Patients with presumed tuberculosis in sub-Saharan Africa that are not diagnosed with tuberculosis: a systematic review and meta-analysis (statistical appendix)

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Contents

Pre-amble

This document is generated from an R script in literate programming fashion. Some code, output and figures are specified for inclusion of the output document. The script and data are publicly available on GitHub at https://github.com/petedodd/NotTB and once the repository is downloaded, it should be possible to generate this document using R with the command `rmarkdown::render('NotTBmeta.R')` within R, or from a unix-like command line with `R -q -e "rmarkdown::render(\"NotTBmeta.R\",output_dir=\"./output\")"`. Alternatively, the R script can be run in whole or part as a conventional R script.

Dependencies

To compile this document, the rmarkdown & knitr packages must be installed. The other R packages required to run this analysis should be installed if necessary, and loaded, with:

```
pkgs.needed <- c("ggplot2","scales","cowplot","ggpubr", #graphs
                 "data.table","here",                   #data mgt
                 "metafor")                             #metaanalysis
install.packages(setdiff(pkgs.needed, rownames(installed.packages())))
suppressMessages(
    devnull <- lapply(pkgs.needed, require, character.only = TRUE) #load for use
)
```

This analysis was run using:

```
sI <- sessionInfo()
dI <- data.frame(
    item=c('R version','platform','OS','metafor version'),
    version=c(
        sI$R.version$version.string, #R version
        sI$platform,                 #platofm
        sI$running,                  #OS
        sI$otherPkgs$metafor$Version #metafor version
    )
)
knitr::kable(dI)
```

item	version
R version	R version 4.1.0 (2021-05-18)
platform	x86_64-pc-linux-gnu (64-bit)
OS	Pop!_OS 21.04
metafor version	3.0-2

Main analysis

We use a random-effects meta-analysis assuming a binomial response and logit link.

$$k_i \sim \text{Binomial}(N_i, p_i)$$
$$\text{logit}(p_i) = \mu + \varepsilon_i$$
$$\varepsilon_i \sim \mathcal{N}(0, \sigma)$$

where $k = 1, \ldots, S$ indexes the numbers of studies.

Use of arcinse or double arcsine transformations has been criticized in this context, with the binomial model above recommended.[1]

check formulae

Read in the data and ensure that factors behave as intended:

```
DD <- fread(file=here('SRMAdata.csv'))
DD[,lab:=factor(lab,levels=rev(DD[order(bac)]$lab),ordered = TRUE)]
```

Create exact binomial confidence intervals:

```
ciz <- function(x,y){
    x <- as.integer(x); y <- as.integer(y)
    list(binom.test(x,y)$conf.int[1],binom.test(x,y)$conf.int[2])
}
DD[,`NotTB Proportion`:=NnotTB/N]
for(i in 1:nrow(DD)){ DD[i,c('lo','hi'):=ciz(NnotTB,N)]; }
DD[,SE:=(hi-lo)/3.92]
```

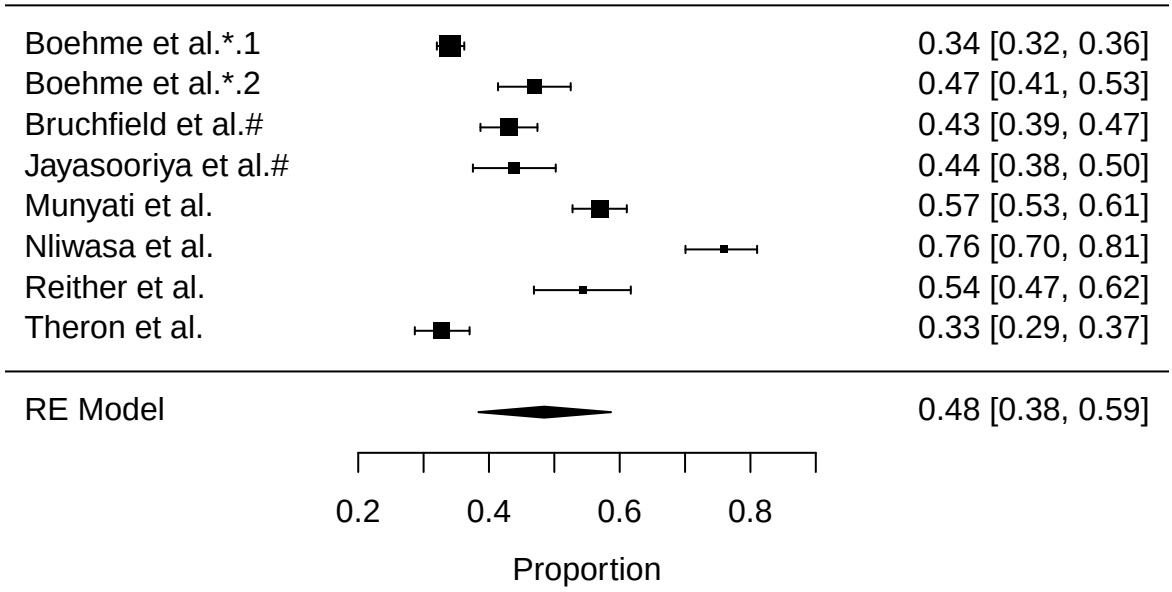
Meta-analysis for passively found TB patients with bacteriologically unconfirmed TB included:

