# Session 4

Multi-test, multi-population models

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2022-09-13

## Why stop at two tests?

In *traditional* diagnostic test evaluation, one test is assumed to be a gold standard from which all other tests are evaluated

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Using a latent class model each new test adds new information - so we should analyse all available test results in the same model

# Simulating data: simple example

Simulating data using an arbitrary number of independent tests is quite straightforward:

```
# Parameter values to simulate:
N <- 200
sensitivity <- c(0.8, 0.9, 0.95)
specificity <- c(0.95, 0.99, 0.95)

Populations <- 2
prevalence <- c(0.25,0.5)

data <- tibble(Population = sample(seq_len(Populations), N, replace=TRUE)) %>%
  mutate(Status = rbinom(N, 1, prevalence[Population])) %>%
  mutate(Test1 = rbinom(N, 1, sensitivity[1]*Status + (1-specificity[1])*(1-Status))) %>%
  mutate(Test2 = rbinom(N, 1, sensitivity[2]*Status + (1-specificity[2])*(1-Status))) %>%
  mutate(Test3 = rbinom(N, 1, sensitivity[3]*Status + (1-specificity[3])*(1-Status))) %>%
  select(-Status)
```

## Model specification

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```
Tally[1:8,p] ~ dmulti(prob[1:8,p], TotalTests[p])

# Probability of observing Test1- Test2- Test3-
prob[1,p] <-  prev[p] * ((1-se[1])*(1-se[2])*(1-se[3]) +
              (1-prev[p]) * (sp[1]*sp[2]*sp[3])

# Probability of observing Test1+ Test2- Test3-
prob[2,p] <-  prev[p] * (se[1]*(1-se[2])*(1-se[3])) +
              (1-prev[p]) * ((1-sp[1])*sp[2]*sp[3])

## snip ##

# Probability of observing Test1+ Test2+ Test3+
prob[3,p] <-  prev[p] * (se[1]*se[2]*se[3]) +
              (1-prev[p]) * ((1-sp[1])*(1-sp[2])*(1-sp[3]))
```

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# Probability of observing Test1- Test2- Test3-
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prob[3,p] <-  prev[p] * (se[1]*se[2]*se[3]) +
              (1-prev[p]) * ((1-sp[1])*(1-sp[2])*(1-sp[3]))
```

- We need to take **extreme** care with these equations, and the multinomial tabulation!!!

## Degrees of freedom

- The amount of information (degrees of freedom) in the data depends on the number of tests and number of populations:
  - 1 test, 1 population: 1 d.f.
  - 2 tests, 1 population: 2 d.f.
  - 2 tests, 2 populations: 3 d.f.
  - 2 tests, 3 populations: 5 d.f.

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  - 2 tests, 2 populations: 3 d.f.
  - 2 tests, 3 populations: 5 d.f.
- In general:
  - d.f. $=$ (2^tests - 1) x populations
  - See: Cheung et al, 2021

## Are the tests conditionally independent?

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- Example: we test people for COVID using an antigen test on a nasal swab, a PCR test on a throat swab, and the same antigen test on the same throat swab
  - The virus may be present in the throat, nose, neither, or both
  - But we use the same antigen test twice
    - Might it cross-react with the same non-target virus?

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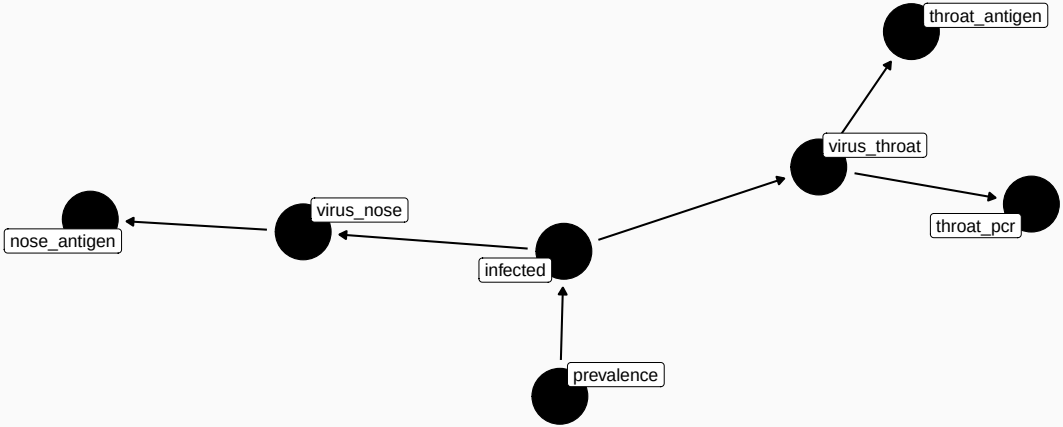
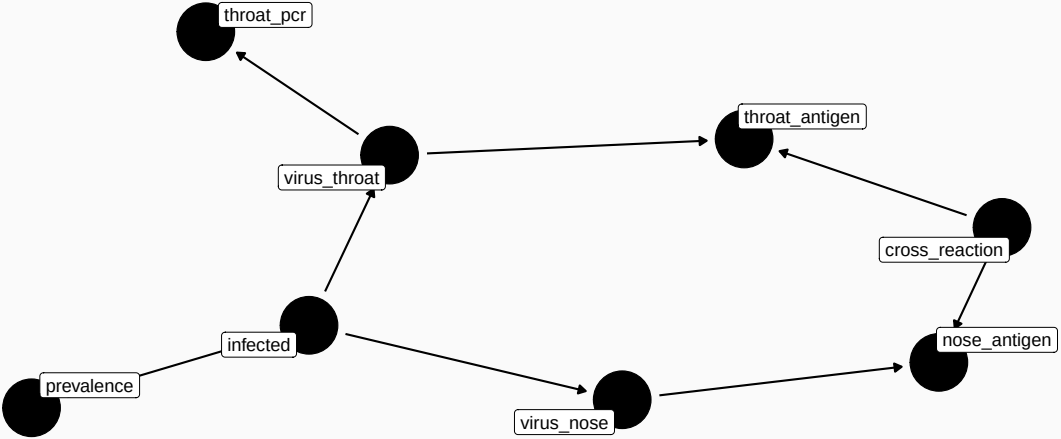
  - The virus may be present in the throat, nose, neither, or both
  - But we use the same antigen test twice
    - Might it cross-react with the same non-target virus?
- In both situations we have pairwise correlation between some of the tests

