Example 1

Vaccine effectiveness

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TND studies on vaccine effectiveness

- The objective of a TND study is to assess the effectiveness of vaccines by comparing the odds of testing positive among vaccinated patients with the odds of positive testing among unvaccinated patients.

A TND study on Covid-19 effectiveness

A TND study conducted in Ontario, Canada, (Chung et al. 2021) investigated the effectiveness of mRNA Covid-19 vaccines (bnt162b2 and mrna-1273) against symptomatic SARS-CoV-2 infection.

	T+	T-
V-	51220	251541
V+	57	3817

$$OR = \frac{57/3817}{51220/251541} = 0.073$$

$$VE = (1 - OR) \cdot 100 = 92.7\%$$

TND studies on vaccine effectiveness

- If a perfect diagnostic assay is available (i.e. sensitivity and specificity equal to 1), we can assume that the results of the test follow an independent binomial sampling distribution for both unvaccinated ($V-$) or vaccinated ($V+$) sub-groups:

$$y_{V_+} \sim Bin(n_{V_+}, p_{V_+})$$

$$y_{V_-} \sim Bin(n_{V_-}, p_{V_-})$$

TND studies on vaccine effectiveness

- The Odds Ratio (OR) and the Vaccine Effectiveness (VE) are defined as follows:

$$OR = \frac{p_{V+}/(1 - p_{V+})}{p_{V-}/(1 - p_{V-})}$$

$$VE = (1 - OR) \cdot 100$$

Bayesian modeling for addressing misclassification bias

- In the simple case of nondifferential misclassification bias, the following relationships hold:

$$Se_{V_+} = Se_{V_-} = Se$$
$$Sp_{V_+} = Sp_{V_-} = Sp$$

Bayesian modeling for addressing misclassification bias

- We can therefore assume that for each of the two sub-groups (vaccinated and unvaccinated) the results of the test follow an independent binomial sampling distribution:

$$y_{*V_+} \sim Bin(n_{*V_+}, p_{*V_+})$$
$$y_{*V_-} \sim Bin(n_{*V_-}, p_{*V_-})$$

with

$$p_{*V_+} = p_{V_+} \cdot Se + (1 - p_{V_+}) \cdot (1 - Sp)$$
$$p_{*V_-} = p_{V_-} \cdot Se + (1 - p_{V_-}) \cdot (1 - Sp)$$

Bayesian modeling for addressing misclassification bias

- This model is over-parameterized with four parameters (p_{V_+}, p_{V_-}, Se, Sp) but only two independent pieces of information provided by the data, i.e. the apparent prevalences in the vaccinated (y_{V_+}/n_{V_+}) and unvaccinated (y_{V_-}/n_{V_-}) sub-groups.

- As such, these models are only of practical use within a Bayesian framework of inference, as this allows for prior information on diagnostic test characteristics (sensitivty and specificity) to be used along with the observed data.

Bayesian model assuming perfect classification

```
bm_1t_perf <- " model {
   for (i in 1:2) {
 # likelihood
   y[i,1] ~ dbin(pi[i], N[i])
 # priors for prevalence parameters
   pi[i] ~ dbeta(2,2)}
 # Computing OR/VE
   OR <- (pi[2]/(1-pi[2])) / (pi[1]/(1-pi[1]))
   VE <- (1-OR)*100
 #data# N, y
 #inits#
 #monitor# pi, OR, VE
 }"
```

Bayesian model for non-differential misclassification

```
bm_1t_nondif <- " model {
    for (i in 1:2) {
  # likelihood
    y[i,1] ~ dbin(prob[i], N[i])
    prob[i] <- pi[i]*Se + (1-pi[i])*(1-Sp)
  # priors for prevalence parameters
    pi[i] ~ dbeta(2,2)}
  # priors for Se and Sp
    Se~dbeta(HPSe[1], HPSe[2])
    Sp~dbeta(HPSp[1], HPSp[2])
  # Computing OR/VE
    OR <- (pi[2]/(1-pi[2])) / (pi[1]/(1-pi[1]))
    VE <- (1-OR)*100
  #data# N, y, HPSe, HPSp
  #inits#
  #monitor# Se, Sp, pi, OR, VE
    }"
```

