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

S Jayasooriya, F Dimambro-Denson, C Beecroft, J Balen, B Awokola, C Mitchell, B Kampmann, F Campbell, PJ Dodd, K Mortimer

August, 2021

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.

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

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

link to paper 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:

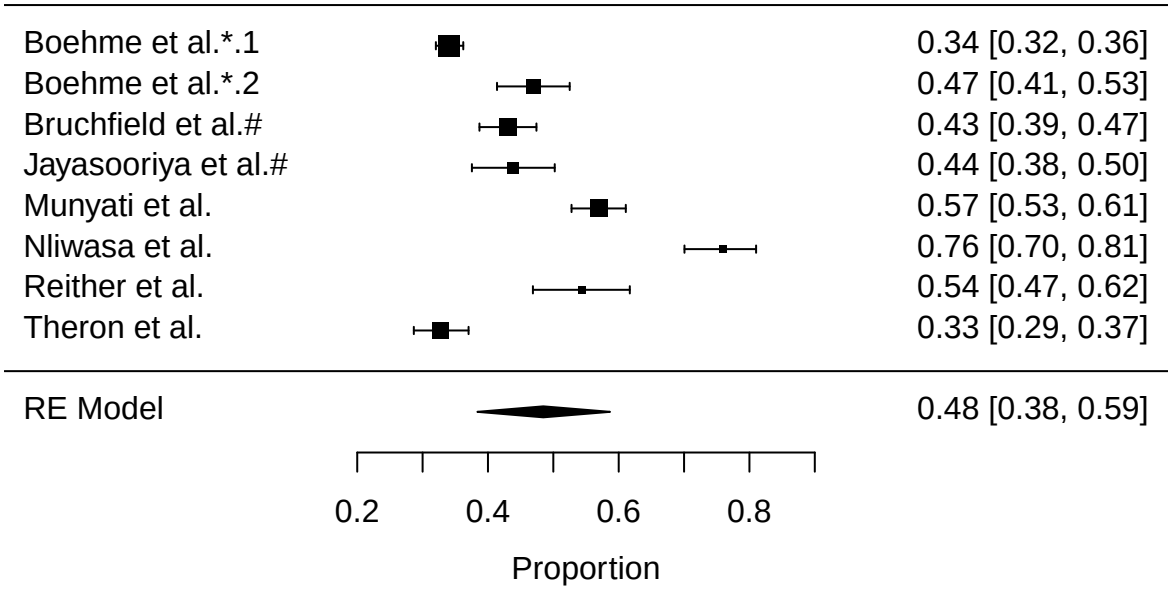
```
ciz <- function(x,y){
    x <- as.integer(x); y <- as.integer(y)
    list(binom.test(x,y)$conf.int[1],binom.test(x,y)$conf.int[2])
}
DD[,`NotTB Proportion`:=NnotTB/N]
for(i in 1:nrow(DD)){ DD[i,c('lo','hi'):=ciz(NnotTB,N)]; }
DD[,SE:=(hi-lo)/3.92]
```

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

```
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)
```



