

COVID-19 Mortality Excess and Cost-Effective Analysis of Different Treatments

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Course: Decision Sciences

**Introduction**

COVID-19 pandemic has created a public health crisis with serious consequences in most countries worldwide, and Mexico has been one of the most affected. On November 19, 2020, the Mexican government reported 1,019,543 accumulated cases of Covid-19 and 100,104 deaths.1 This makes it the eleventh country in the world in the number of confirmed cases and the fourth in reported deaths.2 The current situation has created the urgency to study mortality associated to Covid-19. Usually, studies focus in factors often associated with critical illness and fatal outcome such as age, sex or comorbidities. 3–6 However, these risk factors could be associated with mortality in other serious infectious diseases that require hospitalization and UCI care8 and they are not specific to covid-19.

There are methods that can help calculate the specific effects of Covid-19 and calculate the excess risk or mortality caused by this disease. Excess mortality from a disease can be a very useful measure for decision makers, since it allows to evaluate different strategies that attempt to modify and mitigate directly this specific risk in the population. Currently, there are neither studies that have estimated the excess mortality from Covid-19, nor that attempt to evaluate the effectiveness of various strategies to reduce mortality from Covid-19. The estimation of this excess mortality for the Mexican population provides an opportunity to evaluate possible strategies to reduce the mortality of Covid-19 even if they have not yet been applied in the country.

The aim of this analysis is twofold. First, to estimate the Covid-19 specific mortality for the population over 45 years of age in Mexico using relative survival methods. Second, to quantify the costs, effectiveness and cost-effectiveness using a microsimulation model of two different treatments that aim to reduce the Covid-19-specific mortality: Dexamethasone and Remdesivir. All calculations, models and graphs were done using R7 and Rstudio software.8

**Data**

I used information from the National Epidemiological Surveillance System base for monitoring possible cases of Covid-19. This dataset includes people tested for SARS-CoV-2 in Mexico and contains only data obtained from studies done on suspicious persons when detected in the medical units of the health sector.9 It is daily updated, and this work’s particular database has information until November 21, 2020 and has 2,892,449 individuals and 40 variables.

For analysis purposes, the database is filtered to select only people with a positive test result to SARS-CoV-2 and older than 44 years. Individuals in the database are divided in four age groups: “45 - 54”, “55 - 64”, “65 - 69”, “70 +”. Total individuals with these characteristics are 481,353. To build variable “Death” I use the date of death from the original database. Individuals with fatal outcome have a real date of death while individuals hospitalized or recovered have NA´s instead. The new column death takes 1 on the if the individual has a real date. Otherwise, it is 0.

Background mortality rates for Mexican population in 2020 come from the National Population Council demographic indicators.11 Data bases includes mortality projections until 2050 which were modified to produced time series of mortal cases by sex and age at the national, state and county level. Daily mortality rates by sex and age for 2020 at a national level were used for the models in this work.

**Methods**

*Relative survival and specific probabilities of death*

Relative survival and excess mortality analysis is a methodology that deals with registries of a cohort diagnosed with a disease and follow up its time and vital status, though causes of death are unknown or not clear.12 This methodology is usually used in cancer studies,12,13 but it has been used in other diseases in national analysis such as HIV14 or in cohort of people infected with Hepatitis.15

Relative survival, crude probability of death and net survival are often reported in relative survival analysis.12 The first one consists in the ratio between the survival of the cohort analyzed and the expected survival of the population normally obtained from population mortality information. Relative survival is defined as 12,16 This methodology allows to report overall hazard over time, which could be written as the sum of the disease-specific hazard and the hazard of the population 12. Disease specific hazard or “excess-hazard” is an estimate of great importance since from its calculation the disease specific and background cumulative probabilities of death can be obtained.12

Package *reslsurv*17 for R software contains the function *cmp.rel,* which allows computing cause-specific and background probabilities of death as long as is provided with data from a cohort and background mortality rates. I estimate Covid-19-specific and background probabilities of death for 60 days using the Mexican population positive for Covid-19 as a cohort and the expected mortality as the daily death rates projected for 2020.

Derivation of Covid-19 specific and background population hazards were obtained using the following equation:

18

where is the derivative of the cumulative probability of death, in this case .

.

Overall hazard is the sum of previous hazards.

*Microsimulation and Cost-Effective Analysis*

Previous outputs are sufficient for implement a microsimulation model. The purpose of this model is to simulate the trajectory of individuals infected with covid-19 in Mexico for 60 days and incorporate the effects of two treatments that have shown promising evidence in reducing mortality in people with Covid-1919–21: Dexamethasone and Remdesivir.

The microsimulation model utilized in this analysis is an adaptation of the state-transition microsimulation algorithm proposed for modeling for health decision sciences 22 and is implemented in R. Implementation requires a model of the life cycle of a sick individual. This life cycle should be divided into mutually exclusive and collectively exhaustive states. For cases, I propose three states: Sick of Covid-19, the initial state for all the individuals in the cohort, death from Covid-19 and death from other causes.

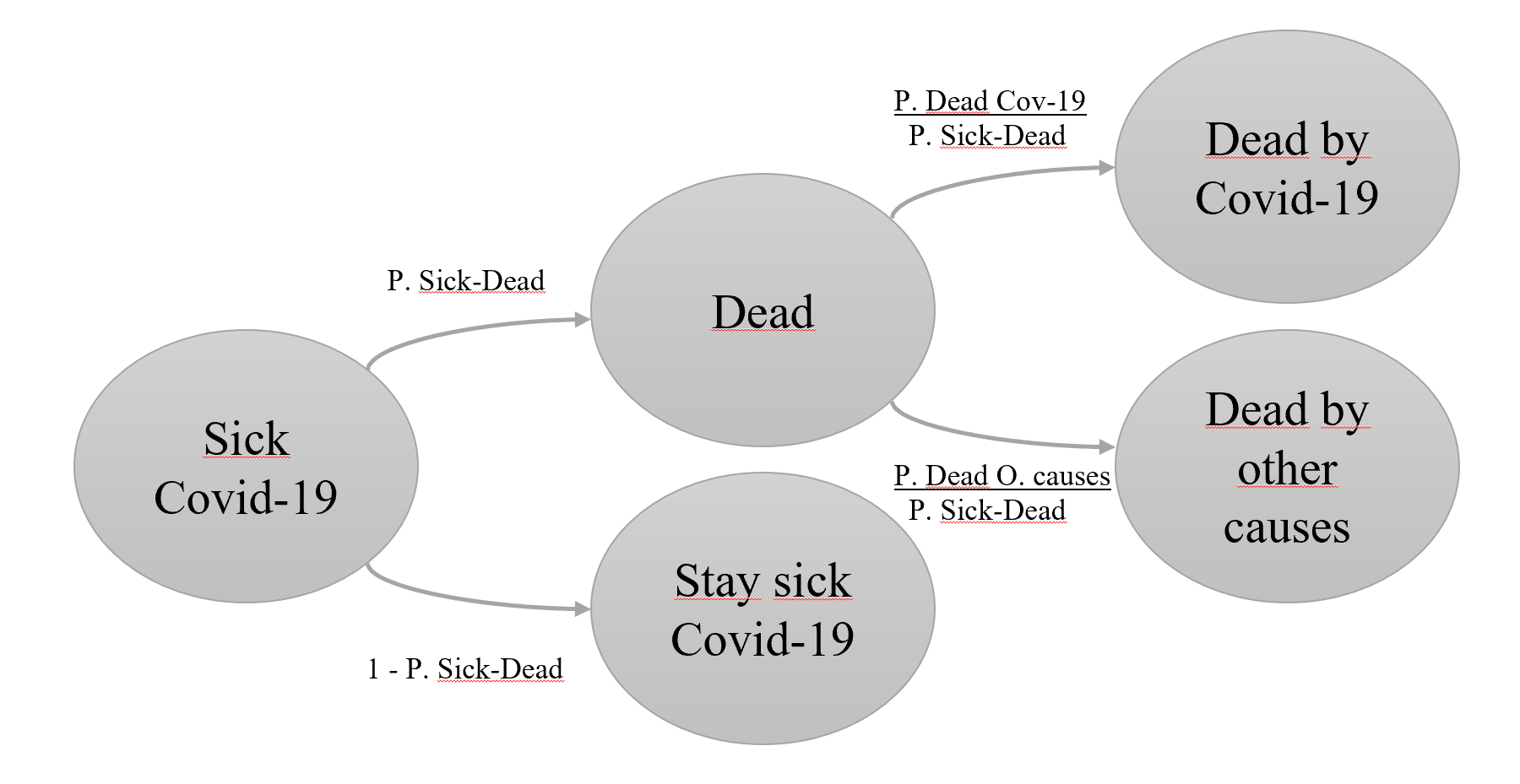
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Figure 1: Three state model for infected individuals with transition probabilities.

Both transition probabilities to death states are conditional on dying. To transition to death from Covid-19 is the conditional probability of having died from covid-19 given that you have died, similar for dead by other causes.

The probability that death was from covid-19 is the ratio of covid-19 specific hazard and overall hazard, while probability for other causes is the ratio between background and overall hazard, .

where the total probability of dead

Microsimulation algorithm allows the calculation of several outcomes at individual level and for the entire cohort 22 such as costs and benefits of different strategies. For this is needed the individual costs and utilities for each cycle, in this case days. The following parameters are the necessary elements to implement three models of simulation models for each strategy: Do not apply treatment, treat with dexamethasone or treat with remdesivir. The description of how they were obtained is found in appendix A of this work

|  |  |
| --- | --- |
| **Table 1: Parameter microsimulation model** | |
| **Parameters** | **Value** |
| *Number of individuals* | 481,353 |
| *Time horizon* | 60 days |
| *Number of states* | 3 |
| *Name of states* | Cov-19 + |
| Cov-19 Dead |
| Dead Other causes |
| *Annual discount rate for costs* | 0.0165 |
| *Annual discount rate for efectiveness* | 0.0165 |
| **Daily healthcare costs** | |
| *Ambulatory Covid 19 patient* | $14,500.00 |
| *Hospitalized Covid-19 patient* | $58,750.00 |
| *Average national Covid-19 patient* | $30,780.00 |
| *Dead patient* | $0.00 |
| **Daily utility weights** | |
| *Mean QALD(Qality Adjusted Life Days) loss* | 2.5 |
| *Covid-19 patient* | 0.975 |
| *Dead patient* | 0 |
| **Intervention daily costs** | |
| *Dexamethasone* | $4.40 |
| *Remdesivir* | $1,040.00 |
| **Intervention Effect** | |
| *Risk reduction of COVID-19 mortality with Dexamethasone* | 3.52% |
| *Risk reduction of COVID-19 mortality with Remdesivir* | 28.04% |
| **Daily transition probabilities** | |
| *dt\_p\_CoV* | Database; age, sex and day dependent |
| *dt\_p\_CoV\_dex* |
| *dt\_p\_CoV\_red* |
| \*All monetary amounts are expressed in Mexican pesos | |



Final results are used to make a Cost-Effectiveness Analysis for three strategies. R package *dampack* 23 is used to estimate Incremental Cost Effectiveness Ratio (ICER) and determine which one is the more cost-effective.

**Results**

*Covid-19 specific mortality*

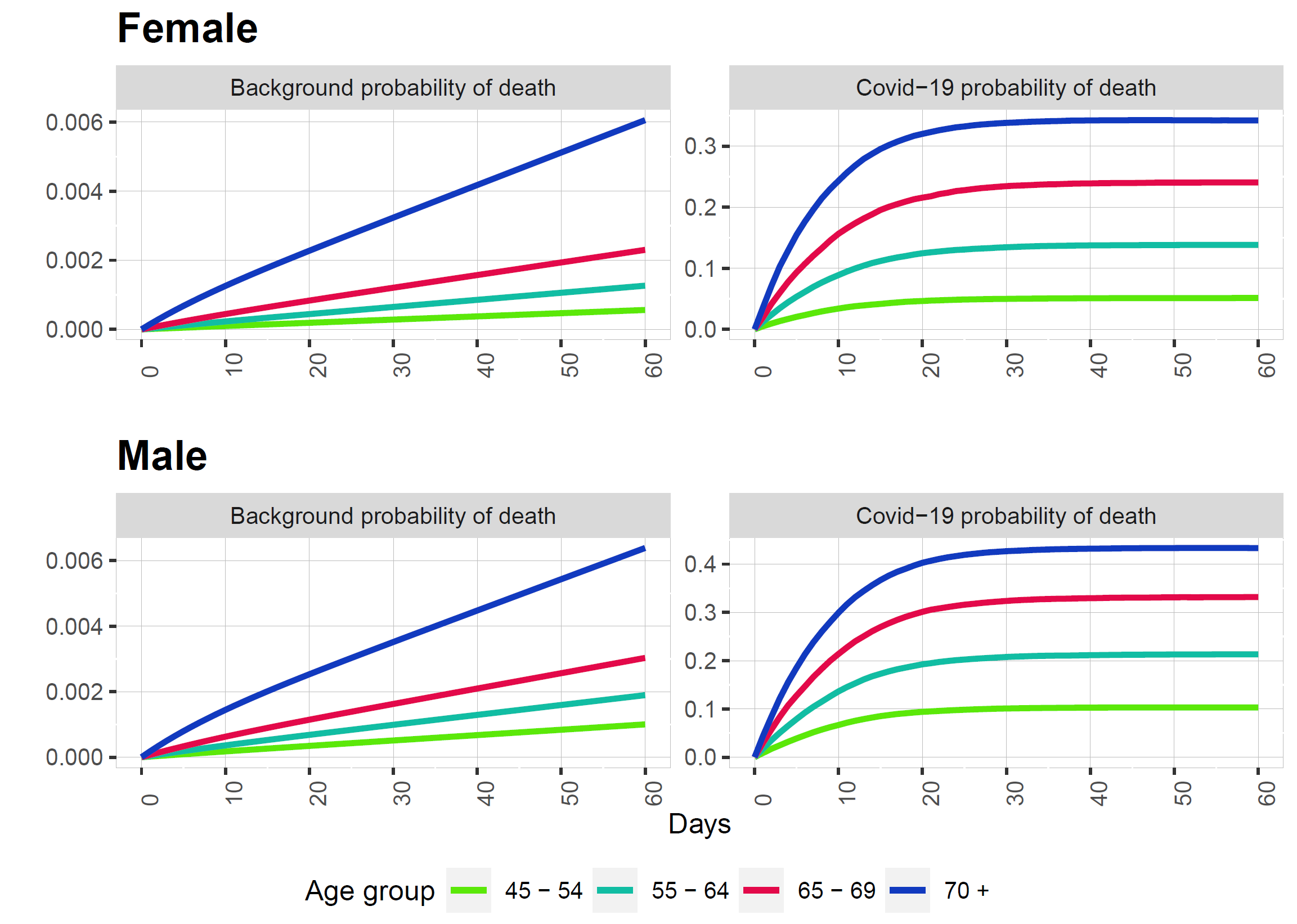
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Figure 2:Background and COVID-19 specific probability of death by sex and age group.

The cumulative probability of death is minimal compared to the probability of death from Covid-19 in all age groups and both sexes. This should be reflected in a much higher death rate from Covid-19 on microsimulation. It can also be observed that the background probability of death is very similar in men and women. However, the probability of death from COVID-19 in men is higher in all age groups. The growth between groups is similar for both sexes.