[1] link to paper

```
maPU <- rma(measure = "PLO", #  binomial w/ logit link
            xi = NnotTB,     # numerator
            ni = N,          # denominator
            data = DD[mode=='Passive' &
                      clinical=='(Unconfirmed TB included)'],
            slab = Author)      # what to use as labels on graphs
summary(maPU)
```

```
##
## Random-Effects Model (k = 8; tau^2 estimator: REML)
##
##   logLik  deviance       AIC       BIC      AICc
##  -6.3265   12.6530   16.6530   16.5448   19.6530
##
## tau^2 (estimated amount of total heterogeneity): 0.3403 (SE = 0.1888)
## tau (square root of estimated tau^2 value):      0.5833
## I^2 (total heterogeneity / total variability):   97.41%
## H^2 (total variability / sampling variability):  38.63
##
## Test for Heterogeneity:
## Q(df = 7) = 221.8886, p-val < .0001
##
## Model Results:
##
## estimate      se     zval    pval    ci.lb   ci.ub
##  -0.0614  0.2101  -0.2920  0.7703  -0.4732  0.3505
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
forest(maPU,transf = transf.ilogit,refline=NA)
```



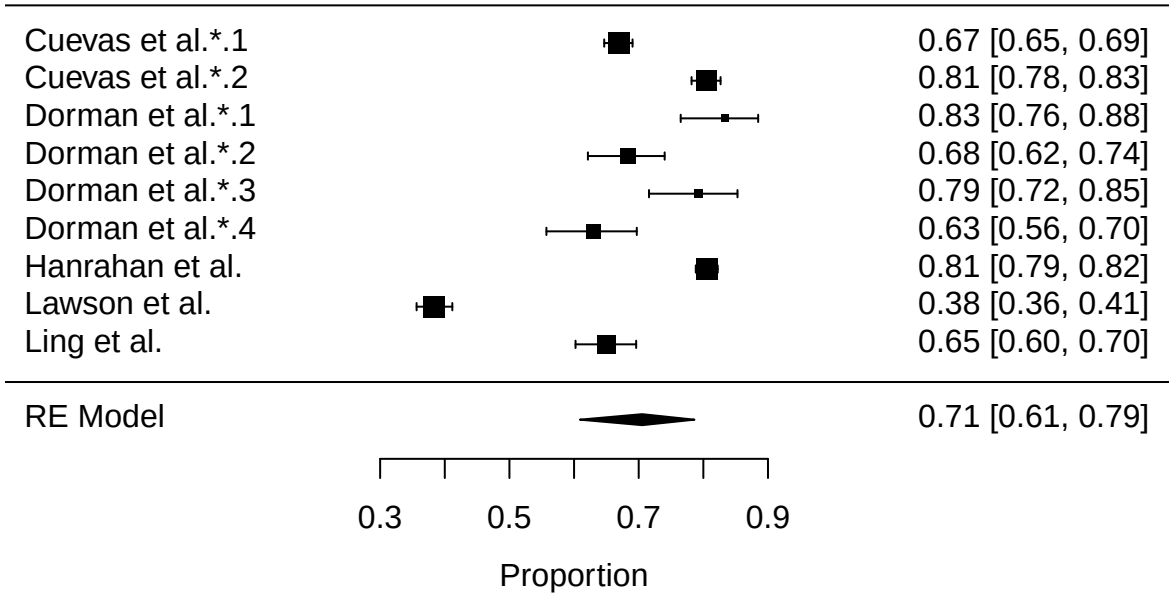
Meta-analysis for passively found TB patients with bacteriologically unconfirmed TB excluded:

```
maPN <- rma(measure = "PLO", #  binomial w/ logit link
            xi = NnotTB,     # numerator
```

```
            ni = N,          # denominator
            data = DD[mode=='Passive' &
                      clinical=='(No unconfirmed TB)'],
            slab = Author)      # what to use as labels on graphs
summary(maPN)
```

```
##
## Random-Effects Model (k = 9; tau^2 estimator: REML)
##
##   logLik  deviance       AIC       BIC      AICc
##  -7.9621   15.9243   19.9243   20.0832   22.3243
##
## tau^2 (estimated amount of total heterogeneity): 0.4153 (SE = 0.2163)
## tau (square root of estimated tau^2 value):      0.6445
## I^2 (total heterogeneity / total variability):   98.34%
## H^2 (total variability / sampling variability):  60.10
##
## Test for Heterogeneity:
## Q(df = 8) = 679.9414, p-val < .0001
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   0.8728  0.2193  3.9803  <.0001  0.4430  1.3025  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
forest(maPN,transf = transf.ilogit,refline=NA)
```



