The 2017 plague outbreak in Madagascar & the Madagascar Plague Model

true true

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Abstract

During this experiment the plague that occurred in Madagascar in 2017 was used as a means to understand plague transmission as real-time data was collected from official reports, described the outbreak's characteristics and estimated transmission parameters using statistical and mathematical models.

Contents

Introduction

The goal of this experiment was to learn more about the behaviour and the way the plague spreads and then modelling our findings about the plague. Due to the fact that Madagascar has annual plague outbreaks, it was decided to use their outbreak information/data as data for this experiment.

The plague has once been one of the deadliest natural disasters in human history, referred to as the Black Death, attributed to the gram-negative bacterium 'Yersinia pestis'. (Boire et al., 2014), it's life-cycle typically starts within an insect vector, in our case: fleas. After which transmission occurs to a mammalian host, typically rodents or other wild animals. Humans are then only affected as incidental hosts. Although the disease was widespread in ancient times, nowadays, plague epidemics still pose a threat to humans, as there are reports of continues annual infections in the following 5 countries: Madagascar, Tanzania, Vietnam, China & the USA. (Boire et al., 2014; Dennis et al., 1999) The disease can manifest in different clinical forms of plague: bubonic, pneumonic and septic, as a result of being bitten by infected fleas. Additionally, direct contamination with infective materials can be an alternative transmission route (Boire et al., 2014). Patients who contract bubonic plague develop a sudden onset of fever, headache, chills, tender and painful lymph nodes (Robert L. Dillard; Andrew L. Juergens, 2022). While plague can be successfully treated with

antibiotics, if left untreated, the bacteria can disseminate from the lymph nodes into the bloodstream causing secondary septicemic plague. Which in addition to the symptoms already present in bubonic plague, patients with septicemic plague undergo abdominal pain and most likely bleeding into the skin and other organs, next to that skin and other tissues may undergo necrosis, especially the fingers, toes and the nose (Centers for Disease Control and Prevention, 2005). However, the most deadly form of the disease is driven by the pneumonic plague and is the only form of plague that can be spread from person to person by infectious droplets caused by sneezing, coughing or being together in an enclosed space. This form of disease has an average incubation time of 4 days and progresses rapidly and is almost always fatal without sufficient antibiotic treatment (Mead, 2017).

One of the goals set for this experiment is to recreate the model and results that the researchers gained from their experiments. To remake the model, the formula's used in the document have been used and adapted to R code, so they can be used with the Desolve package in R. To help with this, the researchers published their code on github, although their code was written in python and had to be adapted to R. Due to that, we also used the same parameters & data the researchers used.

Methods

Outbreak data The outbreak data was manually inputted from separate reports of WHO (World Health Organization), including the cumulative total numbers of clinical cases.

Temperature & Precipation data Data used is the same as the researchers requested from the National Centers for Environmental Information.

Plague transmission model (PTM) The plague transmission model used is a modified SEIR (Susceptible-Exposed-Infectious-Removed) model, it contains 2 additional components reflecting the seasonal from infected rat fleas and the imperfect effects of public health interventions.

Formulas

The following formulas were used to model the PTM.

$$\frac{dS_b}{dt} = -S_b * \alpha f_{irf} - \beta S_b \frac{I_p}{N} f_{itv,h}$$

$$\frac{dS_p}{dt} = -\beta S_p \frac{I_p}{N} f_{itv,h}$$

$$\frac{dE_b}{dt} = S_b \alpha f_{irf} f_{irv,f} - \gamma_b E_b$$

$$\frac{dE_p}{dt} = \beta (S_b + S_p) \frac{I_p}{N} f_{itv,h} - \gamma_p E_p$$

$$\frac{dI_b}{dt} = \gamma_b E_b - \epsilon I_b - \delta_b I_b$$

$$\frac{dI_p}{dt} = \gamma_p E_p - \epsilon I_b - \delta_p I_p$$

Herein the S, E, I describe Susceptible, Exposed, and Infectious and the subscripts b & p denote the bubonic and pneumonic form. The model assumes that there is a fixed population of size N, where only a small part $S_b = pN$ is exposed to infected rat fleas. The transmission rates of the flea-to-human and human-to-human are denoted by α and β. Next to that, the flea density fluctuates due to the season's temperature and

the breeding pattern of the rats. Due to that, the density of infected rat fleas is described as a sinusoidal function $f_{irf} = A + b\sin(2\pi/12t) + C\cos(2\pi/12t)$ that follows the temperature fluctuations. Due to this, the flea-to-human transmission parameter α incorporates a scaling factor from temperature to rat fleas.