Gibbs sampling set-up

```r
inits1 <- list(".RNG.name" = "base::Mersenne-Twister", ".RNG.seed" = 100022)
inits2 <- list(".RNG.name" = "base::Mersenne-Twister", ".RNG.seed" = 300022)

n_thin <- 25
n_burnin <- 50000
n_samples <- 100000
```
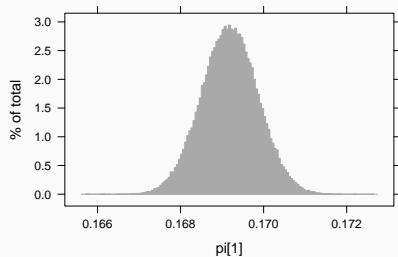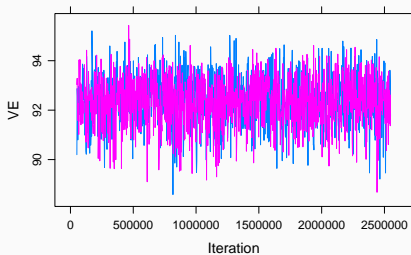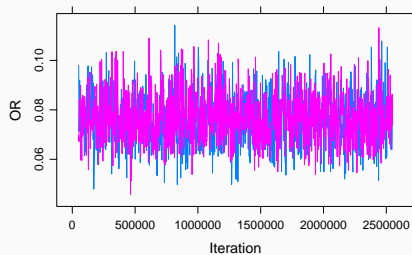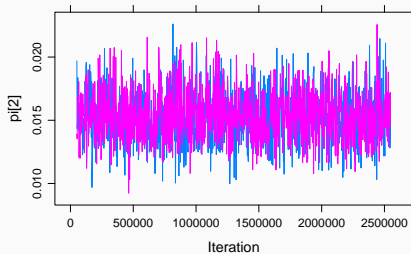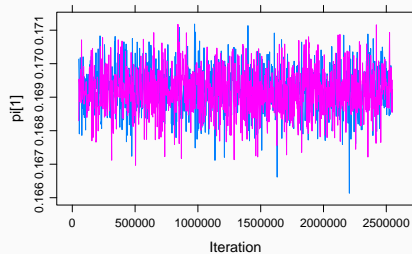
Model 1: perfect classification

```
res_perfect <- run.jags(
  bm_1t_perf,
  n.chains = 2,
  inits = list(inits1, inits2),
  burnin = n_burnin,
  sample = n_samples,
  thin = n_thin
)
## Loading required namespace: rjags
round(summary(res_perfect), 3) |>
  kable()
```

|	Lower95	Median	Upper95	Mean	SD	Mode	MCerr	MC%ofSD	SSeff	AC.250	psrf
pi[1]	0.168	0.169	0.171	0.169	0.001	NA	0.000	0.7	20000	0.002	1
pi[2]	0.012	0.015	0.019	0.015	0.002	NA	0.000	0.7	20405	0.002	1
OR	0.057	0.075	0.096	0.076	0.010	NA	0.000	0.7	20382	0.002	1
VE	90.409	92.460	94.269	92.404	0.996	NA	0.007	0.7	20382	0.002	1