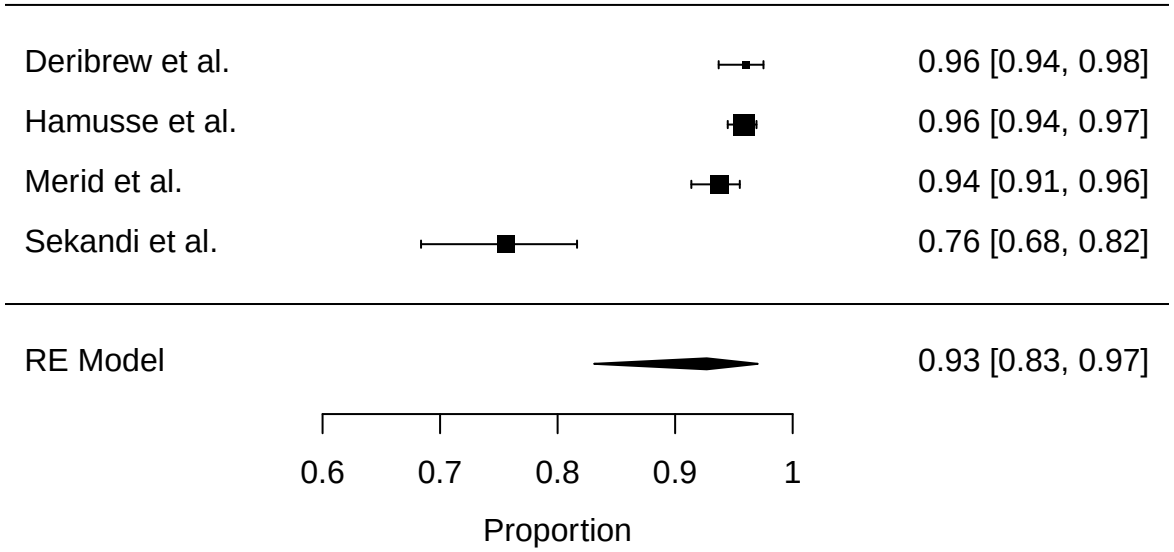
Meta-analysis for actively found TB patients:

```
maA <- rma(measure = "PLO", #  binomial w/ logit link
            xi = NnotTB,     # numerator
            ni = N,          # denominator
            data = DD[mode=='Active'],
```

```
            slab = Author)      # what to use as labels on graphs
summary(maA)
```

```
##
## Random-Effects Model (k = 4; tau^2 estimator: REML)
##
##   logLik  deviance       AIC       BIC      AICc
##  -4.1508    8.3015   12.3015   10.4987   24.3015
##
## tau^2 (estimated amount of total heterogeneity): 0.8952 (SE = 0.7615)
## tau (square root of estimated tau^2 value):      0.9462
## I^2 (total heterogeneity / total variability):   96.27%
## H^2 (total variability / sampling variability):  26.82
##
## Test for Heterogeneity:
## Q(df = 3) = 81.2135, p-val < .0001
##
## Model Results:
##
## estimate      se    zval    pval   ci.lb   ci.ub
##   2.5396  0.4829  5.2593  <.0001  1.5932  3.4861  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
forest(maA,transf = transf.ilogit,refline=NA)
```



