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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Pre-amble

This document is generated from an R script in literate programming fashion. All R code is quoted in this document, together with output (preceded by '##') and figures. The article forest plot is saved to the output folder but not included in the document since it is too cramped. 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:

```
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$cotherPkgs$metafor$Version #metafor version
)
)
knitr::kable(dI)</pre>
```

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 analyses

Approach

We use a generalized linear mixed effects (GLMM) approach to meta-analysis assuming a binomial response and logit link¹. This means we assume

$$k_i \sim \text{Binomial}(N_i, p_i)$$

$$\log \text{it}(p_i) = \mu + \varepsilon_i$$

$$\varepsilon_i \sim \mathcal{N}(0, \tau^2)$$

where i = 1, ..., S indexes the numbers of studies.

Use of arcsine or double arcsine transformations has been criticized in this context, with the GLMM.²

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])</pre>
```

¹Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data.

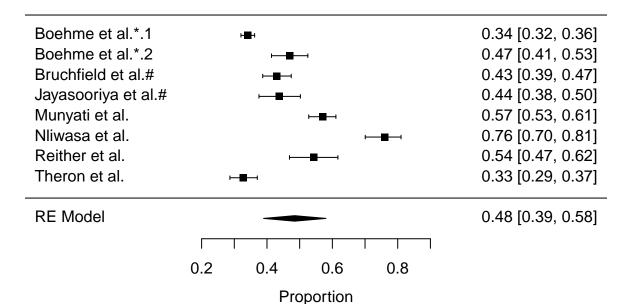
²Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions

```
}
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-analyses

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

```
maPU <- rma.glmm(measure = "PLO", # binomial w/ logit link</pre>
           xi = NnotTB,  # numerator
           ni = N,
                            # denominator
            data = DD[mode=='Passive' &
                     clinical=='(Unconfirmed TB included)'],
            slab = Author) # what to use as labels on graphs
## Registered S3 methods overwritten by 'lme4':
##
    method
                                     from
     cooks.distance.influence.merMod car
##
##
     influence.merMod
##
     dfbeta.influence.merMod
##
    dfbetas.influence.merMod
                                     car
summary(maPU)
## Random-Effects Model (k = 8; tau^2 estimator: ML)
   logLik deviance
                           AIC
                                     BIC
                                               AICc
## -25.7259
              0.4121
                       55.4518
                                 55.6107
                                           57.8518
##
## tau^2 (estimated amount of total heterogeneity): 0.2977
## tau (square root of estimated tau^2 value):
## I^2 (total heterogeneity / total variability):
                                                   97.0524%
## H^2 (total variability / sampling variability): 33.9255
##
## Tests for Heterogeneity:
## Wld(df = 7) = 221.8886, p-val < .0001
## LRT(df = 7) = 243.5648, p-val < .0001
##
## Model Results:
##
                               pval
                                        ci.lb
## estimate
                                               ci.ub
                se
                       zval
## -0.0619 0.1971 -0.3140 0.7535 -0.4482 0.3244
##
## ---
## Signif. codes: 0 '***' 0.001 '**' 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.glmm(measure = "PLO", # binomial w/ logit link
            xi = NnotTB,
                            # numerator
           ni = N,
                            # denominator
            data = DD[mode=='Passive' &
                      clinical=='(No unconfirmed TB)'],
                           # what to use as labels on graphs
            slab = Author)
summary(maPN)
##
## Random-Effects Model (k = 9; tau^2 estimator: ML)
##
                                      BIC
                                               AICc
##
     logLik deviance
                            AIC
## -28.8910
               0.2865
                        61.7821
                                  62.1765
                                            63.7821
##
## tau^2 (estimated amount of total heterogeneity): 0.3714
## tau (square root of estimated tau^2 value):
                                                    0.6094
## I^2 (total heterogeneity / total variability):
                                                    98.1427%
## H^2 (total variability / sampling variability):
                                                   53.8403
## Tests for Heterogeneity:
## Wld(df = 8) = 679.9414, p-val < .0001
## LRT(df = 8) = 727.2051, p-val < .0001
## Model Results:
##
## estimate
                       zval
                               pval
                                      ci.lb
                                              ci.ub
##
     0.8757 0.2078 4.2139 <.0001 0.4684 1.2830
##
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
```