To test these estimates, the probabilities are transformed to be used in the microsimulation of the transition model. Micro-simulated cohort produces a Kaplan-Meier curve very similar to Kaplan-Meier curve of the real population:

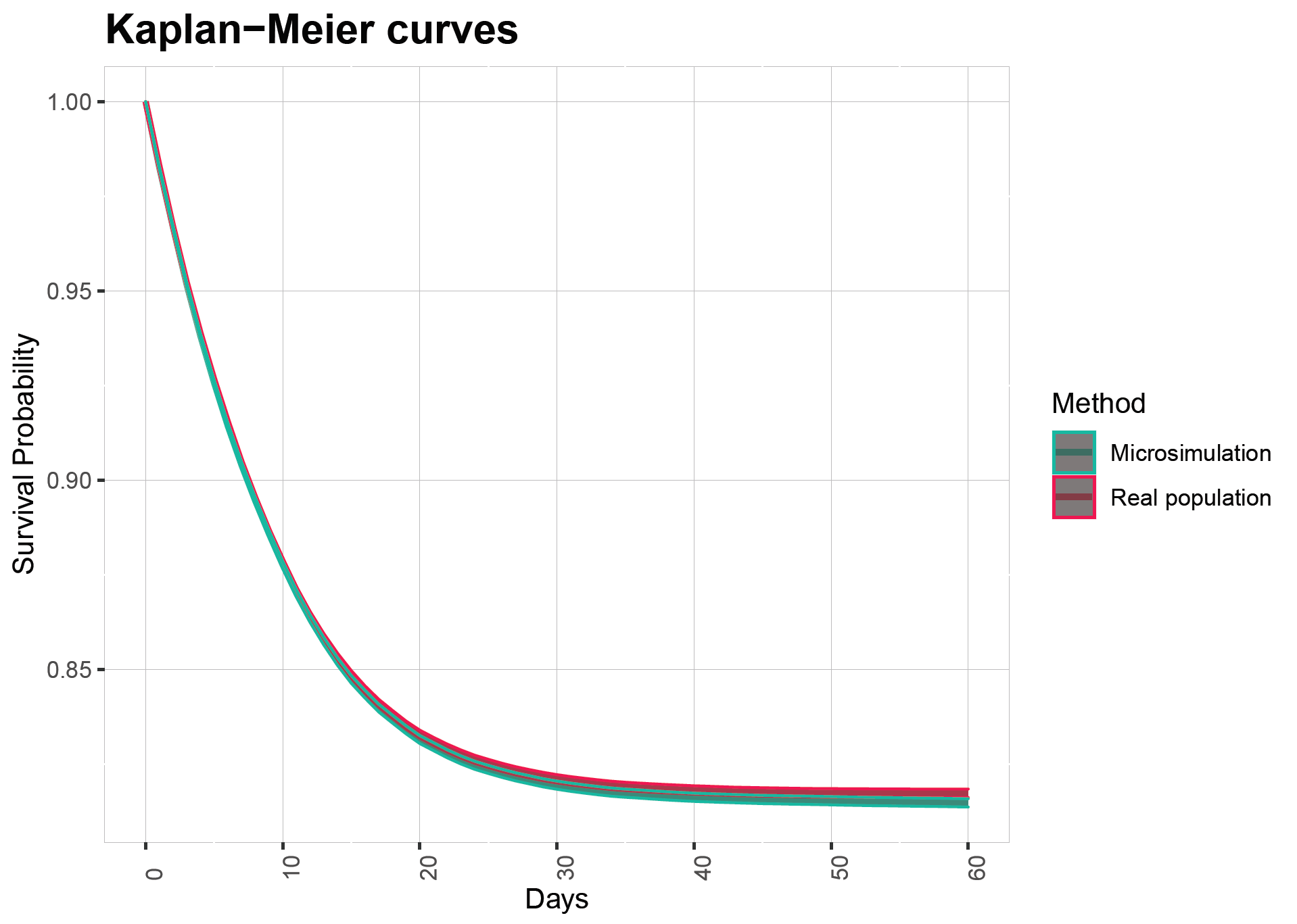
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Figure 3: Comparison of the Kaplan Meier curve of the real and micro-simulated cohort

Both curves have very similar survival probabilities, this indicates that the transition probabilities determined from the excess mortality methodology appear to be adequate. Both have practically the same values in the first 20 days, and from that point on, there is a minimal separation, although the confidence intervals include this gap and results could be modified by the aleatory effect of the microsimulation or by errors in estimates of specific probabilities of death.

*Microsimulation and Cost-Effectiveness Analysis of Remdesivir and Dexamethasone treatment effects.*

Effects of treatments with Remsidivir and Dexamethasone reduced Covid-19-specific mortality rate.

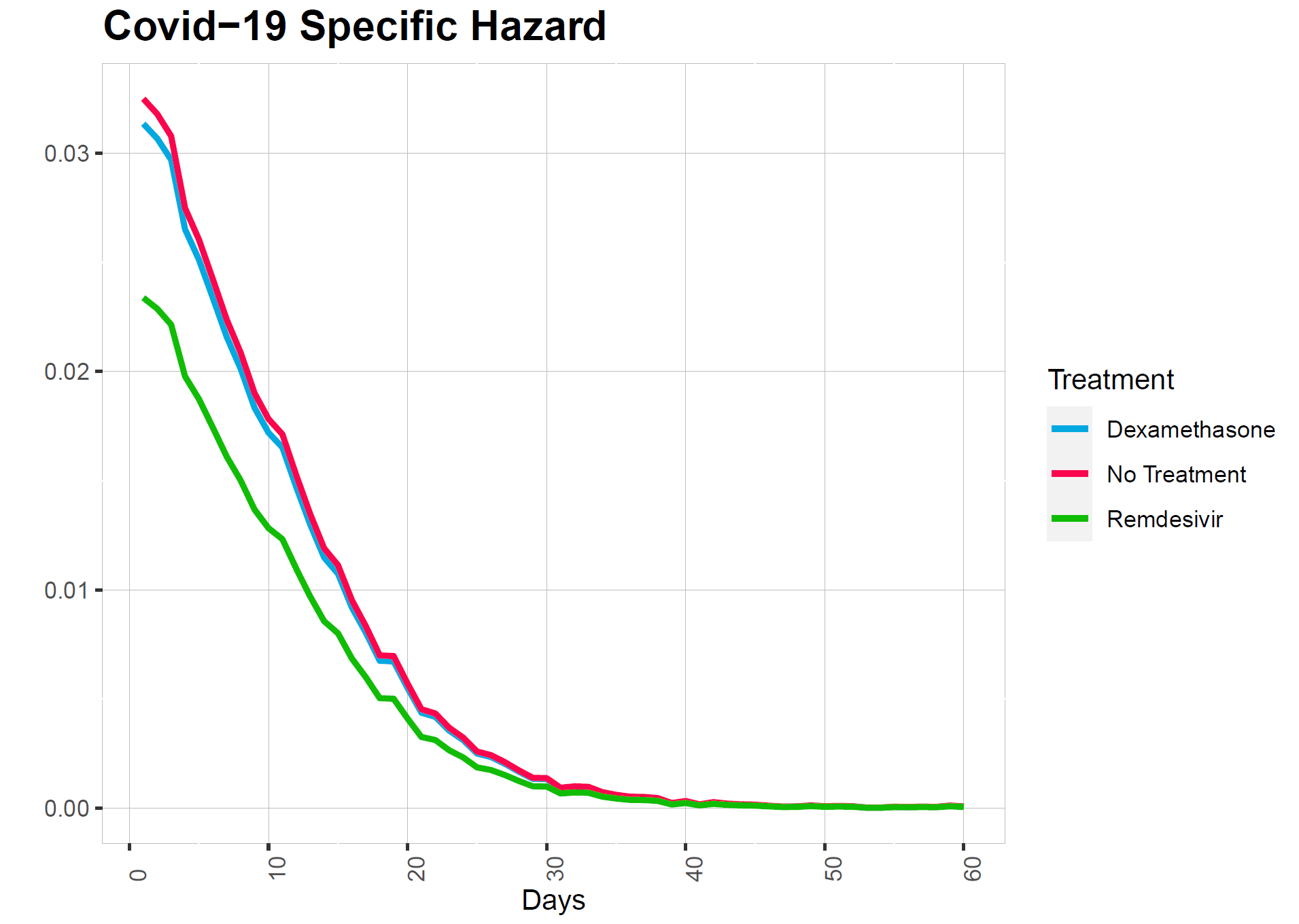
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Figure 4: Covid-19 specific Hazard by treatment. Notes: Dexamethasone and Remdesivir effects only modified Covid-19 specific hazard. The effect of dexamethasone was greatly attenuated because its effectiveness has only been tested in critical patients with assisted breathing.

Covid-19 specific hazard curve, just like the survival curve, has a downward trend. This is explained because the vast majority of deaths in confirmed cases are occurring in the first days. Covid-19 specific hazard estimates are smaller when the application of the treatment is considered, although the effect of dexamethasone is much more tenuous, what is reflected in the survival curves of the simulated cohorts:

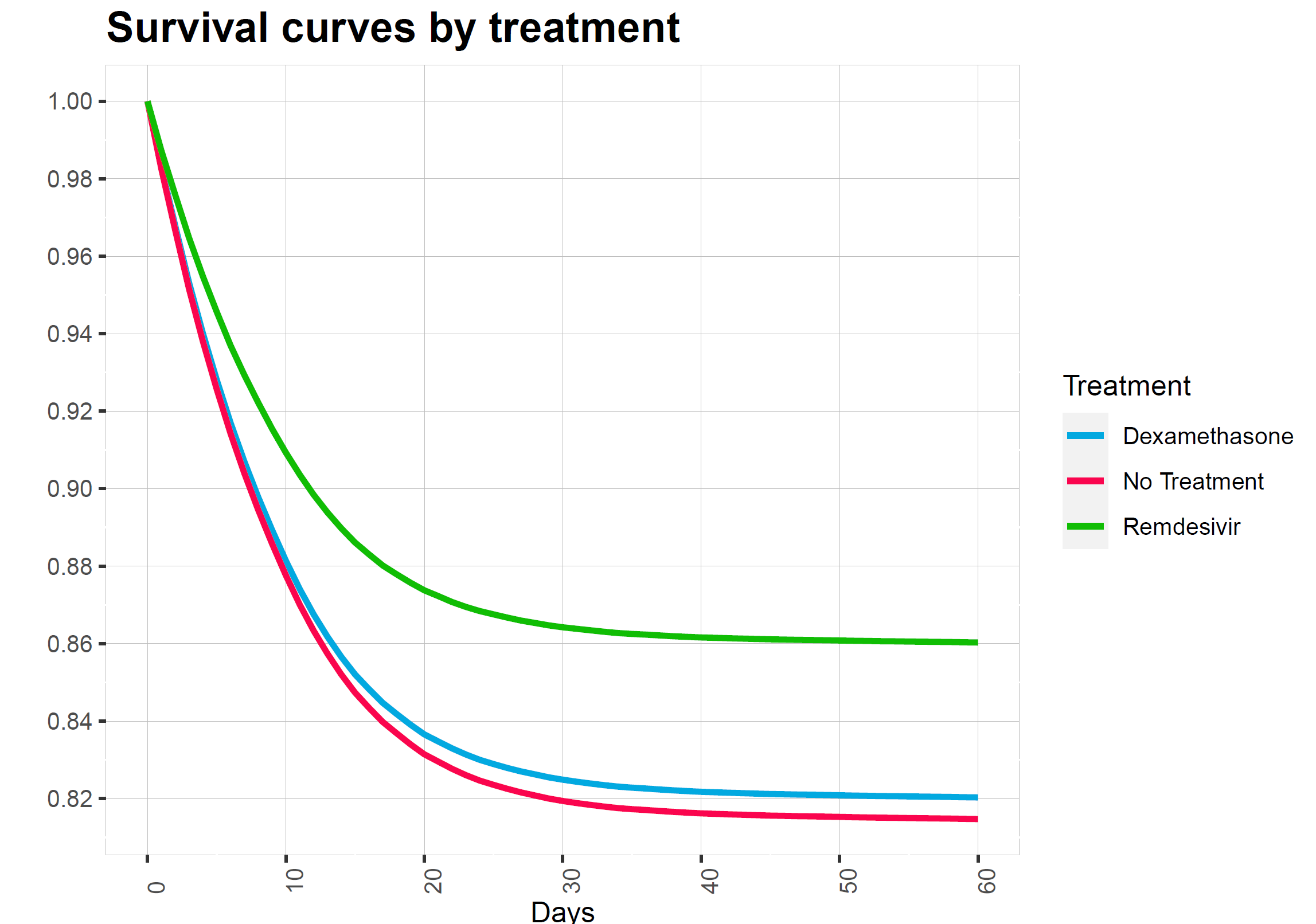
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Figure 5: Survival curves generated by microsimulation of three strategies, No treatment, Dexamethasone and Remdesivir.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 2: Results** | | | | | | | |
| Cycle | Sick  No treatment | Sick Dexamethasone | Sick Remdesivir | Dead Cov-19 No treatment | Dead Cov-19 Dexamethasone | Dead Cov-19 Remdesivir | Dead other Causes |
| *Day 5* | 445,561 | 446,740 | 455,189 | 35,681 | 34,502 | 26,050 | 114 |
| *Day 15* | 407,865 | 410,123 | 426,518 | 73,221 | 70,962 | 54,558 | 277 |
| *Day 30* | 394,418 | 397,061 | 415,996 | 86,455 | 83,807 | 64,847 | 510 |
| *Day 60* | 392,167 | 394,856 | 414,106 | 88,341 | 85,644 | 66,335 | 912 |



Dexamethasone results are much closer to the cohort with no treatment strategy than the cohort Remdesivir. Total deaths prevented by Remdesivir amounts to 22,006 in comparison with 2,697 of Dexamethasone treatment in microsimulated scenarios. If one seeks to reduce the number of deaths as much as possible, the first treatment would undoubtedly be the one to choose. However, the price of Dexamethasone is noticeably lower than Remdesivir, which is 200 times more expensive19. The cost-effectiveness analysis is necessary to know which one offers a higher return for each monetary unit invested.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 3: Cost Effectiveness Analysis** | | | | | |
| Strategy | Cost | Effect | Incremental Cost | Incremental Effect | ICER |
| *No Treatment* | $1,022,965.00 | - | - | - | - |
| *Dexamethasone* | $1,028,455.00 | 32.57286 | 5489.985 | 0.1692426 | 32438.56 |
| *Remdesivir* | $1,102,802.00 | 33.79081 | 74346.512 | 1.2179505 | 61042.31 |



Remdesivir is a more cost-effective treatment than Dexamethasone even its higher prices are considered. Increments in effects are big enough so that the efficiency per monetary is greater than the benefits shown by dexamethasone when is compared to an untreated stage

**Discussion**

The specific probabilities of death from Covid-19 for the analyzed population are much higher for the first few days, where most of the cohort's deaths are concentrated. This specific probability of death from Covid-19 represents almost the total probability of death for the population in the first 30 days; from this point, the probability of death is practically the background population probability for Mexico. For a budget-minded decision maker, this exercise suggests that the best strategy would be to invest resources in Remdesivir treatment for Covid-19 infected patients, even considering its high costs.

