Bayesian meta-analysis and meta-regression for proportion studies: *The example of neurocysticercosis among people with epileptic seizures*

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Presentation objectives

- What is the **traditional methods** of meta-analysis?
- What is **Bayesian random effect model (or Bayesian hierarchical model**)?
- How have we **used** Bayesian models to conduct **meta-analysis, stratified meta-analysis and meta-regression**?

What is Neurocysticercosis (NCC)?

"Neurocysticercosis (NCC) is a zoonotic helminthic infection of the human central nervous system (CNS) caused by larval cyst of *Taenia solium.*".....*Adapted from CDC*

Fig: *Taenia solium*

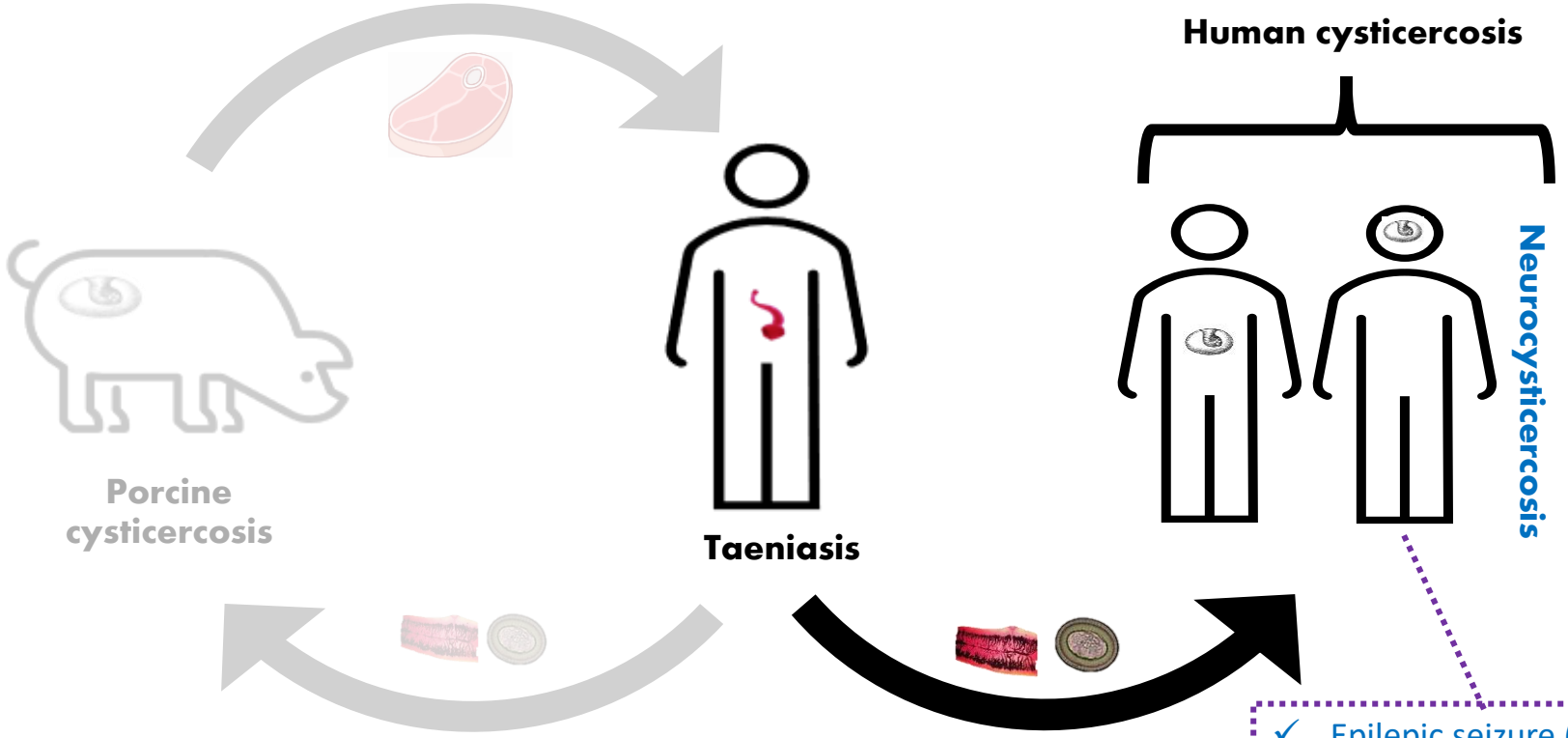


Fig: Life cycle of *Taenia solium*

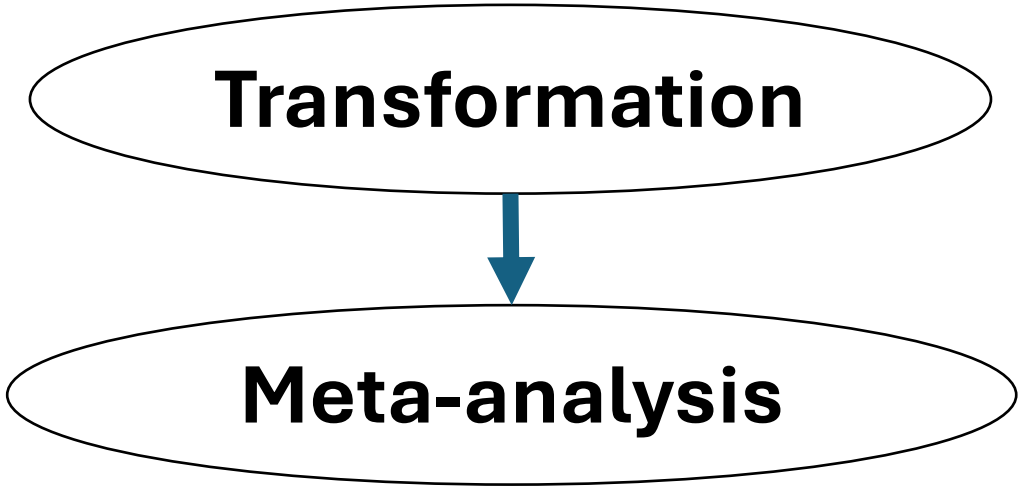
- ✓ Epilepic seizure (~79%)
- ✓ Severe headache (~38%)
- ✓ Hydrocephaly
- ✓ Death (~10%)

