A Probabilistic Assessment of Multiple Sclerosis Treatments in the Age of Covid-19

Jasmine Bilir
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Sunet: jbilir

1 Project Overview

For the CS 109 probility in the world contest, I wanted to answer the question: **What treatment option poses the least risk for MS patients given the risks of disease progression and having a more severe response to the covid-19 virus?** (Different MS drugs compromise the immune system and the body's ability to fight infection. For more background on MS and why answering this question is important see sections 8 and 9 below)

I tackled this problem in few steps:

1. Developed a Bayesian network to describe the various paths and probabilities that would lead an MS patient in various treatments to a severe covid case (i.e. hospitalization or ICU admission).

2. Coded a rejection sampling program to approximate the joint probability table entries (represented in my Bayesian network) that were important to my question

3. Updated my Bayesian network and rejection sampling program to incorporate information regarding vaccination and breakthrough cases and how this changed in relation to severe cases.

4. Utilized poisson random variable where $\lambda = \textit{annual relapse rate}$ to model the probabilities for number of relapses (mostly focusing on 0 or 1 relapses) in the next year given the

treatment options.

5. Modeled the number of trips to the ICU and hospital with respect to number of exposure cases for an MS patient as a binomial random variable. Then, approximated using the number of severe covid cases (again hospitalization or ICU) in the next year given each treatment options using the Poisson approximation of a binomial.

6. I provide my (entirely non-medical licensed) analysis and comparison for what treatments lead to the greatest risk potentials for covid and relapse for the patient.

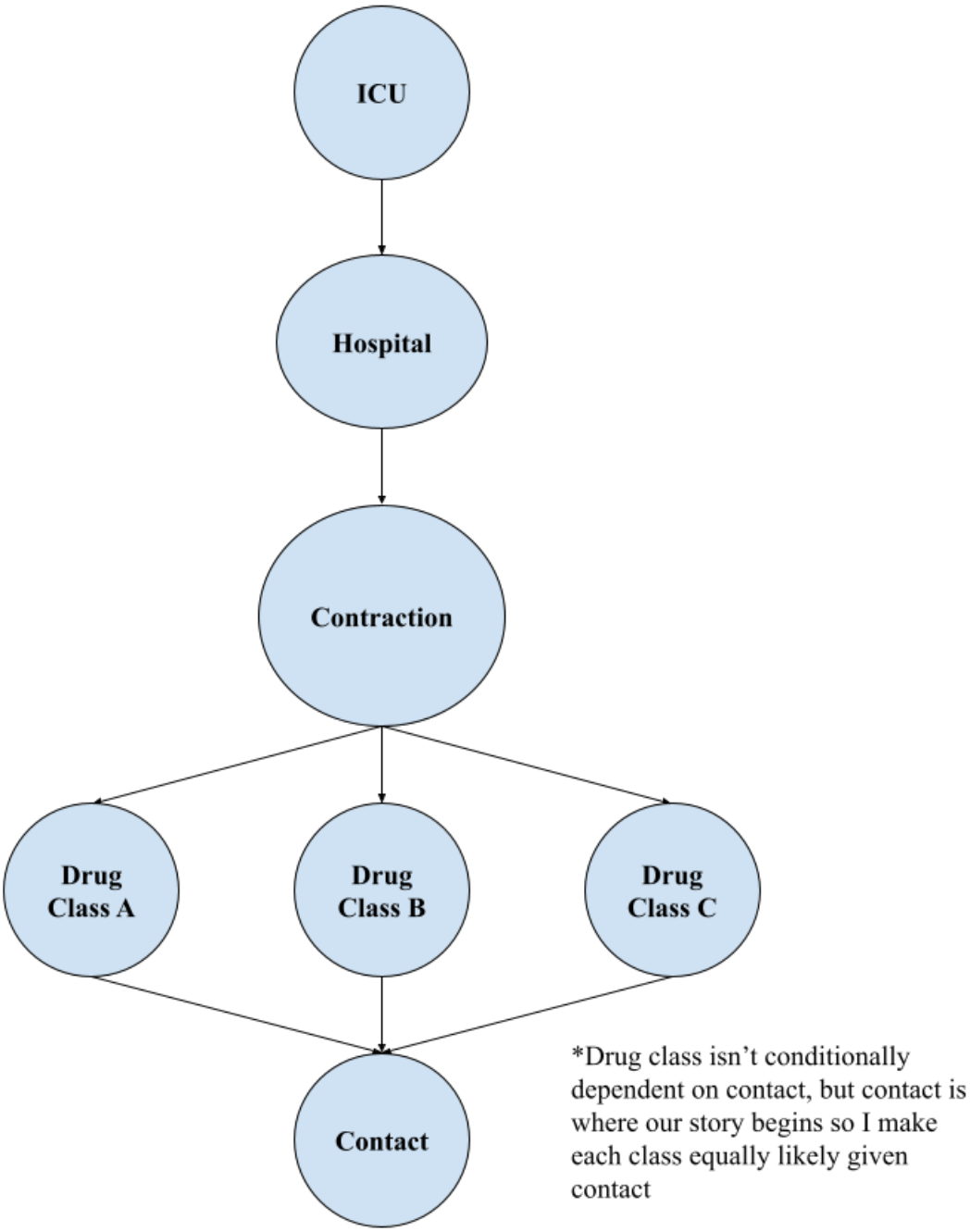
My overall conclusion is that immune suppressant drugs of class b may not be best for the patient as the likelihood of having a severe case of covid is approximately the same as the likelihood of having an MS relapse while on the drug. (Meaning additional risk is taken on by the patient in regards to covid without significant risk reduction for MS). Additionally, I discovered that patients in drug class A were less likely to have a severe case of covid than patients who recieved no medication, potentially indicating that this class of durg may be protective to MS patients against covid.