Due to there going to be interventions that would reduce flea-to-human and human-to-human transmission rates via rodent and flea control. However, these effects have been considered imperfect and has a logistical form as $f_{itv,h,f} = 2 - 2/[1 + \theta + \exp(\tau_h, f - t)]$, where $\tau > 0$ denotes the time at which the interventions reached half maximum effect in controlling human-to-human $(/tau_h)$ and flea-to-human (τ_f) transmission. The reduction from a perfect intervention is defined by $\theta \geq 0$, where $\theta = 0$ means a perfect scenario. The infected cases are assumed to recover and die with the total rate of removal from the infected pool being δ_b and δ_p for bubonic and pneumonic cases.

Libraries • pander -This library is used to print out data/R-code in an alternative way, usually easier to read.

- deSolve -This library contains the ODE that was used to recreate the model in the R language.

Results

```
# get the working directory
# Make sure the working directory is the main_folder containing all the folders, assignment1-3 & projec
working_directory <- getwd()
# get the directory for the data_file
data_file_bugfix <- paste(working_directory, "/Project_madagascar/deterministic_model_data.csv", sep = 
#data <- read.csv(file= data_file_bugfix, col.names=c('Sb','Sy','Eb','Ey','Ib','Ip', 'tijd'))
# The hashed code underneath is for ease of use importing the data at home.
# If none of the data-imports above are working, get the "deterministic_model_data.csv" in the same fol
data <- read.csv(file="deterministic_model_data.csv", col.names=c('Sb','Sy','Eb','Ey','Ib','Ip', 'tijd'

# Run a test to see if the data imported correctly
pander(head(data))
```

Sb	Sy	Eb	Ey	Ib	Ip	tijd
1651	25569244	0.3886	0.217	0.9754	0.9726	0.005
1650	25569244	0.7683	0.4225	0.9602	0.9521	0.02
1650	25569243	1.139	0.6185	0.9539	0.9378	0.045
1649	25569243	1.502	0.8064	0.9561	0.9295	0.08
1649	25569243	1.856	0.9878	0.9663	0.9266	0.125
1649	25569243	2.203	1.164	0.9842	0.9289	0.18

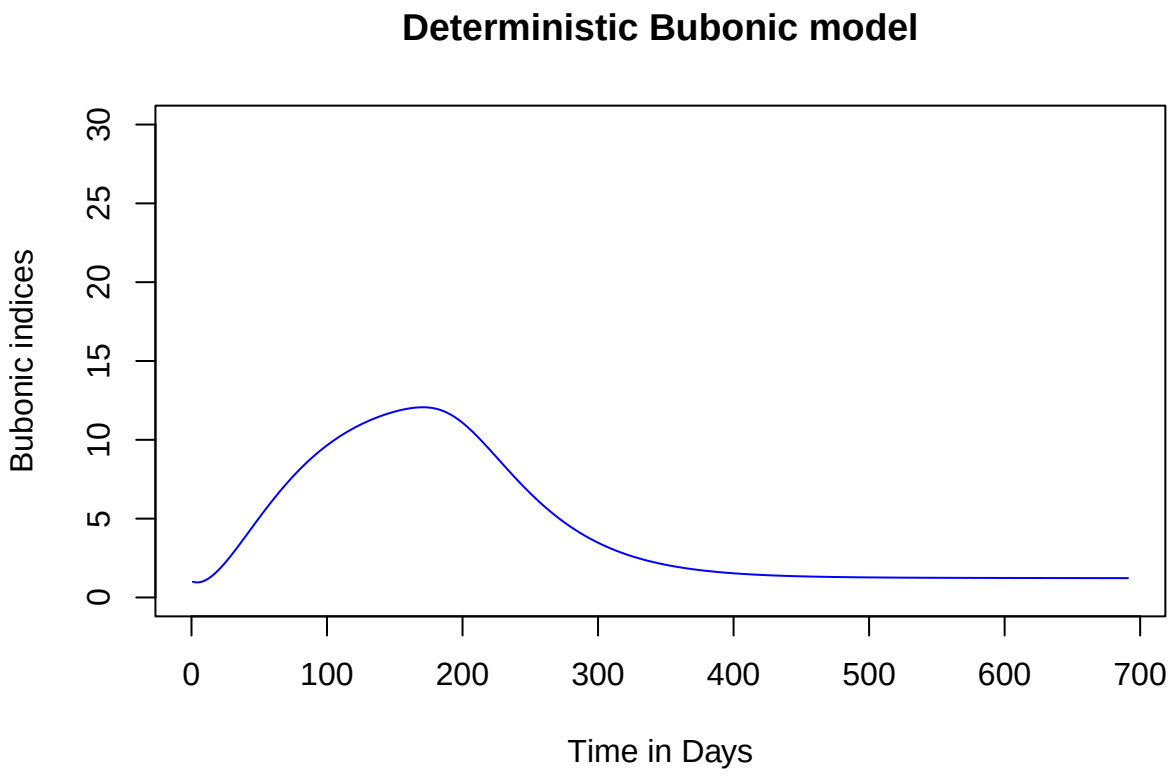
In the table above, the imported data is visible.

```
# Define the variables, parameters, state & time.
tau_p <- 8.893084e+00
tau_b <- 1.793090e+01

A <- 1.15
B <- 0.08
C <- 0.1
```