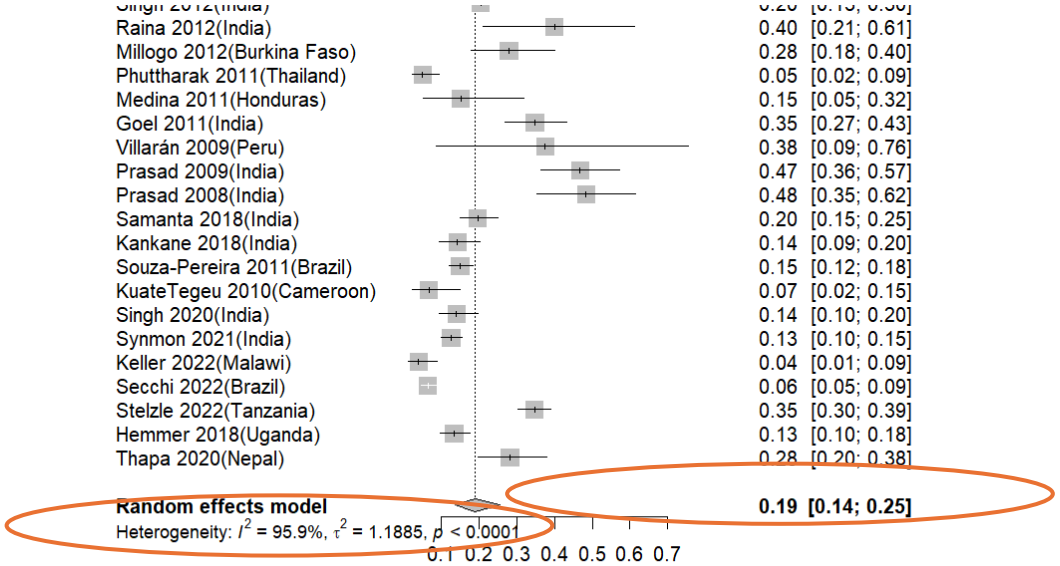
Source: https://steemit.com/,

Life cycle was adapted from: https://www.cdc.gov/dpdx/cysticercosis/index.html

What is the traditional method of meta-analysis? –Frequentist approach

"Two-steps method"





Generalized linear mixed model (with *logit* link)

$$yi \sim Binomial\ (ni, pi)$$

$$logit\ (pi) = P + ui$$

$$ui \sim Normal(0, \tau^2)$$

Here,
yi = # of cases
ni = # of samples
pi = study-level proportion,
P = overall proportion
ui = random effect
τ^2 = between-study variance (heterogeneity).

Major limitation:

"*The frequentist approaches use* ***the point estimate of the heterogeneity variance as a fixed quantity****, which leads to variability underestimation*" – Hackenberger (2020)

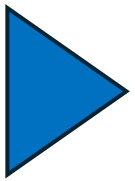
Ref: Lin and Chu (2020); Wang (2023), Hackenberger (2020)

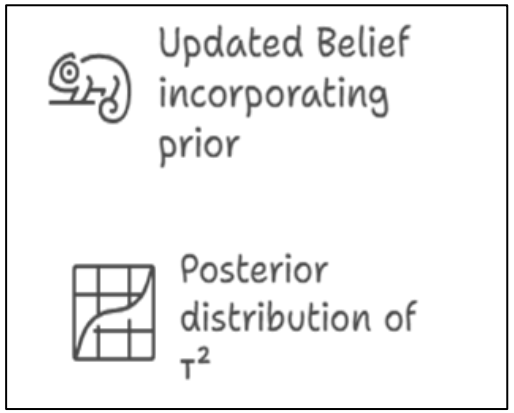
What is Bayesian random-effects model (BREM) ?

$$yi \sim Binomial\ (ni, pi)$$

$$logit\ (pi) = P + ui \rightarrow P \sim logistic\ (0,1)$$

$$ui \sim Normal(0, \tau^2) \rightarrow \tau \sim Half\_Cauchy\ (0,0.5)$$





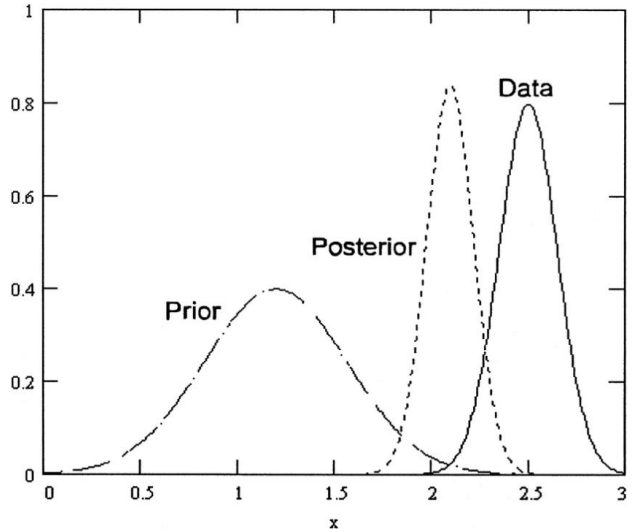
For meta-regression

$$yi \sim Binomial\ (ni, pi)$$

$$logit\ (pi) = P + \boldsymbol{\beta}X + ui \rightarrow \beta \sim Normal\ (0,1)$$

$$ui \sim Normal(0, \tau^2)$$

Main advantages



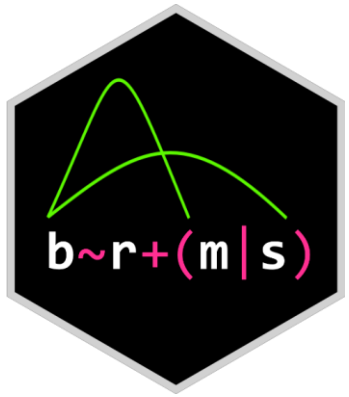
Source of Fig: Linkedin

How have we used BREM in our study?

Research objectives:

*1. To estimate **proportion of neurocysticercosis (NCC)** among people with **epileptic seizure***

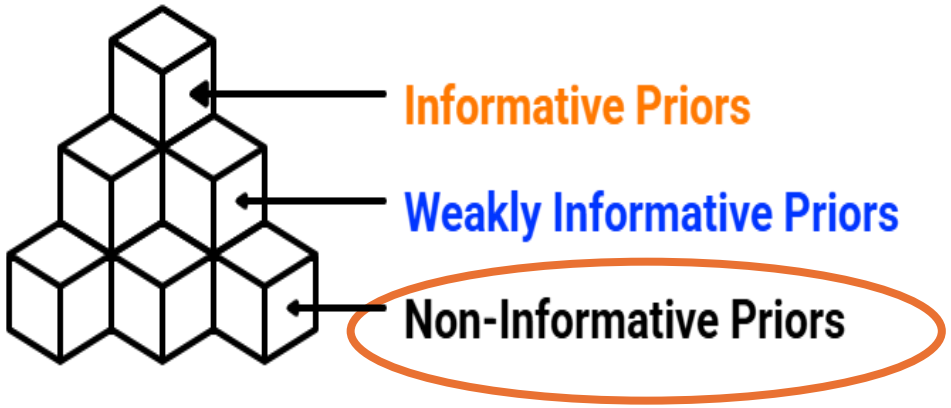
Meta-analysis of studies included in 2010's study (Ndimubanzi et al., 2010)



