NDVTransmissionTrial

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Short summary

The transmission parameter β (unit = day^{-1}), reproduction number R (dimensionless) and the infectious period (unit = day) for vaccinated and unvaccinated chickens was estimated. The vaccination reduced the infectious period and transmission parameter substantially and thus also the reproduction number. The reproduction number was, however, not smaller than 1. This indicates that the vaccination will reduce transmission speed, but cannot prevent an outbreak NDV in this setting. Additional measures such as compartimentalization can contribute to further reduction of spread and thus lower the reproduction number.

Introduction

- Background trial
- Background transmission models

Objectives

- Estimation of infectious period for vaccinated and unvaccinated
- Estimation of transmission parameter beta for vaccinated and unvaccinated
- Estimation of R0 for vaccinated and unvaccinated

Material and methods

Four different assumptions were used to estimate the transmission parameter. An animal is positive if:

1. one or both samples are positive
2. both samples are positive
3. the ON sample is positive
4. the CLO sample is positive

For each of these assumptions we estimated the infectious period, the transmission parameter β the basic reproduction number R_0. The infectious period was estimated assuming that these are normally distributed. The transmission parameter β is estimated using the generalized linear model with a complementary loglog-link function:

```
glm(cbind(C, S-C) ~ 1,offset = log(I/N), family = binomial(link = "cloglog"), data =
out.nona, na.action = na.omit)
```

The basic reproduction number R_0 is than estimated by multiplying the β with the mean infectious period. The confidence interval is calculated by $\log(R) = \log(\beta) + \log(T_{inf}) \pm Z_{0.05} \cdot (\log(SE(\beta)) + \log(SE(T_{inf}))$, which thus assumes independence between the transmission parameter and the infectious period.

Results

Load and organize data

The data sets consist of two separate data files in 'xlsx' format. These files need to be combined to form one data set

with variables

```
names(cevadata)
```

```
##  [1] "Group"      "Vaccinated" "Challenge"  "bird.id"    "Sample"
##  [6] "1.dpch"     "2.dpch"     "3.dpch"     "4.dpch"     "5.dpch"
## [11] "6.dpch"     "7.dpch"     "8.dpch"     "9.dpch"     "10.dpch"
## [16] "11.dpch"    "12.dpch"    "13.dpch"    "14.dpch"    "NP.ELISA"
```

Define a function `reform.data` to rearrange the data for analyses. The function takes the data and use the names of the sampledays, determine positivity based on one or all positive samples, and define the cutt-off value for positivity.

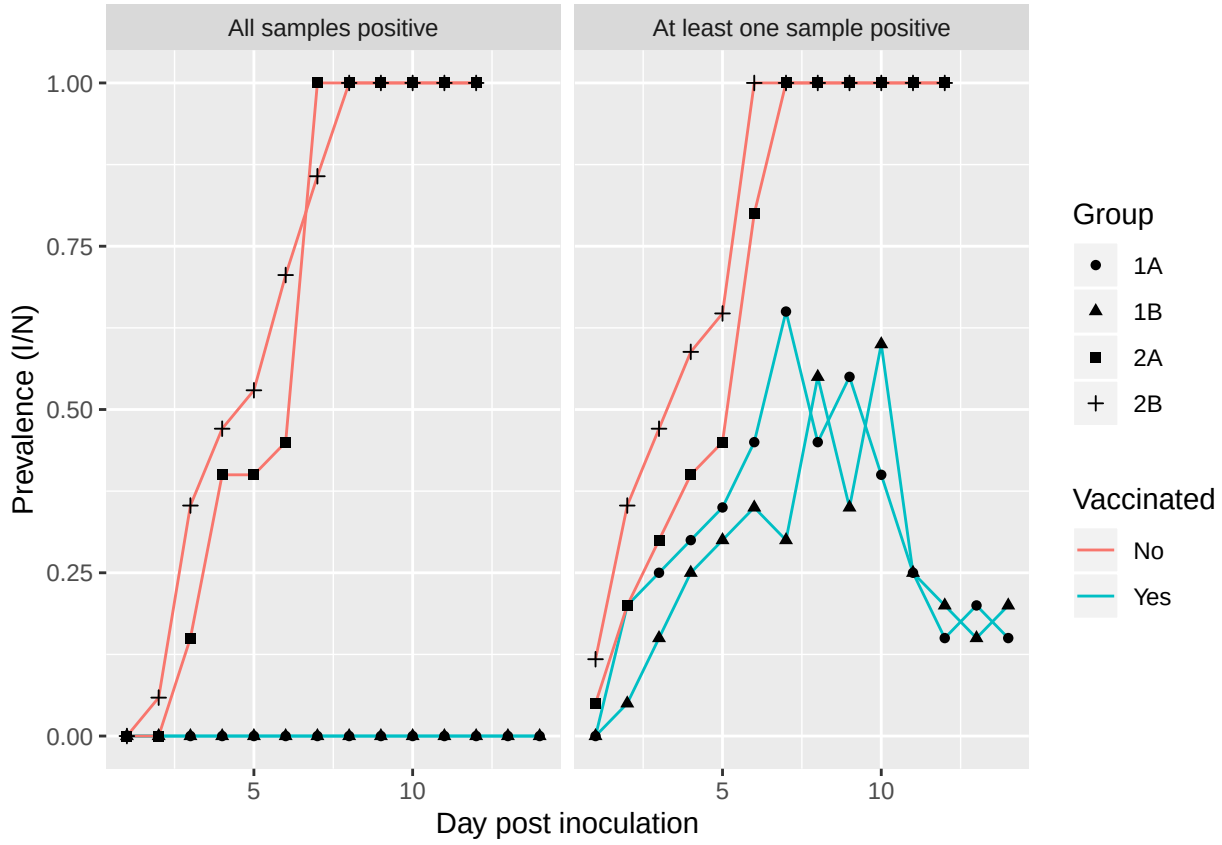
Descriptive data

Epidemic curves

```
epicurveplot
```

```
## Warning: Removed 4 rows containing missing values (geom_path).
```

```
## Warning: Removed 8 rows containing missing values (geom_point).
```



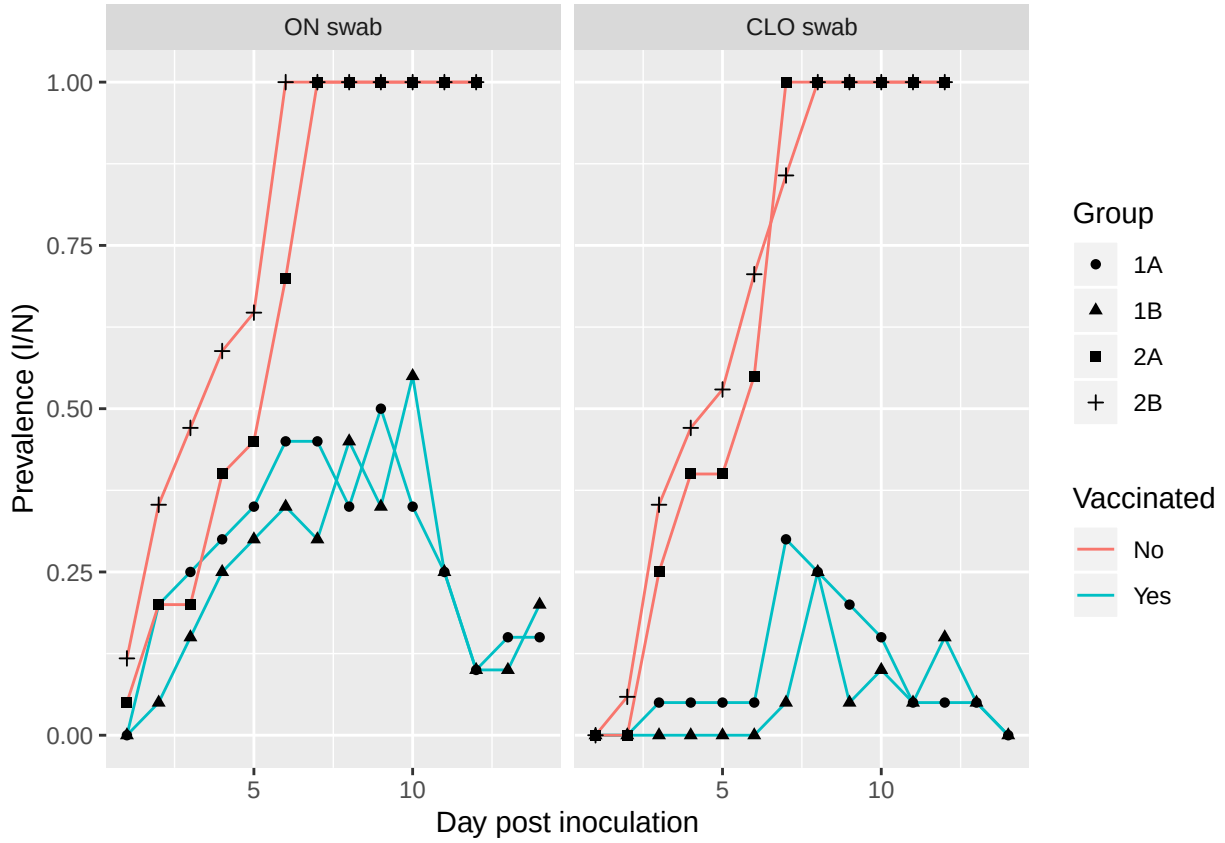
In some stable all chickens died, so that I/N was "NA" causing a message that these were not plotted. The vaccinated groups are found all to be positive in both swaps (CLO swab and NO swab), while non of the unvaccinated were positive.