Model 1: perfect classification
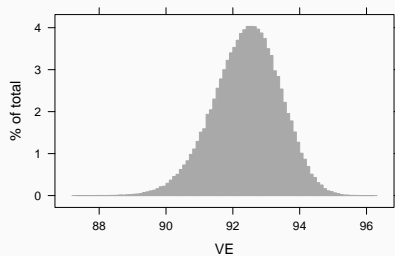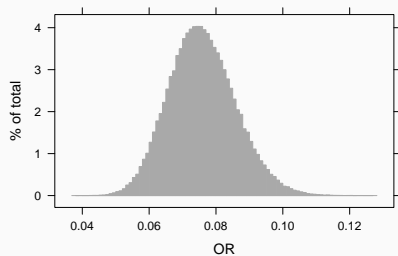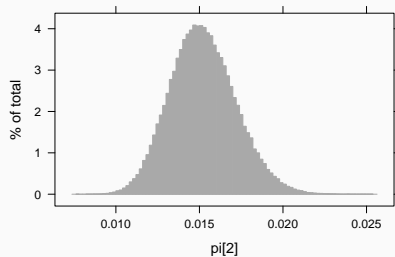
Model 1: perfect classification

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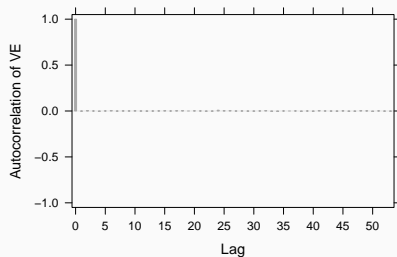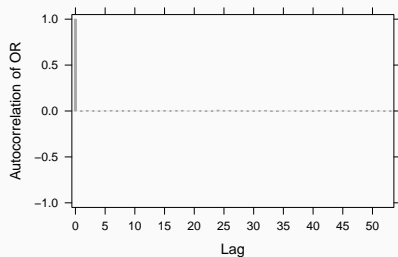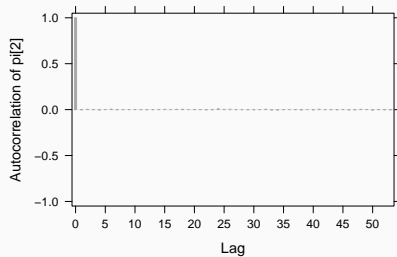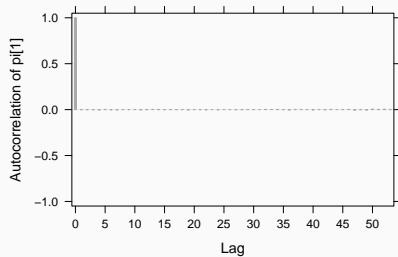
Model 2: sensitivity and specificity from Kostoulas et al. (2021)

- Kostoulas and colleagues (Kostoulas, Eusebi, and Hartnack 2021) used a Bayesian latent class model to estimate the diagnostic accuracy of RT-PCR and lateral flow immunoassay tests for Covid-19.
- The sensitivity of RT-PCR was 0.68 (95% PrI=0.63-0.73), while the specificity was 0.99 (95% PrI=0.98-1.00).
- We plugged-in this prior information in our model by using