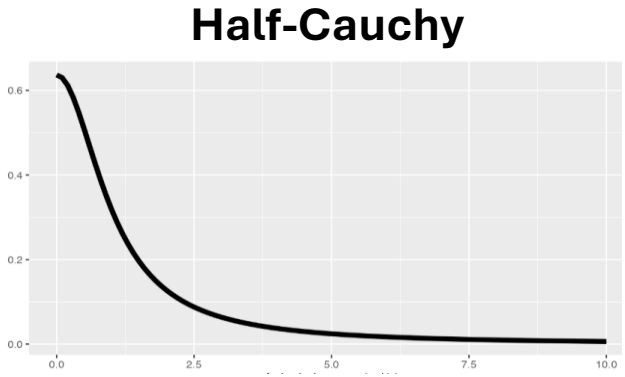
*2. To assess how the NCC proportion has changed over **time and regions.***

How we selected priors?

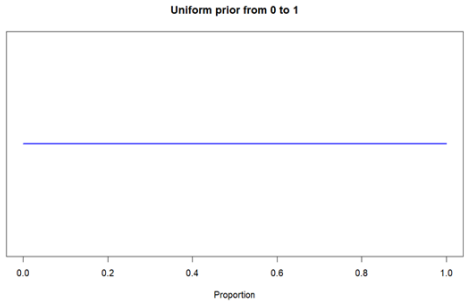
P



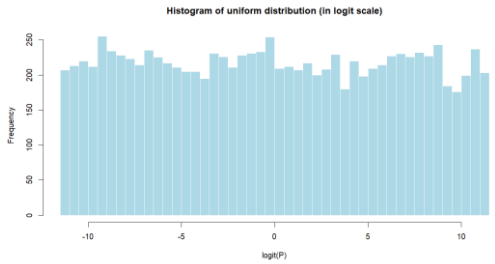
τ

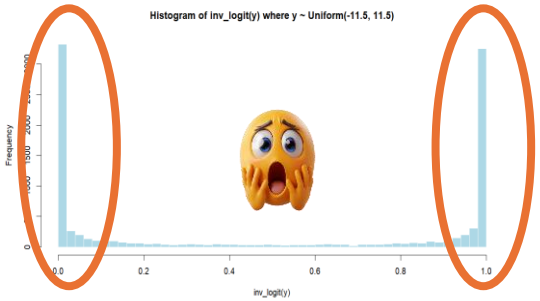


β

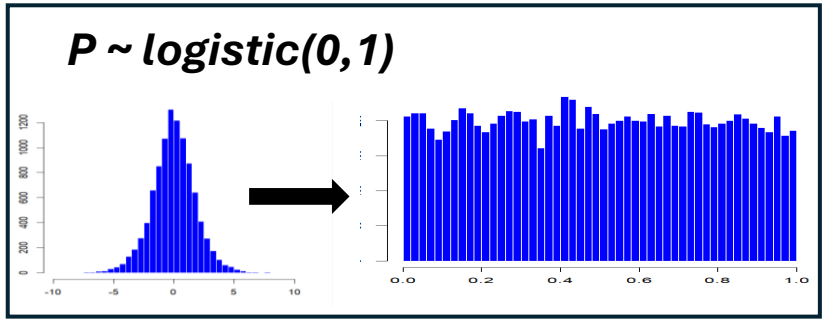


P ~ Uniform (0,1)



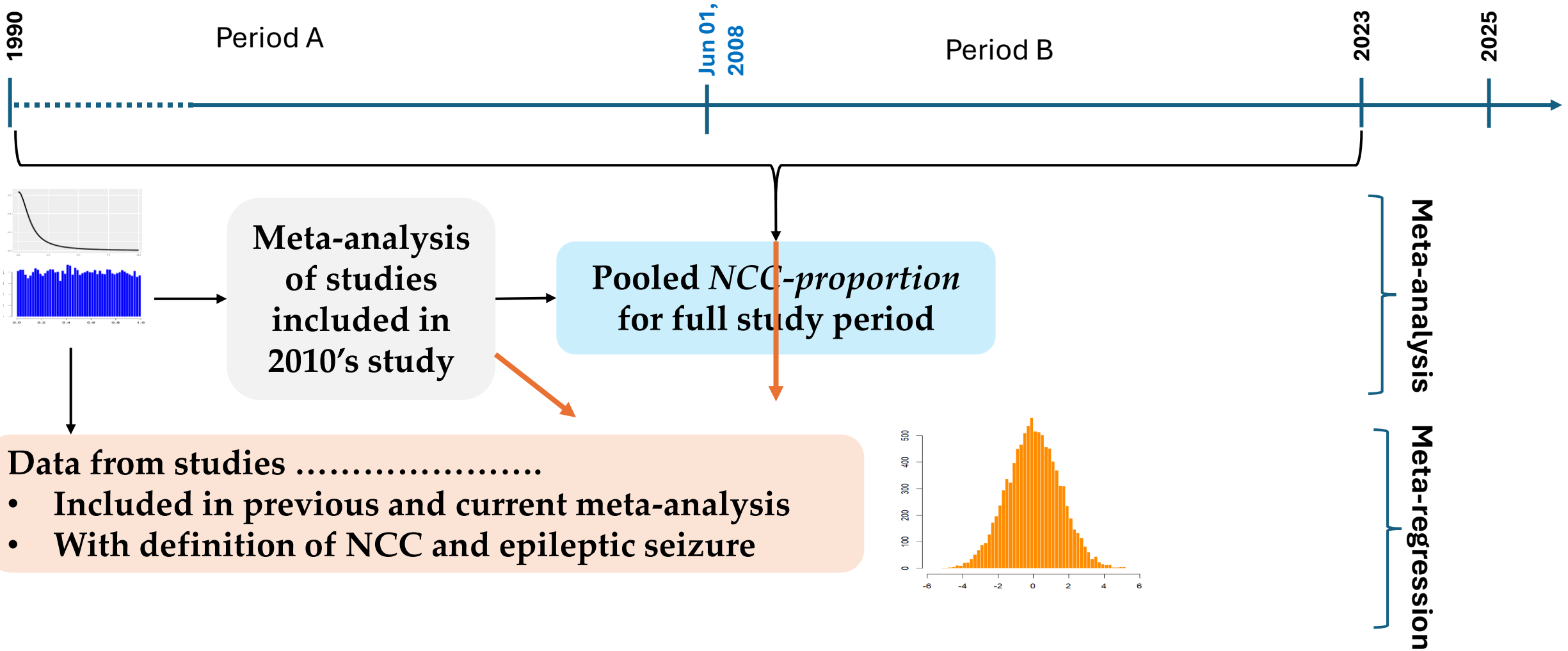


P ~ Uniform (logit (0), logit(1))