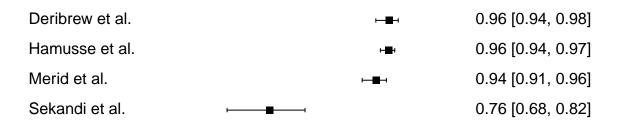
```
Cuevas et al.*.1
                                                                 0.67 [0.65, 0.69]
                                          H
Cuevas et al.*.2
                                                                 0.81 [0.78, 0.83]
Dorman et al.*.1
                                                                 0.83 [0.76, 0.88]
Dorman et al.*.2
                                                                 0.68 [0.62, 0.74]
Dorman et al.*.3
                                                                 0.79 [0.72, 0.85]
Dorman et al.*.4
                                                                 0.63 [0.56, 0.70]
Hanrahan et al.
                                                                 0.81 [0.79, 0.82]
Lawson et al.
                                                                 0.38 [0.36, 0.41]
Ling et al.
                                                                 0.65 [0.60, 0.70]
RE Model
                                                                 0.71 [0.62, 0.78]
```

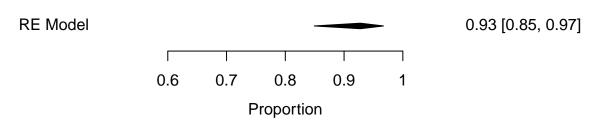
0.3 0.5 0.7 0.9

Proportion

Meta-analysis for actively found TB patients:

```
maA <- rma.glmm(measure = "PLO", # binomial w/ logit link
            xi = NnotTB,
                             # numerator
                             # denominator
            ni = N,
            data = DD[mode=='Active'],
            slab = Author)
                                # what to use as labels on graphs
summary(maA)
##
## Random-Effects Model (k = 4; tau^2 estimator: ML)
##
    logLik deviance
                            AIC
                                               AICc
                                      BIC
## -10.4692
               0.2060
                        24.9385
                                  23.7111
                                            36.9385
##
## tau^2 (estimated amount of total heterogeneity): 0.6678
## tau (square root of estimated tau^2 value):
                                                    0.8172
## I^2 (total heterogeneity / total variability):
                                                    95.0642%
## H^2 (total variability / sampling variability):
                                                    20.2600
##
## Tests for Heterogeneity:
## Wld(df = 3) = 81.2135, p-val < .0001
## LRT(df = 3) = 67.4266, p-val < .0001
## Model Results:
##
## estimate
                 se
                       zval
                               pval
                                      ci.lb
                                              ci.ub
##
     2.5537 0.4199 6.0817 <.0001 1.7307 3.3767 ***
##
## ---
## Signif. codes: 0 '***' 0.001 '**' 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)</pre>
```