This work can be considered as a preliminary cost-effectiveness analysis that will lead to more extensive and deep work in the future. Currently, the work holds certain limitations that will be addressed in future reviews. First, the evidence of treatment effects is limited at the time and the effects in Covid-19 specific hazard might be affected by this. Although the treatments with the most promising results so far were included, studies on these treatments are still few and new evidence may emerge in the future to modify the conclusions of the analysis. As new information emerges in relation to Covid-19 available treatments, this can be included in this study. Second, we do not include potential new treatments. The pandemic is relatively recent, so new treatments with similar or higher effectiveness than Remdesivir or Dexamethasone may appear in the future. If new evidence emerges in this field, it will also be included in future document versions. Potential harmful side effects of the treatments were not included. Dexamethasone has shown evidence of potentially harmful side effects in patients in non-severe states of the disease, and this effect is not considered in the microsimulation models for this version. Transition model can be modified to add more health states that reflects different stages of the illness. This modification allows modifying the effect of the treatment depending on the stage of the individual.

It is important to notice that this work is the first to estimate specific mortality for Covid-19 in Mexico and the world with the relative risks and disease-specific-hazard methodology. The calculation covid-19 specific mortality allows exploring different strategies and determining which is the best to implement in the Mexican population in a context of very little information and much uncertainty and where some of these treatments have not even been applied. This is precious information to the scientific community in charge of studying this phenomenon and decision-makers who are in charge of managing this pandemic.

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**Appendix A**

*Parameters for microsimulation model*

Discount rates corresponded to inflation rates expected for Mexico for December and January and are obtained from the publications made by Mexico's central bank. 24 Quality Adjusted Life Days loss by patient is acquired from a study of the impact of seasonal influenza in age groups “45 – 64 years old” and “65 + years old” 25 a very similar classification to the one used in this work. Influenza was chosen for being a disease that has similar manifestations to covid-19: respiratory disease; fever; chills; feeling tired,25,26 although they differ in various aspects such as transmission, mortality and that COVID-19 appears to have higher impact on older age26. Costs of hospitalization and treaments for patients with covid-19 in Mexico are obtained from several internet prices searches27,28 and press notes.20,29,30 Due to the above it is recommended to take these estimates with caution.

Treatment effects are calculated incorporating the efficacy of each policy with the excess mortality additive model 31. First I computed risk reduction of covid-19 mortality percentage reduction with information with information from studies on the efficacy of remdesivir and dexamethasone in infected patients for 28 and 29 days20,21 In the case of dexamethasone it only affects patients with assisted breathing 21:

|  |  |  |
| --- | --- | --- |
| Treatment | Group | Proportion of surviving patients |
| Dexamethasone | Treatment | 0.77 |
| Placebo | 0.74 |
| Remdesivir | Treatment | 0.89 |
| Placebo | 0.85 |

With this information and the population mortality rates, the following equations can be substituted and the treatment effects can be calculated.

Where is the proportion of treated patients surviving to day t and is the expected proportion of persons with certain age, sex and day characteristics without disease that survives to day t.31

Where is the proportion of not treated patients (placebo group) surviving to day t and is the expected proportion of persons with certain age, sex and day characteristics without disease that survives to day t.31 Reduction of Covid-19 mortality is:

Overall hazard:

**Appendix B: Code**

#### Final project script. Author: Hirvin Azael Diaz Zepeda ####  
  
#### Clean Worsk - pace ####  
rm(list = ls()) # to clean the work - space  
  
#### Load Packages ####  
library(dplyr)  
library(ggplot2)  
library(utils)  
library(scales)  
library(dampack)  
library(chron)  
library(tibble)  
library(knitr)  
library(pander)  
library(kableExtra)  
library(CEAutil)  
library(tidyr)  
library(dampack)  
library(data.table)  
library(reshape2)  
library(survival)  
library(survPen)  
library(relsurv)  
library(readr)  
library(readxl)  
library(lubridate)  
library(muhaz)  
library(ggpubr)  
###### Load data bases ######  
  
# Data base of people suspected of COVID-19 published by Mexico´s Ministry of   
# Health at a national level  
  
Covid <- read\_csv("data-raw/201201COVID19MEXICO.csv") # data base of november 15th  
  
Covid\_p <- Covid %>%   
 filter(RESULTADO\_LAB == 1) %>% # Choose only positives  
 rename(ID = ID\_REGISTRO,  
 sector\_h = SECTOR,  
 sex = SEXO,  
 state = ENTIDAD\_RES,  
 county = MUNICIPIO\_RES,  
 type = TIPO\_PACIENTE,  
 date\_admission = FECHA\_INGRESO,  
 date\_symptoms = FECHA\_SINTOMAS,  
 date\_death = FECHA\_DEF,  
 intubated = INTUBADO,  
 age = EDAD,  
 pregnancy = EMBARAZO,  
 lang\_indigenous = HABLA\_LENGUA\_INDIG,  
 diabetes = DIABETES,  
 copd = EPOC,  
 asthma = ASMA,  
 inmunocompromised = INMUSUPR,  
 hypertension = HIPERTENSION,  
 cardiovascular = CARDIOVASCULAR,  
 obesity = OBESIDAD,  
 kidney\_d = RENAL\_CRONICA,  
 smoking = TABAQUISMO,  
 icu = UCI  
 ) %>%   
 filter(date\_admission <= max(date\_admission) - 10) %>% # Filter to recover just data  
 filter(age >= 45 & age <=100) # from 10 days before   
 # than the last date  
  
max(Covid\_p$date\_admission)  
  
# Create column of death  
Covid\_p <- Covid\_p %>%   
 mutate(death = ifelse(is.na(date\_death), 0, 1))  
  
save(Covid\_p, file = "data/Covid\_p.Rdata")  
  
##### Disease-specific hazard #####  
  
# Data base with national mortality data from repo of PADECI demog-mx created   
# from CONAPO data bases  
df\_mortrate\_state\_age\_sex <- read\_csv("data-raw/df\_mortrate\_state\_age\_sex.csv")  
  
# Create Mortality rates for Mexico  
# Data frame with population mortality rates in 2020 at a national level by sex   
# and age  
Mort\_mx <- df\_mortrate\_state\_age\_sex %>%   
 filter(year == 2020) %>%   
 group\_by(age, sex) %>%   
 summarise(mort\_rate = mean(mort\_rate)) %>%   
 filter(age <= 100)   
Mort\_mx <- as.data.frame(Mort\_mx)  
  
# Reshape data to have every row by sex and age  
Mort\_mx\_wide <- reshape(data = Mort\_mx, idvar = "age",   
 v.names = "mort\_rate",  
 timevar = "sex",   
 direction = "wide")  
  
Mort\_mx\_wide <- Mort\_mx\_wide %>%   
 rename(female = mort\_rate.Female,  
 male = mort\_rate.Male)  
  
#### Population survival rates  
male\_mex <- matrix(exp(- Mort\_mx\_wide$male))  
female\_mex <- matrix(exp(- Mort\_mx\_wide$female))  
  
# Create rate data frame in the format relsurv needs  
rate\_exp\_mx\_2020 <- transrate(men = male\_mex,   
 women = female\_mex,  
 yearlim = c(2020,2020),   
 int.length = 100)  
head(rate\_exp\_mx\_2020, 20)  
# Create database of the cohort in the format of relsurv  
x <- as.Date(max(Covid\_p$date\_admission), format = "%Y-%m-%d")  
  
Covid\_rr <- Covid\_p %>%   
 mutate(stat = ifelse(is.na(date\_death), 0, 1)) %>%   
 select(c("sex", "age", "date\_admission", "date\_death", "date\_symptoms", "stat"))%>%   
 mutate(sex = ifelse(sex == 1, 2, 1))%>% # recode 1 is male and 2 female  
 mutate(time = ifelse(is.na(date\_death),x - date\_admission,   
 date\_death - date\_admission)) %>% # time of observation is   
 rename(diag = date\_symptoms) %>% # date of death minus date of   
 # admission, if censored  
 # last date minus doa.  
 mutate(diag =   
 as.numeric(diag, origin = "1960-01-01")) %>% # diagnostic date = date\_symptoms  
 filter(time >= 1) %>% # eliminate negative times  
 mutate(original\_age = age) %>%   
 mutate(age = original\_age\*365.25) %>% # age needs to be in days for relsurv  
 mutate(age\_range = ifelse(original\_age >= 45 & original\_age <= 54, "45 - 54",   
 ifelse(original\_age >= 55 & original\_age <= 64, "55 - 64",  
 ifelse(original\_age >= 65 & original\_age <= 69, "65 - 69", "70 +"))))  
  
# Survival additive model for all individuals  
fit\_rsadd\_mx\_cov <- rsadd(Surv(time, stat) ~ 1,   
 data = Covid\_rr,   
 ratetable = rate\_exp\_mx\_2020,   
 method = "EM",# Exp Max   
 rmap = list(age = age, sex = sex, year = diag))  
  
# Estimates of Covid-specific Hazard   
sm <- epa(fit\_rsadd\_mx\_cov, times = c(1:60)) # 60 days  
# Plot of Covid-specific Hazard   
plot(x = sm$times, y = sm$lambda)  
  
# Survival model for all individuals (to compute overall hazard)  
ov\_haz <- kphaz.fit(time = Covid\_rr$time,   
 status = Covid\_rr$stat,  
 q =1,  
 method = "nelson")  
haz\_fit <- ov\_haz$haz  
haz\_fit <- as.data.frame(haz\_fit)  
haz\_fit <- head(haz\_fit, 60)  
  
  
# Plot comparing the two  
exc\_h <- as.data.frame(sm$lambda)  
  
df\_exc\_h <- cbind(exc\_h, haz\_fit)  
  
df\_exc\_h <- df\_exc\_h %>%   
 mutate(time = row\_number()) %>%   
 rename(`Covid-19 hazard` = V1,  
 `Overall Hazard` = haz\_fit)  
  
df\_exc\_ov\_h\_long <- gather(data = df\_exc\_h,   
 key = "Hazard",   
 value = "rates", -time)  
  
ggplot(data = df\_exc\_ov\_h\_long,   
 aes(x = time,   
 y = rates,  
 fill = Hazard,  
 color = Hazard))+   
 geom\_point(size = 1.5)+  
 geom\_line(size = 1)+  
 theme(plot.title = element\_text(face = "bold",   
 size = 16,  
 family =),  
 plot.caption = element\_text(hjust = 0,  
 colour = "#777777",  
 size = 10),  
 panel.background = element\_rect(fill = "white",   
 colour = "gray",   
 size = 0.15,   
 linetype = "solid"),  
 panel.grid.major = element\_line(size = 0.15,   
 linetype = 'solid',  
 colour = "gray"),   
 axis.text.x = element\_text(angle = 90, hjust = 0))+  
 scale\_fill\_manual(values=c ("#a9e309", "#11bda3", "#e3094a","#f0189d",   
 "#e918f0", "#9a18f0" ,"#6309e0","#113abf",  
 "#1380bf", "#11b9bf", "#11bda3", "#0fbd71",  
 "#0be357", "#5be809", "#a9e309", "#e8e40c")) +  
 labs(title = "Overall and disease specific hazard",  
 x = "Days",  
 y = "Hazard")  
  
ggsave(paste0("figs/DSH male",  
 format(Sys.Date(), "%F"), ".pdf"),   
 width = 7, height = 5)  
  
# I does not show meaninguful results  
  
#### Net survival and crude probability of death ####  
# Survival additive model for all individuals  
fit\_rsadd\_mx\_cov <- rsadd(Surv(time, stat) ~ sex,   
 data = Covid\_rr,   
 ratetable = rate\_exp\_mx\_2020,   
 method = "EM",# Exp Max   
 rmap = list(age = age, sex = sex, year = diag))  
  
plot(fit\_rsadd\_mx\_cov)  
  
summary(fit\_rsadd\_mx\_cov, times = c(5, 10))  
  
fit\_net <- rs.surv(Surv(time, stat) ~ sex,   
 data = Covid\_rr,  
 ratetable = rate\_exp\_mx\_2020,   
 method = "pohar-perme",   
 add.times = c(20, 40),  
 rmap = list(age = age, sex = sex, year = diag))  
  
summary(fit\_net,   
 times = c(20, 40))  
  
plot(fit\_net,   
 conf.int = TRUE,   
 xlim = c(0,60),   
 ylim = c(0.7,1))  
  
fit\_net\_ages <- rs.surv(Surv(time, stat) ~ age\_range,   
 data = Covid\_rr,  
 ratetable = rate\_exp\_mx\_2020,   
 method = "pohar-perme",   
 add.times = c(20, 40),  
 rmap = list(age = age, sex = sex, year = diag))  
  
plot(fit\_net\_ages,   
 conf.int = TRUE,   
 xlim = c(0,60),   
 ylim = c(0.58,1))  
  
fit\_net\_ages\_sex <- rs.surv(Surv(time, stat) ~ age\_range\*sex,   
 data = Covid\_rr,  
 ratetable = rate\_exp\_mx\_2020,   
 method = "pohar-perme",   
 add.times = c(20, 40),  
 rmap = list(age = age, sex = sex, year = diag))  
  
plot(fit\_net\_ages\_sex,   
 conf.int = TRUE,   
 xlim = c(0,60),   
 ylim = c(0.58,1))  
  
#### Crude (cause-specific) probability of death ####  
  
cmp\_fit <- cmp.rel(Surv(time, stat) ~ sex,   
 data = Covid\_rr,  
 ratetable = rate\_exp\_mx\_2020,   
 rmap = list(age = age, sex = sex, year = diag))  
  
summary(cmp\_fit,   
 times = c(30, 40),   
 scale = 1,   
 area = TRUE)  
  
plot(cmp\_fit,   
 ylim = c(0,0.22),   
 xlim = c(0,60))  
  
  
cmp\_fit\_age <- cmp.rel(Surv(time, stat) ~ age\_range,   
 data = Covid\_rr,  
 ratetable = rate\_exp\_mx\_2020,   
 rmap = list(age = age, sex = sex, year = diag))  
  
summary(cmp\_fit\_age,   
 times = c(30, 40),   
 scale = 1,   
 area = TRUE)  
  
plot(cmp\_fit\_age,   
 ylim = c(0,0.40),   
 xlim = c(0,60))  
  
  
cmp\_fit\_age\_sex <- cmp.rel(Surv(time, stat) ~ age\_range + sex,   
 data = Covid\_rr,  
 ratetable = rate\_exp\_mx\_2020,   
 rmap = list(age = age, sex = sex, year = diag))  
  
summary(cmp\_fit\_age\_sex,   
 times = c(30, 40),   
 scale = 1,   
 area = TRUE)  
  
plot(cmp\_fit\_age\_sex,   
 ylim = c(0,0.40),   
 xlim = c(-1,60))  
  
  
#### Prob of death pop and covid Age group 5 ####  
df\_cmp\_age5\_male <- as.data.frame(cbind(cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=0, sex=1`$time,  
 cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=0, sex=1`$est,  
 cmp\_fit\_age\_sex$`population age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=0, sex=1`$est) )  
  
df\_cmp\_age5\_male <- df\_cmp\_age5\_male %>%   
 mutate(Pop = "45 - 54") %>%  
 mutate(sex = "male") %>%   
 slice\_head(n = 61)  
  
df\_cmp\_age5\_female <- as.data.frame(  
 cbind(cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=0, sex=2`$time,  
 cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=0, sex=2`$est,  
 cmp\_fit\_age\_sex$`population age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=0, sex=2`$est) )  
  
df\_cmp\_age5\_female <- df\_cmp\_age5\_female %>%   
 mutate(Pop = "45 - 54") %>%  
 mutate(sex = "female") %>%   
 slice\_head(n = 61)  
  