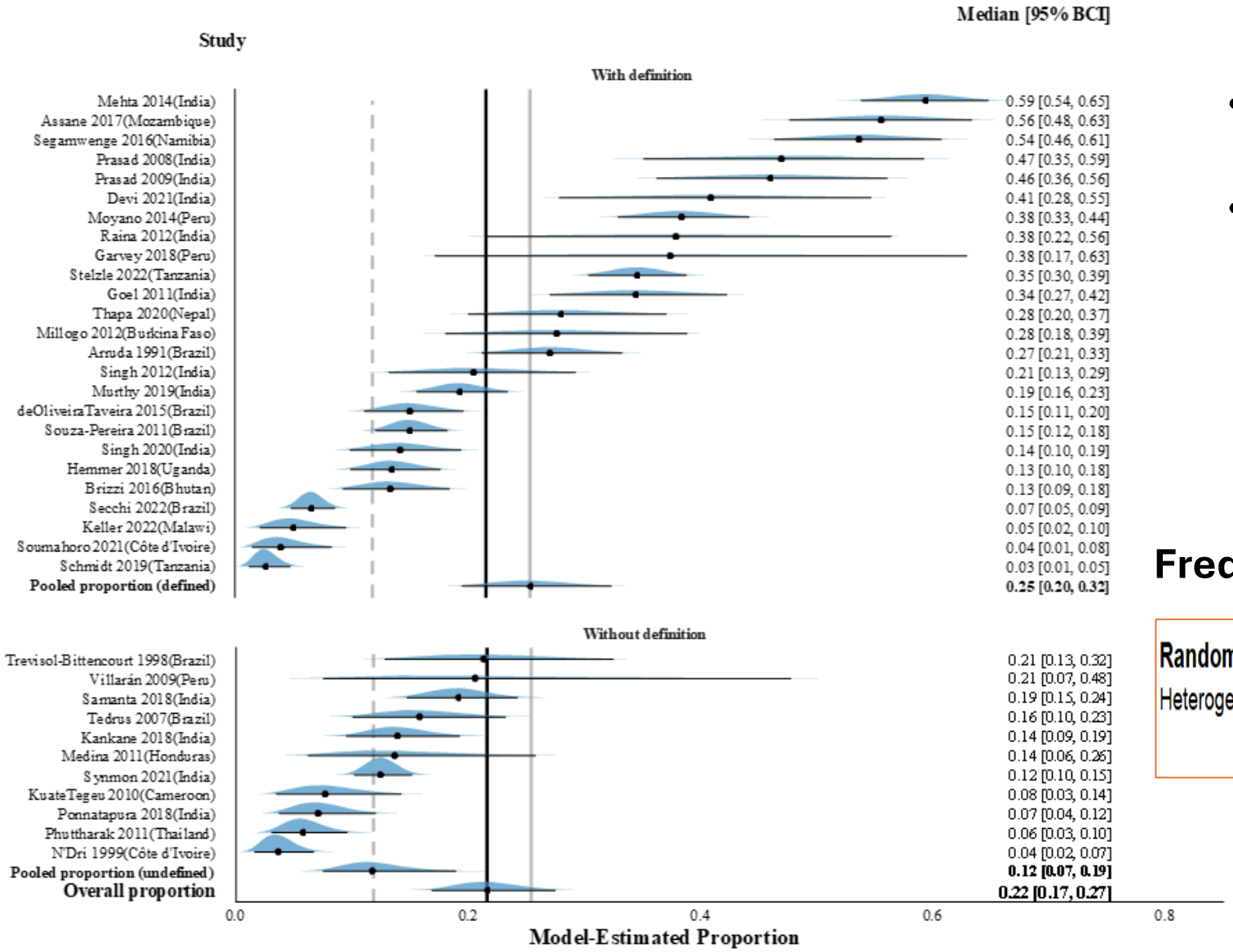


Credit: Some visual created in https://www.napkin.ai/
Ref: Reis, et al (2023).

How we used priors & data from a meta-analysis published in 2010? – Informative prior



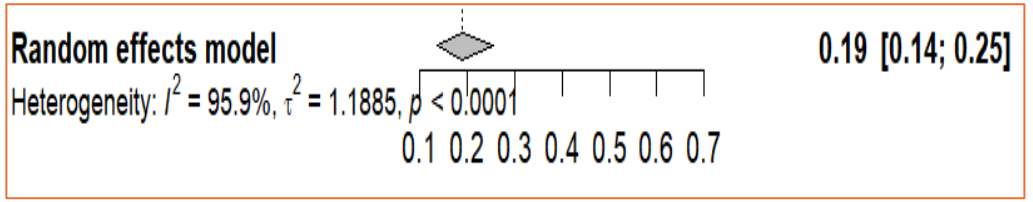
What have we found? – Bayesian meta-analysis



- **The overall median proportion:**
  22% (95%BCI: 17 – 27%)
- **Between-study heterogeneity (τ):**
  1.1 (95%BCI: 0.9 – 1.5)