Creation of combined forest plot

Summary data for combined forest plot:

```
f1 <- function(x)format(round(x,1),nsmall=1)</pre>
cnz <- c('(Unconfirmed TB included)',</pre>
          '(No unconfirmed TB)',
          '(No unconfirmed TB)')
predz <- data.table(mode=c('Passive', 'Passive', 'Active'),</pre>
                     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$12,maPN$12,maPU$12)),'%)')
predz[,SE:=(hi-lo)/3.92]
predz[,qty:<u>=</u>'summary']
predz[,bac:=0]
predz[,mid:=`NotTB Proportion`]
predz[,CI:=paste0(f1(1e2*mid),' (',f1(1e2*lo),' - ',f1(1e2*hi),')')]
predz[,wt:<u>=</u>'100.0%']
predz[,w:=1]
Appending plot data to inputs:
DD[,qty:='study']
DD[,mid:=`NotTB Proportion`]
DD[,CI:=pasteO(f1(1e2*mid),' (',f1(1e2*lo),' - ',f1(1e2*hi),')')]
DD[,wt:=1/SE<sup>2</sup>]
DD[,wtt:=sum(wt),by=.(mode,clinical)]
DD[,wt:=1e2*wt/wtt]
```

```
DD[,wt:<u>=</u>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)</pre>
1bz2 \leftarrow c(1bz[1:3], rev(1bz[-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]</pre>
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

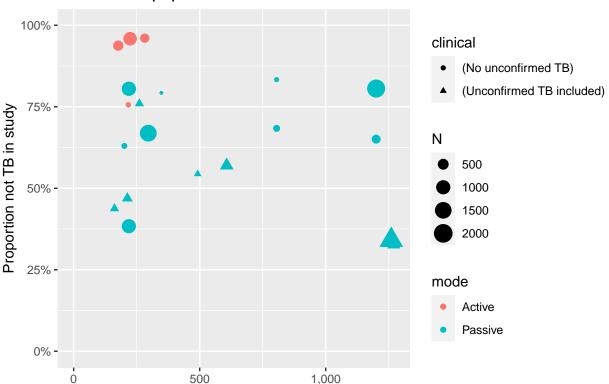
In this section we consider various potential sources of heterogeneity through scatter plots and meta-regression.

TB prevalence

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

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

Influence of population TB burden



WHO estimate of TB prevalence per 100,000 for country-year

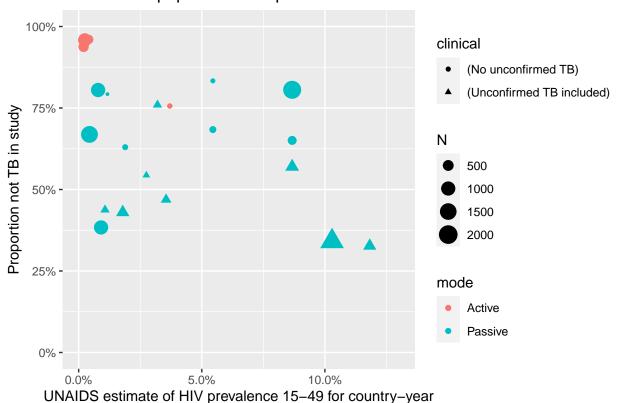
We can formally investigating the influence of TB burden in explaining heterogeneity with a meta-regression:

```
## Warning: Studies with NAs omitted from model fitting.
## Warning: Some yi/vi values are NA.
## Warning: Redundant predictors dropped from the model.
summary(tbmr)
##
## Mixed-Effects Model (k = 20; tau^2 estimator: ML)
##
##
     logLik
             deviance
                            AIC
                                       BIC
                                                AICc
                       133.5982 138.5769
## -61.7991
               0.9638
                                            137.8839
##
                                                            0.4095
## tau^2 (estimated amount of residual heterogeneity):
## tau (square root of estimated tau^2 value):
                                                            0.6399
## I^2 (residual heterogeneity / unaccounted variability): 97.6536%
## H^2 (unaccounted variability / sampling variability):
##
## Tests for Residual Heterogeneity:
## Wld(df = 16) = 973.5088, p-val < .0001
## LRT(df = 16) = 1028.1407, p-val < .0001
##
## Test of Moderators (coefficients 2:4):
## QM(df = 3) = 38.8326, p-val < .0001
## Model Results:
##
##
                                                                             ci.lb
                                       estimate
                                                     se
                                                            zval
                                                                     pval
                                                                  <.0001
## intrcpt
                                         2.5877
                                                 0.3453
                                                          7.4931
                                                                            1.9109
## modePassive
                                        -1.6174
                                                 0.4233
                                                         -3.8210
                                                                  0.0001
                                                                           -2.4471
## clinical(Unconfirmed TB included)
                                        -0.8999
                                                 0.3286
                                                         -2.7386
                                                                  0.0062
                                                                          -1.5439
## tb
                                        -0.0002
                                                0.0004 -0.4084 0.6830
##
                                         ci.ub
## intrcpt
                                        3.2646
## modePassive
                                       -0.7878
## clinical(Unconfirmed TB included)
                                       -0.2559
## tb
                                        0.0006
##
## ---
                  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## Signif. codes:
```

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.

Influence of population HIV prevalence



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

Warning: Redundant predictors dropped from the model.
summary(hivmr)

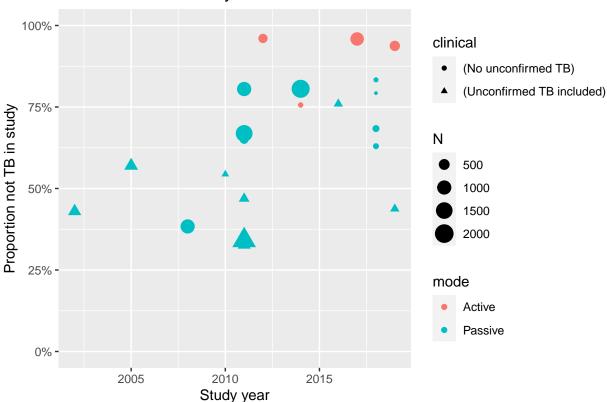
```
##
## Mixed-Effects Model (k = 21; tau^2 estimator: ML)
##
##
     logLik deviance
                            AIC
                                      BIC
                                               AICc
## -65.1479
               1.0280 140.2958 145.5184
                                           144.2958
## tau^2 (estimated amount of residual heterogeneity):
                                                           0.3839
## tau (square root of estimated tau^2 value):
                                                           0.6196
## I^2 (residual heterogeneity / unaccounted variability): 97.5586%
## H^2 (unaccounted variability / sampling variability):
                                                           40.9604
## Tests for Residual Heterogeneity:
## Wld(df = 17) = 973.1809, p-val < .0001
## LRT(df = 17) = 1025.3297, p-val < .0001
## Test of Moderators (coefficients 2:4):
```

```
## QM(df = 3) = 44.7803, p-val < .0001
##
## Model Results:
##
                                    estimate
                                                 se
                                                        zval
                                                                pval
                                                                        ci.lb
## intrcpt
                                      2.5888 0.3279 7.8949 <.0001
                                                                       1.9461
## modePassive
                                     -1.5920 0.4019 -3.9609 <.0001 -2.3798
## clinical(Unconfirmed TB included)
                                     -0.8801 0.3153 -2.7914 0.0052 -1.4981
                                     -0.0325 0.0420 -0.7730 0.4395 -0.1149
##
                                      ci.ub
## intrcpt
                                     3.2315 ***
## modePassive
                                    -0.8042 ***
## clinical(Unconfirmed TB included) -0.2622
## hiv
                                     0.0499
##
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
```

Calendar time

To explore whether there has been any change over time, we consider calendar year

Influence of calendar year



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

Warning: Redundant predictors dropped from the model.
summary(yearmr)

```
##
## Mixed-Effects Model (k = 21; tau^2 estimator: ML)
##
##
     logLik deviance
                            AIC
                                      BIC
                                               AICc
## -65.2094
               1.1510 140.4188 145.6414
                                           144.4188
## tau^2 (estimated amount of residual heterogeneity):
                                                            0.3586
## tau (square root of estimated tau^2 value):
                                                            0.5989
## I^2 (residual heterogeneity / unaccounted variability): 97.5232%
## H^2 (unaccounted variability / sampling variability):
                                                            40.3748
## Tests for Residual Heterogeneity:
## Wld(df = 17) = 882.4776, p-val < .0001
## LRT(df = 17) = 919.1171, p-val < .0001
## Test of Moderators (coefficients 2:4):
```