The separate swabs represent the following epidemic curves:

```
epicurveplot
```

```
## Warning: Removed 4 rows containing missing values (geom_path).
```

```
## Warning: Removed 8 rows containing missing values (geom_point).
```



On first sight the curves are similar for the unvaccinated groups, but the CLO swab are less likely and later positive than the ON swab in the vaccinated groups.

Transmission parameters

At the end of this section all results will be summarized.

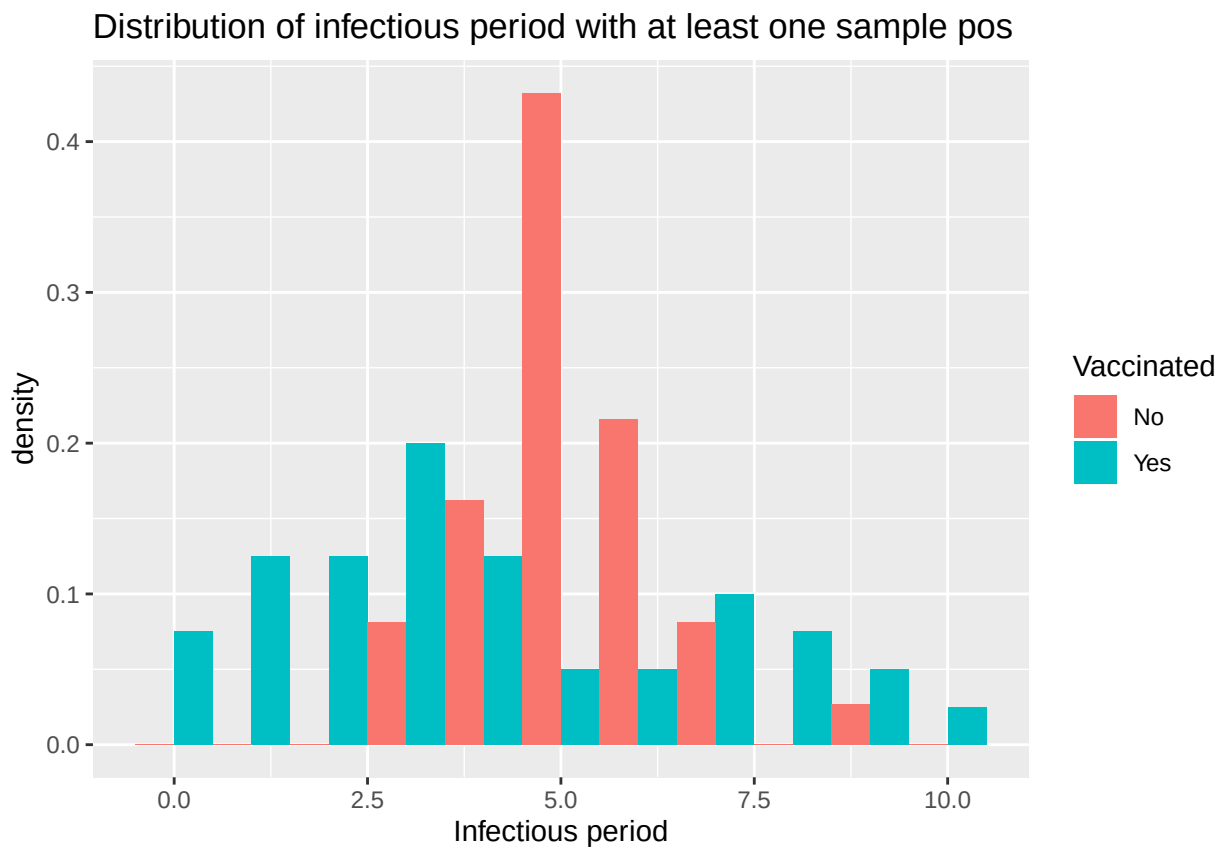
```
all.results <- NULL
```

One positive sample

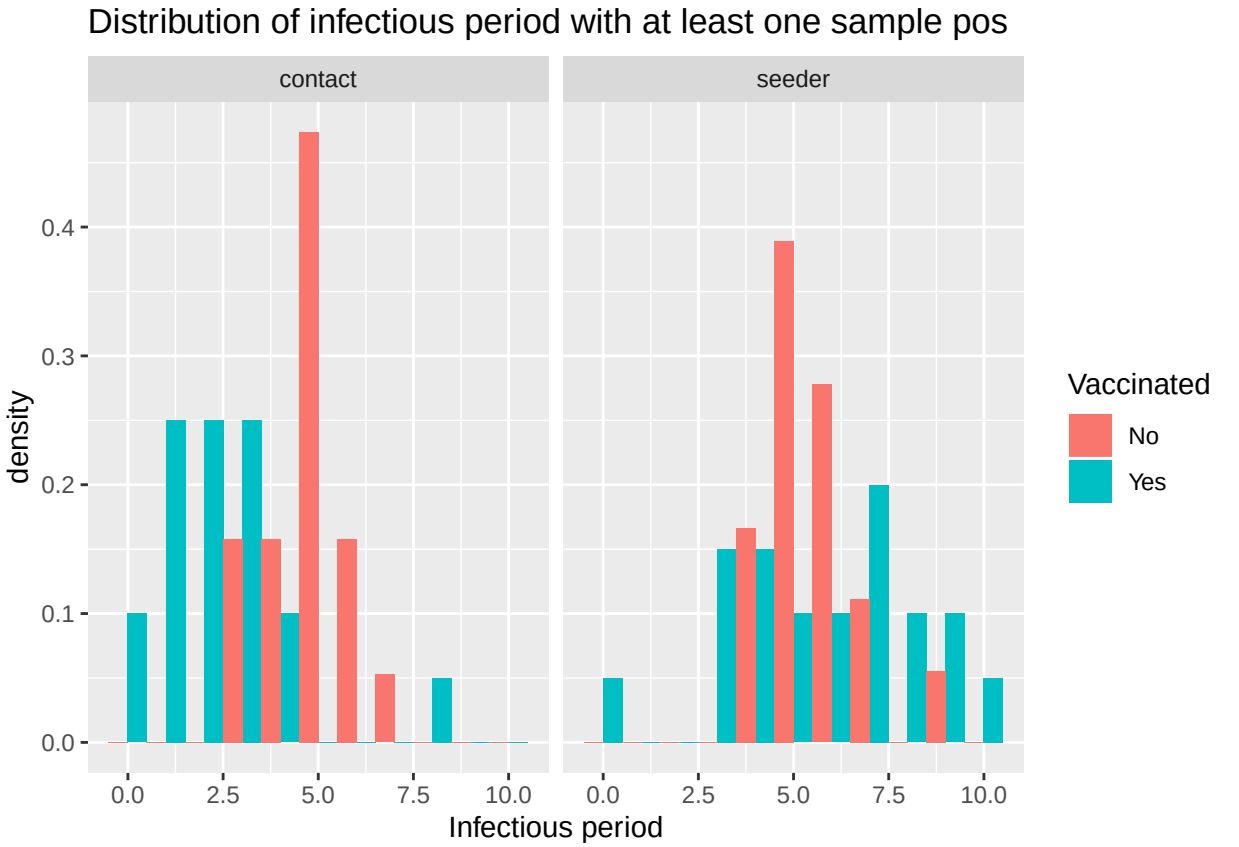
Infectious period

```
#visualize
ggplot(data = out.indiv) +
  geom_histogram(aes(x = infper, y = ..density.., fill = Vaccinated),
                 position = "dodge",binwidth = 1)+
```

```
  ggtitle("Distribution of infectious period with at least one sample pos")+
  xlab("Infectious period")
```




```
ggplot(data = out.indiv) +
  geom_histogram(aes(x = infper, y = ..density.., fill = Vaccinated),
                 position = "dodge",binwidth = 1)+
  ggtitle("Distribution of infectious period with at least one sample pos")+
  xlab("Infectious period") +facet_grid(.~Challenge)
```



Descriptive statistics for the infectious period.

```
table.infper
```

```
##          Group     Mean       SD
## 1      Overall 4.571429 2.232703
## 2 Unvaccinated 5.162162 1.213661
## 3   Vaccinated 4.025000 2.778004
```

From the table it already seems that the variances are not equal. Therefor we first test for equality of variance and than do the appropriate test to compare means.

```
#test for equal variances
fligner.test(out.indiv$infper, out.indiv$Vaccinated)
```

```
##
##  Fligner-Killeen test of homogeneity of variances
##
## data:  out.indiv$infper and out.indiv$Vaccinated
## Fligner-Killeen:med chi-squared = 13.666, df = 1, p-value = 0.0002184
```

```
#Compare the mean infectious period
t.test(out.indiv$infper~out.indiv$Vaccinated,var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## t = 2.3571, df = 54.253, p-value = 0.02205
```

```
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  0.170043 2.104281
## sample estimates:
##  mean in group No mean in group Yes
##          5.162162          4.025000
```

```
#Compare the sd infectious period
var.test(out.indiv$infper~out.indiv$Vaccinated)
```

```
##
##  F test to compare two variances
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## F = 0.19087, num df = 36, denom df = 39, p-value = 2.188e-06
## alternative hypothesis: true ratio of variances is not equal to 1
## 95 percent confidence interval:
##  0.1000171 0.3673606
## sample estimates:
## ratio of variances
##          0.1908662
```

The vaccinated group has a lower mean infectious period, but a larger variance.