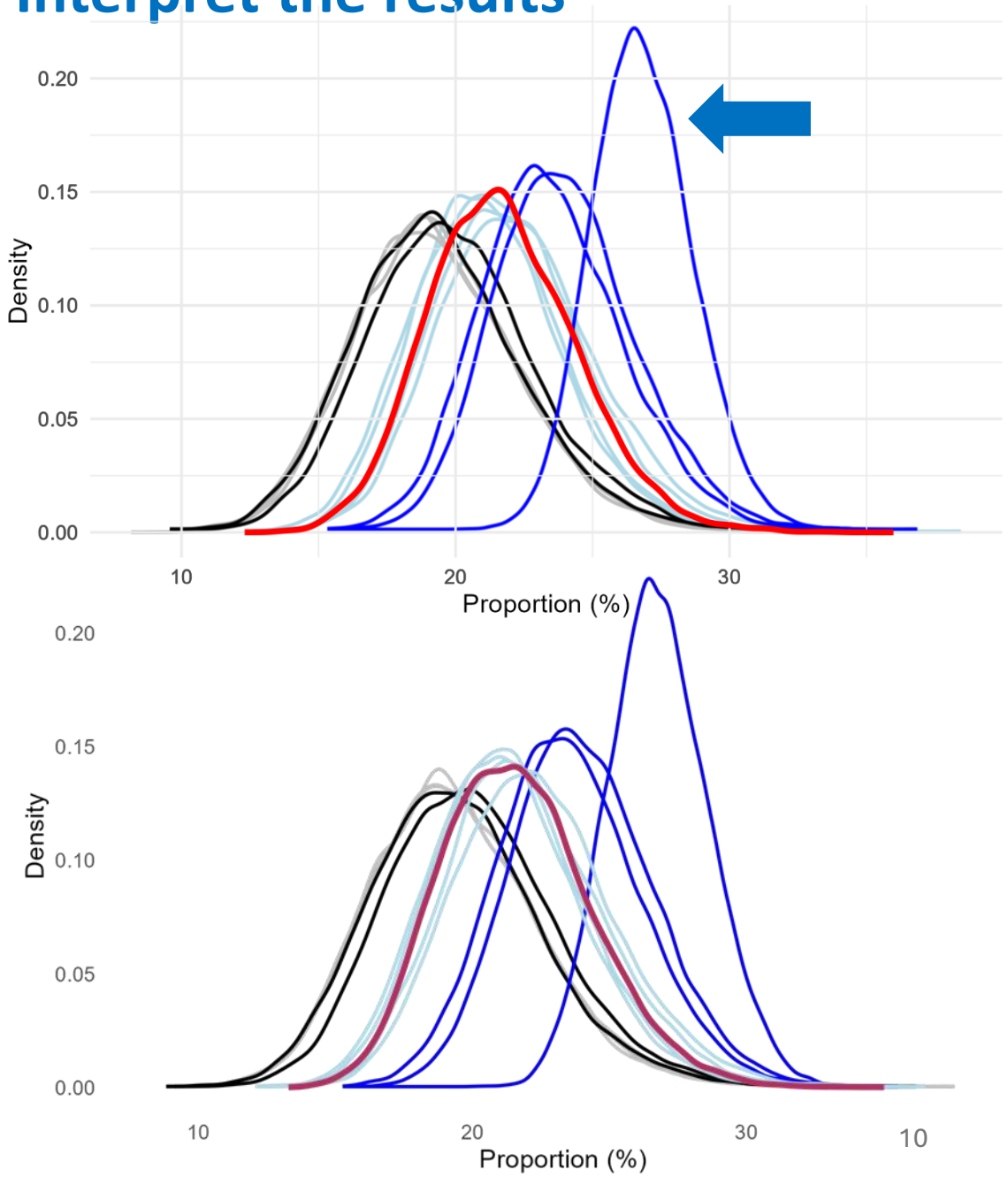
?

Frequentist meta-analysis results



How sensitive the data to the prior? – Interpret the results

Prior distribution of NCC-proportion (P)	Half-Cauch (0, 0.5)	Half-Cauchy (0, 1)
	Posterior P	Posterior P
Non-informative priors		
Student_t(3, 0, 2.5)	19 (14 – 26)	19 (14 – 26)
Prior for SD only	19 (14 – 26)	19 (14 – 26)
Logistic (0,1)	19 (14 – 26)	19 (14 – 26)
Weakly-informative priors		
Normal (0, 1.8)	19 (14 – 26)	19 (14 – 26)
Normal (0,1)	20 (14 – 26)	20 (15 – 27)
Informative priors		
Normal (logit(0.29),0.1)	27 (23 – 31)	27 (23 – 31)
Normal (logit(0.29),0.183)	24 (19 – 29)	24 (19 – 29)
Normal (logit(0.29),0.2)	23 (19 – 29)	23 (19 – 29)
Normal (logit(0.29),0.3)	**22 (17 – 27)**	**21 (17 – 28)**
Normal (logit(0.28),0.3)	21 (17 – 27)	21 (16 – 27)
Normal (logit(0.30),0.3)	22 (17 – 28)	22 (17 – 28)
…….	…….	…….



How sensitive the data to the prior? – Interpret the results

τ:

1.1 (95%BCI: 0.9 – 1.5)

τ	Heterogeneity
0.1 – 0.5	"reasonable"
0.5 - 1.0	"fairly high"
1.0 <	"fairly extreme"

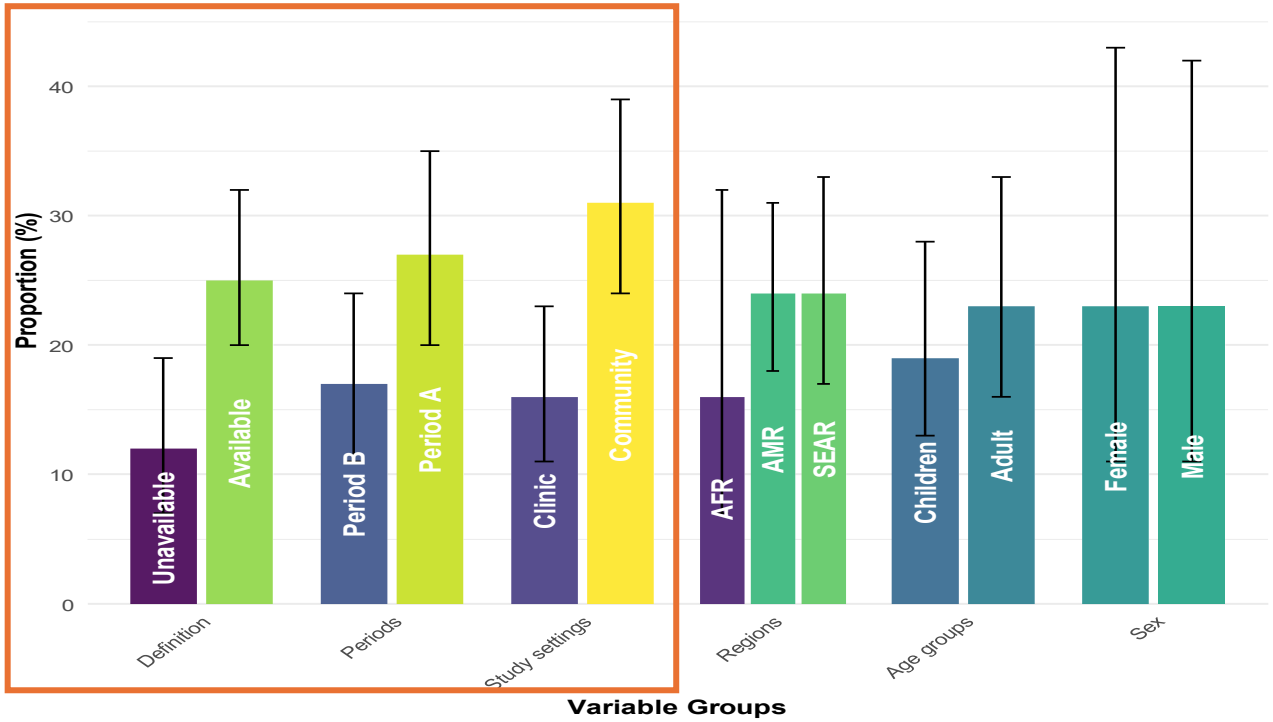
P	Posterior τ	Posterior τ
t(3, 0, 2.5)	1.1 (0.9 – 1.5)	1.1 (0.9 – 1.5)
L(0,1)	1.1 (0.9 – 1.5)	1.1 (0.9 – 1.5)
N (0, 1.8)	1.1 (0.9 – 1.5)	1.1 (0.9 – 1.5)
N(0,1)	1.1 (0.9 – 1.5)	1.1 (0.9 – 1.5)
N (logit(0.29),0.1)	1.2 (0.9 – 1.5)	1.2 (0.9 – 1.6)
N (logit(0.29),0.183)	1.1 (0.9 – 1.5)	1.2 (0.9 – 1.5)
N (logit(0.29),0.2)	1.1 (0.9 – 1.5)	1.1 (0.9 – 1.5)
N (logit(0.29),0.3)	1.1 (0.9 – 1.5)	1.1 (0.9 – 1.5)
N (logit(0.28),0.3)	1.1 (0.9 – 1.5)	1.1 (0.9 – 1.5)
N (logit(0.30),0.3)	1.1 (0.9 – 1.5)	1.1 (0.9 – 1.5)