# Directed Acyclic Graphs

- It may help you to visualise the relationships as a DAG:



- Or with explicit antigen test crossreaction:



## Dealing with correlation: Covid example

It helps to consider the data simulation as a (simplified) biological process (where my parameters are not representative of real life!):

```
# The probability of infection with COVID in two populations:
prevalence <- c(0.01,0.05)
# The probability of shedding COVID in the nose conditional on infection:
nose_shedding <- 0.8
# The probability of shedding COVID in the throat conditional on infection:
throat_shedding <- 0.8
# The probability of detecting virus with the antigen test:
antigen_detection <- 0.75
# The probability of detecting virus with the PCR test:
pcr_detection <- 0.999
# The probability of random cross-reaction with the antigen test:
antigen_crossreact <- 0.05
# The probability of random cross-reaction with the PCR test:
pcr_crossreact <- 0.01
```

## Dealing with correlation: Covid example

It helps to consider the data simulation as a (simplified) biological process (where my parameters are not representative of real life!):

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# The probability of infection with COVID in two populations:
prevalence <- c(0.01,0.05)
# The probability of shedding COVID in the nose conditional on infection:
nose_shedding <- 0.8
# The probability of shedding COVID in the throat conditional on infection:
throat_shedding <- 0.8
# The probability of detecting virus with the antigen test:
antigen_detection <- 0.75
# The probability of detecting virus with the PCR test:
pcr_detection <- 0.999
# The probability of random cross-reaction with the antigen test:
antigen_crossreact <- 0.05
# The probability of random cross-reaction with the PCR test:
pcr_crossreact <- 0.01
```

Note: cross-reactions are assumed to be independent here!

Simulating latent states:

```
N <- 20000
Populations <- length(prevalence)

covid_data <- tibble(Population = sample(seq_len(Populations), N, replace=TRUE)) %>%
  ## True infection status:
  mutate(Status = rbinom(N, 1, prevalence[Population])) %>%
  ## Nose shedding status:
  mutate(Nose = Status * rbinom(N, 1, nose_shedding)) %>%
  ## Throat shedding status:
  mutate(Throat = Status * rbinom(N, 1, throat_shedding))
```

Simulating test results:

```
covid_data <- covid_data %>%
  ## The nose swab antigen test may be false or true positive:
  mutate(NoseAG = case_when(
    Nose == 1 ~ rbinom(N, 1, antigen_detection),
    Nose == 0 ~ rbinom(N, 1, antigen_crossreact)
  )) %>%
  ## The throat swab antigen test may be false or true positive:
  mutate(ThroatAG = case_when(
    Throat == 1 ~ rbinom(N, 1, antigen_detection),
    Throat == 0 ~ rbinom(N, 1, antigen_crossreact)
  )) %>%
  ## The PCR test may be false or true positive:
  mutate(ThroatPCR = case_when(
    Throat == 1 ~ rbinom(N, 1, pcr_detection),
    Throat == 0 ~ rbinom(N, 1, pcr_crossreact)
  ))
```

The overall sensitivity of the tests can be calculated as follows:

```
covid_sensitivity <- c(
  # Nose antigen:
  nose_shedding*antigen_detection + (1-nose_shedding)*antigen_crossreact,
  # Throat antigen:
  throat_shedding*antigen_detection + (1-throat_shedding)*antigen_crossreact,
  # Throat PCR:
  throat_shedding*pcr_detection + (1-throat_shedding)*pcr_crossreact
)
covid_sensitivity
## [1] 0.6100 0.6100 0.8012
```

The overall specificity of the tests is more straightforward:

```
covid_specificity <- c(
  # Nose antigen:
  1 - antigen_crossreact,
  # Throat antigen:
  1 - antigen_crossreact,
  # Throat PCR:
  1 - pcr_crossreact
)
covid_specificity
## [1] 0.95 0.95 0.99
```

The overall specificity of the tests is more straightforward:

```
covid_specificity <- c(
  # Nose antigen:
  1 - antigen_crossreact,
  # Throat antigen:
  1 - antigen_crossreact,
  # Throat PCR:
  1 - pcr_crossreact
)
covid_specificity
## [1] 0.95 0.95 0.99
```

However: this assumes that cross-reactions are independent!

# Model specification

```
prob[1,p] <-  prev[p] * ((1-se[1])*(1-se[2])*(1-se[3])
                         +covse12 +covse13 +covse23) +
              (1-prev[p]) * (sp[1]*sp[2]*sp[3]
                             +covsp12 +covsp13 +covsp23)

prob[2,p] <- prev[p] * (se[1]*(1-se[2])*(1-se[3])
                           -covse12 -covse13 +covse23) +
               (1-prev[p]) * ((1-sp[1])*sp[2]*sp[3]
                              -covsp12 -covsp13 +covsp23)

## snip ##

# Covariance in sensitivity between tests 1 and 2:
covse12 ~ dunif( (se[1]-1)*(1-se[2]) ,
                 min(se[1],se[2]) - se[1]*se[2] )
# Covariance in specificity between tests 1 and 2:
covsp12 ~ dunif( (sp[1]-1)*(1-sp[2]) ,
                 min(sp[1],sp[2]) - sp[1]*sp[2] )
```

# Model specification

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prob[1,p] <-  prev[p] * ((1-se[1])*(1-se[2])*(1-se[3])
                         +covse12 +covse13 +covse23) +
              (1-prev[p]) * (sp[1]*sp[2]*sp[3]
                             +covsp12 +covsp13 +covsp23)

prob[2,p] <- prev[p] * (se[1]*(1-se[2])*(1-se[3])
                           -covse12 -covse13 +covse23) +
               (1-prev[p]) * ((1-sp[1])*sp[2]*sp[3]
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## snip ##

# Covariance in sensitivity between tests 1 and 2:
covse12 ~ dunif( (se[1]-1)*(1-se[2]) ,
                      min(se[1],se[2]) - se[1]*se[2] )
# Covariance in specificity between tests 1 and 2:
covsp12 ~ dunif( (sp[1]-1)*(1-sp[2]) ,
                      min(sp[1],sp[2]) - sp[1]*sp[2] )
```

It is quite easy to get the terms slightly wrong!