```
## QM(df = 3) = 49.0787, p-val < .0001
##
## Model Results:
##
##
                                     estimate
                                                    se
                                                           zval
                                                                   pval
## intrcpt
                                     -88.8442 64.9689
                                                        -1.3675 0.1715
## modePassive
                                              0.3784 -4.2400 <.0001
                                      -1.6045
## clinical(Unconfirmed TB included)
                                      -0.7813
                                                0.3167
                                                        -2.4673 0.0136
## Year
                                       0.0453
                                                0.0322
                                                         1.4068 0.1595
##
                                         ci.lb
                                                  ci.ub
## intrcpt
                                      -216.1809 38.4926
## modePassive
                                                -0.8628
                                       -2.3462
## clinical(Unconfirmed TB included)
                                       -1.4019
                                                -0.1606
## Year
                                       -0.0178
                                                 0.1085
##
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
```

Sensitivity analyses

Dorman et al. by country only

In the main analysis, we considered the different sites in the 2018 study by Dorman et al to be separate data. This included considering the two sites in South Africa - Cape Town and Johannesburg - as different, which was motivated by the very distinct TB epidemiology in the Western Cape. Here we investigate the impact of aggregating the two South African sites in Dorman et al on the meta-analysis for studies with passive case finding excluding clinically diagnosed TB.

Restrict to relevant data & aggregate over Dorman in South Africa:

```
tmp <- DD[mode=='Passive' & clinical=='(No unconfirmed TB)']
tmp[,Country.Simple:=gsub(" \\-.+$","",Country)]  #remove cities
tmp[,authorcountry:=paste(gsub("^([A-Za-z]+).*","\\1",Author),Country.Simple,sep = ", ")] #new label
tmp <- tmp[,.(NnotTB=sum(NnotTB),N=sum(N)),by=authorcountry]
knitr::kable(tmp) #check</pre>
```

authorcountry	NnotTB	N
Cuevas, Ethiopia	1184	1770
Cuevas, Nigeria	963	1196
Dorman, South Africa	285	384
Dorman, Kenya	107	135
Dorman, Uganda	114	181
Hanrahan, South Africa	1685	2091
Lawson, Nigeria	455	1186
Ling, South Africa	257	395

Rerun this meta-analysis with the new data:

```
##
## Random-Effects Model (k = 8; tau^2 estimator: ML)
##
##
                            AIC
                                      BIC
                                               AICc
     logLik deviance
  -26.5760
               0.1654
                        57.1519
                                  57.3108
##
                                            59.5519
##
## tau^2 (estimated amount of total heterogeneity): 0.3563
## tau (square root of estimated tau^2 value):
                                                    0.5969
## I^2 (total heterogeneity / total variability):
                                                    98.3044%
## H^2 (total variability / sampling variability): 58.9761
##
## Tests for Heterogeneity:
## Wld(df = 7) = 671.4861, p-val < .0001
## LRT(df = 7) = 716.0656, p-val < .0001
## Model Results:
##
## estimate
                 se
                       zval
                               pval
                                      ci.lb
                                              ci.ub
##
     0.8252 0.2149
                    3.8406
                            0.0001 0.4041
                                            1.2463
##
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
forest(maPNsa,transf = transf.ilogit,refline=NA)
 Cuevas, Ethiopia
                                                                  0.67 [0.65, 0.69]
 Cuevas, Nigeria
                                                                  0.81 [0.78, 0.83]
 Dorman, South Africa
                                                                  0.74 [0.70, 0.78]
 Dorman, Kenya
                                                                  0.79 [0.72, 0.85]
 Dorman, Uganda
                                                                  0.63 [0.56, 0.70]
 Hanrahan, South Africa
                                                                  0.81 [0.79, 0.82]
 Lawson, Nigeria
                                                                  0.38 [0.36, 0.41]
 Ling, South Africa
                                                                  0.65 [0.60, 0.70]
 RF Model
                                                                  0.70 [0.60, 0.78]
                                   0.5
                                             0.7
                         0.3
                                                       0.9
                                    Proportion
```

This is very similar to the main analysis above.

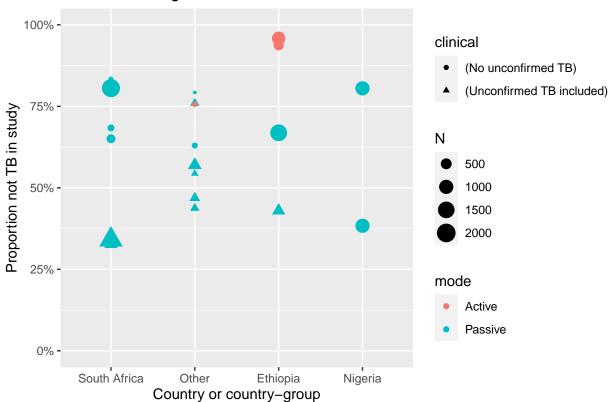
Regional groupings

Here we investigate whether country can explain some heterogeneity. Since when countries have occur only once, it is not possible to identify a country coefficient, we these countries into an "Other" category.