What are the sources of BS heterogeneity?

Bayesian meta-regression

Variables	OR (95%BCI)
Definition (yes)	2.4 (1.2 – 4.6)
Period B	0.5 (0.3 – 0.9)
S. Setting (Com.)	1.7 (1.0 – 3.0)
AMR	1.3 (0.7 – 2.7)
SEAR	2.0 (0.9 – 4.4)
MRI	0.8 (0.3 – 1.9)
CT/MRI	1.3 (0.6 – 2.6)

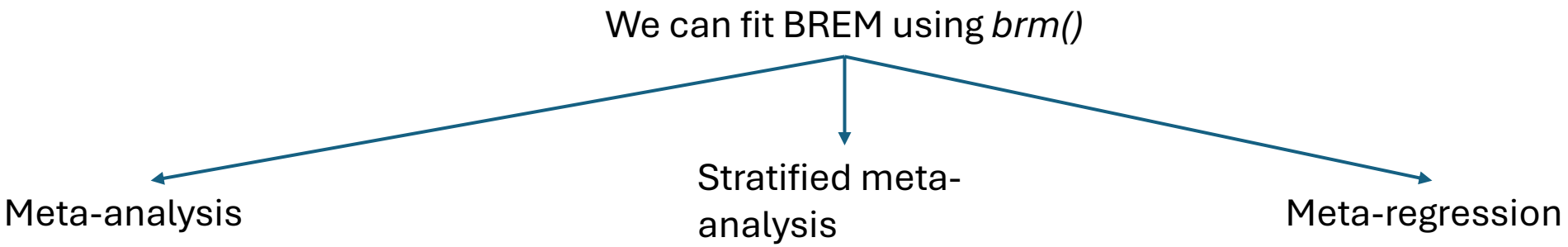
Stratified Bayesian meta-analysis



How has the NCC-proportion changed over time and across regions? – Bayesian meta-regression

Region	Proportion of NCC among PWES			OR (95%BCI)	% of OR less than 1.0
	Period A % (95%BCI)	Period B % (95%BCI)	Period A & B % (95%BCI)		
AFR	35 (18 – 57)	14 (4 – 44)	20 (8 – 40)	0.3 (0.1 – 1.9)	91
AMR	30 (22 – 40)	16 (8 – 36)	25 (18 – 34)	0.4 (0.2 – 0.9)	98
SEAR	39 (26 – 54)	26 (17 – 39)	32 (24 – 41)	0.5 (0.3 – 1.2)	95

In a nutshell……



Major challenges

- ✓ **Assigning prior** is not straight forward
- ✓ No standard for interpreting between-study heterogeneity for proportion studies

Still, we can …….

- ✓ **Combine *priori*** with recent data
- ✓ **Quantify the uncertainty** around the estimates, specially between heterogeneity estimate (τ)

References

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Protocol

To know more about me and my work

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What are the challenges related to NCC?

