The global burden of latent tuberculosis infection (supporting information)

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Methods

Systematic review

Literature search

We searched the literature for papers reporting on nationally representative LTBI survey results and provide an estimate of the ARI for that country. In addition we scanned references from two papers that explored the Styblo rule (Bourdin-Trunz *et al*. and van Leth *et al.* The focus of the search was to identify data to supplement the period where our ARI estimates relied on GTB estimates of prevalence, i.e. 1990 onwards. This review was not registered in a formal database.

Papers were included if the aim of their sampling method was to provide a representative national level estimate, so they could be combined with the existing data from existing reviews.

To be included, papers had to report the minimum required data needed in the model, which included year of survey, average age or range of years in the cohort, the number of participants in the analysis, the number positive or prevalence of infection and the estimated annual risk of infection. If the number tested and positive were missing, an estimate of the ARI with a 95% confidence interval was also acceptable.

We restricted the search to papers available through online databases. If the required data was not available from the abstract, electronic full text was searched for. If this was not available, the record was dropped from the review.

We searched Pubmed with the following query:

(((TB or Tuberculosis)) AND (ARI OR "Annual Risk of Infection" OR LTBI OR "latent tuberculosis infection")) AND (Survey OR population OR community OR representative) Filters: Publication date from 1990/01/01 to 2017/12/31

This yielded 1159 hits (query run on 10th March 2016). In addition, 14 (Bourdin-Trunz *et al.*)+ 7 (van Leth) = 21 potential records were considered.

Paper selection and data extraction was done by RMGJH. Forty-three papers were included for full review, of which 23 contributed data. The selection process, and reasons for exclusion are shown in Figure . Papers were evaluated for bias with regard to representativeness of their sampling by reviewing the methods section, but not for methods used in the TST survey. This was in line with the other reviews that provided data. To reduce the risk of overestimation of infection prevalence due to BCG, we recorded the ARI estimate from BCG-scar negative individuals where possible.

Each study provided a single data point and confidence interval for a specific country to inform the ARI model, there was no attempt or need to combine results across studies, or do further analysis. This was in line with the other reviews that provided data

No funding was provided for this review.