Separate Seeder and contact birds Descriptive statistics for the infectious period.

```
table.infper
```

```
##   Vaccination Challenge     Mean       SD
## 1     Overall   Overall 4.571429 2.232703
## 2          No   contact 4.789474 1.084176
## 3         Yes   contact 2.300000 1.780006
## 4          No    seeder 5.555556 1.247219
## 5         Yes    seeder 5.750000 2.531382
```

From the table it already seems that the variances are not equal. Therefor we first test for equality of variance and than do the appropriate test to compare means.

```
#test for equal variances
#vaccinated vs unvaccinated
fligner.test(out.indiv$infper, out.indiv$Vaccinated)
```

```
##
##  Fligner-Killeen test of homogeneity of variances
##
## data:  out.indiv$infper and out.indiv$Vaccinated
## Fligner-Killeen:med chi-squared = 13.666, df = 1, p-value = 0.0002184
```

```
#seeder vs contact
fligner.test(out.indiv$infper, out.indiv$Challenge)
```

```
##
##  Fligner-Killeen test of homogeneity of variances
##
## data:  out.indiv$infper and out.indiv$Challenge
## Fligner-Killeen:med chi-squared = 0.085416, df = 1, p-value = 0.7701
```

```r
#all four groups
fligner.test(out.indiv$infper, mapply(paste0,out.indiv$Challenge,out.indiv$Vaccinated))
```

```
##
##  Fligner-Killeen test of homogeneity of variances
##
## data:  out.indiv$infper and mapply(paste0, out.indiv$Challenge, out.indiv$Vaccinated)
## Fligner-Killeen:med chi-squared = 14.32, df = 3, p-value = 0.002501
```

Variances between vaccine groups are not equal. Between challenge groups there are no differences.

```r
#Compare the mean infectious period
"vaccinated versus unvaccinated"
```

```
## [1] "vaccinated versus unvaccinated"
```

```r
t.test(out.indiv$infper~out.indiv$Vaccinated,var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## t = 2.3571, df = 54.253, p-value = 0.02205
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  0.170043 2.104281
## sample estimates:
##  mean in group No mean in group Yes
##          5.162162          4.025000
```

```r
"seeder versus contact"
```

```
## [1] "seeder versus contact"
```

```r
t.test(out.indiv$infper~out.indiv$Challenge,var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
## data:  out.indiv$infper by out.indiv$Challenge
## t = -4.781, df = 74.703, p-value = 8.542e-06
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  -3.038918 -1.251231
## sample estimates:
## mean in group contact  mean in group seeder
##              3.512821              5.657895
```

```r
"vaccinated versus unvaccinated in contacts"
```

```
## [1] "vaccinated versus unvaccinated in contacts"
```

```r
t.test(infper~Vaccinated ,
       data = out.indiv[out.indiv$Challenge == "contact", ],
       var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
```

```
## data:  infper by Vaccinated
## t = 5.3041, df = 31.643, p-value = 8.467e-06
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  1.533023 3.445924
## sample estimates:
##  mean in group No mean in group Yes
##          4.789474          2.300000
```

```
"vaccinated versus unvaccinated in seeders"
```

```
## [1] "vaccinated versus unvaccinated in seeders"
```

```
t.test(infper~Vaccinated ,
       data = out.indiv[out.indiv$Challenge == "seeder", ],
       var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
## data:  infper by Vaccinated
## t = -0.30486, df = 28.329, p-value = 0.7627
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  -1.500277  1.111389
## sample estimates:
##  mean in group No mean in group Yes
##          5.555556          5.750000
```

```
#Compare the sd infectious period
var.test(out.indiv$infper~out.indiv$Vaccinated)
```

```
##
##  F test to compare two variances
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## F = 0.19087, num df = 36, denom df = 39, p-value = 2.188e-06
## alternative hypothesis: true ratio of variances is not equal to 1
## 95 percent confidence interval:
##  0.1000171 0.3673606
## sample estimates:
## ratio of variances
##          0.1908662
```

Transmission parameters β

```
#test glm
fit.full <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~ out.nona$Vaccinated+
                  out.nona$Group,
                offset = log(out.nona$I/out.nona$N),
                family = binomial(link = "cloglog"), data = out.nona, na.action = na.omit)
drop1(fit.full)
```

```
## Single term deletions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated +
```

```
##     out.nona$Group
##                       Df Deviance    AIC
## <none>                     81.620 168.00
## out.nona$Vaccinated  0   81.620 168.00
## out.nona$Group       2   85.748 168.13
```

In backward selection Group falls out, but vaccination stays in.

```
fit.empty <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~1,
                 offset = log(out.nona$I/out.nona$N),
                 family = binomial(link = "cloglog"),
                 data = out.nona,
                 na.action = na.omit)
add1(fit.empty, ~. + out.nona$Vaccinated + out.nona$Group)
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ 1
##                       Df Deviance    AIC
## <none>                     91.283 171.66
## out.nona$Vaccinated  1   85.748 168.13
## out.nona$Group       3   81.620 168.00
```

```
fit.vac <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~out.nona$Vaccinated,
               offset = log(out.nona$I/out.nona$N),
               family = binomial(link = "cloglog"),
               data = out.nona, na.action = na.omit)
add1(fit.vac, scope = ~.+na.omit(out.nona$Group))
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated
##                           Df Deviance    AIC
## <none>                         85.748 168.13
## na.omit(out.nona$Group)  2   81.620 168.00
```

```
fit.group <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~out.nona$Group,
                 offset = log(out.nona$I/out.nona$N),
                 family = binomial(link = "cloglog"),
                 data = out.nona, na.action = na.omit)
add1(fit.group, ~.+out.nona$Vaccinated)
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Group
##                       Df Deviance AIC
## <none>                     81.62 168
## out.nona$Vaccinated  0    81.62 168
```

In forward selection both groups and vaccination are added as single terms to improve the empty model, but the addition of Group in the vaccine model or vaccination in the group model shows that Group should not be included in the model.

```
summary(fit.vac)
```

```
##
## Call:
## glm(formula = cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated,
##     family = binomial(link = "cloglog"), data = out.nona, na.action = na.omit,
##     offset = log(out.nona$I/out.nona$N))
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -2.5373  -1.1985  -0.3804   1.0257   3.2453
##
## Coefficients:
##                         Estimate Std. Error z value Pr(>|z|)
## (Intercept)               0.1185     0.1708   0.694   0.4879
## out.nona$VaccinatedYes   -0.5181     0.2146  -2.414   0.0158 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 91.283  on 36  degrees of freedom
## Residual deviance: 85.748  on 35  degrees of freedom
## AIC: 168.13
##
## Number of Fisher Scoring iterations: 5
```

Vaccination lowers the infeection parameter β.

```
beta.table
```

```
##        beta      2.5%     97.5
## 1 1.1257870 0.7899902 1.547889
## 2 0.6705952 0.4431067 1.030285
```

Basic reproduction number R_0

```
mean.R0[, c(1,2,3,4)]
```

```
##   Vaccinated      beta    llbeta   ulbeta
## 1         No 1.1257870 0.7899902 1.547889
## 2        Yes 0.6705952 0.4431067 1.030285
## 3         No 1.1257870 0.7899902 1.547889
## 4        Yes 0.6705952 0.4431067 1.030285
```

```
mean.R0[, c(1,5,6,7)]
```

```
##   Vaccinated   infper llinfper ulinfper
## 1         No 4.789474 4.301977 5.276970
## 2        Yes 2.300000 1.519892 3.080108
## 3         No 5.555556 4.979380 6.131731
## 4        Yes 5.750000 4.640593 6.859407
```

```
mean.R0[, c(1,11,12,13)]
```

```
##   Vaccinated        R       llR      ulR
## 1         No 5.251570 3.3702032 8.183183
## 2        Yes 1.248118 0.5977554 2.606082
## 3         No 6.119101 3.9703039 9.430864
```

```
## 4         Yes 3.355453 1.6471712 6.835393
```