- Reported in 70+ countries
- 1.24 to 2.8 million DALYs

Distribution Unknown

✓ Pleomorphic disease

✓ No rapid test, require CT/MRI

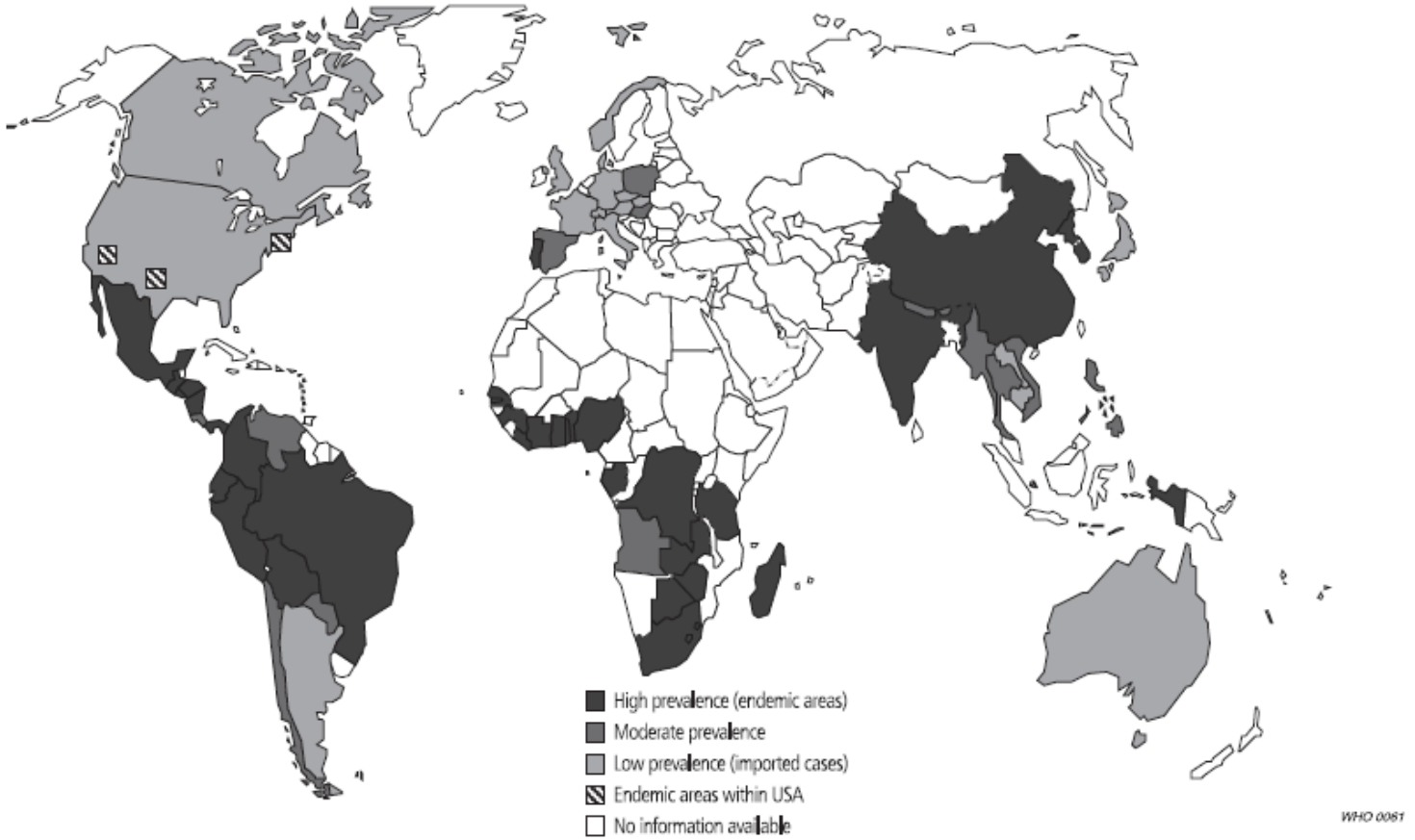
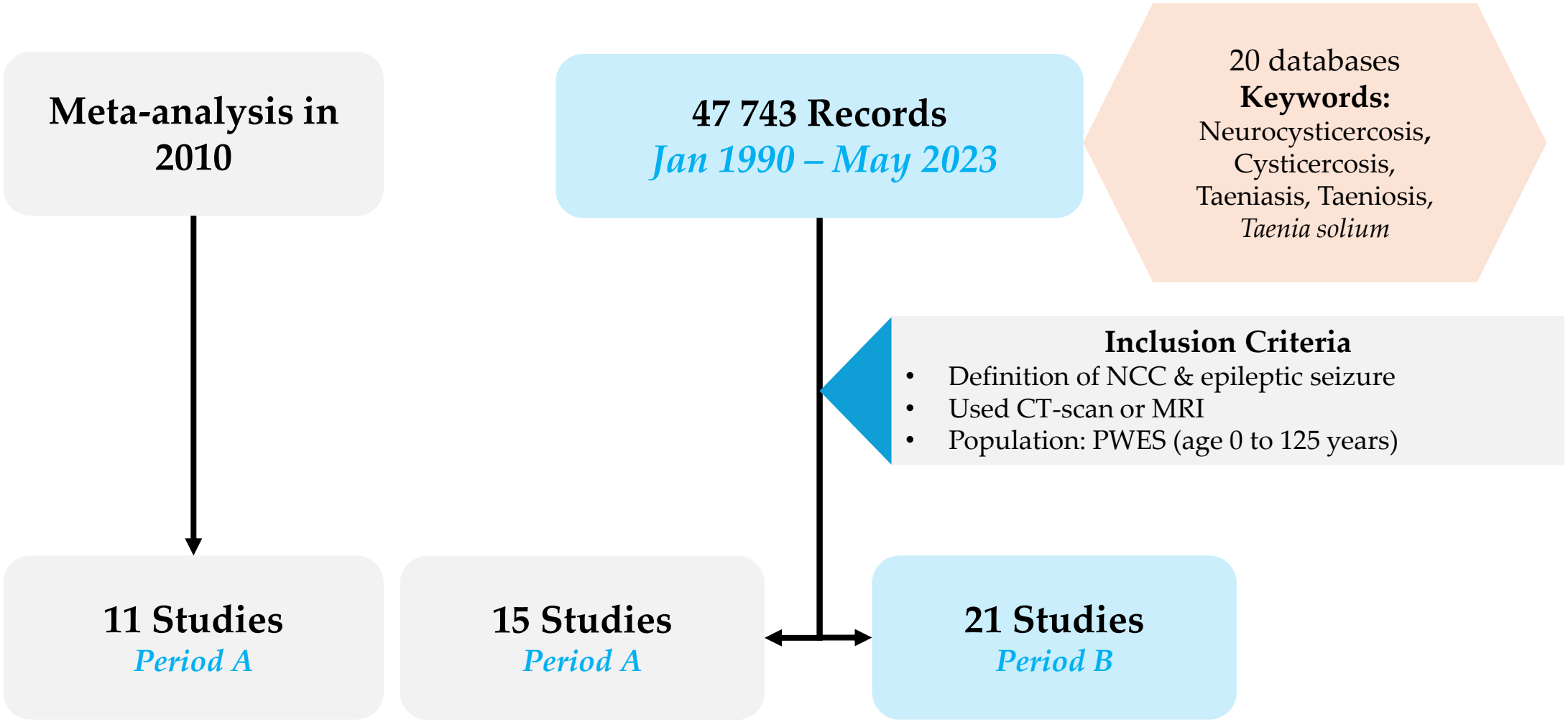


Fig. Map showing areas where cysticercosis is endemic (black) or reported (grey) (Román, et al., 2000).

What have we found? –Systematic review



Why we use GLMM with logit link?

- Directly models binomial data without transformation, avoids bias from approximate methods.
- Proportions are constrained between 0 and 1
- Stabilizes variance

Why we use Bayesian model?

+

- Combine *priori* with data
- Assume random parameter
- Interpretation of 95% credible interval

Why not Bernoulli?

- No individual level data

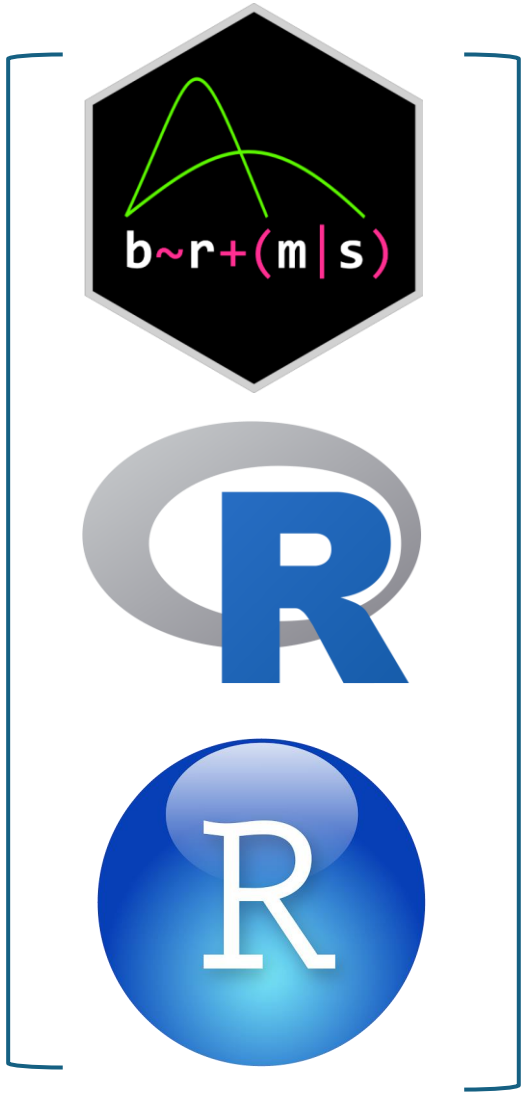
Why need transformation if the proportion?

