty, as it is only making predictions which can only be verified with the passing of time and the coming of the events. Even though no concrete results can be concluded by these models, hopefully they may be used to bring about new predictions that may be considered 'very likely'. It is possible that a pandemic of H5N1 never does occur. But if a human-to-human airborne H5N1 strain does come into existence, the United States and the world may be better prepared to prevent another pandemic with computer simulations such as these.

VI. Using the Application

Due to the computational demand of this simulation, it could not be written completely in Mathematica. To circumvent this problem, the computationally expensive portion of the code was written in C++, and the analysis (plots and graphs) were performed in Mathematica. Even so, with the initial parameters used in this report, the simulation takes approximately 40 minutes.

The ideal situation would be to input the parameters into Mathematica, which passes them to the C++ .exe as command line arguments. Due to a bug in the Mathematica Run[] command, this was not possible.

In order to run the application, the parameters should be entered in the params.txt file. This file simply contains the values to be used in the simulation. The value meanings are specified in an accompanying text file, paramsExplanation.txt. Once the parameters are entered, 3 files should be in the same directory: the Mathematica notebook, the .exe program, and params.txt.

Once all files are in the same directory, and the parameters are set, the Mathematica notebook can be opened. If run in a top-down manner, the notebook will run the C++ program. The C++ program will read in the parameters from params.txt. The C++ program will generate various text files in the same directory, which are the results of the simulation. The Mathematica notebook will then read in these results and perform various type of analysis on the data. The only file that should ever need modification is the params.txt file, as it is utilized by both the notebook and the .exe.

VII. References

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