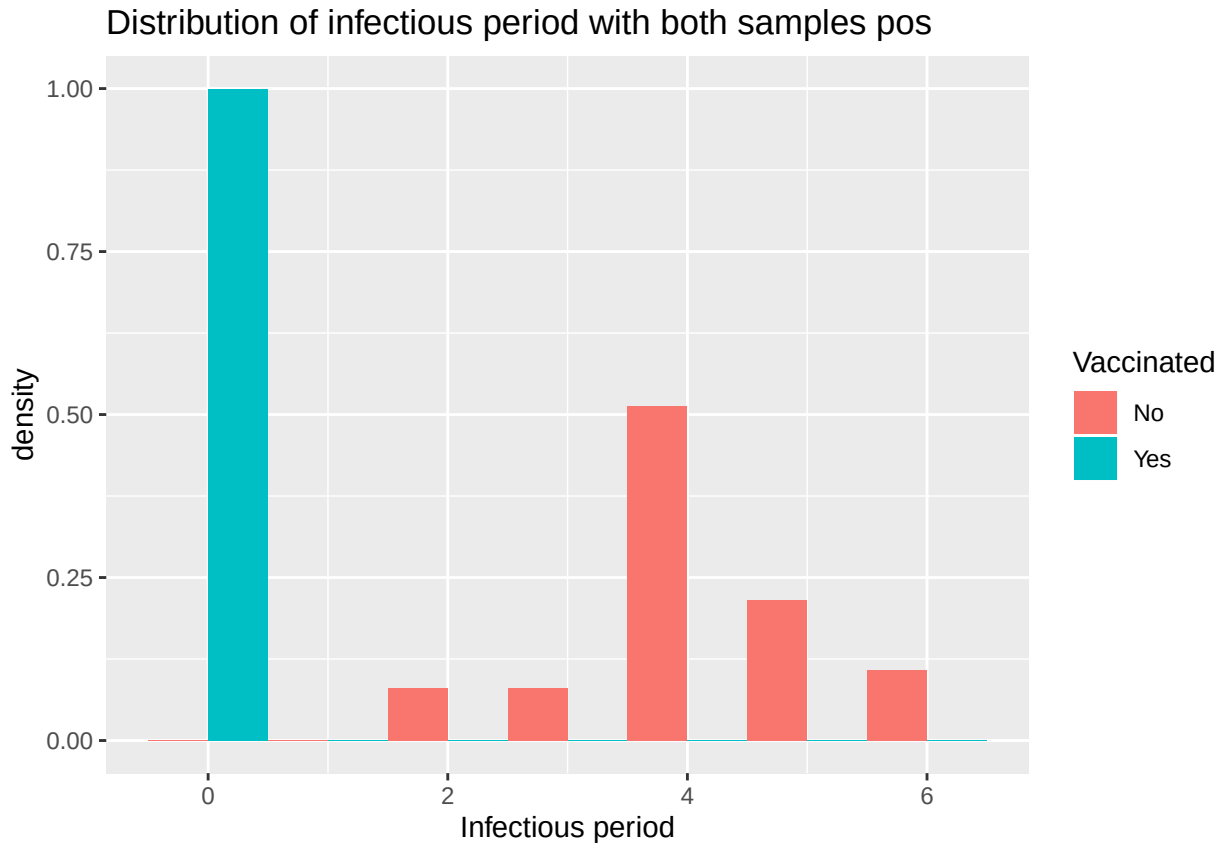
Based on the assumption of one of both samples required to be positive, we find that the transmission parameter β and the mean infectious period are lower, which results in a reproduction number R which is more than 4 times smaller, but is not lower than the threshold $R \leq 1$.

For all other options I have until now only used the overall infectious period!!!

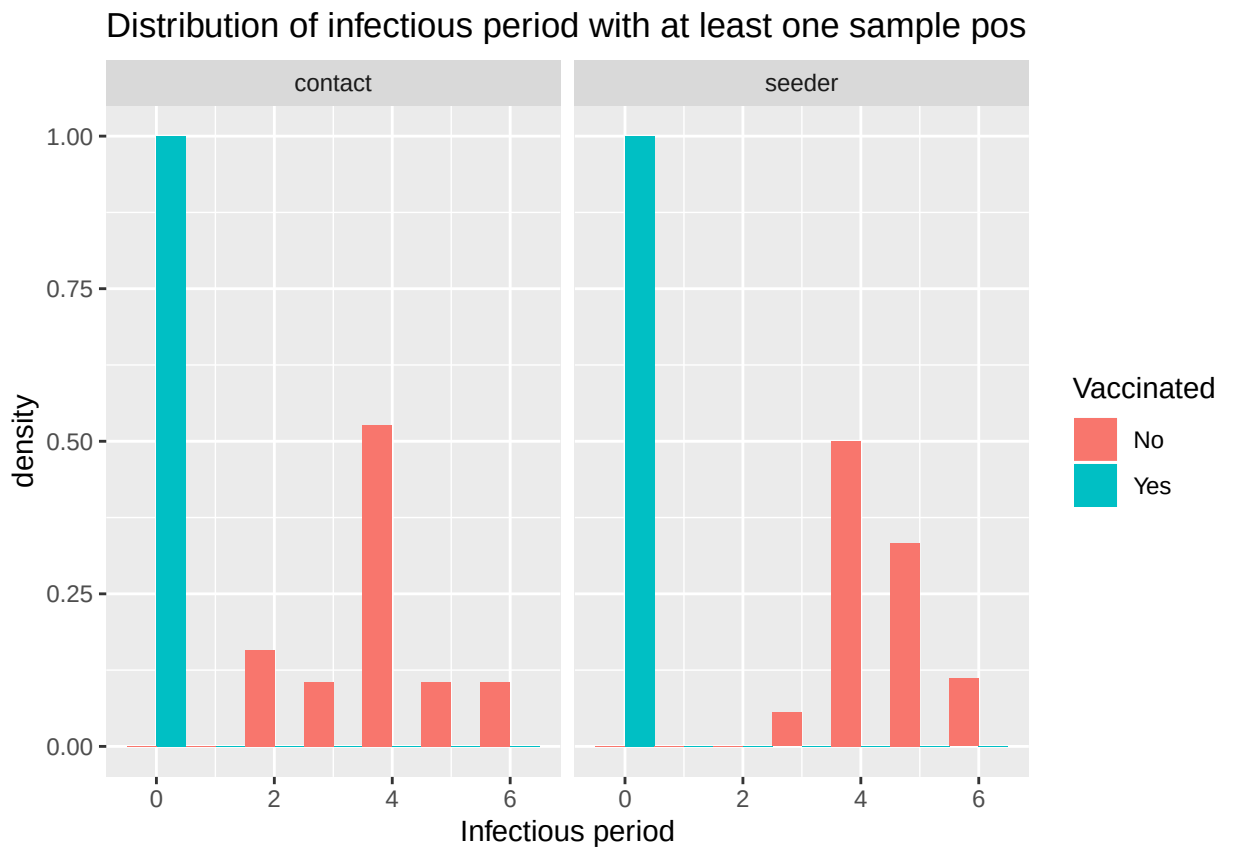
Both positive samples

Infectious period

```
#visualize
ggplot(data = out.indiv) +
  geom_histogram(aes(x = infper, y = ..density.., fill = Vaccinated),
                 position = "dodge",binwidth = 1)+
  ggtitle("Distribution of infectious period with both samples pos")+
  xlab("Infectious period")
```




```
ggplot(data = out.indiv) +
  geom_histogram(aes(x = infper, y = ..density.., fill = Vaccinated),
                 position = "dodge",binwidth = 1)+
  ggtitle("Distribution of infectious period with at least one sample pos")+
  xlab("Infectious period") +facet_grid(.~Challenge)
```



Descriptive statistics for the infectious period.

```
table.infper
```

```
##          Group     Mean       SD
## 1      Overall 2.012987 2.221270
## 2 Unvaccinated 4.189189 1.023009
## 3   Vaccinated 0.000000 0.000000
```

Using the assumption that both swabs need a positive result, the vaccinated group is never infectious. #### Separate Seeder and contact birds

Descriptive statistics for the infectious period.

```
table.infper
```

```
##   Vaccination Challenge     Mean        SD
## 1     Overall   Overall 2.012987 2.2212698
## 2          No   contact 3.894737 1.1496249
## 3         Yes   contact 0.000000 0.0000000
## 4          No    seeder 4.500000 0.7859052
## 5         Yes    seeder 0.000000 0.0000000
```