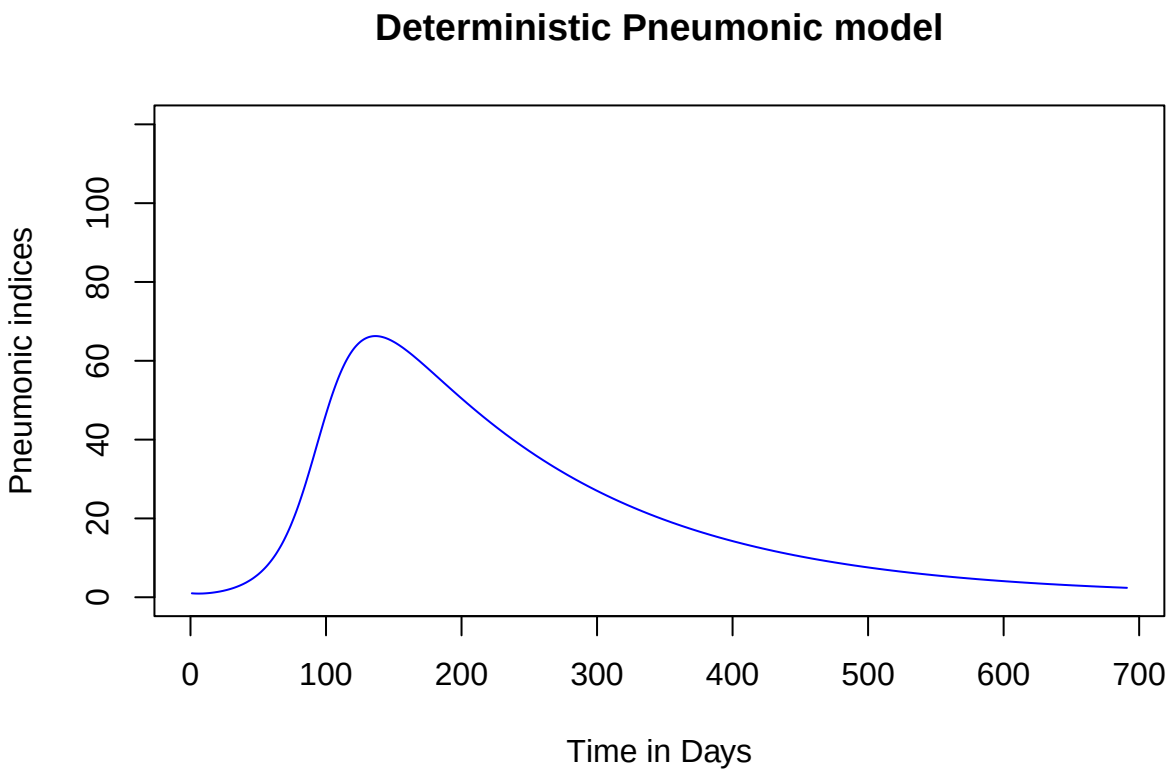
```r
parameters <- c(p       = 6.459494e-05, # fraction susceptible to bite
                alpha   = 1.904753e-03, # rate of bites
                beta    = 2.233049e+00, # between-host infection
                gamma_b = 2.293953e-01, # E to I
                gamma_p = 2.863875e-01, # E to I
                delta_b = 2.626527e-01, # recovery + death
                delta_p = 3.413748e-01, # recovery + death
                epsilon = 3.204494e-02, # I_b to I_p
                kk      = 1.105443e+00, # Imperfect intervention
                N       = 25570895     # population size
                )

S_b_0 <- 1651
S_p_0 <- 25569244

state <- c(Sb = S_b_0, Sy = S_p_0, Eb = 0, Ey =  0, Ib = 1, Ip = 1)

times <- seq(0, 70 - 1, by = 0.1)

# Define the flea function for the flea population
flea <- function (t){
  x <- A + B * sin((pi/180.) * t) + C * cos((pi/180.) * t )

  return (x)
}
# Define the intervention functions of human intervention on the disease
intervention_p <- function (t){
  return (1 - 1/(as.numeric(parameters["kk"]) + exp(tau_p - t)))
}
intervention_b <- function (t){
  return (1 - 1/(as.numeric(parameters["kk"]) + exp(tau_b - t)))
}
```

```r
# Define the function for the model of the deterministic data runs
deterministic_model <- function(t, y, parms){
  with(as.list(c(parms, y, t)),{
    flea_t <- flea(t)
    intervention_b1 <- intervention_b(t)
    intervention_p1 <- intervention_p(t)

    delta.Sb <- -alpha * flea_t * intervention_b1 * Sb - -beta * intervention_p1 * Sb * Ip/N
    delta.Sy <- -beta * intervention_p1 * Sy * Ip/N
    delta.Eb <- alpha * flea_t * intervention_b1 * Sb - gamma_b * Eb
    delta.Ey <- beta * intervention_p1 * (Sb+Sy) * Ip/N - gamma_p * Ey
    delta.Ib <- gamma_b * Eb - epsilon * Ib - delta_b * Ib
    delta.Ip <- gamma_p * Ey + epsilon * Ib - delta_p * Ip

        return(list(c(delta.Sb, delta.Sy, delta.Eb, delta.Ey, delta.Ib, delta.Ip)))
       })
}

# Run the ode model and save the output to the out variable
out <- ode(times = times, y = state,   parms = parameters, func = deterministic_model, method = "lsoda"
```

```
plot(as.data.frame(out)$Ib, type = "l", xlab = "Time in Days", ylab = "Bubonic indices", col = "blue", y
```