#### Prob of death pop and covid Age group 6 ####  
  
df\_cmp\_age6\_male <- as.data.frame(  
 cbind(cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=1, age\_range65 - 69=0, age\_range70 +=0, sex=1`$time,  
 cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=1, age\_range65 - 69=0, age\_range70 +=0, sex=1`$est,  
 cmp\_fit\_age\_sex$`population age\_range55 - 64=1, age\_range65 - 69=0, age\_range70 +=0, sex=1`$est) )  
  
df\_cmp\_age6\_male <- df\_cmp\_age6\_male %>%   
 mutate(Pop = "55 - 64") %>%   
 mutate(sex = "male") %>%   
 slice\_head(n = 61)  
  
df\_cmp\_age6\_female <- as.data.frame(  
 cbind(cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=1, age\_range65 - 69=0, age\_range70 +=0, sex=2`$time,  
 cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=1, age\_range65 - 69=0, age\_range70 +=0, sex=2`$est,  
 cmp\_fit\_age\_sex$`population age\_range55 - 64=1, age\_range65 - 69=0, age\_range70 +=0, sex=2`$est) )  
  
df\_cmp\_age6\_female <- df\_cmp\_age6\_female %>%   
 mutate(Pop = "55 - 64") %>%   
 mutate(sex = "female") %>%   
 slice\_head(n = 61)  
  
#### Prob of death pop and covid Age group 7 ####  
  
df\_cmp\_age7\_male <- as.data.frame(  
 cbind(cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=1, age\_range70 +=0, sex=1`$time,  
 cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=1, age\_range70 +=0, sex=1`$est,  
 cmp\_fit\_age\_sex$`population age\_range55 - 64=0, age\_range65 - 69=1, age\_range70 +=0, sex=1`$est) )  
  
df\_cmp\_age7\_male <- df\_cmp\_age7\_male %>%   
 mutate(Pop = "65 - 69") %>%   
 mutate(sex = "male") %>%   
 slice\_head(n = 61)  
  
df\_cmp\_age7\_female <- as.data.frame(  
 cbind(cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=1, age\_range70 +=0, sex=2`$time,  
 cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=1, age\_range70 +=0, sex=2`$est,  
 cmp\_fit\_age\_sex$`population age\_range55 - 64=0, age\_range65 - 69=1, age\_range70 +=0, sex=2`$est) )  
  
df\_cmp\_age7\_female <- df\_cmp\_age7\_female %>%   
 mutate(Pop = "65 - 69") %>%   
 mutate(sex = "female") %>%   
 slice\_head(n = 61)  
  
#### Prob of death pop and covid Age group 8 ####  
  
df\_cmp\_age8\_male <- as.data.frame(  
 cbind(cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=1, sex=1`$time,  
 cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=1, sex=1`$est,  
 cmp\_fit\_age\_sex$`population age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=1, sex=1`$est) )  
  
df\_cmp\_age8\_male <- df\_cmp\_age8\_male %>%   
 mutate(Pop = "70 +") %>%   
 mutate(sex = "male") %>%   
 slice\_head(n = 61)  
  
df\_cmp\_age8\_female <- as.data.frame(  
 cbind(cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=1, sex=2`$time,  
 cmp\_fit\_age\_sex$`causeSpec age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=1, sex=2`$est,  
 cmp\_fit\_age\_sex$`population age\_range55 - 64=0, age\_range65 - 69=0, age\_range70 +=1, sex=2`$est) )  
  
df\_cmp\_age8\_female <- df\_cmp\_age8\_female %>%   
 mutate(Pop = "70 +") %>%   
 mutate(sex = "female") %>%   
 slice\_head(n = 61)  
  
df\_probs\_agegsex <- rbind(df\_cmp\_age5\_female, df\_cmp\_age5\_male, df\_cmp\_age6\_female,  
 df\_cmp\_age6\_male, df\_cmp\_age7\_female, df\_cmp\_age7\_male,  
 df\_cmp\_age8\_female, df\_cmp\_age8\_male)  
df\_probs\_agegsex <- df\_probs\_agegsex %>%   
 rename(time = V1,  
 `Covid-19 probability of death` = V2,  
 `Background probability of death` = V3)  
  
df\_probs\_agegsex\_long <- gather(data = df\_probs\_agegsex,   
 key = "type",   
 value = "prob", -c("time","Pop","sex"))  
  
  
#### Visualization ####  
  
male\_prob <- ggplot(data = filter(df\_probs\_agegsex\_long,  
 sex == "male"),   
 aes(x = time,   
 y = prob,  
 # fill = Pop,  
 color = Pop))+   
 # geom\_point(size = 1.5)+  
 geom\_line(size = 1.1)+  
 facet\_wrap(~type, scales = "free")+  
 theme(plot.title = element\_text(face = "bold",   
 size = 16,  
 family =),  
 plot.caption = element\_text(hjust = 0,  
 colour = "#777777",  
 size = 10),  
 panel.background = element\_rect(fill = "white",   
 colour = "gray",   
 size = 0.15,   
 linetype = "solid"),  
 panel.grid.major = element\_line(size = 0.15,   
 linetype = 'solid',  
 colour = "gray"),   
 axis.text.x = element\_text(angle = 90, hjust = 0))+  
 scale\_x\_continuous(breaks = number\_ticks(6))+  
 scale\_color\_manual(values=c ("#5be809", "#11bda3", "#e3094a","#113abf",   
 "#e918f0", "#9a18f0" ,"#6309e0","#113abf",  
 "#1380bf", "#11b9bf", "#11bda3", "#0fbd71",  
 "#0be357", "#5be809", "#a9e309", "#e8e40c")) +  
 labs(title = "Male",  
 x = "Days",  
 y = " ",  
 color = "Age group")  
  
female\_prob <- ggplot(data = filter(df\_probs\_agegsex\_long,  
 sex == "female"),   
 aes(x = time,   
 y = prob,  
 # fill = Pop,  
 color = Pop))+   
 # geom\_point(size = 1.5)+  
 geom\_line(size = 1.1)+  
 facet\_wrap(~type, scales = "free")+  
 theme(plot.title = element\_text(face = "bold",   
 size = 16,  
 family =),  
 plot.caption = element\_text(hjust = 0,  
 colour = "#777777",  
 size = 10),  
 panel.background = element\_rect(fill = "white",   
 colour = "gray",   
 size = 0.15,   
 linetype = "solid"),  
 panel.grid.major = element\_line(size = 0.15,   
 linetype = 'solid',  
 colour = "gray"),   
 axis.text.x = element\_text(angle = 90, hjust = 0))+  
 scale\_x\_continuous(breaks = number\_ticks(6))+  
 scale\_color\_manual(values=c ("#5be809", "#11bda3", "#e3094a","#113abf",   
 "#e918f0", "#9a18f0" ,"#6309e0","#113abf",  
 "#1380bf", "#11b9bf", "#11bda3", "#0fbd71",  
 "#0be357", "#5be809", "#a9e309", "#e8e40c")) +  
 labs(title = "Female",  
 x = " ",  
 y = " ",  
 color = "Age group")  
  
ggarrange(female\_prob, male\_prob,  
 #labels = c("Females", "Males"),  
 ncol = 1,   
 common.legend = TRUE,  
 label.y = c(1,0),  
 legend = "bottom")  
ggsave(paste0("figs/Covid-19 and background PoD",  
 format(Sys.Date(), "%F"), ".pdf"),   
 width = 7, height = 5)  
  
#### Transform to hazard ####  
  
# Fromula from Lee, Wang:  
## h(t) = f(t)/ 1 - F(t)  
male\_haz <- df\_probs\_agegsex %>%   
 filter(Pop == "45 - 54" & sex == "male") %>%   
 select(1,2)  
  
f\_x <- diff(male\_haz$`Covid-19 probability of death`)  
  
f\_x <- c(0, diff(male\_haz$`Covid-19 probability of death`))  
  
male\_haz$f\_x <- f\_x  
  
male\_haz <- male\_haz %>%   
 mutate(hazard = ((f\_x)/(1 - `Covid-19 probability of death`)))  
  
  
Covid\_rr\_ag5 <- Covid\_rr %>%   
 filter(sex == 1) %>%   
 filter(age\_range == "45 - 54")  
  
# Survival additive model for all individuals  
fit\_rsadd\_mx\_cov\_agsex<- rsadd(Surv(time, stat) ~ 1,   
 data = Covid\_rr\_ag5,   
 ratetable = rate\_exp\_mx\_2020,   
 method = "EM",# Exp Max   
 rmap = list(age = age, sex = sex, year = diag))  
  
# Estimates of Covid-specific Hazard   
sm <- epa(fit\_rsadd\_mx\_cov\_agsex, times = c(0:60)) # 60 days  
  
sm$lambda  
male\_haz$sm <- c(0,sm$lambda)  
  
male\_haz\_comp <- male\_haz %>%   
 select(1,4,5)  
  
male\_haz\_comp <- gather(male\_haz\_comp, key = "Est", value = "hz",-time)   
  
  
ggplot(data = male\_haz\_comp,   
 aes(x = time,   
 y = hz,  
 # fill = Pop,  
 color = Est))+   
 # geom\_point(size = 1.5)+  
 geom\_line(size = 1.1)  
# Values are pretty similar between transformation with formula and excess  
# obtained by rsadd and excess hazard functions smoothing  
  
  
# Survival additive model for all individuals  
  
Covid\_rr$age\_range <- as.factor(Covid\_rr$age\_range)   
fit\_rsadd\_mx\_cov\_agsex<- rsadd(Surv(time, stat) ~ age\_range + sex,   
 data = Covid\_rr,   
 ratetable = rate\_exp\_mx\_2020,  
 method = "EM",# Exp Max   
 rmap = list(age = age, sex = sex, year = diag))  
  
  
sm <- epa(fit\_rsadd\_mx\_cov\_agsex, times = c(0:60)) # 60 days  
sm$lambda  
  
summary(fit\_rsadd\_mx\_cov\_agsex, times = c(50, 60))  
  
#### Turn probs of death to hazard ####  
  
male\_haz\_a5 <- df\_probs\_agegsex %>%   
 filter(Pop == "45 - 54" & sex == "male")  
  
f\_x\_cov <- abs(c(0, diff(male\_haz\_a5$`Covid-19 probability of death`)))  
f\_x\_pop <- abs(c(0, diff(male\_haz\_a5$`Background probability of death`)))  
  
male\_haz\_a5$f\_x\_cov <- f\_x\_cov  
male\_haz\_a5$f\_x\_pop <- f\_x\_pop  
  
male\_haz\_a5 <- male\_haz\_a5 %>%   
 mutate(hazard\_cov = ((f\_x\_cov)/(1 - `Covid-19 probability of death`))) %>%   
 mutate(hazard\_pop = ((f\_x\_pop)/(1 - `Background probability of death`)))  
  
female\_haz\_a5 <- df\_probs\_agegsex %>%   
 filter(Pop == "45 - 54" & sex == "female")  
  
f\_x\_cov <- abs(c(0, diff(female\_haz\_a5$`Covid-19 probability of death`)))  
f\_x\_pop <- abs(c(0, diff(female\_haz\_a5$`Background probability of death`)))  
  
female\_haz\_a5$f\_x\_cov <- f\_x\_cov  
female\_haz\_a5$f\_x\_pop <- f\_x\_pop  
  
female\_haz\_a5 <- female\_haz\_a5 %>%   
 mutate(hazard\_cov = ((f\_x\_cov)/(1 - `Covid-19 probability of death`))) %>%   
 mutate(hazard\_pop = ((f\_x\_pop)/(1 - `Background probability of death`)))  
  
  
  
male\_haz\_a6 <- df\_probs\_agegsex %>%   
 filter(Pop == "55 - 64" & sex == "male")  
  
f\_x\_cov <- abs(c(0, diff(male\_haz\_a6$`Covid-19 probability of death`)))  
f\_x\_pop <- abs(c(0, diff(male\_haz\_a6$`Background probability of death`)))  
  
male\_haz\_a6$f\_x\_cov <- f\_x\_cov  
male\_haz\_a6$f\_x\_pop <- f\_x\_pop  
  
male\_haz\_a6 <- male\_haz\_a6 %>%   
 mutate(hazard\_cov = ((f\_x\_cov)/(1 - `Covid-19 probability of death`))) %>%   
 mutate(hazard\_pop = ((f\_x\_pop)/(1 - `Background probability of death`)))  
  
female\_haz\_a6 <- df\_probs\_agegsex %>%   
 filter(Pop == "55 - 64" & sex == "female")  
  
f\_x\_cov <- abs(c(0, diff(female\_haz\_a6$`Covid-19 probability of death`)))  
f\_x\_pop <- abs(c(0, diff(female\_haz\_a6$`Background probability of death`)))  
  
female\_haz\_a6$f\_x\_cov <- f\_x\_cov  
female\_haz\_a6$f\_x\_pop <- f\_x\_pop  
  
female\_haz\_a6 <- female\_haz\_a6 %>%   
 mutate(hazard\_cov = ((f\_x\_cov)/(1 - `Covid-19 probability of death`))) %>%   
 mutate(hazard\_pop = ((f\_x\_pop)/(1 - `Background probability of death`)))  
  
  
  
male\_haz\_a7 <- df\_probs\_agegsex %>%   
 filter(Pop == "65 - 69" & sex == "male")  
  
f\_x\_cov <- abs(c(0, diff(male\_haz\_a7$`Covid-19 probability of death`)))  
f\_x\_pop <- abs(c(0, diff(male\_haz\_a7$`Background probability of death`)))  
  
male\_haz\_a7$f\_x\_cov <- f\_x\_cov  
male\_haz\_a7$f\_x\_pop <- f\_x\_pop  
  
male\_haz\_a7 <- male\_haz\_a7 %>%   
 mutate(hazard\_cov = ((f\_x\_cov)/(1 - `Covid-19 probability of death`))) %>%   
 mutate(hazard\_pop = ((f\_x\_pop)/(1 - `Background probability of death`)))  
  
female\_haz\_a7 <- df\_probs\_agegsex %>%   
 filter(Pop == "65 - 69" & sex == "female")  
  
f\_x\_cov <- abs(c(0, diff(female\_haz\_a7$`Covid-19 probability of death`)))  
f\_x\_pop <- abs(c(0, diff(female\_haz\_a7$`Background probability of death`)))  
  
female\_haz\_a7$f\_x\_cov <- f\_x\_cov  
female\_haz\_a7$f\_x\_pop <- f\_x\_pop  
  
female\_haz\_a7 <- female\_haz\_a7 %>%   
 mutate(hazard\_cov = ((f\_x\_cov)/(1 - `Covid-19 probability of death`))) %>%   
 mutate(hazard\_pop = ((f\_x\_pop)/(1 - `Background probability of death`)))  
  
  
  
male\_haz\_a8 <- df\_probs\_agegsex %>%   
 filter(Pop == "70 +" & sex == "male")  
  
f\_x\_cov <- abs(c(0, diff(male\_haz\_a8$`Covid-19 probability of death`)))  
f\_x\_pop <- abs(c(0, diff(male\_haz\_a8$`Background probability of death`)))  
  
male\_haz\_a8$f\_x\_cov <- f\_x\_cov  
male\_haz\_a8$f\_x\_pop <- f\_x\_pop  
  
male\_haz\_a8 <- male\_haz\_a8 %>%   
 mutate(hazard\_cov = ((f\_x\_cov)/(1 - `Covid-19 probability of death`))) %>%   
 mutate(hazard\_pop = ((f\_x\_pop)/(1 - `Background probability of death`)))  
  
female\_haz\_a8 <- df\_probs\_agegsex %>%   
 filter(Pop == "70 +" & sex == "female")  
  
f\_x\_cov <- abs(c(0, diff(female\_haz\_a8$`Covid-19 probability of death`)))  
f\_x\_pop <- abs(c(0, diff(female\_haz\_a8$`Background probability of death`)))  
  
female\_haz\_a8$f\_x\_cov <- f\_x\_cov  
female\_haz\_a8$f\_x\_pop <- f\_x\_pop  
  
female\_haz\_a8 <- female\_haz\_a8 %>%   
 mutate(hazard\_cov = ((f\_x\_cov)/(1 - `Covid-19 probability of death`))) %>%   
 mutate(hazard\_pop = ((f\_x\_pop)/(1 - `Background probability of death`)))  
  
  
df\_hazards <- rbind(male\_haz\_a5, male\_haz\_a6, male\_haz\_a7, male\_haz\_a8,  
 female\_haz\_a5, female\_haz\_a6, female\_haz\_a7, female\_haz\_a8)  
  
save(df\_hazards, file = "data/df\_hazards.Rdata")