# Template Hui-Walter

The model code and data format for an arbitrary number of populations (and tests) can be determined automatically using the template_huiwalter function from the runjags package:

```
template_huiwalter(
  covid_data %>% select(Population, NoseAG, ThroatAG, ThroatPCR),
  outfile = 'covidmodel.txt')
```

This generates self-contained model/data/initial values etc

```
model{

    ## Observation layer:

    # Complete observations (N=20000):
    for(p in 1:Populations){
        Tally_RRR[1:8,p] ~ dmulti(prob_RRR[1:8,p], N_RRR[p])

        prob_RRR[1:8,p] <- se_prob[1:8,p] + sp_prob[1:8,p]
    }


    ## Observation probabilities:

    for(p in 1:Populations){

        # Probability of observing NoseAG- ThroatAG- ThroatPCR- from a true positive::
        se_prob[1,p] <- prev[p] * ((1-se[1])*(1-se[2])*(1-se[3]) +covse12 +covse13 +covse23)
        # Probability of observing NoseAG- ThroatAG- ThroatPCR- from a true negative::
        sp_prob[1,p] <- (1-prev[p]) * (sp[1]*sp[2]*sp[3] +covsp12 +covsp13 +covsp23)

        # Probability of observing NoseAG+ ThroatAG- ThroatPCR- from a true positive::
        se_prob[2,p] <- prev[p] * (se[1]*(1-se[2])*(1-se[3]) -covse12 -covse13 +covse23)
        # Probability of observing NoseAG+ ThroatAG- ThroatPCR- from a true negative::
        sp_prob[2,p] <- (1-prev[p]) * ((1-sp[1])*sp[2]*sp[3] -covsp12 -covsp13 +covsp23)
```

```
## Data:
data{
"Populations" <- 2
"N_RRR" <- c(10044, 9956)
"Tally_RRR" <- structure(c(8864, 515, 496, 24, 70, 18, 16, 41, 8454, 513, 443, 23, 146, 72,
↪  127, 178), .Dim = c(8, 2))
}
```

And can be run directly from R:

```
results <- run.jags('covidmodel.txt')
## Loading required namespace: rjags
results
```

| | Lower95 | Median | Upper95 | SSeff | psrf |
|---|---|---|---|---|---|
| se[1] | 0.537 | 0.589 | 0.639 | 6806 | 1.000 |
| se[2] | 0.644 | 0.697 | 0.751 | 5335 | 1.000 |
| se[3] | 0.952 | 0.986 | 1.000 | 5525 | 1.002 |
| sp[1] | 0.941 | 0.945 | 0.948 | 12043 | 1.000 |
| sp[2] | 0.946 | 0.949 | 0.952 | 11782 | 1.000 |
| sp[3] | 0.990 | 0.992 | 0.994 | 4930 | 1.000 |
| prev[1] | 0.006 | 0.008 | 0.010 | 8301 | 1.000 |
| prev[2] | 0.039 | 0.044 | 0.049 | 6046 | 1.001 |
| covse12 | 0.000 | 0.000 | 0.000 | NA | NA |
| covsp12 | 0.000 | 0.000 | 0.000 | NA | NA |
| covse13 | 0.000 | 0.000 | 0.000 | NA | NA |
| covsp13 | 0.000 | 0.000 | 0.000 | NA | NA |
| covse23 | 0.000 | 0.000 | 0.000 | NA | NA |
| covsp23 | 0.000 | 0.000 | 0.000 | NA | NA |

## Template Hui-Walter

- Modifying priors must still be done directly in the model file
  - Same for adding .RNG.seed and the deviance monitor
- The model needs to be re-generated if the data changes
  - But remember that your modified priors will be reset
- There must be a single column for the population (as a factor), and all of the other columns (either factor, logical or numeric) are interpreted as being test results

- Covariance terms are also calculated as proportion of possible correlation e.g.:

```
# Covariance in sensitivity between NoseAG and ThroatAG tests:
# covse12 ~ dunif( (se[1]-1)*(1-se[2]) , min(se[1],se[2]) - se[1]*se[2] )  ## if the
↪  sensitivity of these tests may be correlated
covse12 <- 0  ## if the sensitivity of these tests can be assumed to be independent
# Calculated relative to the min/max for ease of interpretation:
corse12 <- ifelse(covse12 < 0, -covse12 / ((se[1]-1)*(1-se[2])), covse12 /
↪  (min(se[1],se[2]) - se[1]*se[2]))
```

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↪  (min(se[1],se[2]) - se[1]*se[2]))
```

- But covariance terms are all deactivated by default!

# Activating covariance terms

Find the lines for the covariances that we want to activate (i.e. the two Throat tests):

```
# Covariance in sensitivity between ThroatAG and ThroatPCR tests:
# covse23 ~ dunif( (se[2]-1)*(1-se[3]) , min(se[2],se[3]) - se[2]*se[3] )  ## if the
↪  sensitivity of these tests may be correlated
covse23 <- 0  ## if the sensitivity of these tests can be assumed to be independent

# Covariance in specificity between ThroatAG and ThroatPCR tests:
# covsp23 ~ dunif( (sp[2]-1)*(1-sp[3]) , min(sp[2],sp[3]) - sp[2]*sp[3] )  ## if the
↪  specificity of these tests may be correlated
covsp23 <- 0  ## if the specificity of these tests can be assumed to be independent
```

And edit so it looks like:

```
# Covariance in sensitivity between ThroatAG and ThroatPCR tests:
covse23 ~ dunif( (se[2]-1)*(1-se[3]) , min(se[2],se[3]) - se[2]*se[3] )  ## if the
↪  sensitivity of these tests may be correlated
 # covse23 <- 0  ## if the sensitivity of these tests can be assumed to be independent