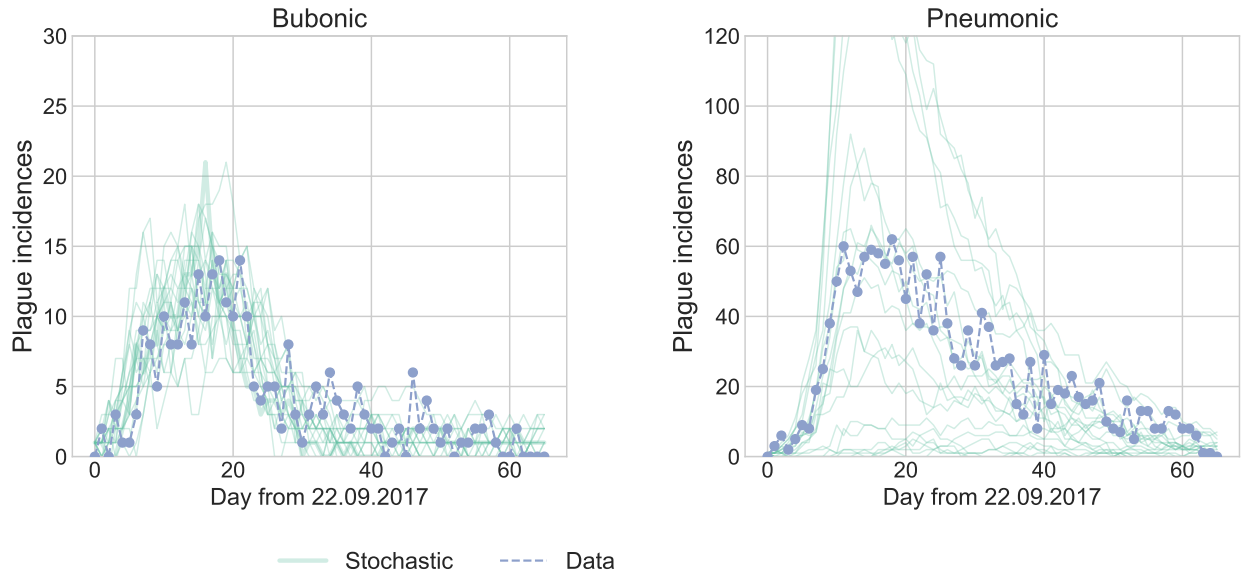



```
plot(as.data.frame(out)$Ip, type = "l", xlab = "Time in Days", ylab = "Pneumonic indices", col = "blue"
```




```
# python code figures


knitr::include_graphics("Deterministic_Fig1.pdf")
```

```
knitr::include_graphics("Stochastic_+_real_data_Fig2.pdf")
```




```
# to test sample differance with a simple T-test
print("bubonic comparison")
```

```
## [1] "bubonic comparison"
```

```
(test_ib <- t.test(as.data.frame(out)$Ib,data$Ib))
```

```
##
##  Welch Two Sample t-test
##
## data:  as.data.frame(out)$Ib and data$Ib
## t = -0.022567, df = 1379, p-value = 0.982
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  -0.4111354  0.4017839
## sample estimates:
## mean of x mean of y
##  4.226284  4.230960
```

```
cat("the P value", test_ib$p.value, "> alpha 0,05")
```

```
## the P value 0.9819993 > alpha 0,05
```

```
print("Puneonic comparison")
```

```
## [1] "Puneonic comparison"
```

```
(test_ip <- t.test(as.data.frame(out)$Ip,data$Ip))
```

```
##
##  Welch Two Sample t-test
##
## data:  as.data.frame(out)$Ip and data$Ip
## t = -0.027568, df = 1379, p-value = 0.978
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  -2.140998  2.081656
## sample estimates:
## mean of x mean of y
##  21.47405  21.50372
```

```
cat("the P value", test_ip$p.value, "> alpha 0,05")
```

```
## the P value 0.9780105 > alpha 0,05
```