###### Load data bases ######  
load("data/Covid\_p.Rdata")  
load("data/df\_hazards.Rdata")  
  
###### synthetic cohort ######  
# Creation of the synthetic cohort  
S\_cohort <- Covid\_rr %>%  
 select(original\_age, sex) %>%   
 mutate(Ind = row\_number()) %>%   
 select(Ind, original\_age, sex) %>%   
 rename(age = original\_age)  
  
## Create data table with hazard by age, day and sex  
# Age group 45 - 54  
df\_hazard\_45\_54 <- df\_hazards %>%   
 filter(Pop == "45 - 54")  
  
x <- seq(45, 54, by = 1)  
y <- seq(0, 60, by = 1)  
  
d1 <- expand.grid(x = x, y = y)  
d2 <- expand.grid(x = x, y = y)  
  
d1 <- d1 %>%   
 mutate(sex = "female")  
  
d2 <- d2 %>%   
 mutate(sex = "male")  
  
d\_p\_HD\_45\_54 <- bind\_rows(d1, d2)  
  
d\_p\_HD\_45\_54 <- d\_p\_HD\_45\_54 %>%   
 rename(day = y,  
 age = x) %>%   
 arrange(age, day)  
  
d\_p\_HD\_45\_54 <- d\_p\_HD\_45\_54 %>%   
 left\_join(df\_hazard\_45\_54, by = c("sex" = "sex", "day" = "time")) %>%   
 select(1,2,3,9,10)  
  
# Age group 55 - 64  
df\_hazard\_55\_64 <- df\_hazards %>%   
 filter(Pop == "55 - 64")  
  
x <- seq(55, 64, by = 1)  
y <- seq(0, 60, by = 1)  
  
d1 <- expand.grid(x = x, y = y)  
d2 <- expand.grid(x = x, y = y)  
  
d1 <- d1 %>%   
 mutate(sex = "female")  
  
d2 <- d2 %>%   
 mutate(sex = "male")  
  
d\_p\_HD\_55\_64 <- bind\_rows(d1, d2)  
  
d\_p\_HD\_55\_64 <- d\_p\_HD\_55\_64 %>%   
 rename(day = y,  
 age = x) %>%   
 arrange(age, day)  
  
d\_p\_HD\_55\_64 <- d\_p\_HD\_55\_64 %>%   
 left\_join(df\_hazard\_55\_64, by = c("sex" = "sex", "day" = "time")) %>%   
 select(1,2,3,9,10)  
  
# Age group 65 - 69  
df\_hazard\_65\_69 <- df\_hazards %>%   
 filter(Pop == "65 - 69")  
  
x <- seq(65, 69, by = 1)  
y <- seq(0, 60, by = 1)  
  
d1 <- expand.grid(x = x, y = y)  
d2 <- expand.grid(x = x, y = y)  
  
d1 <- d1 %>%   
 mutate(sex = "female")  
  
d2 <- d2 %>%   
 mutate(sex = "male")  
  
d\_p\_HD\_65\_69 <- bind\_rows(d1, d2)  
  
d\_p\_HD\_65\_69 <- d\_p\_HD\_65\_69 %>%   
 rename(day = y,  
 age = x) %>%   
 arrange(age, day)  
  
d\_p\_HD\_65\_69 <- d\_p\_HD\_65\_69 %>%   
 left\_join(df\_hazard\_65\_69, by = c("sex" = "sex", "day" = "time")) %>%   
 select(1,2,3,9,10)  
  
# Age group 70 +  
df\_hazard\_70 <- df\_hazards %>%   
 filter(Pop == "70 +")  
  
x <- seq(70, 120, by = 1)  
y <- seq(0, 60, by = 1)  
  
d1 <- expand.grid(x = x, y = y)  
d2 <- expand.grid(x = x, y = y)  
  
d1 <- d1 %>%   
 mutate(sex = "female")  
  
d2 <- d2 %>%   
 mutate(sex = "male")  
  
d\_p\_HD\_70 <- bind\_rows(d1, d2)  
  
d\_p\_HD\_70 <- d\_p\_HD\_70 %>%   
 rename(day = y,  
 age = x) %>%   
 arrange(age, day)  
  
d\_p\_HD\_70 <- d\_p\_HD\_70 %>%   
 left\_join(df\_hazard\_70, by = c("sex" = "sex", "day" = "time")) %>%   
 select(1,2,3,9,10)  
  
d\_p\_HD <- rbind(d\_p\_HD\_45\_54, d\_p\_HD\_55\_64, d\_p\_HD\_65\_69, d\_p\_HD\_70)  
  
d\_p\_HD$hazard\_overall <- d\_p\_HD$hazard\_cov + d\_p\_HD$hazard\_pop  
  
d\_p\_HD <- d\_p\_HD %>%   
 mutate(cov\_prop = hazard\_cov/hazard\_overall) %>%   
 mutate(pop\_prop = 1 - cov\_prop)  
  
d\_p\_HD$cov\_prop[d\_p\_HD$cov\_prop == "NaN"] <- 0   
d\_p\_HD$pop\_prop[d\_p\_HD$pop\_prop == "NaN"] <- 0   
  
#### Microsimulation without treatment ####  
# Parameters set  
# number of simulated individuals, in this case 488,866  
n\_i <- length(S\_cohort$Ind)   
n\_t <- 60 # time horizon, 60 days  
# model states: Positive Case - Cov19+, Death by Covid-19 - CoV19\_Dead,   
# Death by other causes - O\_Causes\_Dead  
v\_names\_states <- c("Cov19+", "CoV19\_Dead", "O\_Causes\_Dead")   
n\_states <- length(v\_names\_states) # the number of states  
d\_c <- d\_e <- (0.017 + 0.016)/2 # Daily discount rates for costs and utilities  
# calculate discount weights for costs for each cycle based on discount rate d\_c  
v\_dwc <- 1 / (1 + d\_c) ^ (0:n\_t)   
# calculate discount weights for effectiveness for each cycle based on discount   
# rate d\_e  
v\_dwe <- 1 / (1 + d\_e) ^ (0:n\_t)  
  
## Costs and utilities inputs (in MX pesos)  
c\_amb <- 14500 # Average cost by ambulatory patient  
# Average cost for patients that require hospitalized care  
c\_hosp <- ((35000 + 50000 + 70000+ 80000)/4)  
# compute proportion of ambulatory and hospitalized patients   
covid\_p\_h <- Covid\_p %>%   
 filter(type == 2)  
# Proportion of hospitalized patients  
p\_hosp <- length(covid\_p\_h$ID) / length(Covid\_p$ID)   
# cost of remaining one cycle sick with COVID-19  
c\_sCov <- p\_hosp\*c\_hosp + (1 - p\_hosp)\* c\_amb   
c\_dCov <- 0 # cost of remaining one cycle Dead  
c\_dPop <- 0 # cost of remaining one cycle Dead  
c\_Trt <- 0  
# Mean QALD (Quality Adjusted Life Days) loss.  
m\_QALD <- 2.5  
u\_sCov <- (100 - m\_QALD)/100 # utility when Sick   
u\_dCov <- 0 # utility when Dead  
u\_dPop <- 0 # utility when Dead  
  
# Create data table with probabilities for each state  
  
d\_p\_Cov <- d\_p\_HD %>%   
 mutate(prob\_dead = (1 - exp(-hazard\_overall))) %>%   
 mutate(p\_dCoV = prob\_dead\*cov\_prop) %>%   
 mutate(p\_dPop = prob\_dead\*pop\_prop)  
  
d\_p\_CoV <- d\_p\_Cov %>%   
 select(1:3,9:11)  
  
# Convert data frame to a data table for efficiency  
dt\_p\_CoV <- data.table(d\_p\_CoV)  
  
# set the data table to be indexed by age, day and Sex  
setkey(dt\_p\_CoV, age, day, sex)  
  
# Create data frame of population from cohort. All begin in day 0  
df\_X <- S\_cohort  
df\_X$sex[df\_X$sex == 1] <- "male"  
df\_X$sex[df\_X$sex == 2] <- "female"  
df\_X <- df\_X %>%   
 mutate(day = 0)  
  
source("R/Functions.R")  
  
Probs <- function(v\_M\_t, df\_X, t) { # t <- 1  
 # Arguments:  
 # v\_M\_t: health state occupied at cycle t (character variable)  
 # df\_X: data frame with individual characteristics data   
 # v\_Ts: vector with the duration of being sick  
 # t: cycle  
 # Returns:   
 # transition probabilities for that cycle  
 # create matrix of state transition probabilities  
 m\_p\_t <- matrix(0, nrow = n\_states, ncol = n\_i)   
 # give the state names to the rows  
 rownames(m\_p\_t) <- v\_names\_states  
   
 # Lookup baseline probability of dying from Covid-19 or other causes based on   
 # individual characteristics of day, sex and age   
 p\_die\_CoV\_all <- dt\_p\_CoV[.(df\_X$age,df\_X$day + t, df\_X$sex), p\_dCoV]   
 p\_die\_Pop\_all <- dt\_p\_CoV[.(df\_X$age,df\_X$day + t, df\_X$sex), p\_dPop]   
 p\_die\_CoV <- p\_die\_CoV\_all[v\_M\_t == "Cov19+"]   
 p\_die\_Pop <- p\_die\_Pop\_all[v\_M\_t == "Cov19+"]   
   
 # update m\_p\_t with the appropriate probabilities   
 # transition probabilities when healthy  
 m\_p\_t[, v\_M\_t == "Cov19+"] <- rbind(1 - (p\_die\_CoV + p\_die\_Pop), p\_die\_CoV, p\_die\_Pop)   
 # transition probabilities when sick   
 m\_p\_t[, v\_M\_t == "CoV19\_Dead"] <- rbind(0, 1 ,0)  
 # transition probabilities when sicker   
 m\_p\_t[, v\_M\_t == "O\_Causes\_Dead"] <- rbind(0, 0, 1)  
   
   
 # t(m\_p\_t[, 1:10]) # Show the probabilities for the first 10 individuals   
   
 return(t(m\_p\_t))  
}   
  
Costs <- function (v\_M\_t, Trt = FALSE) {  
 # v\_M\_t: current health state  
 c\_t <- c()  
 c\_t[v\_M\_t == "Cov19+"] <- c\_sCov + (c\_Trt \* Trt) # costs accrued by being healthy this cycle  
 c\_t[v\_M\_t == "CoV19\_Dead"] <- c\_dCov # costs accrued by being sick this cycle  
 c\_t[v\_M\_t == "O\_Causes\_Dead"] <- c\_dCov # costs accrued by being sicker this cycle  
 return(c\_t) # return costs accrued this cycle  
}  
  
Effs <- function (v\_M\_t, Trt = FALSE) {  
 # v\_M\_t: current health state  
 q\_t <- c()   
 q\_t[v\_M\_t == "Cov19+"] <- u\_sCov   
 # QALYs accrued by being healthy this cycle  
 q\_t[v\_M\_t == "CoV19\_Dead"] <- u\_dCov # QALYs accrued by being healthy this cycle  
 q\_t[v\_M\_t == "O\_Causes\_Dead"] <- u\_dCov # QALYs accrued by being sick this cycle  
 return(q\_t) # return the QALYs accrued this cycle  
}  
  
#### 04.2 Dynamic characteristics   
# These are just starting conditions - they will change with the simulation  
v\_M\_init <- rep("Cov19+", n\_i) # everyone begins in the healthy state  
  
MicroSim <- function(n\_i, df\_X, seed = 1) { #t <- 1  
   
 set.seed(seed) # set the seed  
   
 m\_M <- m\_C <- m\_E <- matrix(NA, nrow = n\_i, ncol = n\_t + 1,   
 dimnames = list(paste("ind" , 1:n\_i, sep = " "),   
 paste("cycle", 0:n\_t, sep = " ")))   
   
 m\_M[, 1] <- v\_M\_init # initial health state  
 m\_C[, 1] <- Costs(m\_M[, 1]) # costs accrued during cycle 0  
 m\_E[, 1] <- Effs(m\_M[, 1]) # QALYs accrued during cycle 0  
   
 # open a loop for time running cycles 1 to n\_t   
 for (t in 1:n\_t) { # t <- 1  
 # calculate the transition probabilities for the cycle based on health state t  
 m\_P <- Probs(v\_M\_t = m\_M[, t], df\_X, t = t)   
 # sample the current health state and store that state in matrix m\_M  
 m\_M[, t + 1] <- samplev(m\_P, 1)   
 # calculate costs per individual during cycle t + 1  
 m\_C[, t + 1] <- Costs(m\_M[, t + 1])   
 # calculate QALYs per individual during cycle t + 1  
 m\_E[, t + 1] <- Effs(m\_M[, t + 1])   
   
 # Display simulation progress  
 if(t/(n\_t/10) == round(t/(n\_t/10), 0)) { # display progress every 10%  
 cat('\r', paste(t/n\_t \* 100, "% done", sep = " "))  
 }  
   
 } # close the loop for the time points   
   
 # calculate   
 tc <- m\_C %\*% v\_dwc # total (discounted) cost per individual  
 te <- m\_E %\*% v\_dwe # total (discounted) QALYs per individual   
 tc\_hat <- mean(tc) # average (discounted) cost   
 te\_hat <- mean(te) # average (discounted) QALYs  
 tc\_sum <- sum(tc) # sum (discounted) cost  
 te\_sum <- sum(te) # sum (discounted) QALYs  
   
 # store the results from the simulation in a list  
 results <- list(m\_M = m\_M,   
 m\_C = m\_C,   
 m\_E = m\_E,   
 tc = tc ,   
 te = te,   
 tc\_hat = tc\_hat,   
 te\_hat = te\_hat,  
 tc\_sum = tc\_sum,   
 te\_sum = te\_sum )   
   
 return(results) # return the results  
   
} # end of the MicroSim function   
  
outcomes <- MicroSim(n\_i, df\_X, seed = 1)  
  
results <- data.frame("Total Cost" = outcomes$tc\_hat,   
 "Total QALYs" = outcomes$te\_hat)  
  
# Create dataframe to transform: alive =1 and death = 0  
state\_m\_s <- as.data.frame(outcomes$m\_M)   
state\_m\_s[state\_m\_s == "Cov19+"] <- 1  
state\_m\_s[state\_m\_s == "CoV19\_Dead"] <- 0   
state\_m\_s[state\_m\_s == "O\_Causes\_Dead"] <- 0   
state\_m\_s <- sapply(state\_m\_s, as.numeric)  
  