# Covariance in specificity between ThroatAG and ThroatPCR tests:
covsp23 ~ dunif( (sp[2]-1)*(1-sp[3]) , min(sp[2],sp[3]) - sp[2]*sp[3] )  ## if the
↪  specificity of these tests may be correlated
 # covsp23 <- 0  ## if the specificity of these tests can be assumed to be independent
```

[i.e. swap the comments around]

You will also need to uncomment out the relevant initial values for BOTH chains (on lines 132-137 and 128-133):

```
# "covse12" <- 0
# "covse13" <- 0
# "covse23" <- 0
# "covsp12" <- 0
# "covsp13" <- 0
# "covsp23" <- 0
```

So that they look like:

```
# "covse12" <- 0
# "covse13" <- 0
"covse23" <- 0
# "covsp12" <- 0
# "covsp13" <- 0
"covsp23" <- 0
```

```
results <- run.jags('covidmodel.txt', sample=50000)
results
##
## JAGS model summary statistics from 100000 samples (chains = 2; adapt+burnin = 5000):
##
##             Lower95     Median    Upper95       Mean
## se[1]       0.53404     0.5882    0.64399    0.58823
## se[2]       0.55629    0.65527    0.73666     0.6509
## se[3]       0.85842    0.96466    0.99999    0.95117
## sp[1]       0.94154    0.94506    0.94867    0.94508
## sp[2]       0.94517    0.94851    0.95177     0.9485
## sp[3]       0.98957    0.99168    0.99374    0.99166
## prev[1]   0.0057376  0.0078993    0.01026  0.0079707
## prev[2]    0.039606   0.045369   0.052683     0.0457
## covse12           0          0          0          0
## corse12           0          0          0          0
## covsp12           0          0          0          0
## corsp12           0          0          0          0
## covse13           0          0          0          0
## corse13           0          0          0          0
## covsp13           0          0          0          0
## corsp13           0          0          0          0
## covse23  -0.0062452   0.010798   0.052363    0.01578
## corse23    -0.56104     0.5141          1    0.41839
## covsp23 -0.00032519 0.00019951 0.00069713 0.00020264
## corsp23    -0.59595    0.025357    0.12289  -0.054898
```