- Approximate study-specific proportion with normal distribution
- Stabilizing their variance

How we specified the model? – using *brm()* function

Bayesian random-effect logistic model

$$y_i = Binomial(n_i, p_i)$$
$$logit\,(p_i) = P + u_i$$
$$P = Normal(0, 1)$$
$$u_i = Normal(0, \tau^2)$$
$$\tau = Half\_Cauchy\,(0, 0{,}5)$$



STAN

- No-U-Turn Sampling (NUTS)

Model convergence?

```
> summary(mod_ip_1)
 Family: binomial
  Links: mu = logit
Formula: y | trials(n) ~ (1 | Study)
   Data: dat_meta (Number of observations: 36)
  Draws: 4 chains, each with iter = 10000; warmup = 5000; thin = 1;
         total post-warmup draws = 20000

Multilevel Hyperparameters:
~Study (Number of levels: 36)
              Estimate Est.Error l-95% CI u-95% CI Rhat Bulk_ESS Tail_ESS
sd(Intercept)     1.12      0.15     0.87     1.45 1.00     2394     4571

Regression Coefficients:
          Estimate Est.Error l-95% CI u-95% CI Rhat Bulk_ESS Tail_ESS
Intercept    -1.29      0.16    -1.60    -0.97 1.00     1911     3541

Draws were sampled using sampling(NUTS). For each parameter, Bulk_ESS
and Tail_ESS are effective sample size measures, and Rhat is the potential
scale reduction factor on split chains (at convergence, Rhat = 1).
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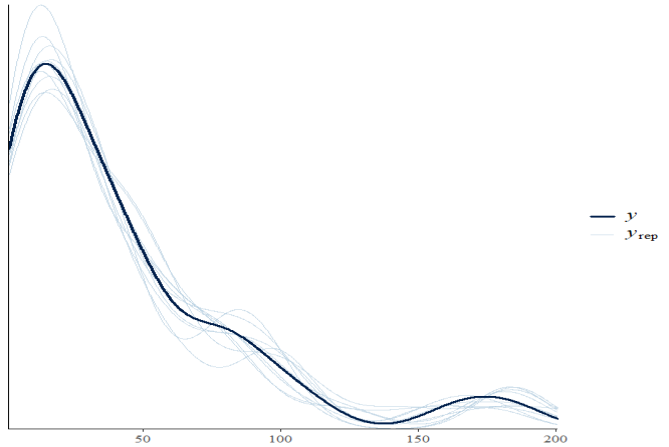

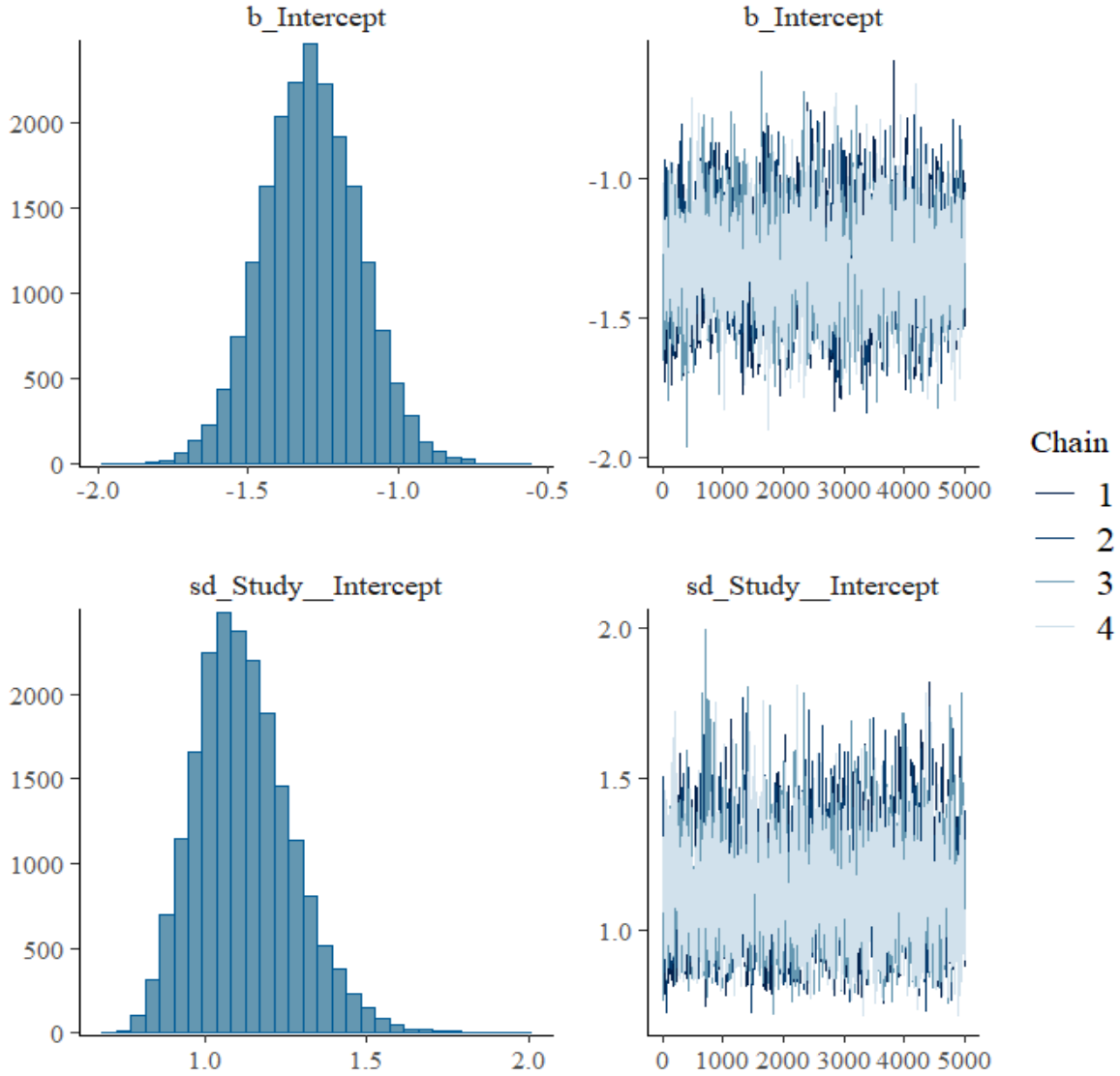

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