Cycle\_sum\_NT <-   
 colSums(state\_m\_s)/n\_i # Compute survival probability for each cycle  
  
fit\_net\_ages\_sex <- rs.surv(Surv(time, stat) ~ 1,   
 data = Covid\_rr,  
 ratetable = rate\_exp\_mx\_2020,   
 method = "pohar-perme",   
 type="kaplan-meier",  
 conf.type="log",  
 conf.int=0.95,  
 rmap = list(age = age, sex = sex, year = diag))  
  
time\_km <- c(0, fit\_net\_ages\_sex$time)  
`Real population` <- c(1, fit\_net\_ages\_sex$surv)  
LB <- c(1, fit\_net\_ages\_sex$lower)  
UB <- c(1, fit\_net\_ages\_sex$upper)  
df\_compare <- as.data.frame(cbind(time\_km, `Real population`, LB, UB))  
df\_compare <- head(df\_compare, 61)  
  
df\_compare$Microsimulation <- Cycle\_sum\_NT  
  
LB\_wald <- function(num){  
 lb <- num - 1.96\*(sqrt((num\*(1-num))/n\_i))  
 return(lb)  
}  
  
UB\_wald <- function(num){  
 ub <- num + 1.96\*(sqrt((num\*(1-num))/n\_i))  
 return(ub)  
}  
  
df\_compare$LB\_wald <- LB\_wald(df\_compare$Microsimulation)  
df\_compare$UB\_wald <- UB\_wald(df\_compare$Microsimulation)  
  
df\_compare\_long <- gather(data = df\_compare,   
 key = KM,   
 value = surv, -c(time\_km, UB, LB, LB\_wald, UB\_wald))  
  
#### Visualization Kplan Meier ####  
ggplot(data = df\_compare\_long,   
 aes(x = time\_km,   
 y = surv,  
 # fill = Pop,  
 color = KM))+   
 # geom\_point(size = 1.5)+  
 geom\_line(size = 1.1)+  
 geom\_ribbon(data = filter(df\_compare\_long,  
 KM == "Real population"),   
 aes(ymin = LB, ymax = UB), alpha = 0.3) +  
 geom\_ribbon(data = filter(df\_compare\_long,  
 KM == "Microsimulation"),   
 aes(ymin = LB\_wald, ymax = UB\_wald), alpha = 0.3) +  
 # facet\_wrap(~type, scales = "free")+  
 theme(plot.title = element\_text(face = "bold",   
 size = 16,  
 family =),  
 plot.caption = element\_text(hjust = 0,  
 colour = "#777777",  
 size = 10),  
 panel.background = element\_rect(fill = "white",   
 colour = "gray",   
 size = 0.15,   
 linetype = "solid"),  
 panel.grid.major = element\_line(size = 0.15,   
 linetype = 'solid',  
 colour = "gray"),   
 axis.text.x = element\_text(angle = 90, hjust = 0))+  
 scale\_x\_continuous(breaks = number\_ticks(6))+  
 scale\_color\_manual(values=c ("#11bda3", "#fa054e", "#e3094a","#113abf",   
 "#e918f0", "#9a18f0" ,"#6309e0","#113abf",  
 "#1380bf", "#11b9bf", "#11bda3", "#0fbd71",  
 "#0be357", "#5be809", "#a9e309", "#e8e40c")) +  
 labs(title = "Kaplan-Meier curves",  
 x = "Days",  
 y = "Survival Probability",  
 color = "Method")   
  
ggsave(paste0("figs/Kaplan\_M\_curves",  
 format(Sys.Date(), "%F"), ".pdf"),   
 width = 7, height = 5)   
   
   
#### Microsimulation with Remdesivir ####  
# Parameters set  
# number of simulated individuals, in this case 488,866  
n\_i <- length(S\_cohort$Ind)   
n\_t <- 60 # time horizon, 60 days  
# model states: Positive Case - Cov19+, Death by Covid-19 - CoV19\_Dead,   
# Death by other causes - O\_Causes\_Dead  
v\_names\_states <- c("Cov19+", "CoV19\_Dead", "O\_Causes\_Dead")   
n\_states <- length(v\_names\_states) # the number of states  
d\_c <- d\_e <- (0.017 + 0.016)/2 # Daily discount rates for costs and utilities  
v\_names\_str = c("No Treatment", "Dexamethasone")  
# calculate discount weights for costs for each cycle based on discount rate d\_c  
v\_dwc <- 1 / (1 + d\_c) ^ (0:n\_t)   
# calculate discount weights for effectiveness for each cycle based on discount   
# rate d\_e  
v\_dwe <- 1 / (1 + d\_e) ^ (0:n\_t)  
  
## Costs and utilities inputs (in dollars)  
c\_amb <- 14500 # Average cost by ambulatory patient  
# Average cost for patients that require hospitalized care  
c\_hosp <- ((35000 + 50000 + 70000+ 80000)/4)  
# compute proportion of ambulatory and hospitalized patients   
covid\_p\_h <- Covid\_p %>%   
 filter(type == 2)  
# Proportion of hospitalized patients  
p\_hosp <- length(covid\_p\_h$ID) / length(Covid\_p$ID)   
# cost of remaining one cycle sick with COVID-19  
c\_sCov <- p\_hosp\*c\_hosp + (1 - p\_hosp)\* c\_amb   
c\_dCov <- 0 # cost of remaining one cycle Dead  
c\_dPop <- 0 # cost of remaining one cycle Dead  
c\_Trt <- (3120\*20)/60 # cost of remdesivir per patient mexican currency  
# Mean QALD (Quality Adjusted Life Days) loss.  
m\_QALD <- 2.5  
u\_sCov <- (100 - m\_QALD)/100 # utility when Sick   
u\_dCov <- 0 # utility when Dead  
u\_dPop <- 0 # utility when Dead  
  
# Create data table with probabilities for each state  
# This part is modified to add treatment effect of Remsedivir  
df\_N\_t <- df\_hazards %>%   
 group\_by(time) %>%   
 summarise(haz\_pop = mean(hazard\_pop))  
  
df\_N\_t <- head(df\_N\_t, 30)  
N\_t <- 1 - sum(df\_N\_t$haz\_pop)  
  
s\_t <- 1 - (59/541)  
s\_p <- 1 - (77/521)  
  
d <- (-1/29)\*log(s\_p/N\_t)  
d\_e\_1 <- (-1/29)\*log(s\_t/N\_t)  
  
e <- 1 - (d\_e\_1/d) # reduction or effect of treatment  
  
d\_p\_HD\_red <- rbind(d\_p\_HD\_45\_54, d\_p\_HD\_55\_64, d\_p\_HD\_65\_69, d\_p\_HD\_70)  
  
d\_p\_HD\_red$hazard\_cov\_red <- d\_p\_HD\_red$hazard\_cov \* (1 - e)  
d\_p\_HD\_red$hazard\_overall <- d\_p\_HD\_red$hazard\_cov\_red + d\_p\_HD\_red$hazard\_pop  
  
d\_p\_HD\_red <- d\_p\_HD\_red %>%   
 mutate(cov\_prop = hazard\_cov\_red/hazard\_overall) %>%   
 mutate(pop\_prop = 1 - cov\_prop)  
  
d\_p\_HD\_red$cov\_prop[d\_p\_HD\_red$cov\_prop == "NaN"] <- 0   
d\_p\_HD\_red$pop\_prop[d\_p\_HD\_red$pop\_prop == "NaN"] <- 0   
  
d\_p\_Cov\_red <- d\_p\_HD\_red %>%   
 mutate(prob\_dead = (1 - exp(-hazard\_overall))) %>%   
 mutate(p\_dCoV = prob\_dead\*cov\_prop) %>%   
 mutate(p\_dPop = prob\_dead\*pop\_prop)  
  
d\_p\_Cov\_red <- d\_p\_Cov\_red %>%   
 select(1:3,10:12)  
  
# Convert data frame to a data table for efficiency  
dt\_p\_Cov\_red <- data.table(d\_p\_Cov\_red)  
  
# set the data table to be indexed by age, day and Sex  
setkey(dt\_p\_Cov\_red, age, day, sex)  
  
# Create data frame of population from cohort. All begin in day 0  
df\_X <- S\_cohort  
df\_X$sex[df\_X$sex == 1] <- "male"  
df\_X$sex[df\_X$sex == 2] <- "female"  
df\_X <- df\_X %>%   
 mutate(day = 0)  
  
source("R/Functions.R")  
  
Probs <- function(v\_M\_t, df\_X, t) { # t <- 1  
 # Arguments:  
 # v\_M\_t: health state occupied at cycle t (character variable)  
 # df\_X: data frame with individual characteristics data   
 # v\_Ts: vector with the duration of being sick  
 # t: cycle  
 # Returns:   
 # transition probabilities for that cycle  
 # create matrix of state transition probabilities  
 m\_p\_t <- matrix(0, nrow = n\_states, ncol = n\_i)   
 # give the state names to the rows  
 rownames(m\_p\_t) <- v\_names\_states  
   
 # Lookup baseline probability of dying from Covid-19 or other causes based on   
 # individual characteristics of day, sex and age   
 p\_die\_CoV\_all <- dt\_p\_Cov\_red[.(df\_X$age,df\_X$day + t, df\_X$sex), p\_dCoV]   
 p\_die\_Pop\_all <- dt\_p\_Cov\_red[.(df\_X$age,df\_X$day + t, df\_X$sex), p\_dPop]   
 p\_die\_CoV <- p\_die\_CoV\_all[v\_M\_t == "Cov19+"]   
 p\_die\_Pop <- p\_die\_Pop\_all[v\_M\_t == "Cov19+"]   
   
 # update m\_p\_t with the appropriate probabilities   
 # transition probabilities when healthy  
 m\_p\_t[, v\_M\_t == "Cov19+"] <- rbind(1 - (p\_die\_CoV + p\_die\_Pop), p\_die\_CoV, p\_die\_Pop)   
 # transition probabilities when sick   
 m\_p\_t[, v\_M\_t == "CoV19\_Dead"] <- rbind(0, 1 ,0)  
 # transition probabilities when sicker   
 m\_p\_t[, v\_M\_t == "O\_Causes\_Dead"] <- rbind(0, 0, 1)  
   
   
 # t(m\_p\_t[, 1:10]) # Show the probabilities for the first 10 individuals   
   
 return(t(m\_p\_t))  
}   
  
Costs <- function (v\_M\_t, Trt = TRUE) {  
 # v\_M\_t: current health state  
 c\_t <- c()  
 c\_t[v\_M\_t == "Cov19+"] <- c\_sCov + (c\_Trt \* Trt) # costs accrued by being healthy this cycle  
 c\_t[v\_M\_t == "CoV19\_Dead"] <- c\_dCov # costs accrued by being sick this cycle  
 c\_t[v\_M\_t == "O\_Causes\_Dead"] <- c\_dCov # costs accrued by being sicker this cycle  
 return(c\_t) # return costs accrued this cycle  
}  
  
Effs <- function (v\_M\_t, Trt = FALSE) {  
 # v\_M\_t: current health state  
 q\_t <- c()   
 q\_t[v\_M\_t == "Cov19+"] <- u\_sCov   
 # QALYs accrued by being healthy this cycle  
 q\_t[v\_M\_t == "CoV19\_Dead"] <- u\_dCov # QALYs accrued by being healthy this cycle  
 q\_t[v\_M\_t == "O\_Causes\_Dead"] <- u\_dCov # QALYs accrued by being sick this cycle  
 return(q\_t) # return the QALYs accrued this cycle  
}  
  
#### 04.2 Dynamic characteristics   
# These are just starting conditions - they will change with the simulation  
v\_M\_init <- rep("Cov19+", n\_i) # everyone begins in the healthy state  
  
MicroSim\_rem <- function(n\_i, df\_X, seed = 1) { #t <- 1  
   
 set.seed(seed) # set the seed  
   
 m\_M <- m\_C <- m\_E <- matrix(NA, nrow = n\_i, ncol = n\_t + 1,   
 dimnames = list(paste("ind" , 1:n\_i, sep = " "),   
 paste("cycle", 0:n\_t, sep = " ")))   
   
 m\_M[, 1] <- v\_M\_init # initial health state  
 m\_C[, 1] <- Costs(m\_M[, 1]) # costs accrued during cycle 0  
 m\_E[, 1] <- Effs(m\_M[, 1]) # QALYs accrued during cycle 0  
   
 # open a loop for time running cycles 1 to n\_t   
 for (t in 1:n\_t) { # t <- 1  
 # calculate the transition probabilities for the cycle based on health state t  
 m\_P <- Probs(v\_M\_t = m\_M[, t], df\_X, t = t)   
 # sample the current health state and store that state in matrix m\_M  
 m\_M[, t + 1] <- samplev(m\_P, 1)   
 # calculate costs per individual during cycle t + 1  
 m\_C[, t + 1] <- Costs(m\_M[, t + 1], Trt = TRUE)   
 # calculate QALYs per individual during cycle t + 1  
 m\_E[, t + 1] <- Effs(m\_M[, t + 1])   
   
 # Display simulation progress  
 if(t/(n\_t/10) == round(t/(n\_t/10), 0)) { # display progress every 10%  
 cat('\r', paste(t/n\_t \* 100, "% done", sep = " "))  
 }  
   
 } # close the loop for the time points   
   
 # calculate   
 tc <- m\_C %\*% v\_dwc # total (discounted) cost per individual  
 te <- m\_E %\*% v\_dwe # total (discounted) QALYs per individual   
 tc\_hat <- (mean(tc)) # average (discounted) cost   
 te\_hat <- (mean(te)) # average (discounted) QALYs  
 tc\_sum <- (sum(tc)) # sum (discounted) cost  
 te\_sum <- (sum(te)) # sum (discounted) QALYs  
   
 # store the results from the simulation in a list  
 results <- list(m\_M = m\_M,   
 m\_C = m\_C,   
 m\_E = m\_E,   
 tc = tc ,   
 te = te,   
 tc\_hat = tc\_hat,   
 te\_hat = te\_hat,  
 tc\_sum = tc\_sum,   
 te\_sum = te\_sum )   
   
 return(results) # return the results  
   
} # end of the MicroSim function   
  
outcomes\_rem <- MicroSim\_rem(n\_i, df\_X, seed = 1)  
  
results\_rem <- data.frame("Total Cost" = outcomes\_rem$tc\_hat,   
 "Total QALYs" = outcomes\_rem$te\_hat)  
  
# Create dataframe to transform: alive =1 and death = 0  
state\_m\_s\_rem <- as.data.frame(outcomes\_rem$m\_M)   
state\_m\_s\_rem[state\_m\_s\_rem == "Cov19+"] <- 1  
state\_m\_s\_rem[state\_m\_s\_rem == "CoV19\_Dead"] <- 0   
state\_m\_s\_rem[state\_m\_s\_rem == "O\_Causes\_Dead"] <- 0   
state\_m\_s\_rem <- sapply(state\_m\_s\_rem, as.numeric)  
  
Cycle\_sum\_rem <-   
 colSums(state\_m\_s\_rem)/n\_i # Compute survival probability for each cycle  
  
# plot(Cycle\_sum)  
plot(Cycle\_sum\_rem,  
 type = 'l',   
 ylim = c(0.70, 1),  
 ylab = "Survival probability",  
 xlab = "Cycle",  
 main = "Overall Survival with remdesivir")   
# Add grid   
grid(nx = n\_t,   
 ny = 10,   
 col = "lightgray",   
 lty = "dotted",  
 lwd = par("lwd"),  
 equilogs = TRUE)   
  