Make predictions for plot data:

```
map <- predict(maA,transf = transf.ilogit)
mup <- predict(maPU,transf = transf.ilogit)
mnp <- predict(maPN,transf = transf.ilogit)
```

Summary data for combined forest plot:

```
f1 <- function(x)format(round(x,1),nsmall=1)
cnz <- c('(Unconfirmed TB included)',
         '(No unconfirmed TB)',
```

```
         '(No unconfirmed TB)')
predz <- data.table(mode=c('Passive','Passive','Active'),
                    clinical=cnz,
                    `NotTB Proportion` = c(mup$pred,mnp$pred,map$pred),
                    lo = c(mup$ci.lb,mnp$ci.lb,map$ci.lb),
                    hi = c(mup$ci.ub,mnp$ci.ub,map$ci.ub),
                    lab=paste0('SUMMARY (',expression(I^2),'=',
                               f1(c(maA$I2,maPN$I2,maPU$I2)),'%)')
                    )
predz[,SE:=(hi-lo)/3.92]
predz[,qty:='summary']
predz[,bac:=0]
predz[,mid:=`NotTB Proportion`]
predz[,CI:=paste0(f1(1e2*mid),' (',f1(1e2*lo),' - ',f1(1e2*hi),')')]
predz[,wt:='100.0%']
predz[,w:=1]
```

Appending plot data to inputs:

```
DD[,qty:='study']
DD[,mid:=`NotTB Proportion`]
DD[,CI:=paste0(f1(1e2*mid),' (',f1(1e2*lo),' - ',f1(1e2*hi),')')]
DD[,wt:=1/SE^2]
DD[,wtt:=sum(wt),by=.(mode,clinical)]
DD[,wt:=1e2*wt/wtt]
DD[,wt:=paste0(f1(wt),'%')]
DD[,w:=0]
```

Combined plot data:

```
B <- rbind(
    DD[,.(lab,`NotTB Proportion`,lo,hi,SE,mode,clinical,
          qty,bac,CI,wt,w)],
    predz[,.(lab,`NotTB Proportion`,lo,hi,SE,mode,clinical,
             qty,bac,CI,wt,w)]
)
lbz <- as.character(B[order(bac)]$lab)
lbz2 <- c(lbz[1:3],rev(lbz[-c(1:3)]))
B[,lab:=factor(lab,levels=lbz2,ordered = TRUE)]
B[,clinical.g:='Clinically diagnosed tuberculosis included']
B[clinical=='(No unconfirmed TB)',
  clinical.g:='No clinically diagnosed tuberculosis included']
B[mode=='Active',clinical.g:='']
B[,mode:=factor(mode,levels=c('Passive','Active'),ordered = TRUE)]
B[,clinical.g:=factor(clinical.g,levels=unique(clinical.g))]
labdat <- B[1]
labdat[,txt:=' weight (%)']
```

Create publication forest plot figure:

```
SA <- ggplot(B,aes(lab,y=`NotTB Proportion`,
                   ymin=lo,
                   ymax=hi,
                   col=qty)) +
    geom_point(aes(size=1/SE^2,shape=qty)) +
    geom_errorbar(aes(width=w/2)) +
```

```
    scale_y_continuous(label=percent,limits = c(0,NA))+
    scale_color_manual(values=c('study'="black",'summary'="blue"))+
    scale_shape_manual(values=c('study'=22,'summary'=23))+
    xlab('') +
    ylab('Proportion of patients with presumptive tuberculosis not diagnosed as tuberculosis')+
    facet_grid(mode + clinical.g ~ .,
               scales = 'free',space='free',
               switch='x'
               )+
    coord_flip() +
    guides(size='none',color='none',shape='none')+
    theme_classic() +
    theme(panel.spacing = unit(2, "lines"), #or 3
          strip.background = element_blank(),
          strip.placement = "outside") +
    geom_text(aes(x=lab,y=1.2,label=CI,hjust='right')) +
    geom_text(aes(x=lab,y=0.0,label=wt))+
    geom_text(data=labdat,aes(x=9.5,y=0,label=txt))+
    ggpubr::grids()

ggsave(SA,file=here('output/ForestPlot.pdf'),h=13,w=12)
ggsave(SA,file=here('output/ForestPlot.eps'),h=13,w=12)
```