$$Sensitivity \sim Beta(226.16, 105.93)$$

$$Specificity \sim Beta(606.34, 6.45)$$

Model 2: sensitivity and specificity from Kostoulas et al. (2021)

```
HPSe <- findbetaqq2(
  percentile.value1 = 0.63,
  percentile1 = 0.025,
  percentile.value2 = 0.73,
  percentile2 = 0.975
)
HPSe
## [1] 226.16 105.93
HPSp <- findbeta2(
    themedian = 0.99,
    percentile = 0.975,
    lower.v = FALSE,
    percentile.value = 0.98
  )
HPSp
## [1] 606.34   6.45
```
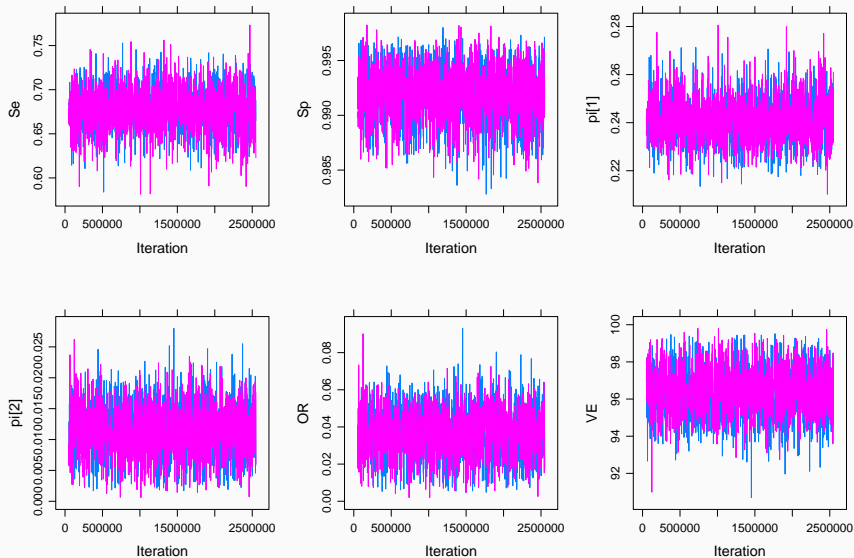
Model 2: sensitivity and specificity from Kostoulas et al. (2021)

	Lower95	Median	Upper95	Mean	SD	Mode	MCerr	MC%ofSD	SSeff	AC.250	psrf
Se	0.626	0.678	0.728	0.677	0.026	NA	0.00	0.8	14469	0.160	1
Sp	0.987	0.992	0.997	0.992	0.003	NA	0.00	0.7	20000	0.004	1
pi[1]	0.223	0.241	0.262	0.241	0.010	NA	0.00	0.8	14725	0.167	1
pi[2]	0.002	0.011	0.020	0.011	0.004	NA	0.00	0.7	20000	0.012	1
OR	0.009	0.036	0.063	0.036	0.014	NA	0.00	0.7	20000	0.004	1
VE	93.700	96.405	99.051	96.384	1.391	NA	0.01	0.7	20000	0.004	1

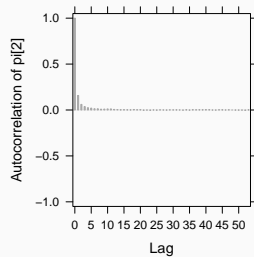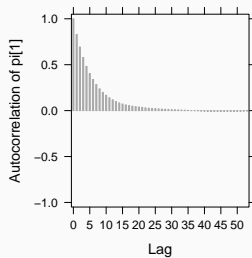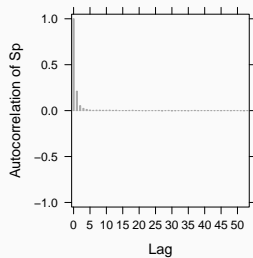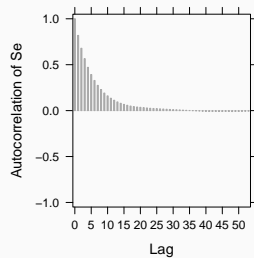# Model 2: sensitivity and specificity from Kostoulas et al. (2021)
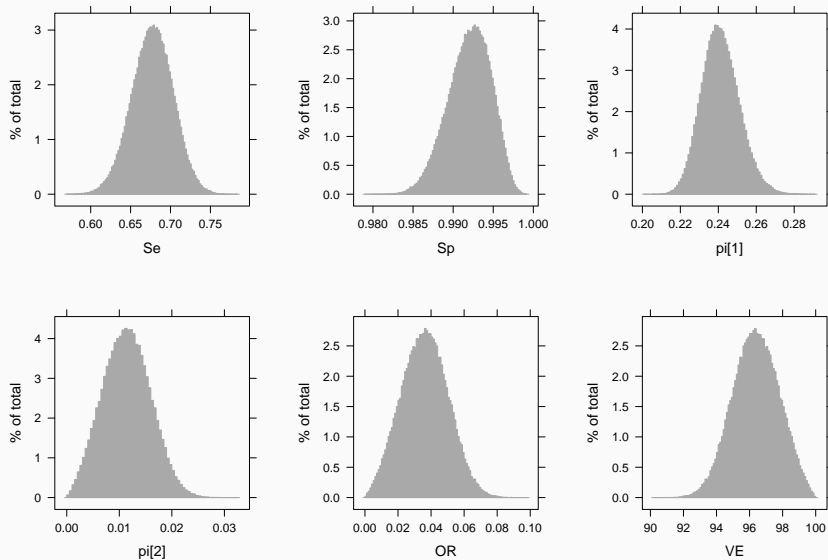
Model 2: sensitivity and specificity from Kostoulas et al. (2021)