From the table it already seems that the variances are not equal. Therefor we first test for equality of variance and than do the appropriate test to compare means.

```
#test for equal variances
#vaccinated vs unvaccinated
fligner.test(out.indiv$infper, out.indiv$Vaccinated)
```

```
##
##  Fligner-Killeen test of homogeneity of variances
##
## data:  out.indiv$infper and out.indiv$Vaccinated
## Fligner-Killeen:med chi-squared = 23.166, df = 1, p-value = 1.486e-06
```

```
#seeder vs contact
fligner.test(out.indiv$infper, out.indiv$Challenge)
```

```
##
##  Fligner-Killeen test of homogeneity of variances
##
## data:  out.indiv$infper and out.indiv$Challenge
## Fligner-Killeen:med chi-squared = 0.42391, df = 1, p-value = 0.515
```

```
#all four groups
fligner.test(out.indiv$infper, mapply(paste0,out.indiv$Challenge,out.indiv$Vaccinated))
```

```
##
##  Fligner-Killeen test of homogeneity of variances
##
## data:  out.indiv$infper and mapply(paste0, out.indiv$Challenge, out.indiv$Vaccinated)
## Fligner-Killeen:med chi-squared = 23.32, df = 3, p-value = 3.464e-05
```

```
#Compare the mean infectious period
"vaccinated versus unvaccinated"
```

```
## [1] "vaccinated versus unvaccinated"
```

```
t.test(out.indiv$infper~out.indiv$Vaccinated,var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## t = 24.909, df = 36, p-value < 2.2e-16
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  3.848101 4.530277
## sample estimates:
##  mean in group No mean in group Yes
##          4.189189          0.000000
```

```
"seeder versus contact"
```

```
## [1] "seeder versus contact"
```

```
t.test(out.indiv$infper~out.indiv$Challenge,var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
## data:  out.indiv$infper by out.indiv$Challenge
## t = -0.45946, df = 73.906, p-value = 0.6473
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  -1.2495719  0.7812858
## sample estimates:
## mean in group contact  mean in group seeder
```

```
##              1.897436              2.131579
```

```
"vaccinated versus unvaccinated in contacts"
```

```
## [1] "vaccinated versus unvaccinated in contacts"
```

```
t.test(infper~Vaccinated ,
       data = out.indiv[out.indiv$Challenge == "contact", ],
       var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
## data:  infper by Vaccinated
## t = 14.767, df = 18, p-value = 1.674e-11
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  3.340635 4.448838
## sample estimates:
##  mean in group No mean in group Yes
##          3.894737          0.000000
```

```
"vaccinated versus unvaccinated in seeders"
```

```
## [1] "vaccinated versus unvaccinated in seeders"
```

```
t.test(infper~Vaccinated ,
       data = out.indiv[out.indiv$Challenge == "seeder", ],
       var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
## data:  infper by Vaccinated
## t = 24.293, df = 17, p-value = 1.221e-14
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  4.109179 4.890821
## sample estimates:
##  mean in group No mean in group Yes
##               4.5               0.0
```

```
#Compare the sd infectious period
var.test(out.indiv$infper~out.indiv$Vaccinated)
```

```
##
##  F test to compare two variances
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## F = Inf, num df = 36, denom df = 39, p-value < 2.2e-16
## alternative hypothesis: true ratio of variances is not equal to 1
## 95 percent confidence interval:
##  Inf Inf
## sample estimates:
## ratio of variances
##                Inf
```

Transmission parameters β

Because there are no chickens that are set to infectious based on the criterium that both need to be positive, parameters can only be estimated for the unvaccinated group.

```
#test glm
fit.full <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~ out.nona$Group,
                offset = log(out.nona$I/out.nona$N),
                family = binomial(link = "cloglog"),
                data = out.nona, na.action = na.omit)
drop1(fit.full)
```

```
## Single term deletions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Group
##                 Df Deviance    AIC
## <none>               54.449 75.570
## out.nona$Group  1   54.574 73.695
```

In backward selection again Group falls out.

```
fit.empty <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~1,
                 offset = log(out.nona$I/out.nona$N),
                 family = binomial(link = "cloglog"),
                 data = out.nona,
                 na.action = na.omit)
add1(fit.empty, ~. +  out.nona$Group)
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ 1
##                 Df Deviance    AIC
## <none>               54.574 73.695
## out.nona$Group  1   54.449 75.570
```

Also in forward selection, Group should not be included in the model.

```
summary(fit.empty)
```

```
##
## Call:
## glm(formula = cbind(out.nona$C, out.nona$S - out.nona$C) ~ 1,
##     family = binomial(link = "cloglog"), data = out.nona, na.action = na.omit,
##     offset = log(out.nona$I/out.nona$N))
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -3.3345  -1.8171  -0.1445   1.3824   4.4520
##
## Coefficients:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept)   0.1469     0.1780   0.825    0.409
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 54.574  on 9  degrees of freedom
```

```
## Residual deviance: 54.574  on 9  degrees of freedom
## AIC: 73.695
##
## Number of Fisher Scoring iterations: 5
```

Vaccination lowers the infeection parameter β.

```
beta.table
```

```
##       beta      2.5%     97.5
## 1 1.158205 0.8038566 1.606461
```

Basic reproduction number R_0

```
mean.R0[, c(1,2,3,4)]
```

```
##   Vaccinated      beta    llbeta   ulbeta
## 1         No 1.1257870 0.8038566 1.606461
## 2        Yes 0.6705952 0.9049713 1.808533
## 3         No 1.1257870 0.8038566 1.606461
## 4        Yes 0.6705952 0.9049713 1.808533
```

```
mean.R0[, c(1,5,6,7)]
```

```
##   Vaccinated   infper llinfper ulinfper
## 1         No 3.894737 3.377812 4.411662
## 2        Yes 0.000000 0.000000 0.000000
## 3         No 4.500000 4.136937 4.863063
## 4        Yes 0.000000 0.000000 0.000000
```

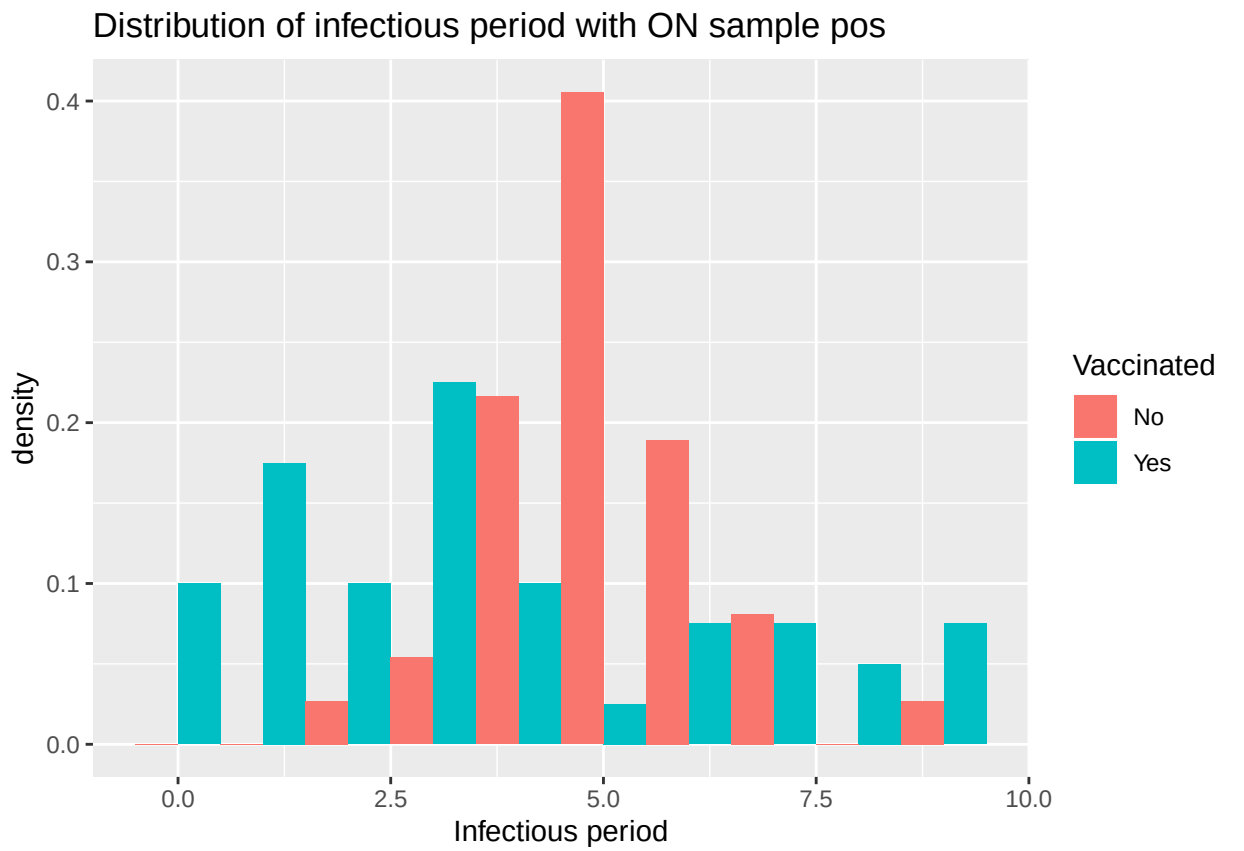
```
mean.R0[, c(1,11,12,13)]
```

```
##   Vaccinated         R       llR       ulR
## 1         No 4.1837981 2.5834457 6.7755117
## 2        Yes 0.3352976 0.2201517 0.5106682
## 3         No 4.9939505 3.2964492 7.5655772
## 4        Yes 0.3352976 0.2201517 0.5106682
```

ON sample positive

Infectious period

```
#visualize
ggplot(data = out.indiv) +
  geom_histogram(aes(x = infper, y = ..density.., fill = Vaccinated),
                 position = "dodge",binwidth = 1)+
  ggtitle("Distribution of infectious period with ON sample pos")+
  xlab("Infectious period")
```



Descriptive statistics for the infectious period.

```
table.infper
```

```
##          Group     Mean       SD
## 1      Overall 4.311688 2.272604
## 2 Unvaccinated 5.054054 1.289831
## 3   Vaccinated 3.625000 2.742706
```

From the table it already seems that the variances are not equal. Therefor we first test for equality of variance and than do the appropriate test to compare means.

```
#test for equal variances
fligner.test(out.indiv$infper, out.indiv$Vaccinated) #conclude unequal variances
```

```
##
##  Fligner-Killeen test of homogeneity of variances
##
## data:  out.indiv$infper and out.indiv$Vaccinated
## Fligner-Killeen:med chi-squared = 12.14, df = 1, p-value = 0.0004936
```

```
#Compare the mean infectious period
t.test(out.indiv$infper~out.indiv$Vaccinated,var.equal = FALSE)
```

```
##
##  Welch Two Sample t-test
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## t = 2.9604, df = 56.387, p-value = 0.004488
```

```
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  0.4621832 2.3959249
## sample estimates:
##  mean in group No mean in group Yes
##          5.054054          3.625000
```

```
#Compare the sd infectious period
var.test(out.indiv$infper~out.indiv$Vaccinated)
```

```
##
##  F test to compare two variances
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## F = 0.22116, num df = 36, denom df = 39, p-value = 1.358e-05
## alternative hypothesis: true ratio of variances is not equal to 1
## 95 percent confidence interval:
##  0.1158917 0.4256676
## sample estimates:
## ratio of variances
##          0.2211602
```

The vaccinated group has a lower mean infectious period, but a larger variance.