  
#### Microsimulation for Dexamethasone ####  
# Parameters set  
# number of simulated individuals, in this case 481,353  
n\_i <- length(S\_cohort$Ind)   
n\_t <- 60 # time horizon, 60 days  
# model states: Positive Case - Cov19+, Death by Covid-19 - CoV19\_Dead,   
# Death by other causes - O\_Causes\_Dead  
v\_names\_states <- c("Cov19+", "CoV19\_Dead", "O\_Causes\_Dead")   
n\_states <- length(v\_names\_states) # the number of states  
d\_c <- d\_e <- (0.017 + 0.016)/2 # Daily discount rates for costs and utilities  
v\_names\_str = c("No Treatment", "Dexamethasone")  
# calculate discount weights for costs for each cycle based on discount rate d\_c  
v\_dwc <- 1 / (1 + d\_c) ^ (0:n\_t)   
# calculate discount weights for effectiveness for each cycle based on discount   
# rate d\_e  
v\_dwe <- 1 / (1 + d\_e) ^ (0:n\_t)  
  
## Costs and utilities inputs (in dollars)  
c\_amb <- 14500 # Average cost by ambulatory patient  
# Average cost for patients that require hospitalized care  
c\_hosp <- ((35000 + 50000 + 70000+ 80000)/4)  
# compute proportion of ambulatory and hospitalized patients   
covid\_p\_h <- Covid\_p %>%   
 filter(type == 2)  
# Proportion of hospitalized patients  
p\_hosp <- length(covid\_p\_h$ID) / length(Covid\_p$ID)   
# cost of remaining one cycle sick with COVID-19  
c\_sCov <- p\_hosp\*c\_hosp + (1 - p\_hosp)\* c\_amb   
c\_dCov <- 0 # cost of remaining one cycle Dead  
c\_dPop <- 0 # cost of remaining one cycle Dead  
c\_Trt <- (264.16)/60 # cost of dexamethasone per patient for one day mexican currency  
# Mean QALD (Quality Adjusted Life Days) loss.  
m\_QALD <- 2.5  
u\_sCov <- (100 - m\_QALD)/100 # utility when Sick   
u\_dCov <- 0 # utility when Dead  
u\_dPop <- 0 # utility when Dead  
  
# Create data table with probabilities for each state  
# This part is modified to add treatment effect of Dexamethasone  
df\_N\_t <- df\_hazards %>%   
 group\_by(time) %>%   
 summarise(haz\_pop = mean(hazard\_pop))  
  
# Data for s\_t, s\_p, d and d\_e\_1 from Dexamethasone in Hospitalized patients  
# with COVID-19 preliminary Report.  
df\_N\_t <- head(df\_N\_t, 29)  
N\_t <- 1 - sum(df\_N\_t$haz\_pop)  
  
s\_t <- 1 - (482/2104)  
s\_p <- 1 - (1110/4321)  
  
d <- (-1/28)\*log(s\_p/N\_t)  
d\_e\_1 <- (-1/28)\*log(s\_t/N\_t)  
  
e <- 1 - (d\_e\_1/d) # reduction or effect of treatment  
  
# Dexamethasone effects appears to be only in for people who needed   
# ventilator-assisted breathing, so the effect is just for sub-population  
  
df\_cov\_dead\_int <- Covid\_p %>%   
 mutate(death = ifelse(is.na(date\_death), 0, 1)) %>%   
 filter(death == 1) %>%   
 mutate(intub = ifelse(intubated == 1, 1, 0))  
  
r\_cov\_dead\_int <- sum(df\_cov\_dead\_int$intub)/sum(df\_cov\_dead\_int$death)  
  
e\_dex <- e\*r\_cov\_dead\_int  
  
d\_p\_HD\_dex <- rbind(d\_p\_HD\_45\_54, d\_p\_HD\_55\_64, d\_p\_HD\_65\_69, d\_p\_HD\_70)  
  
d\_p\_HD\_dex$hazard\_cov\_red <- d\_p\_HD\_dex$hazard\_cov \* (1 - e\_dex)  
d\_p\_HD\_dex$hazard\_overall <- d\_p\_HD\_dex$hazard\_cov\_red + d\_p\_HD\_dex$hazard\_pop  
  
d\_p\_HD\_dex <- d\_p\_HD\_dex %>%   
 mutate(cov\_prop = hazard\_cov\_red/hazard\_overall) %>%   
 mutate(pop\_prop = 1 - cov\_prop)  
  
d\_p\_HD\_dex$cov\_prop[d\_p\_HD\_dex$cov\_prop == "NaN"] <- 0   
d\_p\_HD\_dex$pop\_prop[d\_p\_HD\_dex$pop\_prop == "NaN"] <- 0   
  
d\_p\_Cov\_dex <- d\_p\_HD\_dex %>%   
 mutate(prob\_dead = (1 - exp(-hazard\_overall))) %>%   
 mutate(p\_dCoV = prob\_dead\*cov\_prop) %>%   
 mutate(p\_dPop = prob\_dead\*pop\_prop)  
  
d\_p\_Cov\_dex <- d\_p\_Cov\_dex %>%   
 select(1:3,10:12)  
  
# Convert data frame to a data table for efficiency  
dt\_p\_Cov\_dex <- data.table(d\_p\_Cov\_dex)  
  
# set the data table to be indexed by age, day and Sex  
setkey(dt\_p\_Cov\_dex, age, day, sex)  
  
# Create data frame of population from cohort. All begin in day 0  
df\_X <- S\_cohort  
df\_X$sex[df\_X$sex == 1] <- "male"  
df\_X$sex[df\_X$sex == 2] <- "female"  
df\_X <- df\_X %>%   
 mutate(day = 0)  
  
source("R/Functions.R")  
  
Probs <- function(v\_M\_t, df\_X, t) { # t <- 1  
 # Arguments:  
 # v\_M\_t: health state occupied at cycle t (character variable)  
 # df\_X: data frame with individual characteristics data   
 # v\_Ts: vector with the duration of being sick  
 # t: cycle  
 # Returns:   
 # transition probabilities for that cycle  
 # create matrix of state transition probabilities  
 m\_p\_t <- matrix(0, nrow = n\_states, ncol = n\_i)   
 # give the state names to the rows  
 rownames(m\_p\_t) <- v\_names\_states  
   
 # Lookup baseline probability of dying from Covid-19 or other causes based on   
 # individual characteristics of day, sex and age   
 p\_die\_CoV\_all <- dt\_p\_Cov\_dex[.(df\_X$age,df\_X$day + t, df\_X$sex), p\_dCoV]   
 p\_die\_Pop\_all <- dt\_p\_Cov\_dex[.(df\_X$age,df\_X$day + t, df\_X$sex), p\_dPop]   
 p\_die\_CoV <- p\_die\_CoV\_all[v\_M\_t == "Cov19+"]   
 p\_die\_Pop <- p\_die\_Pop\_all[v\_M\_t == "Cov19+"]   
   
 # update m\_p\_t with the appropriate probabilities   
 # transition probabilities when healthy  
 m\_p\_t[, v\_M\_t == "Cov19+"] <- rbind(1 - (p\_die\_CoV + p\_die\_Pop), p\_die\_CoV, p\_die\_Pop)   
 # transition probabilities when sick   
 m\_p\_t[, v\_M\_t == "CoV19\_Dead"] <- rbind(0, 1 ,0)  
 # transition probabilities when sicker   
 m\_p\_t[, v\_M\_t == "O\_Causes\_Dead"] <- rbind(0, 0, 1)  
   
   
 # t(m\_p\_t[, 1:10]) # Show the probabilities for the first 10 individuals   
   
 return(t(m\_p\_t))  
}   
  
Costs <- function (v\_M\_t, Trt = TRUE) {  
 # v\_M\_t: current health state  
 c\_t <- c()  
 c\_t[v\_M\_t == "Cov19+"] <- c\_sCov + (c\_Trt \* Trt) # costs accrued by being healthy this cycle  
 c\_t[v\_M\_t == "CoV19\_Dead"] <- c\_dCov # costs accrued by being sick this cycle  
 c\_t[v\_M\_t == "O\_Causes\_Dead"] <- c\_dCov # costs accrued by being sicker this cycle  
 return(c\_t) # return costs accrued this cycle  
}  
  
Effs <- function (v\_M\_t, Trt = FALSE) {  
 # v\_M\_t: current health state  
 q\_t <- c()   
 q\_t[v\_M\_t == "Cov19+"] <- u\_sCov   
 # QALYs accrued by being healthy this cycle  
 q\_t[v\_M\_t == "CoV19\_Dead"] <- u\_dCov # QALYs accrued by being healthy this cycle  
 q\_t[v\_M\_t == "O\_Causes\_Dead"] <- u\_dCov # QALYs accrued by being sick this cycle  
 return(q\_t) # return the QALYs accrued this cycle  
}  
  
#### 04.2 Dynamic characteristics   
# These are just starting conditions - they will change with the simulation  
v\_M\_init <- rep("Cov19+", n\_i) # everyone begins in the healthy state  
  
MicroSim\_dex <- function(n\_i, df\_X, seed = 1) { #t <- 1  
   
 set.seed(seed) # set the seed  
   
 m\_M <- m\_C <- m\_E <- matrix(NA, nrow = n\_i, ncol = n\_t + 1,   
 dimnames = list(paste("ind" , 1:n\_i, sep = " "),   
 paste("cycle", 0:n\_t, sep = " ")))   
   
 m\_M[, 1] <- v\_M\_init # initial health state  
 m\_C[, 1] <- Costs(m\_M[, 1]) # costs accrued during cycle 0  
 m\_E[, 1] <- Effs(m\_M[, 1]) # QALYs accrued during cycle 0  
   
 # open a loop for time running cycles 1 to n\_t   
 for (t in 1:n\_t) { # t <- 1  
 # calculate the transition probabilities for the cycle based on health state t  
 m\_P <- Probs(v\_M\_t = m\_M[, t], df\_X, t = t)   
 # sample the current health state and store that state in matrix m\_M  
 m\_M[, t + 1] <- samplev(m\_P, 1)   
 # calculate costs per individual during cycle t + 1  
 m\_C[, t + 1] <- Costs(m\_M[, t + 1], Trt = TRUE)   
 # calculate QALYs per individual during cycle t + 1  
 m\_E[, t + 1] <- Effs(m\_M[, t + 1])   
   
 # Display simulation progress  
 if(t/(n\_t/10) == round(t/(n\_t/10), 0)) { # display progress every 10%  
 cat('\r', paste(t/n\_t \* 100, "% done", sep = " "))  
 }  
   
 } # close the loop for the time points   
   
 # calculate   
 tc <- m\_C %\*% v\_dwc # total (discounted) cost per individual  
 te <- m\_E %\*% v\_dwe # total (discounted) QALYs per individual   
 tc\_hat <- (mean(tc)) # average (discounted) cost   
 te\_hat <- (mean(te)) # average (discounted) QALYs  
 tc\_sum <- (sum(tc)) # sum (discounted) cost  
 te\_sum <- (sum(te)) # sum (discounted) QALYs  
   
 # store the results from the simulation in a list  
 results <- list(m\_M = m\_M,   
 m\_C = m\_C,   
 m\_E = m\_E,   
 tc = tc ,   
 te = te,   
 tc\_hat = tc\_hat,   
 te\_hat = te\_hat,  
 tc\_sum = tc\_sum,   
 te\_sum = te\_sum )   
   
 return(results) # return the results  
   
} # end of the MicroSim function   
  
outcomes\_dex <- MicroSim\_dex(n\_i, df\_X, seed = 1)  
  
results\_dex <- data.frame("Total Cost" = outcomes\_dex$tc\_hat,   
 "Total QALYs" = outcomes\_dex$te\_hat)  
  
# Create dataframe to transform: alive =1 and death = 0  
state\_m\_s\_dex <- as.data.frame(outcomes\_dex$m\_M)   
state\_m\_s\_dex[state\_m\_s\_dex == "Cov19+"] <- 1  
state\_m\_s\_dex[state\_m\_s\_dex == "CoV19\_Dead"] <- 0   
state\_m\_s\_dex[state\_m\_s\_dex == "O\_Causes\_Dead"] <- 0   
state\_m\_s\_dex <- sapply(state\_m\_s\_dex, as.numeric)  
  
Cycle\_sum\_dex <-   
 colSums(state\_m\_s\_dex)/n\_i # Compute survival probability for each cycle  
  
# plot(Cycle\_sum)  
plot(Cycle\_sum\_dex,  
 type = 'l',   
 ylim = c(0.70, 1),  
 ylab = "Survival probability",  
 xlab = "Cycle",  
 main = "Overall Survival with dexamethasone")   
# Add grid   
grid(nx = n\_t,   
 ny = 10,   
 col = "lightgray",   
 lty = "dotted",  
 lwd = par("lwd"),  
 equilogs = TRUE)   
  
  
### Results, Visualization ####  
df\_hzd\_cov\_NT <- d\_p\_HD %>%   
 group\_by(day) %>%   
 summarise(`No Treatment` = mean(hazard\_cov))  
  
df\_hzd\_cov\_dex <- d\_p\_HD\_dex %>%   
 group\_by(day) %>%   
 summarise(`Dexamethasone` = mean(hazard\_cov\_red))  
  
df\_hzd\_cov\_rem <- d\_p\_HD\_red %>%   
 group\_by(day) %>%   
 summarise(`Remdesivir` = mean(hazard\_cov\_red))  
  
df\_hzd\_cov <- df\_hzd\_cov\_NT %>%   
 left\_join(df\_hzd\_cov\_rem, by = c("day" = "day"))  
  
df\_hzd\_cov <- df\_hzd\_cov %>%   
 left\_join(df\_hzd\_cov\_dex, by = c("day" = "day")) %>%   
 filter(day > 0)  
  
df\_hzd\_cov\_long <- gather(data = df\_hzd\_cov,   
 key = "Treatment",   
 value = "Hazard", -day)  
  
ggplot(data = df\_hzd\_cov\_long,   
 aes(x = day,   
 y = Hazard,  
 # fill = Pop,  
 color = Treatment))+   
 # geom\_point(size = 1.5)+  
 geom\_line(size = 1.1)+  
 #geom\_ribbon(data = filter(df\_compare\_long,  
 # KM == "Real population"),   
 # aes(ymin = LB, ymax = UB), alpha = 0.3) +  
 #geom\_ribbon(data = filter(df\_compare\_long,  
 # KM == "Microsimulation"),   
 # aes(ymin = LB\_wald, ymax = UB\_wald), alpha = 0.3) +  
 # facet\_wrap(~type, scales = "free")+  
 theme(plot.title = element\_text(face = "bold",   
 size = 16,  
 family =),  
 plot.caption = element\_text(hjust = 0,  
 colour = "#777777",  
 size = 10),  
 panel.background = element\_rect(fill = "white",   
 colour = "gray",   
 size = 0.15,   
 linetype = "solid"),  
 panel.grid.major = element\_line(size = 0.15,   
 linetype = 'solid',  
 colour = "gray"),   
 axis.text.x = element\_text(angle = 90, hjust = 0))+  
 scale\_x\_continuous(breaks = number\_ticks(6))+  
 scale\_color\_manual(values=c ("#02a9e0", "#fa054e", "#10bd04","#113abf",   
 "#e918f0", "#9a18f0" ,"#6309e0","#113abf",  
 "#1380bf", "#11b9bf", "#11bda3", "#0fbd71",  
 "#0be357", "#5be809", "#a9e309", "#e8e40c")) +  
 labs(title = "Covid-19 Specific Hazard",  
 x = "Days",  
 y = " ")   
  
ggsave(paste0("figs/Covid-19 Specific",  
 format(Sys.Date(), "%F"), ".pdf"),   
 width = 7, height = 5)   
  