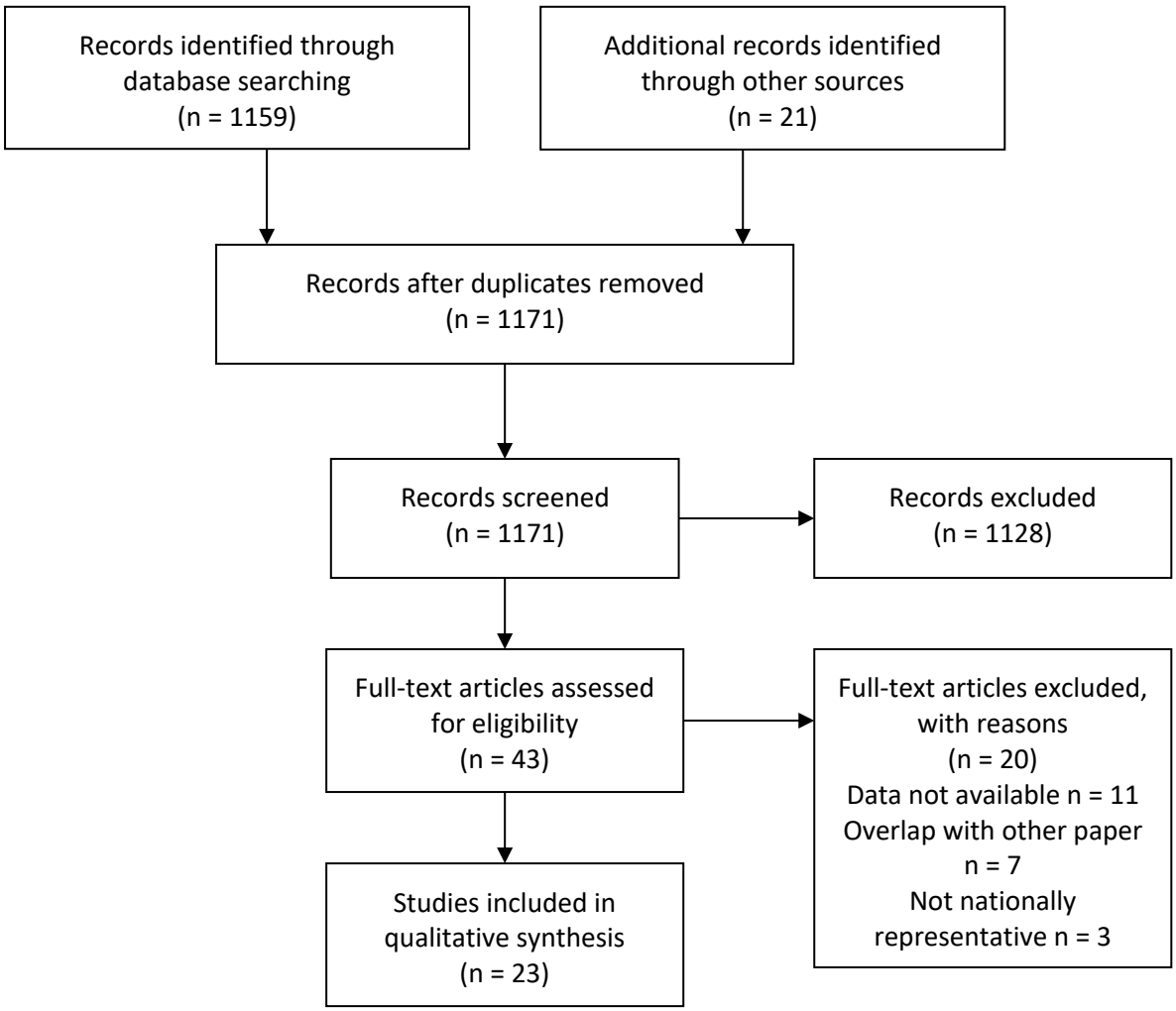

Figure A: PRISMA flow chart for systematic review

References from review (ordered by time of publication)

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Uncertainty in ARI estimates from TST surveys

ARI data were typically reported as a point estimate, together with the sample size and the mean age of participants. We show below how to use this information to construct an approximate data likelihood that conservatively represents the degree of precision of each study.

The force-of-infection, λ, for a given study is effectively estimated from a binomial likelihood:

$$\prod_i Bin(N_i, k_i|(1 - e^{-\lambda a_i}))$$

where N_i, k_i are the number, and number infected in age category *i* and a_i is the age of this category. The derivatives of the loglikelihood, *LL*, are

$$\frac{\partial LL}{\partial \lambda} = \sum_i \left\{ \frac{k_i a_i e^{-\lambda a_i}}{1 - e^{-\lambda a_i}} - (N_i - k_i) a_i \right\}$$

$$\frac{\partial^2 LL}{\partial \lambda^2} = \sum_i -\frac{k_i a_i^2 e^{\lambda a_i}}{(e^{\lambda a_i} - 1)^2}$$

If $1 - e^{-\lambda a} \approx \lambda a$ and $k_i \ll N_i$ then, writing $N = \sum_i N_i$ and $K = \sum_i k_i$, setting the derivative of the loglikelihood to zero gives

$$K \lesssim \lambda N \bar{a}$$

where $\bar{a}$ is the average age of the persons in the study. Similarly, the second equation becomes:

$$-\frac{\partial^2 LL}{\partial \lambda^2} \approx \frac{K}{\lambda^2} \leq \frac{N\bar{a}}{\lambda}$$

so that this last quantity (i.e., $N\bar{a}/\lambda$) gives a conservative estimate of the precision associated with a given study.

Data merging and special cases

24 countries were dropped as they could not be matched across the TB and population data (ISO3 codes: AIA AND ANT ASM BMU COK CYM DMA GRL KNA MCO MHL MNP MSR NIU NRU PLW SMR SXM TCA TKL TUV VGB WLF).

Because of the stochasticity in small populations, we dropped 24 countries with a population size below 500,000 (ISO3 codes: WSM ABW ATG BHS BLZ BRB BRN CUW FSM GRD GUM ISL KIR LCA MDV MLT NCL PYF STP SYC TON VCT VIR VUT). See Figure B.

4 further countries were dropped because they had fewer than 15 data points in total (ISO3 codes: BES CUW SXM TLS).