Transmission parameters β

```
#test glm
fit.full <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~ out.nona$Vaccinated +out.nona$Group,
                offset = log(out.nona$I/out.nona$N),
                family = binomial(link = "cloglog"),
                data = out.nona, na.action = na.omit)
drop1(fit.full)
```

```
## Single term deletions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated +
##     out.nona$Group
##                       Df Deviance    AIC
## <none>                     79.134 165.19
## out.nona$Vaccinated  0   79.134 165.19
## out.nona$Group       2   83.397 165.46
```

```
fit.vac <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~ out.nona$Vaccinated,
               offset = log(out.nona$I/out.nona$N),
               family = binomial(link = "cloglog"),
               data = out.nona, na.action = na.omit)
drop1(fit.vac)
```

```
## Single term deletions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated
##                       Df Deviance    AIC
## <none>                     83.397 165.46
## out.nona$Vaccinated  1   91.087 171.15
```

```r
fit.group <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~ out.nona$Group,
                 offset = log(out.nona$I/out.nona$N),
                 family = binomial(link = "cloglog"),
                 data = out.nona, na.action = na.omit)
drop1(fit.group)
```

```
## Single term deletions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Group
##                Df Deviance    AIC
## <none>              79.134 165.19
## out.nona$Group  3   91.087 171.15
```

In backward selection either group or vaccination should stay in the selection.

```r
fit.empty <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~1,
                 offset = log(out.nona$I/out.nona$N),
                 family = binomial(link = "cloglog"),
                 data = out.nona, na.action = na.omit)
add1(fit.empty, ~. + out.nona$Vaccinated + out.nona$Group)
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ 1
##                      Df Deviance    AIC
## <none>                    91.087 171.15
## out.nona$Vaccinated  1   83.397 165.46
## out.nona$Group       3   79.134 165.19
```

```r
fit.vac <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~out.nona$Vaccinated,
               offset = log(out.nona$I/out.nona$N),
               family = binomial(link = "cloglog"),
               data = out.nona, na.action = na.omit)
add1(fit.vac, scope = ~.+na.omit(out.nona$Group))
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated
##                          Df Deviance    AIC
## <none>                        83.397 165.46
## na.omit(out.nona$Group)  2   79.134 165.19
```

```r
fit.group <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~out.nona$Group,
                 offset = log(out.nona$I/out.nona$N),
                 family = binomial(link = "cloglog"),
                 data = out.nona,
                 na.action = na.omit)
add1(fit.group, ~.+out.nona$Vaccinated)
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Group
```

```
##                       Df Deviance    AIC
## <none>                     79.134 165.19
## out.nona$Vaccinated  0   79.134 165.19
```

In forward selection either groups or vaccination are added as single terms to improve the empty model. We choose to use vaccination as this is the main interest.

```
summary(fit.vac)
```

```
##
## Call:
## glm(formula = cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated,
##     family = binomial(link = "cloglog"), data = out.nona, na.action = na.omit,
##     offset = log(out.nona$I/out.nona$N))
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -2.4911  -1.1414  -0.4031   1.4409   3.2962
##
## Coefficients:
##                          Estimate Std. Error z value Pr(>|z|)
## (Intercept)                0.1487     0.1686   0.882  0.37758
## out.nona$VaccinatedYes    -0.6159     0.2165  -2.844  0.00445 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 91.087  on 36  degrees of freedom
## Residual deviance: 83.397  on 35  degrees of freedom
## AIC: 165.46
##
## Number of Fisher Scoring iterations: 4
```

Vaccination lowers the infection parameter β.

```
beta.table
```

```
##   Vaccination      beta      2.5%      97.5
## 1          No 1.1603785 0.8184697 1.5888716
## 2         Yes 0.6268027 0.4122417 0.9646928
```

The transmission parameter β is lower for the vaccinated group.

Basic reproduction number R_0

```
mean.R0[, c(1,2,3,4)]
```

```
##             Vaccinated      beta    llbeta    ulbeta
## (Intercept)         No 1.1603785 0.8184697 1.5888716
##                    Yes 0.6268027 0.4122417 0.9646928
```

```
mean.R0[, c(1,5,6,7)]
```

```
##             Vaccinated   infper llinfper ulinfper
## (Intercept)         No 5.054054 4.638450 5.469658
##                    Yes 3.625000 2.775042 4.474958
```

```
mean.R0[, c(1,11,12,13)]
```

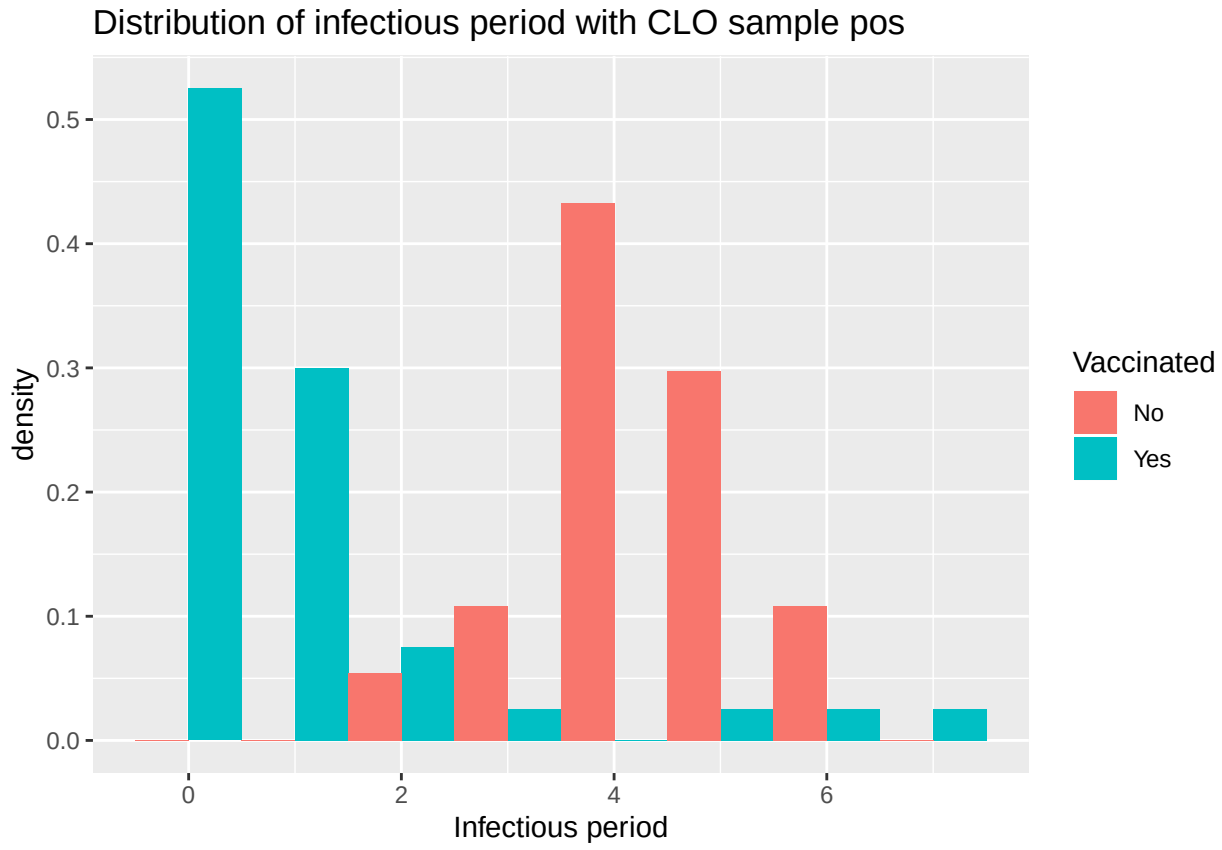
```
##             Vaccinated        R       llR     ulR
## (Intercept)         No 5.670181 3.7331690 8.61224
##                    Yes 1.661995 0.8244941 3.35021
```

Based on the assumption of ON samples required to be positive, we find that the transmission parameter β and the mean infectious period are lower, which results in a reproduction number R which is less than one thirth, but is not lower than the threshold $R \leq 1$.