In the following sections of this write-up, I describe my results, my math, my program, my motivations, and each step in greater detail below. Additionally, I list the sources I used for data, assumptions that I made, and other facets of this topic I wish I could have explored.

2 Covid Risk Bayesian Network For MS Patients Pre-vaccination

I made the following Bayesian network to represent the relationships of the various stages in the path of an MS patient catching covid and being hospitalized or going to the ICU. Because the data I found regarding this subject was in terms of strict probabilities and not distributions, I chose to

include the following random variables all as Bernoulli indicator variables: ICU (1=a MS patient is admitted to the ICU with Covid), Hospitalization (1=MS patient is hospitalized with covid), Contraction (1=MS patient contracted covid given exposure and susceptibility given treatment), drug class A, B, C (1=MS patient receives that treatment), and contact (1=MS patient came into contact with an individual with covid).



Like we learned in class the graph's edges represent conditional dependency, however I should note that drug class isn't dependent on contact. The reason I drew the graph in this manner is because contraction, hospitalization, and icu are conditionally dependent on which drug class an MS patient is in, and the probability of contact is the same for all three individuals. Thus, I consider the edges from the classes to contact to be weighted equally (i.e. $P(drugClass = A|contact = 1) = P(drugClass = B|contact = 1) = P(drugClass = C|contact = 1) = \frac{1}{3}$). Additionally, I used research from medical studies to find the following probabilities to weight my graph.

- $P(contact = 1) = 0.67$ – the general risk for coming into contact with 1 infected person in a gathering of 50 people, like a trip to the supermarket, in Jefferson County Colorado where my mother resides (source 1)
- $P(contraction = 1|contact = 1, drugClass = A) = P(contraction = 1|contact = 1, drugClass = C) = 0.026$ – the likelihood of contracting covid given moderate exposure to an infected individual for a non-immune compromised person (source 2)
- $P(contraction = 1|contact = 1, drugClass = B) = 2 * P(contraction = 1|contact = 1, drugClass = C)$ – *ASSUMPTION* In my research I could not find an exact value for how much more susceptible or how likely an immune compromised individual is to contract covid, only that they are "more likely". Accordingly, I have made the assumption that they are twice as susceptible (assumption based on information in source 3)
- $P(hospital = 1|contraction = 1, drugClass = A) = 0.133$ – likelihood of MS patient in drug class A that has covid to be hospitalized (source 3)
- $P(hospital = 1|contraction = 1, drugClass = B) = 0.251$ – likelihood of MS patient in drug class B that has covid to be hospitalized (source 3)
- $P(hospital = 1|contraction = 1, drugClass = C) = 0.372$ – likelihood of MS patient in drug class C that has covid to be hospitalized (source 3)
- $P(ICU = 1|hospital = 1, contraction = 1, drugClass = A) = 0.194$ – likelihood of MS patient in drug class A that has been hospitalized for covid to be admitted to the ICU (source 3)
- $P(ICU = 1|hospital = 1, contraction = 1, drugClass = B) = 0.319$ – likelihood of MS patient in drug class B that has been hospitalized for covid to be admitted to the ICU (source 3)

- $P(ICU = 1|hospital = 1, contraction = 1, drugClass = C) = 0.175$ – likelihood of MS patient in drug class C that has been hospitalized for covid to be admitted to the ICU (source 3)

3 Calculating Risk Using Rejection Sampling

Because I couldn't find and calculate all the information in the joint distribution table for my Bayesian network, I used rejection sampling in order to calculate different values from the joint that were important to me. Namely, I used my rejection sampling program to calculate the following.