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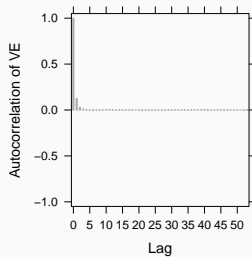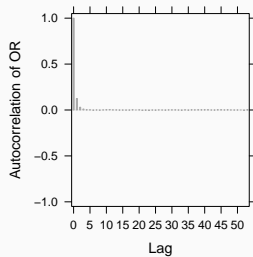
Model 3: sensitivity and specificity from Staerk et al. (2022)

- A recent report using Danish registries data used a Bayesian latent class model to estimate the diagnostic accuracy of RT-PCR and antigen tests for Covid-19. (Stærk-Østergaard et al. 2022)
- The specificity of RT-PCR was estimated to be close to 1.00.
- The sensitivity estimates were 0.957 (95% PrI=0.928-0.984).
- We plugged-in this prior information in our model by using:

$$Sensitivity \sim Beta(3040.61, 3.64)$$

$$Specificity \sim Beta(168.66, 6.84)$$

Model 3: sensitivity and specificity from Staerk et al. (2022)

```r
# Sp
HPSp <- findbetaqq2(
  percentile.value1 = 0.9973,
  percentile1 = 0.025,
  percentile.value2 = 0.9997,
  percentile2 = 0.975)
HPSp
## [1] 3040.61    3.64
round(qbeta(c(0.025, 0.5, 0.975), HPSp[1], HPSp[2]), 4)