CLO sample positive

Infectious period

```
#visualize
ggplot(data = out.indiv) +
  geom_histogram(aes(x = infper, y = ..density.., fill = Vaccinated),
                 position = "dodge",binwidth = 1)+
  ggtitle("Distribution of infectious period with CLO sample pos")+
  xlab("Infectious period")
```



Descriptive statistics for the infectious period.

```
table.infper
```

```
##          Group     Mean        SD
## 1      Overall 2.571429 2.1547290
## 2 Unvaccinated 4.297297 0.9962392
```

```
## 3   Vaccinated 0.975000 1.6406300
```

From the table it already seems that the variances are not equal. Therefor we first test for equality of variance and than do the appropriate test to compare means.

```
#test for equal variances
fligner.test(out.indiv$infper, out.indiv$Vaccinated)
```

```
##
##  Fligner-Killeen test of homogeneity of variances
##
## data:  out.indiv$infper and out.indiv$Vaccinated
## Fligner-Killeen:med chi-squared = 0.0073488, df = 1, p-value = 0.9317
```

```
#Compare the mean infectious period
t.test(out.indiv$infper~out.indiv$Vaccinated,var.equal = F)
```

```
##
##  Welch Two Sample t-test
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## t = 10.829, df = 65.086, p-value = 3.346e-16
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  2.709625 3.934970
## sample estimates:
##  mean in group No mean in group Yes
##          4.297297          0.975000
```

```
t.test(out.indiv$infper~out.indiv$Vaccinated,var.equal = T)
```

```
##
##  Two Sample t-test
##
## data:  out.indiv$infper by out.indiv$Vaccinated
## t = 10.634, df = 75, p-value < 2.2e-16
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  2.699926 3.944669
## sample estimates:
##  mean in group No mean in group Yes
##          4.297297          0.975000
```

The vaccinated group has a lower mean infectious period, but no difference in variance found.

Transmission parameters β

```
#test glm
fit.full <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~ out.nona$Vaccinated +out.nona$Group,
                offset = log(out.nona$I/out.nona$N),
                family = binomial(link = "cloglog"),
                data = out.nona,
                na.action = na.omit)
drop1(fit.full)
```

```
## Single term deletions
##
```

```
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated +
##     out.nona$Group
##                       Df Deviance    AIC
## <none>                     87.014 132.33
## out.nona$Vaccinated  0   87.014 132.33
## out.nona$Group       2   87.043 128.36
```

```
fit.vac <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~ out.nona$Vaccinated,
               offset = log(out.nona$I/out.nona$N),
               family = binomial(link = "cloglog"),
               data = out.nona,
               na.action = na.omit)
drop1(fit.vac)
```

```
## Single term deletions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated
##                       Df Deviance    AIC
## <none>                     87.043 128.36
## out.nona$Vaccinated  1   90.679 130.00
```

```
fit.group <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~ out.nona$Group,
                 offset = log(out.nona$I/out.nona$N),
                 family = binomial(link = "cloglog"),
                 data = out.nona,
                 na.action = na.omit)
drop1(fit.group)
```

```
## Single term deletions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Group
##                 Df Deviance    AIC
## <none>               87.014 132.33
## out.nona$Group  3   90.679 130.00
```

In backward selection either group or vaccination should stay in the selection.

```
fit.empty <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~1,
                 offset = log(out.nona$I/out.nona$N),
                 family = binomial(link = "cloglog"),
                 data = out.nona,
                 na.action = na.omit)
add1(fit.empty, ~. + out.nona$Vaccinated + out.nona$Group)
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ 1
##                       Df Deviance    AIC
## <none>                     90.679 130.00
## out.nona$Vaccinated  1   87.043 128.36
## out.nona$Group       3   87.014 132.33
```

```
fit.vac <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~out.nona$Vaccinated,
               offset = log(out.nona$I/out.nona$N),
               family = binomial(link = "cloglog"),
               data = out.nona,
               na.action = na.omit)
add1(fit.vac, scope = ~.+na.omit(out.nona$Group))
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated
##                          Df Deviance    AIC
## <none>                        87.043 128.36
## na.omit(out.nona$Group)  2   87.014 132.33
```

```
fit.group <- glm(cbind(out.nona$C, out.nona$S-out.nona$C) ~out.nona$Group,
                 offset = log(out.nona$I/out.nona$N),
                 family = binomial(link = "cloglog"),
                 data = out.nona,
                 na.action = na.omit)
add1(fit.group, ~.+out.nona$Vaccinated)
```

```
## Single term additions
##
## Model:
## cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Group
##                       Df Deviance    AIC
## <none>                     87.014 132.33
## out.nona$Vaccinated  0   87.014 132.33
```

In forward selection either groups or vaccination are added as single terms to improve the empty model. We choose to use vaccination as this is the main interest.

```
summary(fit.vac)
```

```
##
## Call:
## glm(formula = cbind(out.nona$C, out.nona$S - out.nona$C) ~ out.nona$Vaccinated,
##     family = binomial(link = "cloglog"), data = out.nona, na.action = na.omit,
##     offset = log(out.nona$I/out.nona$N))
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -3.1887  -1.0778  -0.8148   0.4695   3.8361
##
## Coefficients:
##                          Estimate Std. Error z value Pr(>|z|)
## (Intercept)               0.05745    0.18170   0.316   0.7519
## out.nona$VaccinatedYes -0.54945    0.29381  -1.870   0.0615 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 90.679  on 27  degrees of freedom
## Residual deviance: 87.043  on 26  degrees of freedom
```

```
## AIC: 128.36
##
## Number of Fisher Scoring iterations: 5
```

Vaccination lowers the infection parameter β, but this not statistically significant.

```
beta.table
```

```
##   Vaccination      beta      2.5%     97.5
## 1         Yes 1.0591299 0.7260748 1.483655
## 2          No 0.6113985 0.3386858 1.075261
```

The transmission parameter β is lower for the vaccinated group, but the confidence intervals overlap largely.

Basic reproduction number R_0

```
mean.R0[, c(1,2,3,4)]
```

```
##             Vaccinated      beta    llbeta   ulbeta
## (Intercept)         No 1.0591299 0.7260748 1.483655
##                    Yes 0.6113985 0.3386858 1.075261
```

```
mean.R0[, c(1,5,6,7)]
```

```
##             Vaccinated   infper  llinfper ulinfper
## (Intercept)         No 4.297297 3.9762930 4.618302
##                    Yes 0.975000 0.4665729 1.483427
```

```
mean.R0[, c(1,11,12,13)]
```

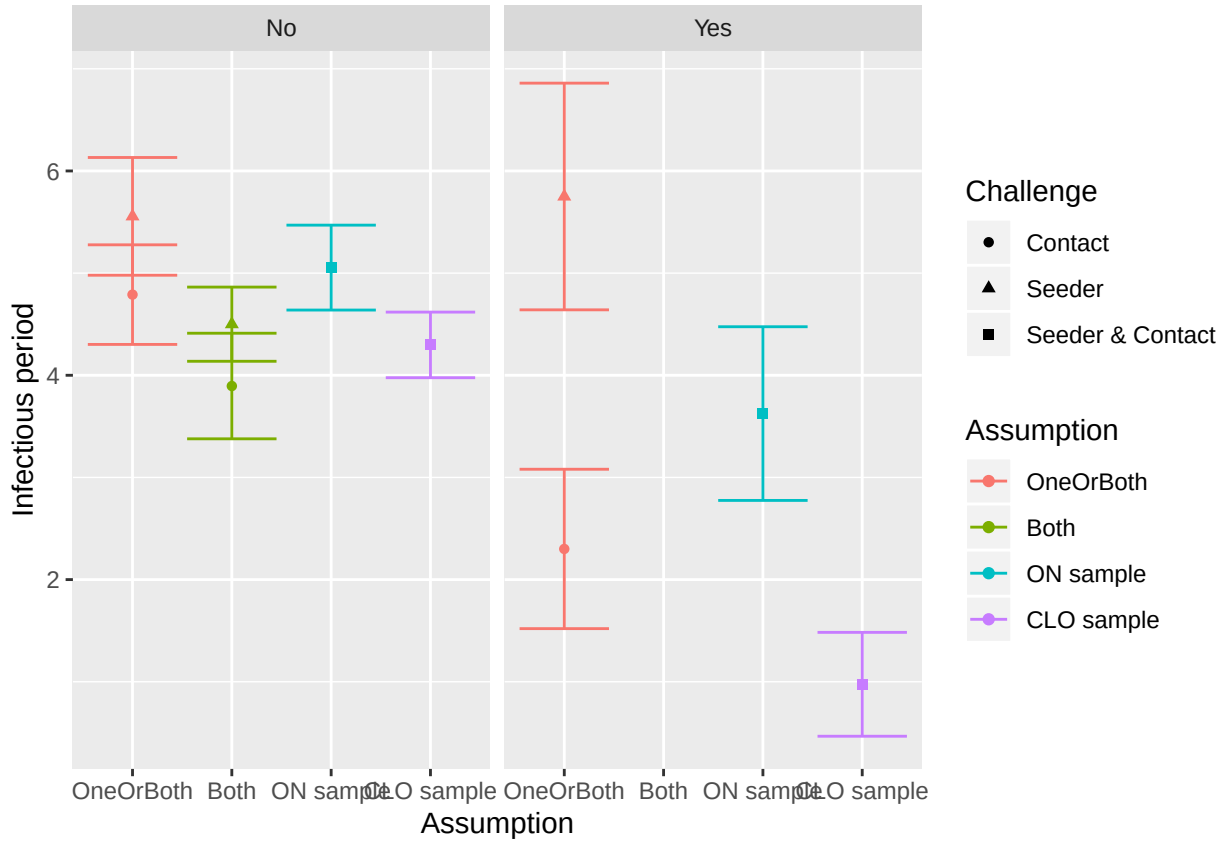
```
##             Vaccinated         R       llR      ulR
## (Intercept)         No 4.4165020 2.8446651 6.856867
##                    Yes 0.5258288 0.2349727 1.176715
```

Based on the assumption of CLO samples required to be positive, we find that the transmission parameter β and the mean infectious period are lower, although teh transmission parameter is not statistically significant. The reproduction number R is one nineth, and lower than the threshold $R < 1$ although the confidence interval incorporates 1.