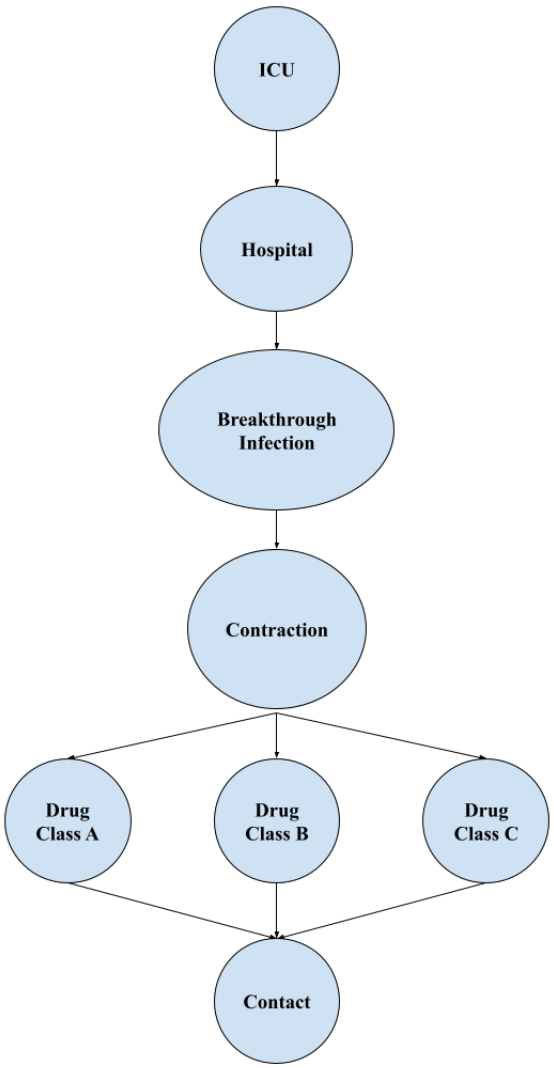
Table 1 MS Patient Covid Risk in Relation to Treatment

Approximated Probabilities	x = Class A	x = Class B	x = Class C
$P(hospital = 1\|drugClass = x)$	0.0025364	0.0091178	0.0071738
$P(ICU = 1\|drugClass = x)$	0.0005669	0.0031688	0.0015437
$P(drugClass = x\|hospital = 1)$	0.12420382	0.49363057	0.38216561
$P(drugClass = x\|ICU = 1)$	0.10077519	0.60465116	0.29457364

I followed the standard procedure of rejection sampling that we used in class and I have included all my code in the gradescope submission with this write-up.

4 Considering Vaccination in the Bayesian Network

After initially exploring the non-vaccinated case, I also wanted to explore how risks were altered given the presence of a vaccine. So I made the following alteration to my Bayesian network where breakthrough infections under the vaccine is another Bernoulli (1=has a breakthrough case when fully vaccinated).



From further research, I learned that the breakthrough rate of covid cases for a fully vaccinated and non-immune compromised individual is $P(breakthrough = 1|contact = 1) = 0.06$ (source 4). Because Drug classes A and C do not reduce the capacity of the immune system they fall into this category. For immune compromised individuals like those in drug class B, they are 3 times more likely to have a breakthrough (source 4). To compare the results, I used rejection sampling to create vaccinated samples and see the difference in the two groups. I measured and graphed the following results.