## [1] 0.9973 0.9989 0.9997
# Se
HPSe <- findbetaqq2(
  percentile.value1 = 0.9279,
  percentile1 = 0.025,
  percentile.value2 = 0.9843,
  percentile2 = 0.975)
HPSe
## [1] 168.66    6.84
round(qbeta(c(0.025, 0.5, 0.975), HPSe[1], HPSe[2]), 4)
## [1] 0.9279 0.9628 0.9843
```
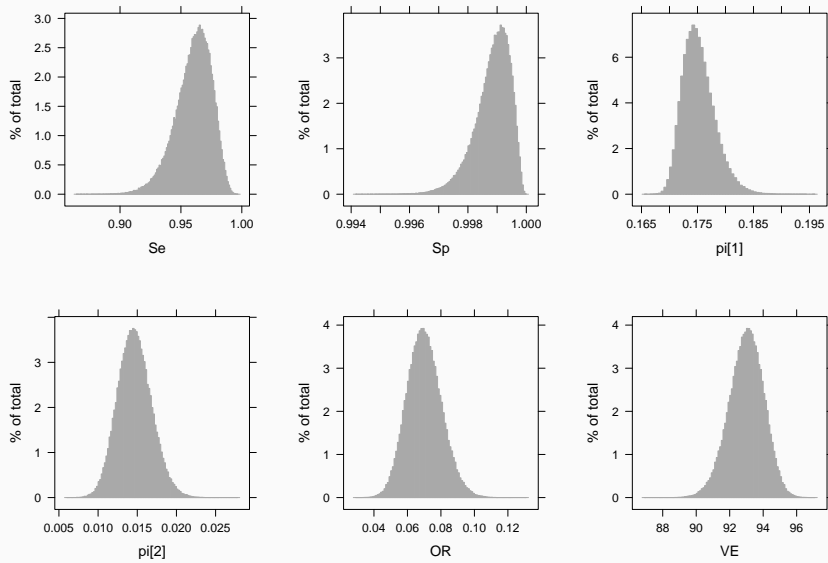
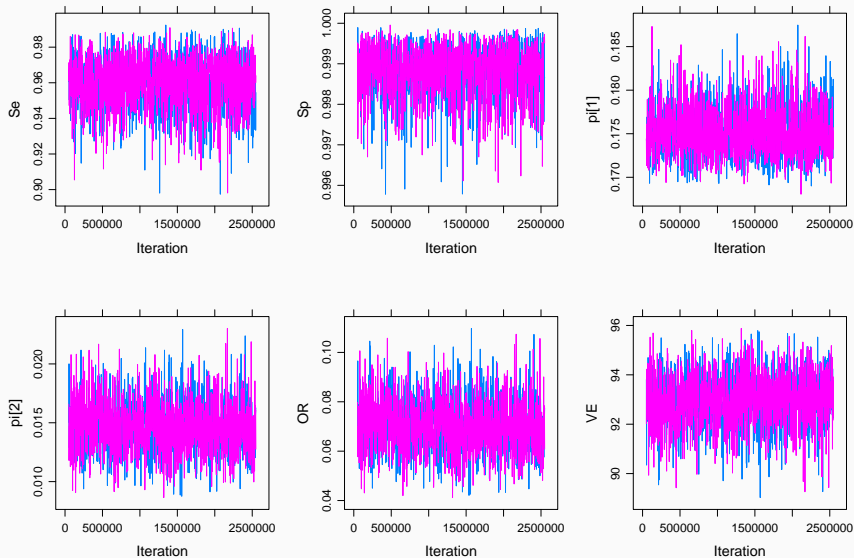## Model 3: sensitivity and specificity from Staerk et al. (2022)

|	Lower95	Median	Upper95	Mean	SD	Mode	MCerr	MC%ofSD	SSeff	AC.250	psrf
Se	0.931	0.962	0.987	0.960	0.015	NA	0.000	0.7	20000	0.000	1
Sp	0.998	0.999	1.000	0.999	0.001	NA	0.000	0.7	20598	0.000	1
pi[1]	0.170	0.175	0.181	0.175	0.003	NA	0.000	0.7	20000	0.002	1
pi[2]	0.011	0.015	0.019	0.015	0.002	NA	0.000	0.7	20000	0.000	1
OR	0.050	0.070	0.090	0.070	0.010	NA	0.000	0.7	20000	0.000	1
VE	90.965	93.030	95.006	92.993	1.033	NA	0.007	0.7	20000	0.000	1

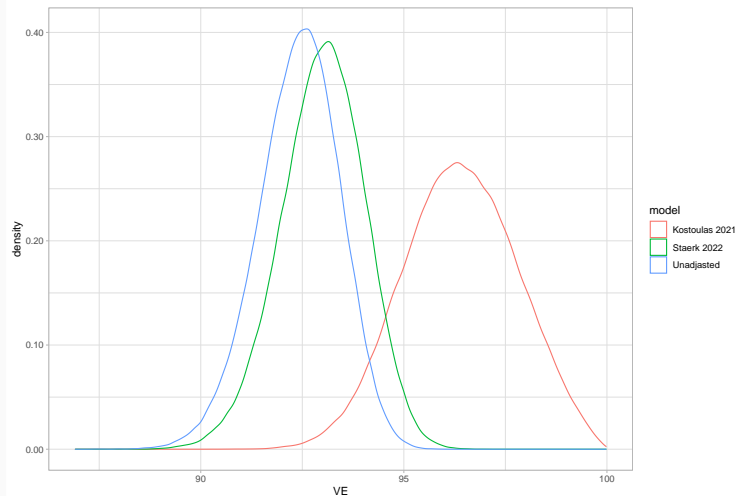## Model 3: sensitivity and specificity from Staerk et al. (2022)