Meta-regressions

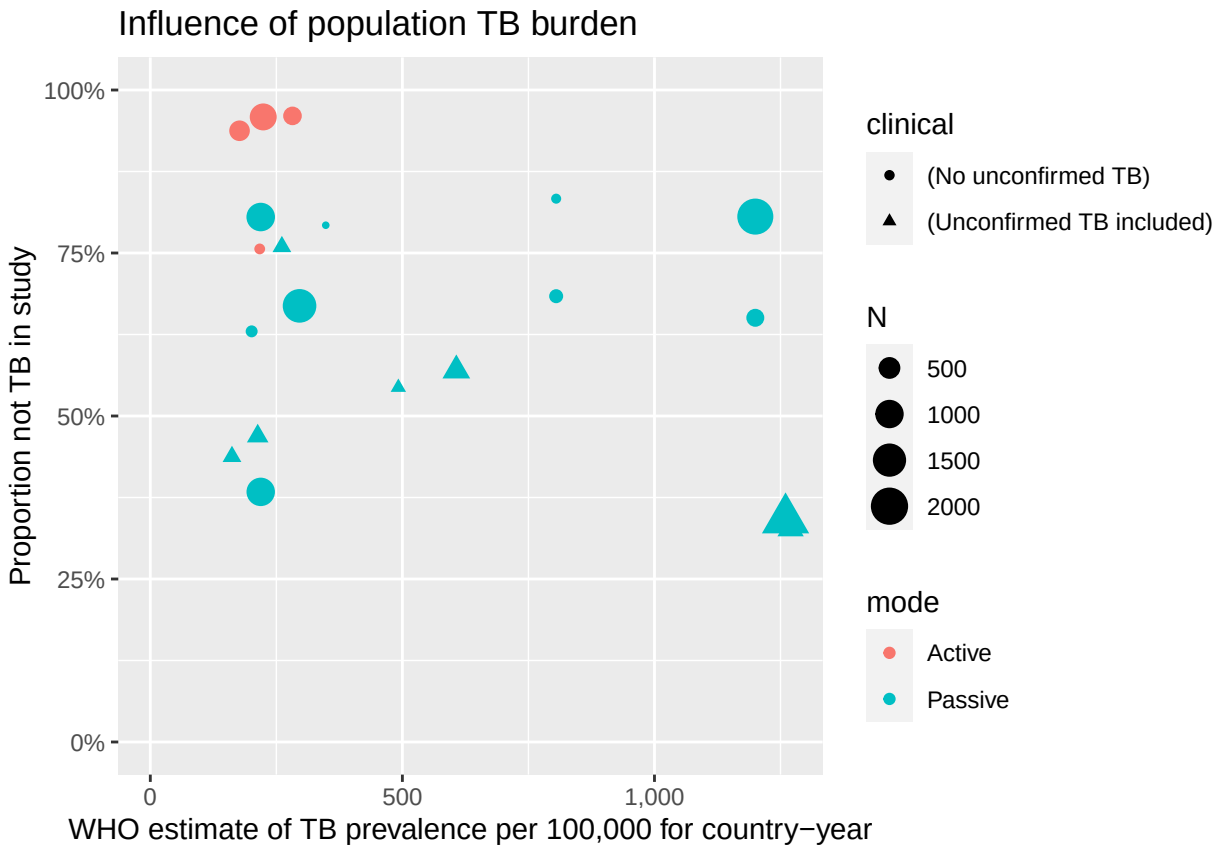
TB prevalence

The burden of TB in a population might reasonably be expected to influence the proportion of presumptive TB that is not TB.

```
DD[,tb:=`WHO TB estimate (per 100 000 year of study)`]

ggplot(DD,aes(tb,`NotTB Proportion`,
              size=N,col=mode,shape=clinical))+
    scale_x_continuous(label=comma,limits=c(0,NA))+
    scale_y_continuous(label=percent,limits=c(0,1))+
    geom_point()+
    xlab('WHO estimate of TB prevalence per 100,000 for country-year')+
    ylab('Proportion not TB in study')+
    ggtitle('Influence of population TB burden')
```

```
## Warning: Removed 1 rows containing missing values (geom_point).
```