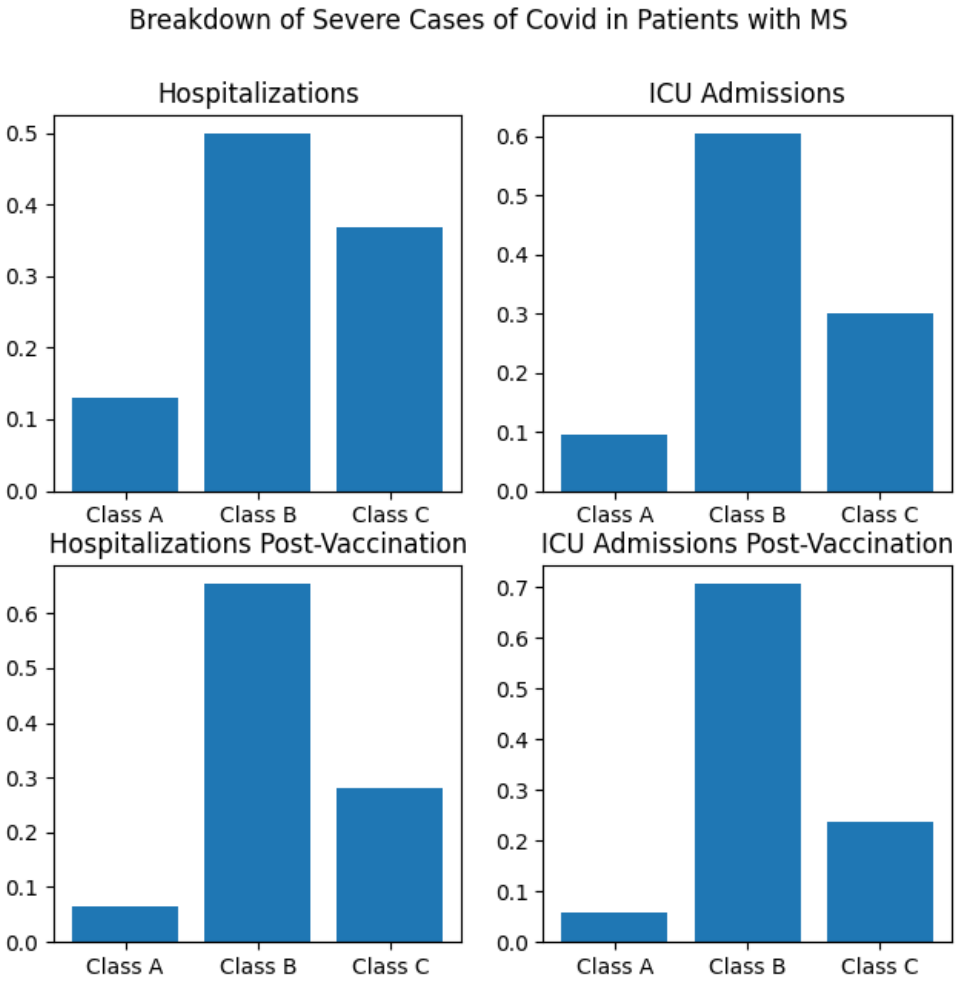


Table 2 MS Patient Covid Risk in Relation to Treatment Post-vaccination

Approximated Probabilities	x = Class A	x = Class B	x = Class C
$P(hospital = 1 \mid drugClass = x)$	0.0002102	0.0020194	0.0005073
$P(ICU = 1 \mid drugClass = x)$	9.006575e-05	0.0005425	5.96783e-05
$P(drugClass = x \mid hospital = 1)$	0.06976744	0.73255814	0.19767442
$P(drugClass = x \mid ICU = 1)$	0.04545455	0.72727273	0.22727273

5 Using Poisson to Approximate Number of Relapses in a Year

In order to compare the risk of relapse to the risk a severe covid case, I wanted to know the likelihood of having a relapse in a year time interval for each treatment type. In order to measure this, I found data regarding the annual relapse rates for the three treatments types. A has annual relapse rate of 0.33 (source 5), B has an annual relapse rate of 0.15 (source 6), C has an annual relapse rate (on average) of 0.5 (source 7). Using the PMF of a Poisson where lambda was equal to the annual relapse rate for each case, I found the following probabilities:

Table 3 Probability of MS Relapse for a Given Year Given Treatment Type

Approximated Probabilities	x = Class A	x = Class B	x = Class C
$P(relapses = 0 \| drugClass = x)$	0.7189237	0.8607079	0.6065307
$P(relapses = 1 \| drugClass = x)$	0.2372448	0.1291062	0.3032653

This helped give me an idea of the different benefits of the treatment options in terms of keeping MS controlled.

6 Using Binomial and Poisson to Approximate Number of Severe Covid Cases in a Year

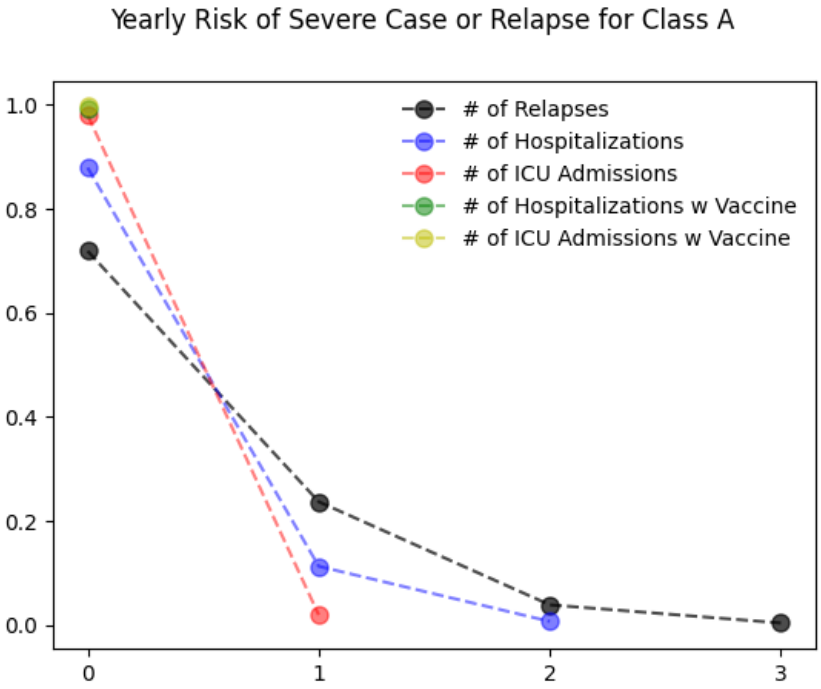
In order compare the risks of each treatment and compare annual relapse probabilities to covid risk, I used a binomial to approximate the number of exposures someone had over a year and a hit on the binomial to indicate a severe case (either hospitalization or ICU). Thus, my binomial would be $severeCase \sim Bin(n = 52, p =$ *probability from table1 or table2)*. I choose n=52 as an example exposure because the $P(exposure = 1)$ I used in the first step was the likelihood of coming into contact with covid in a group of 50 people. This is roughly the risk of coming into contact with covid when entering a medium sized grocery store. Thus, this scenario assumes that