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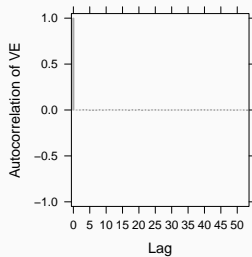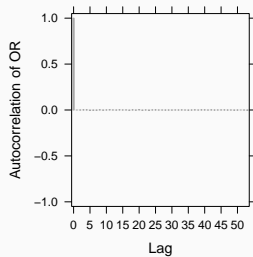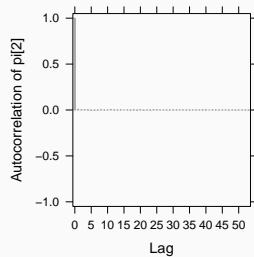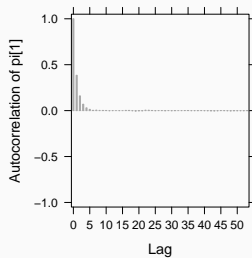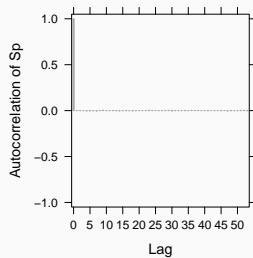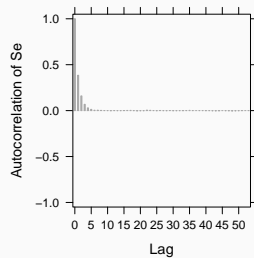
Posterior: vaccine effectiveness

Preprint and code

Addressing Misclassification Bias in Vaccine Effectiveness Studies with an Application to Covid-19 (Eusebi et al. 2022)

https://www.researchsquare.com/article/rs-1799561/v1

https://github.com/paoloeusebi/tnd-vaccine-effectiveness/

Chung, Hannah, Siyi He, Sharifa Nasreen, Maria E Sundaram, Sarah A Buchan, Sarah E Wilson, Branson Chen, et al. 2021. "Effectiveness of BNT162b2 and mRNA-1273 Covid-19 Vaccines Against Symptomatic SARS-CoV-2 Infection and Severe Covid-19 Outcomes in Ontario, Canada: Test Negative Design Study." *BMJ*, August, n1943. https://doi.org/10.1136/bmj.n1943.

Eusebi, Paolo, Nico Speybroeck, Sonja Hartnack, Jacob Staerk-Østergaard, Matthew D. Denwood, and Polychronis Kostoulas. 2022. "Addressing Misclassification Bias in Vaccine Effectiveness Studies with an Application to Covid-19." http://dx.doi.org/10.21203/rs.3.rs-1799561/v1.

Kostoulas, Polychronis, Paolo Eusebi, and Sonja Hartnack. 2021. "Diagnostic Accuracy Estimates for COVID-19 Real-Time Polymerase Chain Reaction and Lateral Flow Immunoassay Tests With Bayesian Latent-Class Models." *American Journal of Epidemiology* 190 (8): 1689–95. https://doi.org/10.1093/aje/kwab093.

Stærk-Østergaard, Jacob, Carsten Kirkeby, Lasse E. Christiansen, Michael A. Andersen, Camilla H. Møller, Marianne Voldstedlund, and Matthew J. Denwood. 2022. "Evaluation of Diagnostic Test Procedures for SARS-CoV-2 Using Latent Class Models." *Journal of Medical Virology* 94 (10): 4754–61. https://doi.org/10.1002/jmv.27943.