## Overall ##  
df\_hzd\_ovll\_NT <- d\_p\_HD %>%   
 group\_by(day) %>%   
 summarise(`No Treatment` = mean(hazard\_overall))  
  
df\_hzd\_ovll\_dex <- d\_p\_HD\_dex %>%   
 group\_by(day) %>%   
 summarise(`Dexamethasone` = mean(hazard\_overall))  
  
df\_hzd\_ovll\_rem <- d\_p\_HD\_red %>%   
 group\_by(day) %>%   
 summarise(`Remdesivir` = mean(hazard\_overall))  
  
df\_hzd\_ovll <- df\_hzd\_ovll\_NT %>%   
 left\_join(df\_hzd\_ovll\_rem, by = c("day" = "day"))  
  
df\_hzd\_ovll <- df\_hzd\_ovll %>%   
 left\_join(df\_hzd\_ovll\_dex, by = c("day" = "day")) %>%   
 filter(day > 0)  
  
df\_hzd\_ovll\_long <- gather(data = df\_hzd\_ovll,   
 key = "Treatment",   
 value = "Hazard", -day)  
  
Ovll\_ggplot <- ggplot(data = df\_hzd\_ovll\_long,   
 aes(x = day,   
 y = Hazard,  
 # fill = Pop,  
 color = Treatment))+   
 # geom\_point(size = 1.5)+  
 geom\_line(size = 1.1)+  
 #geom\_ribbon(data = filter(df\_compare\_long,  
 # KM == "Real population"),   
 # aes(ymin = LB, ymax = UB), alpha = 0.3) +  
 #geom\_ribbon(data = filter(df\_compare\_long,  
 # KM == "Microsimulation"),   
 # aes(ymin = LB\_wald, ymax = UB\_wald), alpha = 0.3) +  
 # facet\_wrap(~type, scales = "free")+  
 theme(plot.title = element\_text(face = "bold",   
 size = 16,  
 family =),  
 plot.caption = element\_text(hjust = 0,  
 colour = "#777777",  
 size = 10),  
 panel.background = element\_rect(fill = "white",   
 colour = "gray",   
 size = 0.15,   
 linetype = "solid"),  
 panel.grid.major = element\_line(size = 0.15,   
 linetype = 'solid',  
 colour = "gray"),   
 axis.text.x = element\_text(angle = 90, hjust = 0))+  
 scale\_x\_continuous(breaks = number\_ticks(6))+  
 scale\_color\_manual(values=c ("#02a9e0", "#fa054e", "#10bd04","#113abf",   
 "#e918f0", "#9a18f0" ,"#6309e0","#113abf",  
 "#1380bf", "#11b9bf", "#11bda3", "#0fbd71",  
 "#0be357", "#5be809", "#a9e309", "#e8e40c")) +  
 labs(title = "Overall Hazard",  
 x = "Days",  
 y = " ")   
  
  
## Population ##  
  
df\_hzd\_pop\_NT <- d\_p\_HD %>%   
 group\_by(day) %>%   
 summarise(`No Treatment` = mean(hazard\_pop))  
  
df\_hzd\_pop\_dex <- d\_p\_HD\_dex %>%   
 group\_by(day) %>%   
 summarise(`Dexamethasone` = mean(hazard\_pop))  
  
df\_hzd\_pop\_rem <- d\_p\_HD\_red %>%   
 group\_by(day) %>%   
 summarise(`Remdesivir` = mean(hazard\_pop))  
  
df\_hzd\_pop <- df\_hzd\_pop\_NT %>%   
 left\_join(df\_hzd\_pop\_rem, by = c("day" = "day"))  
  
df\_hzd\_pop <- df\_hzd\_pop %>%   
 left\_join(df\_hzd\_pop\_dex, by = c("day" = "day")) %>%   
 filter(day > 0)  
  
df\_hzd\_pop\_long <- gather(data = df\_hzd\_pop,   
 key = "Treatment",   
 value = "Hazard", -day)  
  
ggplot(data = df\_hzd\_pop\_long,   
 aes(x = day,   
 y = Hazard,  
 # fill = Pop,  
 color = Treatment))+   
 # geom\_point(size = 1.5)+  
 geom\_line(size = 1.1)+  
 #geom\_ribbon(data = filter(df\_compare\_long,  
 # KM == "Real population"),   
 # aes(ymin = LB, ymax = UB), alpha = 0.3) +  
 #geom\_ribbon(data = filter(df\_compare\_long,  
 # KM == "Microsimulation"),   
 # aes(ymin = LB\_wald, ymax = UB\_wald), alpha = 0.3) +  
 # facet\_wrap(~type, scales = "free")+  
 theme(plot.title = element\_text(face = "bold",   
 size = 16,  
 family =),  
 plot.caption = element\_text(hjust = 0,  
 colour = "#777777",  
 size = 10),  
 panel.background = element\_rect(fill = "white",   
 colour = "gray",   
 size = 0.15,   
 linetype = "solid"),  
 panel.grid.major = element\_line(size = 0.15,   
 linetype = 'solid',  
 colour = "gray"),   
 axis.text.x = element\_text(angle = 90, hjust = 0))+  
 scale\_x\_continuous(breaks = number\_ticks(6))+  
 scale\_color\_manual(values=c ("#02a9e0", "#fa054e", "#10bd04","#113abf",   
 "#e918f0", "#9a18f0" ,"#6309e0","#113abf",  
 "#1380bf", "#11b9bf", "#11bda3", "#0fbd71",  
 "#0be357", "#5be809", "#a9e309", "#e8e40c")) +  
 labs(title = "Population",  
 x = "Days",  
 y = " ")   
  
#ggarrange(Cov\_ggplot, Ovll\_ggplot,  
# #labels = c("Females", "Males"),  
# ncol = 2,   
# common.legend = TRUE,  
# label.y = c(1,0),  
# legend = "bottom")  
  
df\_ov\_surv <- as.data.frame(cbind(Cycle\_sum\_dex,Cycle\_sum\_NT,Cycle\_sum\_rem))  
  
df\_ov\_surv <- df\_ov\_surv %>%   
 mutate(day = row\_number()-1) %>%   
 rename(Dexamethasone = Cycle\_sum\_dex,  
 Remdesivir = Cycle\_sum\_rem,  
 `No Treatment` = Cycle\_sum\_NT)  
  
df\_surv\_long <- gather(data = df\_ov\_surv, key = "Treatment", value = "Hazard", -day)  
  
ggplot(data = df\_surv\_long,   
 aes(x = day,   
 y = Hazard,  
 # fill = Pop,  
 color = Treatment))+   
 # geom\_point(size = 1.5)+  
 geom\_line(size = 1.1)+  
 #geom\_ribbon(data = filter(df\_compare\_long,  
 # KM == "Real population"),   
 # aes(ymin = LB, ymax = UB), alpha = 0.3) +  
 #geom\_ribbon(data = filter(df\_compare\_long,  
 # KM == "Microsimulation"),   
 # aes(ymin = LB\_wald, ymax = UB\_wald), alpha = 0.3) +  
 # facet\_wrap(~type, scales = "free")+  
 theme(plot.title = element\_text(face = "bold",   
 size = 16,  
 family =),  
 plot.caption = element\_text(hjust = 0,  
 colour = "#777777",  
 size = 10),  
 panel.background = element\_rect(fill = "white",   
 colour = "gray",   
 size = 0.15,   
 linetype = "solid"),  
 panel.grid.major = element\_line(size = 0.15,   
 linetype = 'solid',  
 colour = "gray"),   
 axis.text.x = element\_text(angle = 90, hjust = 0))+  
 scale\_x\_continuous(breaks = number\_ticks(6))+  
 scale\_y\_continuous(breaks = number\_ticks(7))+  
 scale\_color\_manual(values=c ("#02a9e0", "#fa054e", "#10bd04","#113abf",   
 "#e918f0", "#9a18f0" ,"#6309e0","#113abf",  
 "#1380bf", "#11b9bf", "#11bda3", "#0fbd71",  
 "#0be357", "#5be809", "#a9e309", "#e8e40c")) +  
 labs(title = "Survival curves by treatment",  
 x = "Days",  
 y = " ")   
  
ggsave(paste0("figs/S\_curves\_byTreat",  
 format(Sys.Date(), "%F"), ".pdf"),   
 width = 7, height = 5)   
  
  
### Vector of costs  
v\_ted\_cost <- c(results$Total.Cost, results\_dex$Total.Cost,results\_rem$Total.Cost)  
### Vector of effectiveness  
v\_ted\_qaly <- c(results$Total.QALYs, results\_dex$Total.QALYs, results\_rem$Total.QALYs)  
### Vector of treatment names  
v\_names\_str <- c("No treatment", "Dexamethasone", "Remdesivir")  
  
### Calculate incremental cost-effectiveness ratios (ICERs)  
df\_cea <- calculate\_icers(cost = v\_ted\_cost,  
 effect = v\_ted\_qaly,  
 strategies = v\_names\_str)  
View(df\_cea)  
  
#### Results Table ####  
### Sick Cov-19  
state\_m\_s\_dex <- as.data.frame(outcomes\_dex$m\_M)  
state\_m\_s\_dex\_S <- state\_m\_s\_dex %>%   
 select(6,16,31,46,61)  
length(state\_m\_s\_dex\_S$`cycle 5`[state\_m\_s\_dex\_S$`cycle 5` == "Cov19+"])  
length(state\_m\_s\_dex\_S$`cycle 15`[state\_m\_s\_dex\_S$`cycle 15` == "Cov19+"])  
length(state\_m\_s\_dex\_S$`cycle 30`[state\_m\_s\_dex\_S$`cycle 30` == "Cov19+"])  
length(state\_m\_s\_dex\_S$`cycle 45`[state\_m\_s\_dex\_S$`cycle 45` == "Cov19+"])  
length(state\_m\_s\_dex\_S$`cycle 60`[state\_m\_s\_dex\_S$`cycle 60` == "Cov19+"])  
  
state\_m\_s <- as.data.frame(outcomes$m\_M)  
state\_m\_s\_S <- state\_m\_s %>%   
 select(6,16,31,46,61)  
length(state\_m\_s\_S$`cycle 5`[state\_m\_s\_S$`cycle 5` == "Cov19+"])  
length(state\_m\_s\_S$`cycle 15`[state\_m\_s\_S$`cycle 15` == "Cov19+"])  
length(state\_m\_s\_S$`cycle 30`[state\_m\_s\_S$`cycle 30` == "Cov19+"])  
length(state\_m\_s\_S$`cycle 45`[state\_m\_s\_S$`cycle 45` == "Cov19+"])  
length(state\_m\_s\_S$`cycle 60`[state\_m\_s\_S$`cycle 60` == "Cov19+"])  
  
state\_m\_s\_rem <- as.data.frame(outcomes\_rem$m\_M)  
state\_m\_s\_rem\_S <- state\_m\_s\_rem %>%   
 select(6,16,31,46,61)  
length(state\_m\_s\_rem\_S$`cycle 5`[state\_m\_s\_rem\_S$`cycle 5` == "Cov19+"])  
length(state\_m\_s\_rem\_S$`cycle 15`[state\_m\_s\_rem\_S$`cycle 15` == "Cov19+"])  
length(state\_m\_s\_rem\_S$`cycle 30`[state\_m\_s\_rem\_S$`cycle 30` == "Cov19+"])  
length(state\_m\_s\_rem\_S$`cycle 45`[state\_m\_s\_rem\_S$`cycle 45` == "Cov19+"])  
length(state\_m\_s\_rem\_S$`cycle 60`[state\_m\_s\_rem\_S$`cycle 60` == "Cov19+"])  
  
### Dead Cov-19  
state\_m\_s\_dex <- as.data.frame(outcomes\_dex$m\_M)  
state\_m\_s\_dex\_S <- state\_m\_s\_dex %>%   
 select(6,16,31,46,61)  
length(state\_m\_s\_dex\_S$`cycle 5`[state\_m\_s\_dex\_S$`cycle 5` == "CoV19\_Dead"])  
length(state\_m\_s\_dex\_S$`cycle 15`[state\_m\_s\_dex\_S$`cycle 15` == "CoV19\_Dead"])  
length(state\_m\_s\_dex\_S$`cycle 30`[state\_m\_s\_dex\_S$`cycle 30` == "CoV19\_Dead"])  
length(state\_m\_s\_dex\_S$`cycle 45`[state\_m\_s\_dex\_S$`cycle 45` == "CoV19\_Dead"])  
length(state\_m\_s\_dex\_S$`cycle 60`[state\_m\_s\_dex\_S$`cycle 60` == "CoV19\_Dead"])  
  
state\_m\_s <- as.data.frame(outcomes$m\_M)  
state\_m\_s\_S <- state\_m\_s %>%   
 select(6,16,31,46,61)  
length(state\_m\_s\_S$`cycle 5`[state\_m\_s\_S$`cycle 5` == "CoV19\_Dead"])  
length(state\_m\_s\_S$`cycle 15`[state\_m\_s\_S$`cycle 15` == "CoV19\_Dead"])  
length(state\_m\_s\_S$`cycle 30`[state\_m\_s\_S$`cycle 30` == "CoV19\_Dead"])  
length(state\_m\_s\_S$`cycle 45`[state\_m\_s\_S$`cycle 45` == "CoV19\_Dead"])  
length(state\_m\_s\_S$`cycle 60`[state\_m\_s\_S$`cycle 60` == "CoV19\_Dead"])  
  
state\_m\_s\_rem <- as.data.frame(outcomes\_rem$m\_M)  
state\_m\_s\_rem\_S <- state\_m\_s\_rem %>%   
 select(6,16,31,46,61)  
length(state\_m\_s\_rem\_S$`cycle 5`[state\_m\_s\_rem\_S$`cycle 5` == "CoV19\_Dead"])  
length(state\_m\_s\_rem\_S$`cycle 15`[state\_m\_s\_rem\_S$`cycle 15` == "CoV19\_Dead"])  
length(state\_m\_s\_rem\_S$`cycle 30`[state\_m\_s\_rem\_S$`cycle 30` == "CoV19\_Dead"])  
length(state\_m\_s\_rem\_S$`cycle 45`[state\_m\_s\_rem\_S$`cycle 45` == "CoV19\_Dead"])  
length(state\_m\_s\_rem\_S$`cycle 60`[state\_m\_s\_rem\_S$`cycle 60` == "CoV19\_Dead"])  
  
  
# Dead Other Causes  
  
state\_m\_s\_rem <- as.data.frame(outcomes\_rem$m\_M)  
state\_m\_s\_rem\_S <- state\_m\_s\_rem %>%   
 select(6,16,31,46,61)  
length(state\_m\_s\_rem\_S$`cycle 5`[state\_m\_s\_rem\_S$`cycle 5` == "O\_Causes\_Dead"])  
length(state\_m\_s\_rem\_S$`cycle 15`[state\_m\_s\_rem\_S$`cycle 15` == "O\_Causes\_Dead"])  
length(state\_m\_s\_rem\_S$`cycle 30`[state\_m\_s\_rem\_S$`cycle 30` == "O\_Causes\_Dead"])  
length(state\_m\_s\_rem\_S$`cycle 45`[state\_m\_s\_rem\_S$`cycle 45` == "O\_Causes\_Dead"])  
length(state\_m\_s\_rem\_S$`cycle 60`[state\_m\_s\_rem\_S$`cycle 60` == "O\_Causes\_Dead"])