## Practical considerations

- Correlation terms add complexity to the model in terms of:
  - Opportunity to make a coding mistake
  - Reduced identifiability

## Practical considerations

- Correlation terms add complexity to the model in terms of:
  - Opportunity to make a coding mistake
  - Reduced identifiability
- The template_huiwalter function helps us with coding mistakes
- Only careful consideration of covariance terms can help us with identifiability

# How to interpret the latent class

## What exactly is our latent class?

Think about what exactly the latent class is in these situations:

1. An antigen plus antibody test

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2. Two antibody tests

## What exactly is our latent class?

Think about what exactly the latent class is in these situations:

1. An antigen plus antibody test

- The latent status is probably close to the true disease status

2. Two antibody tests

- The latent status is actually ‘producing antibodies’
  - And not ‘diseased’ !!!

## What exactly is our latent class?

Think about what exactly the latent class is in these situations:

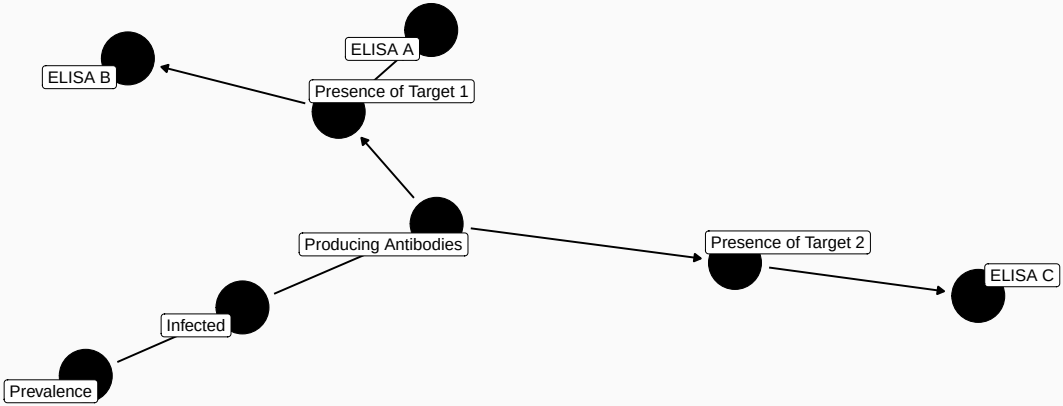
1. An antigen plus antibody test

- The latent status is probably close to the true disease status

2. Two antibody tests

- The latent status is actually ‘producing antibodies’
  - And not ‘diseased’ !!!
- What do we mean by “conditionally independent”?
  - Independent of each other conditional on the latent state