We can formally investigating the influence of TB burden in explaining heterogeneity with a meta-regression:

```
tbmr <-  rma(measure = "PLO",  #binomial w/ logit link
             xi = NnotTB,      # numerator
             ni = N,           # denominator
             data = DD,         # what data to use
             mods = ~mode*clinical + tb)
```

```
## Warning: Studies with NAs omitted from model fitting.
```

```
## Warning: Redundant predictors dropped from the model.
```

```
summary(tbmr)
```

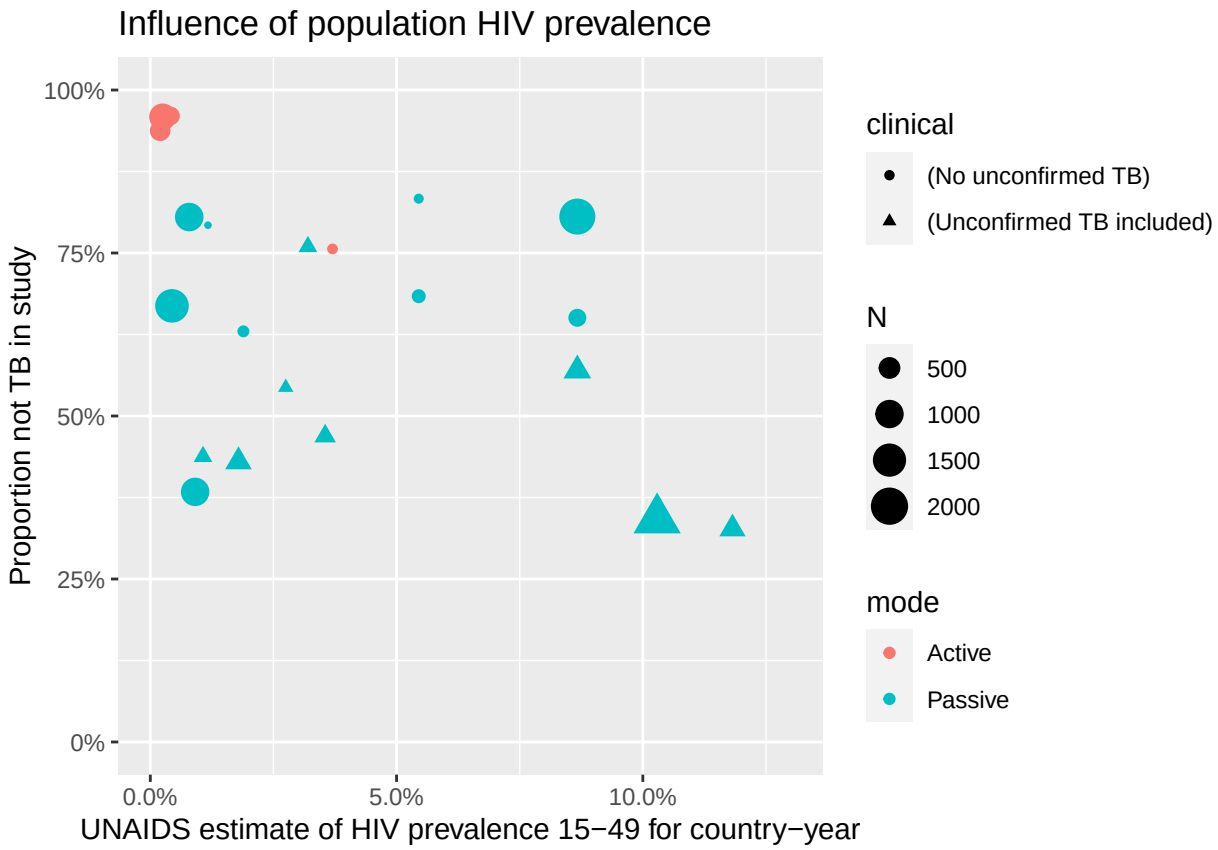
```
##
## Mixed-Effects Model (k = 20; tau^2 estimator: REML)
##
##   logLik  deviance       AIC       BIC      AICc
## -17.6992   35.3984   45.3984   49.2614   51.3984
##
## tau^2 (estimated amount of residual heterogeneity):     0.5137 (SE = 0.1887)
## tau (square root of estimated tau^2 value):             0.7167
## I^2 (residual heterogeneity / unaccounted variability): 98.12%
## H^2 (unaccounted variability / sampling variability):   53.20
## R^2 (amount of heterogeneity accounted for):            60.59%
##
## Test for Residual Heterogeneity:
## QE(df = 16) = 973.5088, p-val < .0001
##
```

```
## Test of Moderators (coefficients 2:4):
## QM(df = 3) = 30.9942, p-val < .0001
##
## Model Results:
##
##                                    estimate      se     zval    pval    ci.lb
## intrcpt                             2.5734  0.3838   6.7055  <.0001   1.8212
## modePassive                        -1.6053  0.4710  -3.4080  0.0007  -2.5286
## clinical(Unconfirmed TB included)  -0.8972  0.3667  -2.4465  0.0144  -1.6159
## tb                                 -0.0002  0.0004  -0.3650  0.7151  -0.0010
##                                     ci.ub
## intrcpt                            3.3256  ***
## modePassive                       -0.6821  ***
## clinical(Unconfirmed TB included) -0.1784    *
## tb                                 0.0007
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

HIV prevalence

Population HIV prevalence may plausibly influence the proportion of presumptives not diagnosed with TB both by inluencing TB burden, but also by changing the typical clinical characteristics of TB and most importantly, the burden of other illness that could be designated presumptive TB.