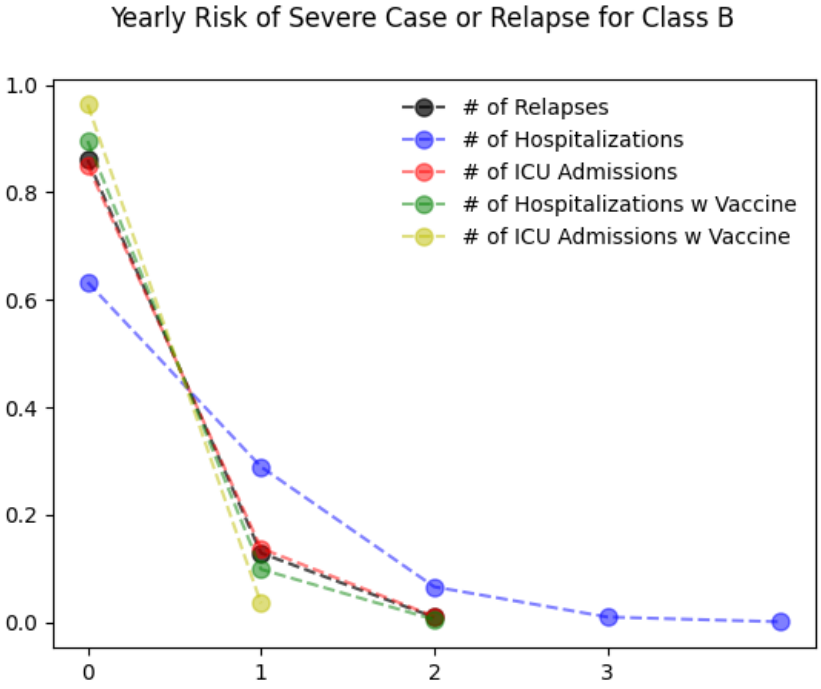
the MS patient is only getting exposed 52 times a year, or roughly on a once a week shopping trip. However, different amounts of exposure or n values would lead to different risks.

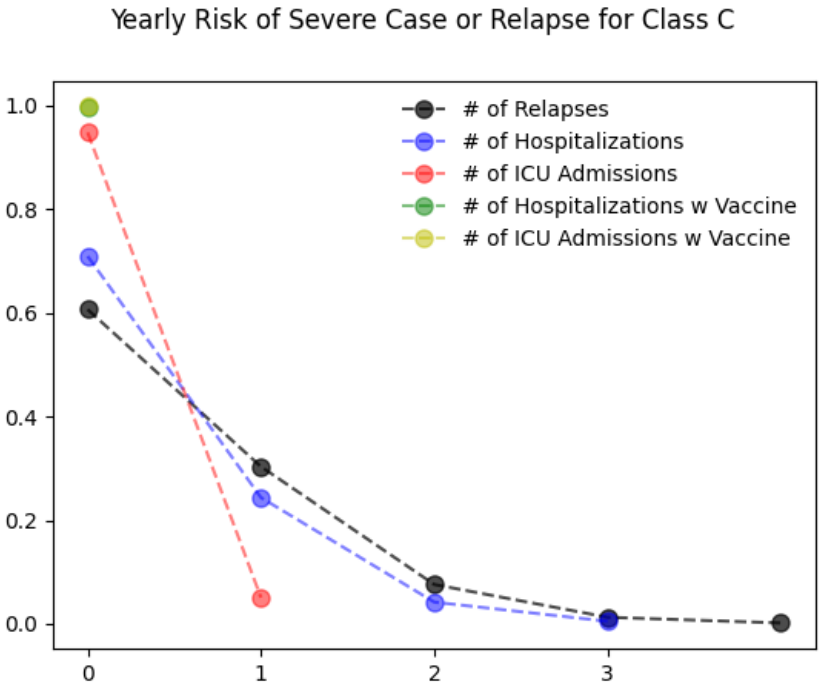
Because I wanted to the likelihood of having 0 or 1 relapses in the next year I approximated my binomial as a poisson where $severeCase \sim Poi(\lambda = np)$. I thought this could be a fair approximation because p is very small relative to n, however, it may be a poor approximation because n isn't very large on the whole. Using this Poisson I calculated the following probabilities and graphed the poisson pmf's for each drug class for comparison.