  - But the latent state is NOT always *disease*

# A hierarchy of latent states



## What is sensitivity and specificity?

- The probability of test status conditional on true disease status?
- The probability of test status conditional on the latent state?

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So is the latent state the same as the true disease state?

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- The probability of test status conditional on true disease status?
- The probability of test status conditional on the latent state?

So is the latent state the same as the true disease state?

Important quote:

"Latent class models involve pulling **something** out of a hat, and deciding to call it a rabbit"

- Nils Toft

# When should we correct for correlation?

Aims:

- To get you to think about when and why we should try to correct for correlation
- To get you to think about what is NOT achieved by including correlation terms

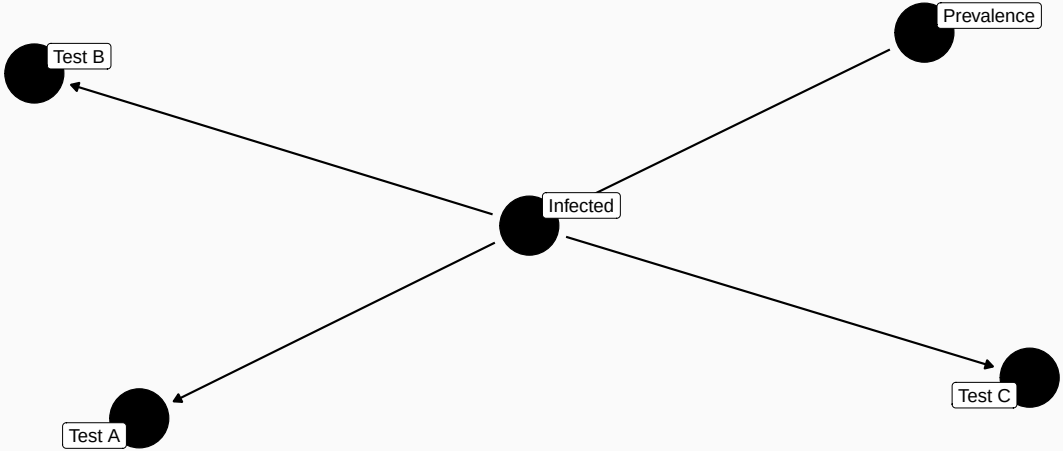
## When should we correct for correlation?

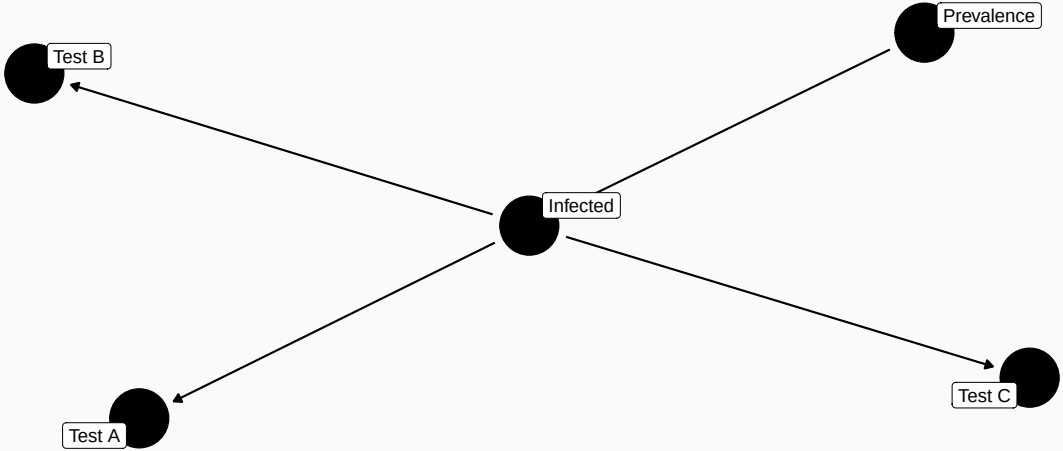
Aims:

- To get you to think about when and why we should try to correct for correlation
- To get you to think about what is NOT achieved by including correlation terms

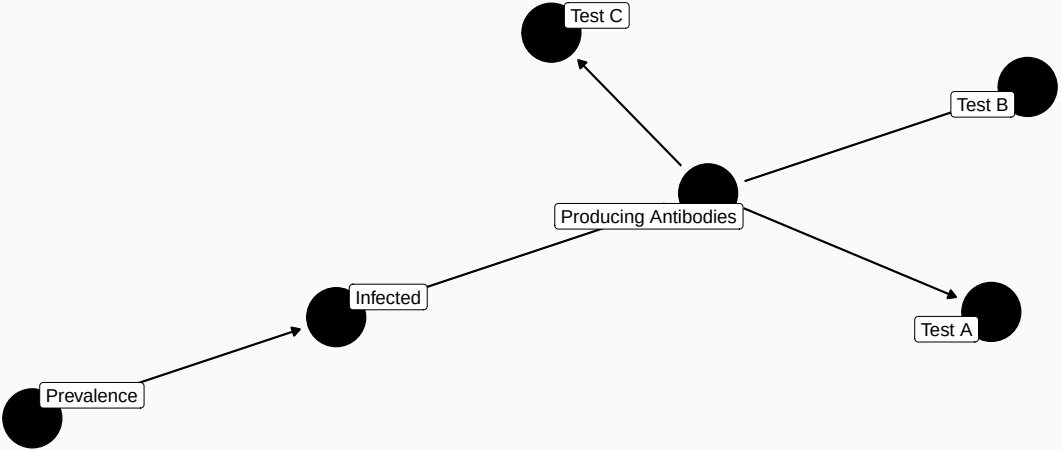
Main discussion points for each example:

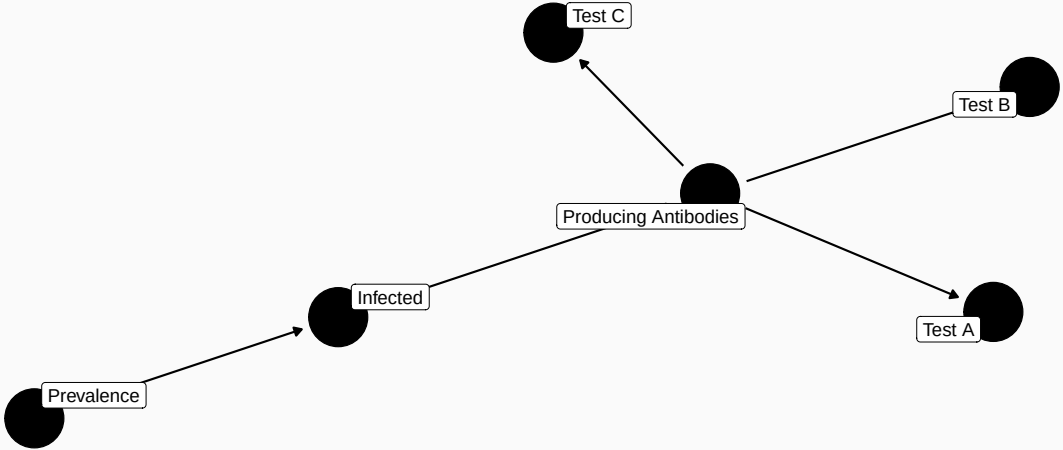
- What is the latent class
- Which correlation terms should we include and why


Prevalence
Test B
Infected
Test A
Test C

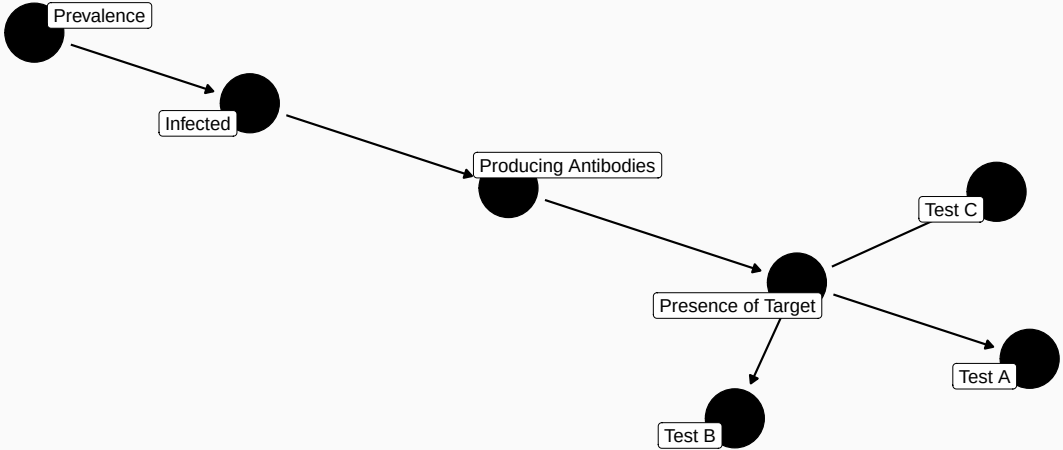


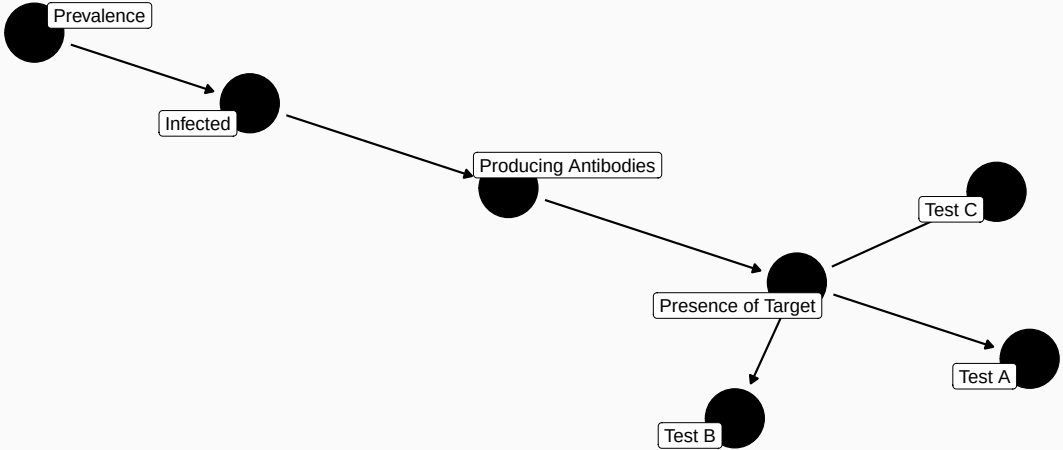

- No correlation to model!


Test C
Test B
Producing Antibodies
Infected
Test A
Prevalence

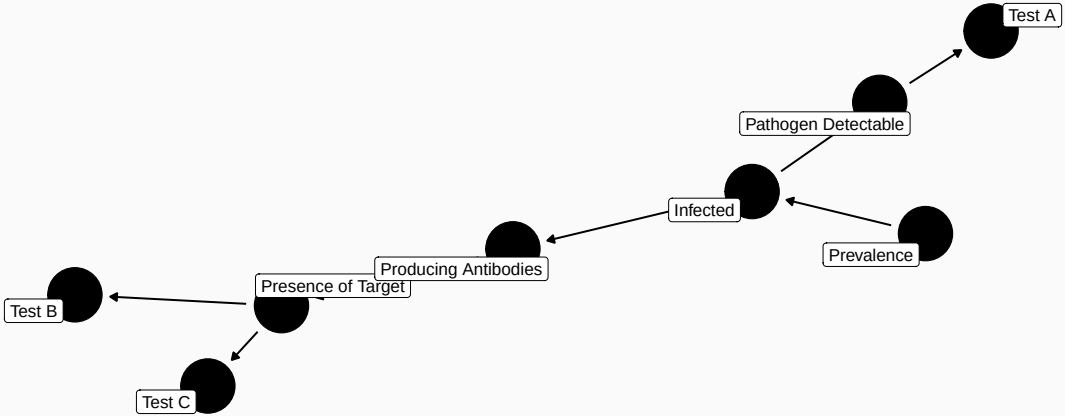


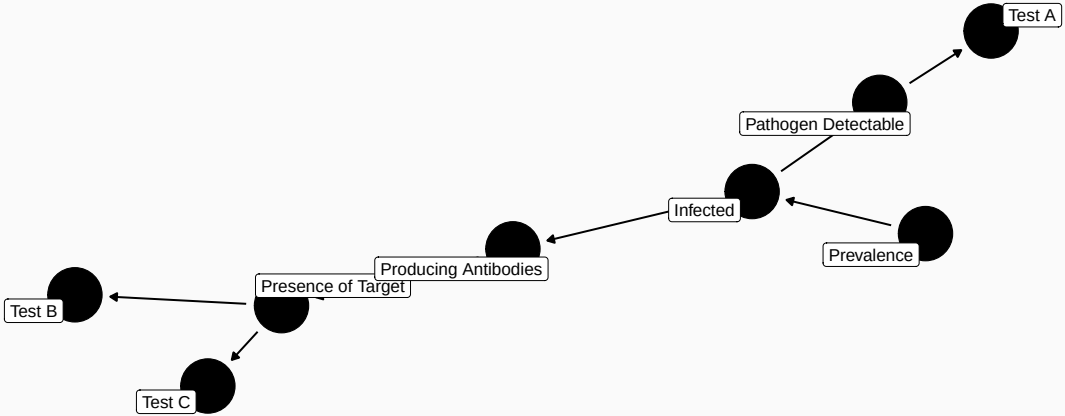

