Dr. M. Baron, Statistical Machine Learning class, STAT-427/627

Bootstrap analysis of efficacy of the Pfizer-BioNTech COVID-19 Vaccine

The Phase III clinical trial of Pfizer vaccine included n=43,448 patients,
randomized into two groups.

Reference: https://www.nejm.org/doi/full/10.1056/nejmoa2034577

Result:
Among 21,720 vaccinated patients, there were 8 cases of COVID-19 within 7 days
after the second dose. Among 21,728 placebo participants, 162 contracted COVID-19
during the same time interval.
A conclusion was made that the Pfizer vaccine is 95% efficient, which means that
this tested vaccine reduces the risk of COVID by the factor of 20.

Vaccine critics point to a small counts of 8 and 162 for any meaningful conclusions.
Here, we explore what confidence statements we can draw from these data.

Construct a Bootstrap confidence interval for p1/p2 = the ratio of probabilities
p1 = P(infection | placebo group), p2 = P(infection | vaccine group)
Vaccine efficacy is defined as 1 – p2/p1, where p2/p1 is the incidence rate ratio

```
V = c(rep(0,21728),rep(1, 21720));                    # 0 = placebo, 1 = treatment
X = rep(0,43448); X[c(1:162, 21729:21736)]=1;         # 1 = contracted covid
XV = data.frame(X,V);

pratio = function(xv,Z){            # function of data xv and a subsample Z
  x = xv[,1]; v = xv[,2];
  Pplacebo = sum(x[Z]==1 & v[Z]==0)/sum(v[Z]==0);
  Pvaccine = sum(x[Z]==1 & v[Z]==1)/sum(v[Z]==1);
  return( Pplacebo/Pvaccine )
}

pratio(XV,)
```

The ratio is estimated as 20.24. This is why the 95% efficacy is concluded. Vaccinated people have
a risk of contracting COVID reduced by an estimated coefficient of 20.24.
We need to supply it with the margin of error and a confidence level.
For this, we use Bootstrap to construct a confidence interval.

```
library(boot)
b = boot( XV, pratio, R=10000 )   # Apply bootstrap
quantile(b$t,c(0.025,0.975))             # This is a 95% confidence interval for p1/p2

#     2.5%    97.5%          # Thus, we can claim with 95% confidence that the ratio of
# 11.27793 55.53106     # probabilities is between 11.3 and 54.5. But do we need an interval,
                   # or should we just find a lower bound?
quantile(b$t,0.05)     # Try a one-sided confidence interval.
#      5%            # We can now claim, also with 95% confidence, that vaccination
# 12.28344       # reduces the chance of COVID-19 infection by at least a factor of 12.

####################################################################################
### Official efficacy of the vaccine                                                          ###
### The efficacy of a vaccine is defined as the difference of risks between                   ###
### the vaccine group and the placebo group, relative to the placebo group.                   ###
####################################################################################

### To study the efficacy of Pfizer, we modify our function:

efficacy = function(xv,Z){ # function of data xv and a subsample Z
  x = xv[,1]; v = xv[,2];
  Pplacebo = sum(x[Z]==1 & v[Z]==0)/sum(v[Z]==0);
  Pvaccine = sum(x[Z]==1 & v[Z]==1)/sum(v[Z]==1);
  return( (Pplacebo - Pvaccine)/Pplacebo ) }

efficacy(XV,)   # This gives the estimated efficacy which you see in all official reports
# 0.9505991   # But we know that it is only based on the sample, so it has a margin of error.

# So, we proceed by building a confidence interval

b = boot( XV, efficacy, 10000 )              # Bootstrap!
hist(b$t)     # This is a histogram of bootstrap efficacy values, it's not very symmetric
          # I'm just checking normality, to see if we can settle with a PARAMETRIC
          # bootstrap confidence interval, which is the mean b$t, plus or minus 1.96
          # standard deviations

shapiro.test(b$t)                      # Shapiro-Wilk test is a rigorous test of normality
Error in shapiro.test(b$t) : sample size must be between 3 and 5000
                 # The way it's built in R does not handle samples > 5000
shapiro.test(b$t[sample(10000,5000)])   # Ok, we select a random sample of n=5000

#       Shapiro-Wilk normality test
#
# data:  b$t[sample(10000, 5000)]
```

```
# W = 0.98926, p-value < 2.2e-16        # Shapiro-Wilk test rejects normal distribution.

# Hence, we construct a NONPARAMETRIC bootstrap confidence interval:
quantile( b$t, c(0.025,0.975) )
#      2.5%     97.5%
# 0.9105982 0.9816955                  # This is a 95% confidence interval for efficacy
quantile( b$t, c(0.005,0.995) )
     0.5%     99.5%
0.8947269 0.9882617                    # This is a 99% confidence interval
```