Table 4 Probability of MS Relapse for a Given Year Given Treatment Type

Approximated Probabilities	x = Class A	x = Class B	x = Class C
$P(hospitalizations = 0 \mid drugClass = x, vaccination = 0)$	0.8881216	0.6211345	0.7125353
$P(hospitalizations = 1 \mid drugClass = x, vaccination = 0)$	0.1053726	0.2957889	0.2432114
$P(hospitalizations = 0 \mid drugClass = x, vaccination = 1)$	0.9953308	0.9244165	0.9798697
$P(hospitalizations = 1 \mid drugClass = x, vaccination = 1)$	0.0046212	0.0726522	0.0199263
$P(icuAdmits = 0 \mid drugClass = x, vaccination = 0)$	0.9631944	0.872446	0.9293170
$P(icuAdmits = 1 \mid drugClass = x, vaccination = 0)$	0.0361197	0.1190491	0.0681238
$P(icuAdmits = 0 \mid drugClass = x, vaccination = 1)$	0.9984449	0.974059	0.993767
$P(icuAdmits = 1 \mid drugClass = x, vaccination = 1)$	0.0015538	0.0256019	0.0062131


Yearly Risk of Severe Case or Relapse for Class A
# of Relapses
# of Hospitalizations
# of ICU Admissions
# of Hospitalizations w Vaccine
# of ICU Admissions w Vaccine
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3


Yearly Risk of Severe Case or Relapse for Class B
# of Relapses
# of Hospitalizations
# of ICU Admissions
# of Hospitalizations w Vaccine
# of ICU Admissions w Vaccine
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3