- No correlation to model . . . but “infected” is not the latent class


Prevalence
Infected
Producing Antibodies
Test C
Presence of Target
Test A
Test B

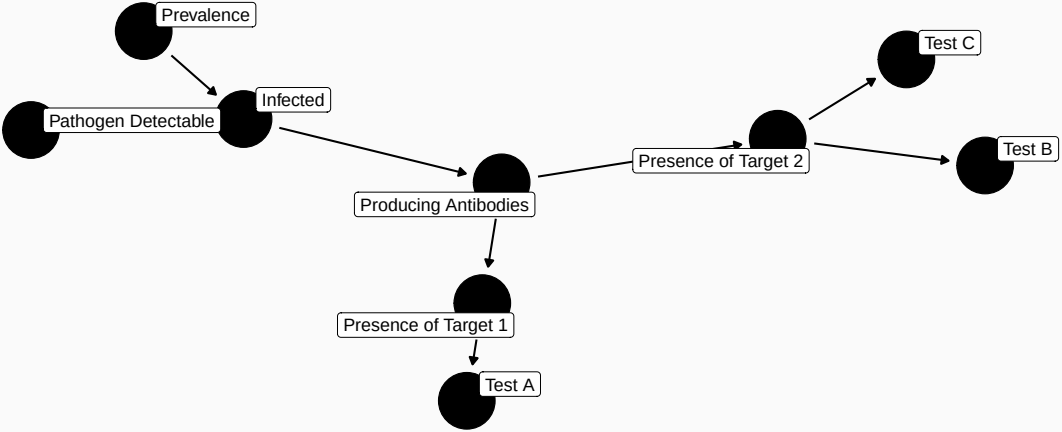


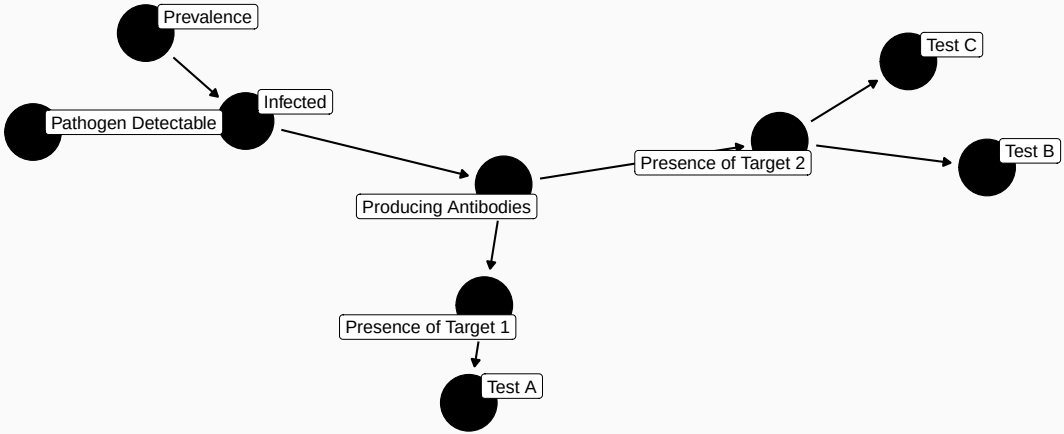

- Same as above!


Test A
Pathogen Detectable
Infected
Prevalence
Producing Antibodies
Presence of Target
Test B
Test C

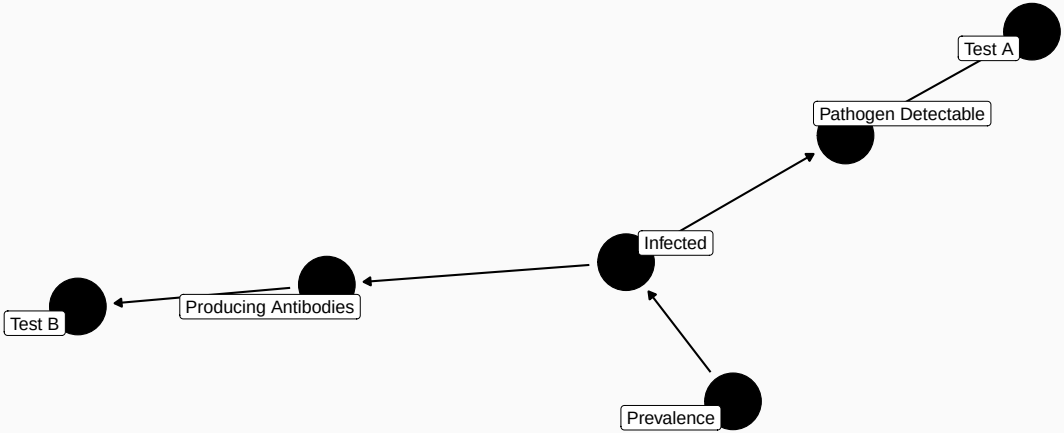


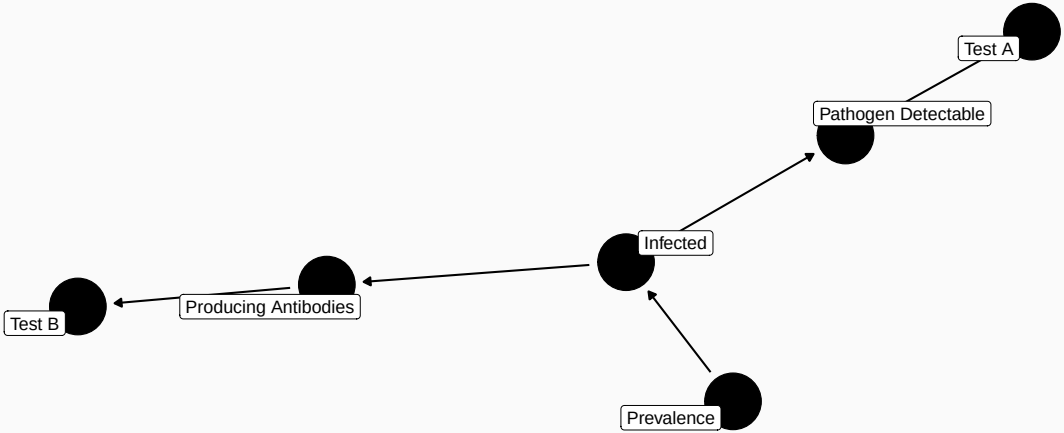

- Tests B and C are correlated


Prevalence
Infected
Pathogen Detectable
Producing Antibodies
Presence of Target 2
Test C
Test B
Presence of Target 1
Test A

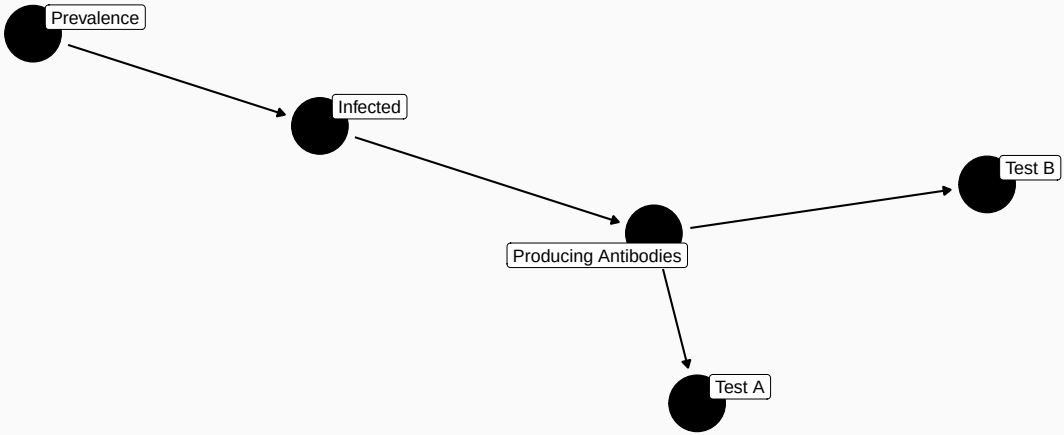


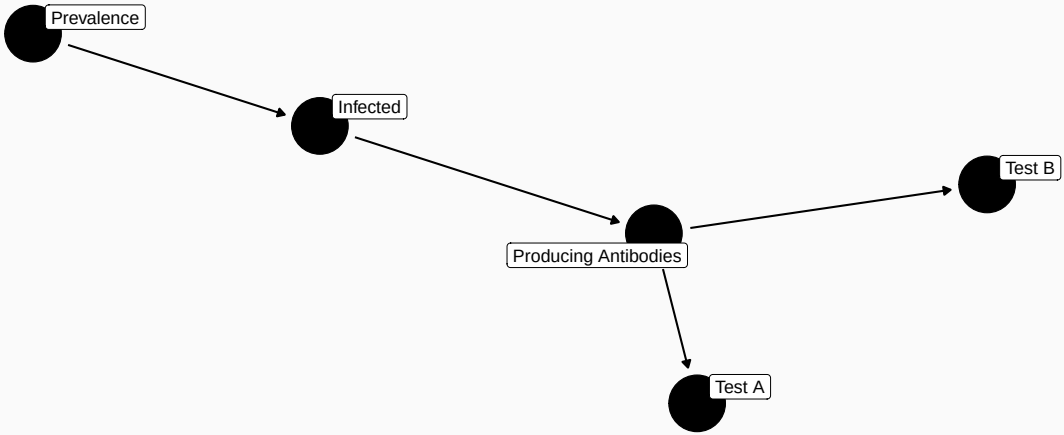

- All tests are correlated with respect to infected BUT infected is not the latent class
- Tests B and C are correlated with respect to antibodies - but maybe not substantially?


Test A
Pathogen Detectable
Infected
Producing Antibodies
Test B
Prevalence




- No correlation to model


Prevalence
Infected
Producing Antibodies
Test B
Test A




- No correlation to model - but “infected” is not the latent class

## Publication of your results

STARD-BLCM: A helpful structure to ensure that papers contain all necessary information

- You should follow this and refer to it in your articles!

## Publication of your results

STARD-BLCM: A helpful structure to ensure that papers contain all necessary information

- You should follow this and refer to it in your articles!

If you use the software, please cite JAGS:

- Plummer, M. (2003). JAGS : A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling JAGS : Just Another Gibbs Sampler. Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003), March 20–22,Vienna, Austria. ISSN 1609-395X. https://doi.org/10.1.1.13.3406

## And R:

```
citation()
##
## To cite R in publications use:
##
##   R Core Team (2022). R: A language and environment
##   for statistical computing. R Foundation for
##   Statistical Computing, Vienna, Austria. URL
##   https://www.R-project.org/.
##
## A BibTeX entry for LaTeX users is
##
##   @Manual{,
##     title = {R: A Language and Environment for Statistical Computing},
##     author = {{R Core Team}},
##     organization = {R Foundation for Statistical Computing},
##     address = {Vienna, Austria},
##     year = {2022},
##     url = {https://www.R-project.org/},
##   }
##
## We have invested a lot of time and effort in creating
## R, please cite it when using it for data analysis.
## See also 'citation("pkgname")' for citing R packages.
```

And runjags:

```
citation("runjags")
##
## To cite runjags in publications use:
##
##   Matthew J. Denwood (2016). runjags: An R Package
##   Providing Interface Utilities, Model Templates,
##   Parallel Computing Methods and Additional
##   Distributions for MCMC Models in JAGS. Journal of
##   Statistical Software, 71(9), 1-25.
##   doi:10.18637/jss.v071.i09
##
## A BibTeX entry for LaTeX users is
##
##   @Article{,
##     title = {{runjags}: An {R} Package Providing Interface Utilities, Model Templates,
↪  Parallel Computing Methods and Additional Distributions for {MCMC} Models in {JAGS}},
##     author = {Matthew J. Denwood},
##     journal = {Journal of Statistical Software},
##     year = {2016},
##     volume = {71},
##     number = {9},
##     pages = {1--25},
##     doi = {10.18637/jss.v071.i09},
```

# Practical session 4

## Points to consider

1. How does including a third test impact the inference for the first two tests?
2. What happens if we include correlation between tests?

## Summary

- Including multiple tests is technically easy
  - But philosophically more difficult!!!
- Complexity of adding correlation terms increases non-linearly with more tests
  - Probably best to stick to correlations with biological justification?
- Adding/removing test results may change the posterior for
  - Other test Se / Sp
  - Prevalence