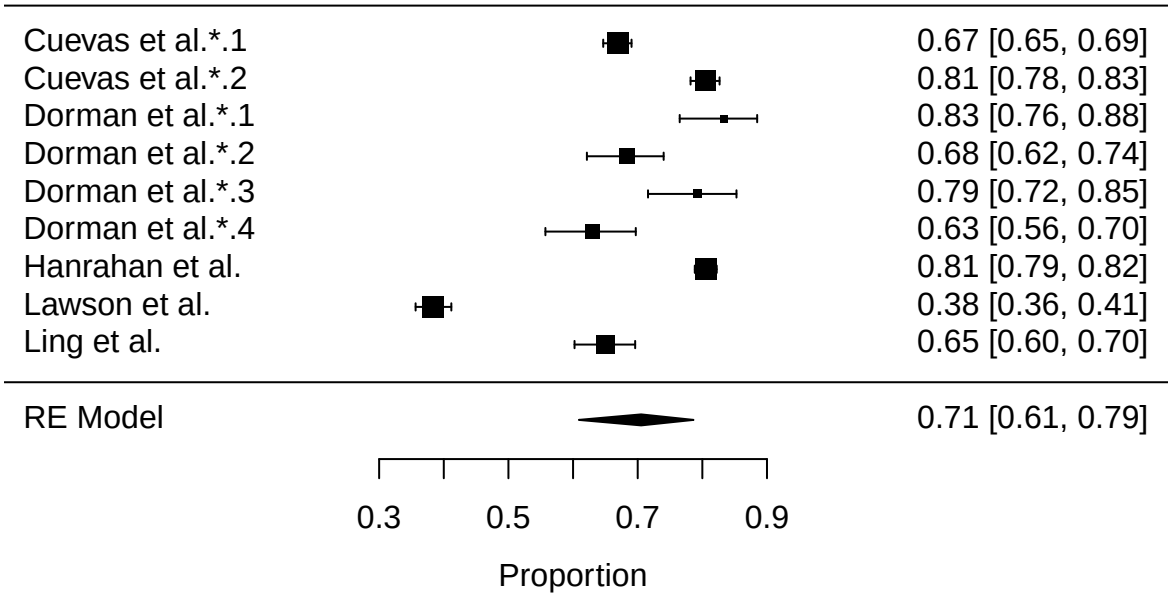
Meta-analysis for passively found TB patients with bacteriologically unconfirmed TB excluded:

```
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)
```



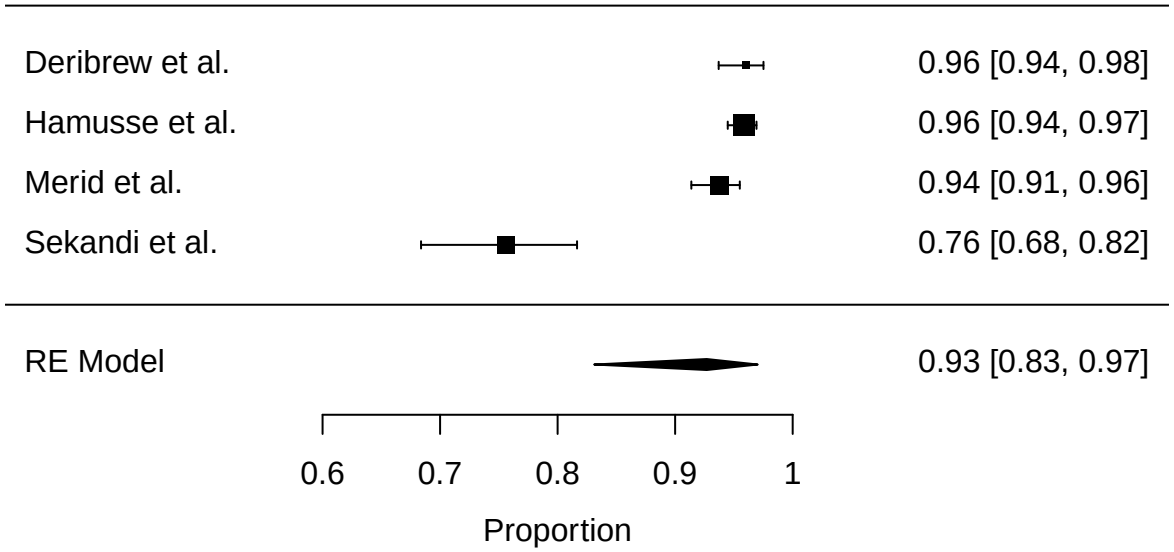
Meta-analysis for actively found TB patients:

```
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

TODO add+annotate from other file

Sensitivity analyses

Regional groupings

TODO

Dorman by country

TODO

Grouping blah as a single study