Graphic summary of results

Infectious period

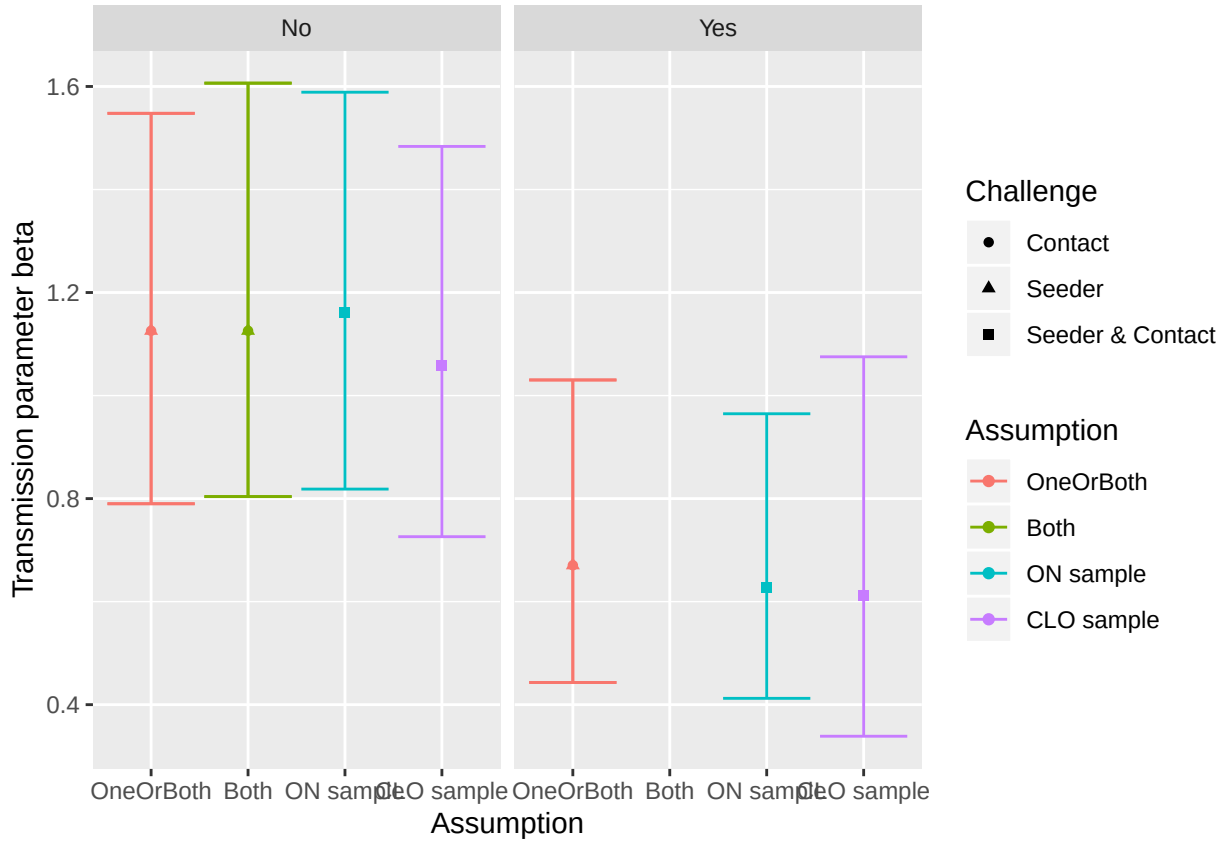
```
ggplot(data = all.results) +
  geom_point(aes(x = Assumption, y =infper,colour = Assumption, shape = Challenge ))+
  geom_errorbar(aes( x = Assumption, ymin = llinfper, ymax = ulinfper,colour = Assumption ))+
  facet_grid(.~Vaccinated)+ylab("Infectious period")
```



The descrepancy between the OneOrBoth and ON/CLO sample is that for the OneOrBoth only contact animals are given.

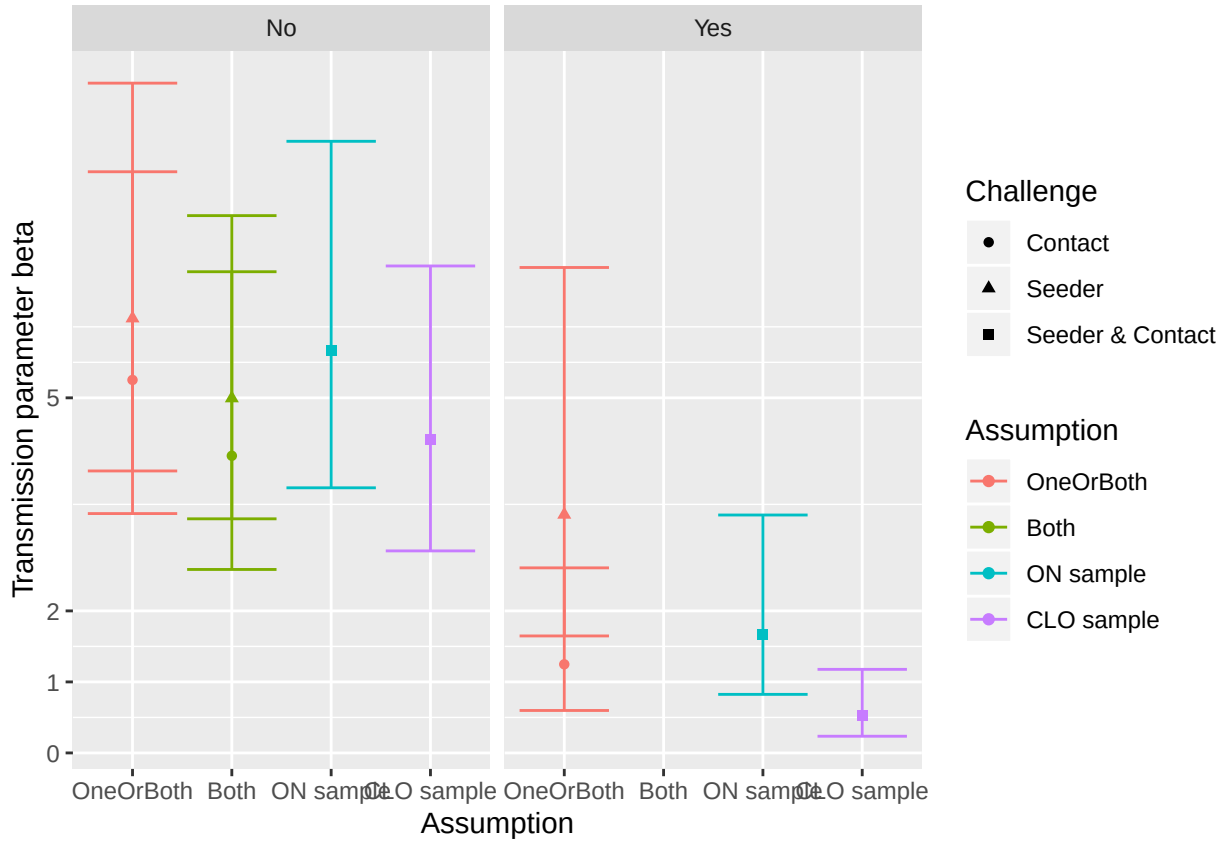
Transmission parameter β

```
ggplot(data = all.results) +
  geom_point(aes(x = Assumption, y = beta,colour = Assumption, shape = Challenge ))+
  geom_errorbar(aes( x = Assumption, ymin = llbeta, ymax = ulbeta,colour = Assumption ))+
  facet_grid(.~Vaccinated)+ylab("Transmission parameter beta")
```



Reproduction number R

```
ggplot(data = all.results) +
  geom_point(aes(x = Assumption, y = R,colour = Assumption, shape = Challenge ))+
  geom_errorbar(aes( x = Assumption, ymin = llR, ymax = ulR,colour = Assumption ))+
  facet_grid(.~Vaccinated)+ylab("Transmission parameter beta")+scale_y_continuous(breaks = c(0,1,2,5,10)
```



Conclusions