```
ggplot(DD,aes(hiv/1e2,`NotTB Proportion`,
              size=N,col=mode,shape=clinical))+
    scale_x_continuous(label=percent,limits=c(0,0.13))+
    scale_y_continuous(label=percent,limits=c(0,1))+
    geom_point()+
    xlab('UNAIDS estimate of HIV prevalence 15-49 for country-year')+
    ylab('Proportion not TB in study')+
    ggtitle('Influence of population HIV prevalence')
```



We can formally investigating the influence of HIV in explaining heterogeneity with a meta-regression:

```
hivmr <-  rma(measure = "PLO",  #binomial w/ logit link
              xi = NnotTB,      # numerator
              ni = N,           # denominator
              data = DD,         # what data to use
              mods = ~mode*clinical + hiv)
```

```
## Warning: Redundant predictors dropped from the model.
```

```
summary(hivmr)
```

```
##
## Mixed-Effects Model (k = 21; tau^2 estimator: REML)
##
##   logLik  deviance       AIC       BIC      AICc
## -18.1622   36.3244   46.3244   50.4904   51.7789
##
## tau^2 (estimated amount of residual heterogeneity):     0.4756 (SE = 0.1697)
## tau (square root of estimated tau^2 value):             0.6896
## I^2 (residual heterogeneity / unaccounted variability): 98.02%
## H^2 (unaccounted variability / sampling variability):   50.50
## R^2 (amount of heterogeneity accounted for):            63.48%
##
## Test for Residual Heterogeneity:
## QE(df = 17) = 973.1809, p-val < .0001
##
## Test of Moderators (coefficients 2:4):
```

```
## QM(df = 3) = 36.2039, p-val < .0001
##
## Model Results:
##
##                                    estimate      se     zval    pval    ci.lb
## intrcpt                              2.5749  0.3620   7.1120  <.0001   1.8653
## modePassive                         -1.5794  0.4443  -3.5546  0.0004  -2.4502
## clinical(Unconfirmed TB included)   -0.8771  0.3497  -2.5085  0.0121  -1.5624
## hiv                                 -0.0327  0.0467  -0.7010  0.4833  -0.1242
##                                      ci.ub
## intrcpt                             3.2845  ***
## modePassive                        -0.7085  ***
## clinical(Unconfirmed TB included)  -0.1918    *
## hiv                                 0.0587
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Sensitivity analyses

Regional groupings

TODO

Dorman by country

TODO

Grouping blah as a single study