In the plots above we can see the R plots of the 2 deterministic models (first two plots & blue line) and the 2 plots from the python code (two last plots with orange line). As we can see, the plots are almost identical, further supported by the t-test's done between the 2 datasets generated from R & python. What is of note however is that there are some minor differences between R & python, but not significant enough for it to be of an issue.

```
# TODO fix logical error with change output "change_func"
state_sto <- c(state[['Sb']],state[['Sy']],state[['Eb']],state[['Ey']],state[['Ib']],state[['Ip']])
D <- 6
# Vectorize the flea & intervention functions
# v_flea <- vectorize(flea)
# v_itv_p <- vectorize(intervention_p)
# v_itv_b <- vectorize(intervention_b)

# Save all the flea/intervention data based on each piece of time
f_irf <- flea(times)
f_itv_b <- intervention_b(times)
f_itv_p <- intervention_p(times)

unit_vector <- function (i, D){
  out <- rep(0, D)
  out[i+1] <- 1
  return (out)
}



transition_rates <- function (state, f_irf, f_itv_p, f_itv_b) {

  return (array(c(parameters[["alpha"]] * f_irf * f_itv_b * state[["Sb"]],
                  parameters[["beta"]] * f_itv_p * state[["Sb"]] * state[["Ip"]]/parameters[["N"]],
                  parameters[["beta"]] * f_itv_p * state[["Sy"]] * state[["Ip"]]/parameters[["N"]],
                  parameters[["gamma_b"]] * state[["Eb"]],
                  parameters[["gamma_p"]] * state[["Ey"]],
```

```
                parameters[["delta_b"]] * state[["Ib"]],
                parameters[["delta_p"]] * state[["Ip"]],
                parameters[["epsilon"]] * state[["Ib"]])))

}

nu <- array(c(unit_vector(2, D) - unit_vector(0, D), unit_vector(3, D) - unit_vector(0, D),
              unit_vector(3, D) - unit_vector(1, D), unit_vector(4, D) - unit_vector(2, D),
              unit_vector(5, D) - unit_vector(3, D), -unit_vector(4, D), -unit_vector(5, D),
              unit_vector(5, D) - unit_vector(4, D)), dim = c(6,8))

change_func <- function(n, firings, nu) {
  prechange <- rep(0,6)

  for (i in seq(1,n)) {
    #print(i)
    prechange <- prechange + (firings[i]*nu[,i])

  }
  return(prechange)
}

plague_tau <- function (parms, t, f_irf, f_itv_p, f_itv_b, nu) {
  x_t <- data.frame(matrix(ncol = 6, nrow = 0))
  colnames(x_t)<- c("Sb", 'Sy', 'Eb', 'Ey', 'Ib', "Ip")
  for (i in seq(0,length(t))){
    x_t[nrow(x_t) + 1,] <- state_sto
    rates <- transition_rates(state, f_irf[i], f_itv_p[i], f_itv_b[i])
    n <- length(rates)
    firings <- rpois(n, max(rates, rep(0, n)*0.1))
    # TODO
    change <- change_func(n, firings, nu)

    state_sto <- state_sto + change

  }
  x_t <- (x_t)
  return(x_t)
}

# Set the seed for the random number generator
set.seed(10042018)
runs <- 20

I_blist <- list()
I_Plist <- list()

runs <- 1
repeat {
  y <- plague_tau(parms, times, f_irf, f_itv_p, f_itv_b, nu)


  I_b <- (y$Ib)
```

```
  I_P <- (y$Ip)

  I_blist <- append(I_blist, list(I_b))
  I_Plist <- append(I_Plist, list(I_P))


  if(runs == 20) {
      break
   }
  runs <- runs +1
}
```