```
DD[,Country.Group:=gsub(" \\-.+$","",Country)] #remove cities
DD[!Country.Group %in% c("South Africa","Ethiopia","Nigeria"),Country.Group:="Other"] #group
DD[,Country.Group:=factor(Country.Group,levels=unique(Country.Group))] #make factor
```

Plot this data:

Influence of region



Perform meta-regression on country-group:

```
cgmr <- rma.glmm(measure = "PLO", #binomial w/ logit link</pre>
               xi = NnotTB,
                                # numerator
               ni = N,
                                # denominator
                                 # what data to use
               data = DD,
               mods = ~mode*clinical + Country.Group)
## Warning: Redundant predictors dropped from the model.
summary(cgmr)
##
## Mixed-Effects Model (k = 21; tau^2 estimator: ML)
##
    logLik deviance
                            AIC
                                      BIC
                                                AICc
## -65.1801
               1.0924 144.3602 151.6718 152.9755
##
## tau^2 (estimated amount of residual heterogeneity):
                                                            0.3559
```

```
## tau (square root of estimated tau^2 value):
                                                         0.5966
## I^2 (residual heterogeneity / unaccounted variability): 96.9246%
## H^2 (unaccounted variability / sampling variability): 32.5156
##
## Tests for Residual Heterogeneity:
## Wld(df = 15) = 776.0219, p-val < .0001
## LRT(df = 15) = 809.5261, p-val < .0001
## Test of Moderators (coefficients 2:6):
## QM(df = 5) = 49.6317, p-val < .0001
## Model Results:
##
                                                                         ci.lb
                                     estimate
                                                  se
                                                         zval
                                                                 pval
                                      2.1567 0.5023 4.2940 <.0001
## intrcpt
                                                                        1.1723
## modePassive
                                     -1.2854 0.4723 -2.7217 0.0065 -2.2110
## clinical(Unconfirmed TB included) -1.1151 0.3371 -3.3082 0.0009 -1.7757
## Country.GroupOther
                                     0.2021 0.3565 0.5669 0.5708 -0.4966
## Country.GroupEthiopia
                                      0.4592 0.4521 1.0158 0.3097 -0.4269
## Country.GroupNigeria
                                     -0.4006 0.5052 -0.7931 0.4277 -1.3908
                                      ci.ub
##
## intrcpt
                                     3.1412 ***
## modePassive
                                     -0.3597
## clinical(Unconfirmed TB included) -0.4544 ***
## Country.GroupOther
                                     0.9008
## Country.GroupEthiopia
                                     1.3453
## Country.GroupNigeria
                                     0.5895
##
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
```