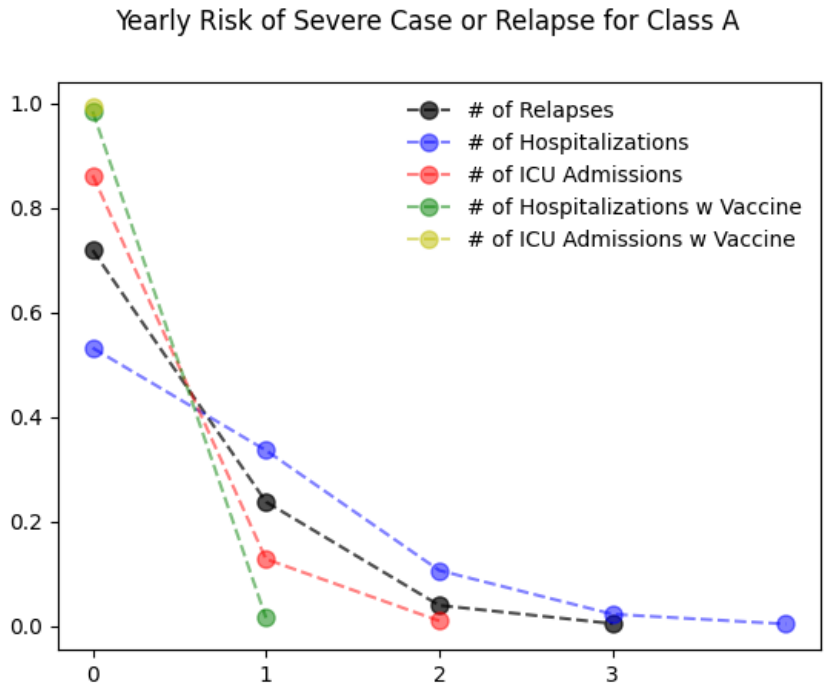
7 Conclusion

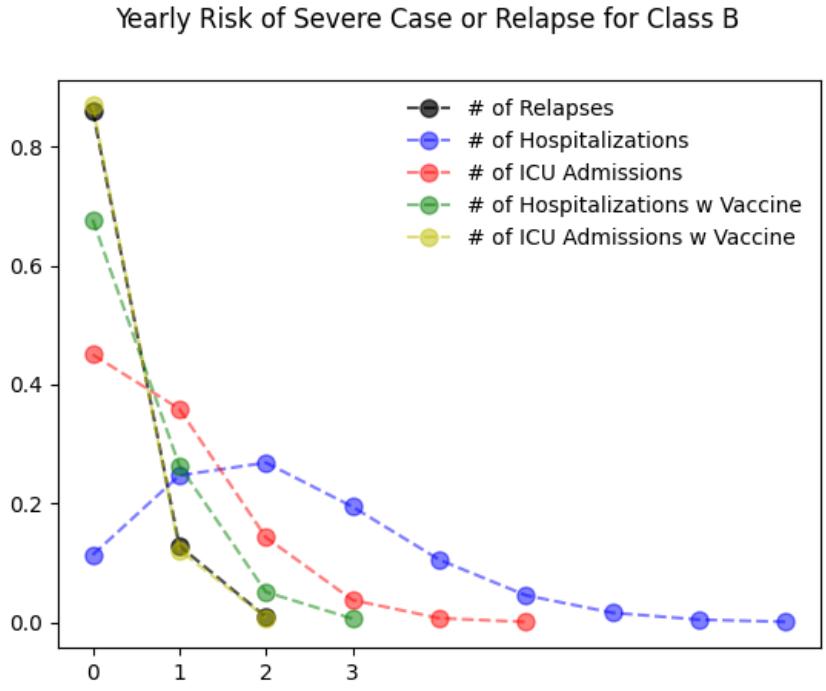
7.1 Analysis

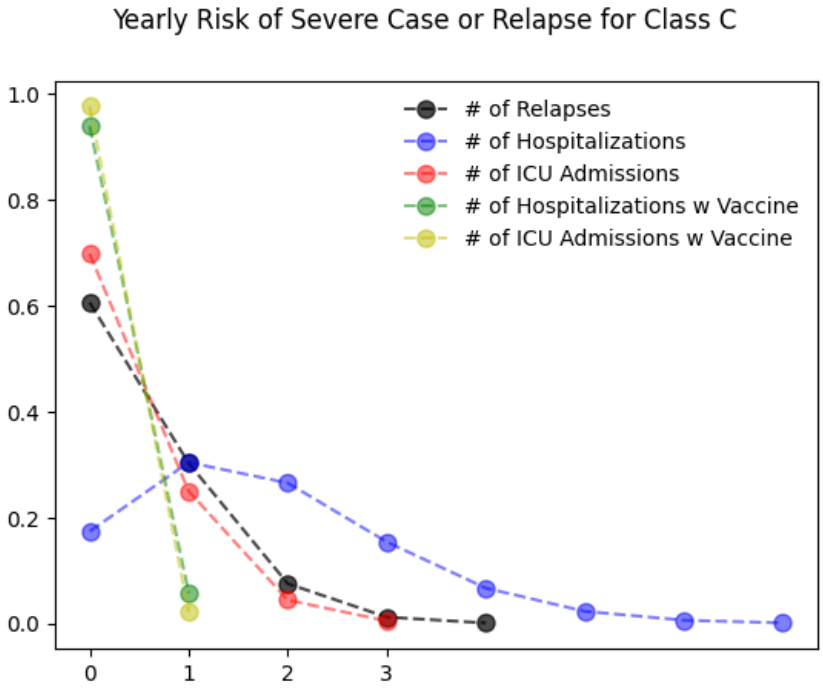
As the graphs show, there are trade offs to the different relapse and covid risks associated with a treatment. However, what I found to be especially noteworthy is that in treatment class B, a patient is nearly just as likely to have a severe case of covid as they are to have a relapse, even when vaccinated. To me, this indicated that treatment B (immune suppression) may not always make sense for a patient given the state of the pandemic. It is also worth noting that treatment class A, was less likely to have a severe covid case than treatment class C and therefore offered some benefit in protection against relapses. Thus, my answer to my initial guiding question is that **a good treatment for MS patients during covid might be a class A drug**.

Additionally, I looked at cases where exposure was greater (52*5 i.e. exposure everyday of the work week) and these correlations seemed to hold, as can be seen below in the following poisson

pmf graphs.


Yearly Risk of Severe Case or Relapse for Class A
# of Relapses
# of Hospitalizations
# of ICU Admissions
# of Hospitalizations w Vaccine
# of ICU Admissions w Vaccine
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3


Yearly Risk of Severe Case or Relapse for Class B
# of Relapses
# of Hospitalizations
# of ICU Admissions
# of Hospitalizations w Vaccine
# of ICU Admissions w Vaccine
0.8
0.6
0.4
0.2
0.0
0
1
2
3



7.2 Assumptions and Constraints

I am in no way, shape, or form qualified to act in place of a neurologist in advising on MS treatment, and in some ways, MS risks are much more complicated than my project considers. For instance, relapses can vary in severity and permanence. Therefore, the comparison between severe covid cases and severe relapses may not be a fair one, and one may be more devastating given the patient and their condition. Likewise, medications affect patients differently and aggregate data may not reflect the individual risk/benefit analysis.