Conclusion

Looking at the deterministic models from both Python and R, it shows that the graphs are identical, which is further supported by the t-test that was performed on the datasets generated from both Python and R. However, due to them not being a 100% match as expected, there are some differences in how Python and R process the exact same mathematical equations and data generation, the suspected cause of this is internal functions unique to each coding language.

Discussion

While translating the python model to R. We found that there are some minor internal rounding differences when calculating floats in R and python, these differences where isolated and removed, simply by comparing each outcome of the R and python equations and we discovered that the outcome of each equation used for calculating the delta value was exactly the same between the 2 languages. Furthermore, we rewrote the R code back to python code to see if there were any differences or mistakes in our code, compared to the document's code. In the end we only managed to find one mistake between the code. Although even after fixing the error, the results in R are slightly different from python, even between our own code. Although the differences aren't statistically significant, as shown by the t-test performed on both generated datasets.

This let to that we found that the DeSolve ode function and the scipy odeint have minor differences in calculating the deltas, that with a given time create a snowball effect.

Also, while converting the stochastic model from python to R. It was apparent that we had to fully rewrite the code that they have used as it wasn't easily use-able in R itself. This has lead to some complications in writing the code in an R-styled manner. Due to unexpected workload in converting the python stochastic code to functional R code, we underestimated the time that was needed. And thus weren't able to fully get the stochastic code running. We managed to isolate the issues to the dynamics in or around calculating the change and the function "change_func" in the "plague_tau" function. Instead of creating a correct delta it only decreases or only increases.

We believe that if we had more time, that the data generated would be similar between both R and Python, although it would be interesting to see what other minor differences between R and Python we could find when running a stochastic model.

Sources

Main article: https://www.sciencedirect.com/science/article/pii/S1755436518300070

Boire et al., 2014; https://www.longdom.org/open-access/lessons-learned-from-historic-plague-epidemics-the-relevance-of-an-ancient-disease-in-modern-times-2329-8731.1000114.pdf Dennis et al., 1999; https://apps.who.int/iris/bitstream/handle/10665/66010/WHO_CDS_CSR_EDC_99.2.pdf?sequence=1&isAllowed=y Robert L. Dillard; Andrew L. Juergens, 2022; https://www.ncbi.nlm.nih.gov/books/NBK549855/ Centers for Disease Control and Prevention, 2005; https://www.cdc.gov/plague/symptoms/index.html Mead, 2017; https://www.nejm.org/doi/10.1056/NEJMp1713881