Additionally, because there isn't much conclusive data on how much better off an MS patient is after having the vaccine, it is possible that the hospitalization and ICU probabilities may be lower given the partial immunity provided even in breakthrough cases. Likewise, I made assumptions about the density of covid cases where the patient is exposed, number of times the patient is exposed per year, and how much more susceptible immune compromised patients are to catching

covid given the data I had available. However, these assumptions might make my project less accurate.

8 Why Does this Project Matter?

Early in January of 2020, my mother's neurologist recommended that she begin receiving an IV immune suppressant drug to more actively address her Multiple Sclerosis. Six months later, when it was time for her to receive her second dose of the drug, the world was in the midst of the covid-19 pandemic and being immune compromised came with an entirely new set of considerations. At this point, my family only had a vague intuition about the treatment trade offs: we knew an immune suppressant meant my mother was at an increased risk for both catching covid and having a severe reaction, but we also believed that she would be at an increased risk for MS relapses without it. There were other forms of MS treatment we could have explored, but we didn't know how to weigh the risks given the new and changing circumstances. Ultimately, we decided, mostly on a gut-hunch and at the suggestion of my mother's doctor, to continue on the immune suppressant drug. However, risk calculation and types of treatment continue to be an ongoing question for my mother and I assume many other individuals dealing with auto-immune disorders. In the end, I wanted to explore this topic because my mother's health is most important real world probability to me and now that I am more mathematically well-versed I think I can make a more analytical and data driven assessment of her options. (– while keeping in mind that I know almost nothing about medicine of course :))

9 Background on MS

9.1 What is MS?

Multiple Sclerosis, more commonly known as MS, is a neurological autoimmune disorder where the immune system mistakenly attacks myelin sheaths (the protective outer coating to all neurons). This causes neural tissue to become exposed, causing communication issues between the brain and the body. This is often due to either temporary or permanent nerve damage in the body.

9.2 How do we measure MS progression?

Disease onset for MS is generally considered to occur when a preliminary event makes the disease known, usually with some form neurological abnormality. (In the case of my mother, it was ongoing numbness in her fingers and toes.) After onset and an identifying diagnosis, any treatment plan is generally focused on preventing any further damage from occurring from this point onward. Thus, MS progression is measured in terms of *relapses*, or events of additional neurological failing. Relapses can vary in severity or permanence, but are a general indicator that neurons and their myelin sheaths are experiencing new and further damage from immune cells. MS progression or treatment success is generally measured as an annual relapse rate, regardless of presentation or severity.

9.3 What are the treatment options for MS?

MS treatment is typically differentiated in two major categories of disease modifying therapies (*DMTS*). For the sake of this project, I also include the third option of no treatment as an additional comparison.

1. **Treament A / Class A: non-suppressing DMTs**

   These are alternative forms of drug treatment that are shown to reduce MS relapse rate without directly suppressing the patient's immune system. A representative drug of this class is dimethyl fumarate, which has been shown to be effective in MS treatment but is still being researched as to why and how.

2. **Treament B / Class B: immune suppressing DMTs**

   The two most common immune suppressant dmts are ocrelizumab and rituximab which come from the same class of drugs. These drugs work to partially inhibit the function of immune cells (B cells specifically) that are targeting the myelin sheaths. However, drugs of this also decrease the body's ability to fight off infection, cause greater susceptibility to infection, and decrease the duration/effectiveness of immunity and vaccines.

3. **Treament C / Class C: No DMTs**

   Because I was able to find data regarding MS patients on no DMT, I included this category as a potential baseline to compare when looking at covid risk.

10 Code

I plan on turning in my .py file in gradescope along with my writeup and screen capture. (Apologies! This template made code pasting finicky!)

11 Sources

1. https://covid19risk.biosci.gatech.edu/ – Stanford and Georgia Tech data project for listing risk of covid contact per state and county

2. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html – CDC website on covid contact and transmission

3. https://n.neurology.org/content/97/19/e1870 – 2021 American Academy of Neurology Study on MS and Severe Cases of Covid

4. https://www.news-medical.net/news/20211019/COVID-19-vaccine-breakthrough-infections-among-immunocompromised-individuals.aspx – Medical Journal Article Regarding Vaccine effectiveness and Immune Compromised Individuals

5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3916439/ – study from 2014 on Non-DMT treatment effectiveness in MS

6. https://www.gene.com/media/press-releases/14905/2021-04-15/new-data-for-genentechs-ocrevus-ocrelizu – Drug Class B Manufacturer Press Release

7. https://mstrust.org.uk/about-ms/ms-symptoms-and-relapses/managing-relapses https://mstrust.org.uk/about-ms/ms-symptoms-and-relapses/managing-relapses – United Kingdom MS foundation information regarding MS relapses