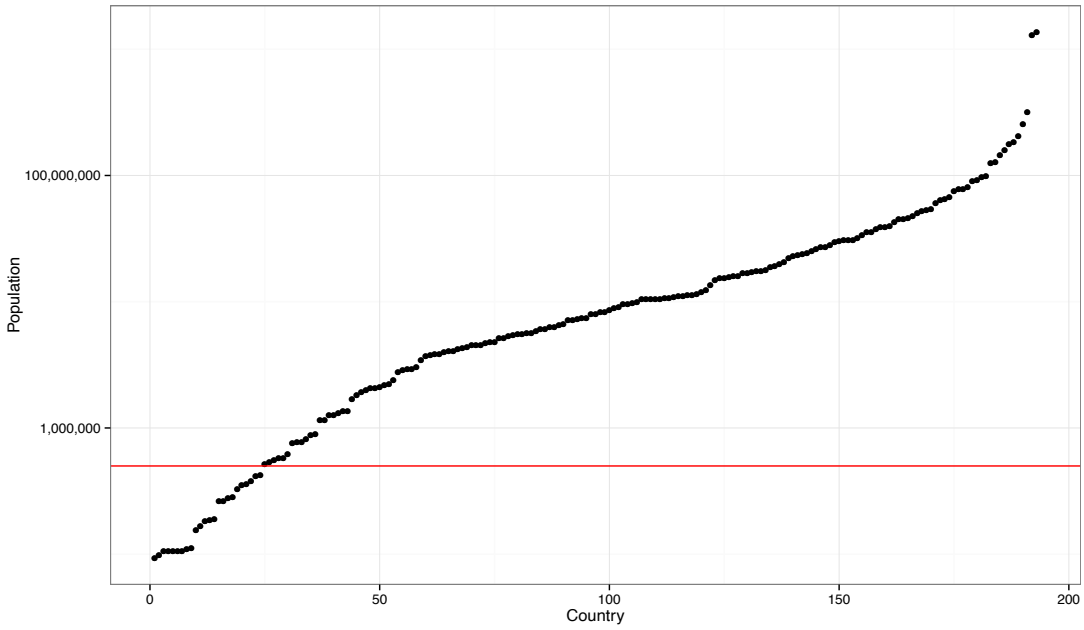

Figure B: Ranked country sizes (500,000 population size cut-off as red line)

168 countries were left, with a total population in 2014 of 7,232,115 thousand (>99.9% of the estimated global population). (ISO3 codes: BWA BDI CMR ETH GMB LSO TZA ARG BRA IND IDN THA DZA AFG BHR KWT LBY PAK SYR CHN MYS KOR PHL AGO ALB ARE ARM AUS AUT AZE BEL BEN BFA BGD BGR BIH BLR BOL BTN CAF CAN CHE CHL CIV COD COG COL COM CPV CRI CUB CYP CZE DEU DJI DNK DOM ECU EGY ERI ESP EST FIN FJI FRA GAB GBR GEO GHA GIN GNB GNQ GRC GTM GUY HKG HND HRV HTI HUN IRL IRN IRQ ISR ITA JAM JOR JPN KAZ KEN KGZ KHM LAO LBN LBR LKA LTU LUX LVA MAC MAR MDA MDG MEX MKD MLI MMR MNE MNG MOZ MRT MUS MWI NAM NER NGA NIC NLD NOR NPL NZL OMN PAN PER PNG POL PRI PRK PRT PRY PSE QAT ROU RUS RWA SAU SDN SEN SGP SLB SLE SLV SOM SRB SSD SUR SVK SVN SWE SWZ TCD TGO TJK TKM TTO TUN TUR UGA UKR URY USA UZB VEN VNM YEM ZAF ZMB ZWE).

For Sudan and South Sudan, we used prevalence estimates for Sudan prior to 2011 for both Sudan and South Sudan, and prevalence estimates specific to each country thereafter. For Serbia and Montenegro we used prevalence estimates reported for the combined country from 1990 to 2004 for the two countries separately, and prevalence estimates specific to each country thereafter.

Modelling ARI from TB prevalence estimates

The Styblo ratio

The Styblo ratio, β, between ARI and the prevalence of smear positive TB was taken to be distributed as

$$\beta \sim LogNormal(1.678,0.371)$$

following Dodd *et al.*

The influence of HIV on smear-positivity

We followed the WHO assumptions for the durations of TB disease stratified by HIV- and notification-status. That is, we assumed these durations to be uniformly distributed

$$T_1^n \sim U[0.2,2]$$
$$T_1^u \sim U[1,4]$$
$$T_2^n \sim U[0.01,1]$$
$$T_2^u \sim U[0.01,0.22]$$

where 1 & 2 denote HIV negative & positive respectively, and *u* and *n* denote un-notified and notified cases, respectively. We used the WHO estimate of case detection ratio to compute the mean TB duration by HIV status for a given country-year

$$T_1 = CDR.T_1^n + (1 - CDR).T_1^u$$
$$T_2 = CDR.T_2^n + (1 - CDR).T_2^u$$

The smear-positivity of TB in people living with HIV was assumed to be a factor *f* less likely, where *f* is taken to be the ratio of two uniform distributions

$$f \sim U[0.3,0.4]/U[0.4,0.5]$$

following Corbett *et al*.

The overall factor reduction *S* in smear-positivity for a country year then

$$S = \frac{(p.f.T_2 + (1 - p).T_1)}{(p.T_2 + (1 - p).T_1)}$$

where p is the WHO estimate of the proportion of incident TB that is HIV-associated.

To assess the sensitivity or results to our assumption that the CDR is independent of HIV-status, we considered the change in the factor S if the CDR in people with HIV was 100%. The proportional change in S across country-years showed a median reduction of 0.14% (IQR: 0.04% - 0.55%).

The influence of age mix on smear-positivity

The proportions p_1, p_2 and p_3 of TB in 0-4, 5-14 and ≥15 age groups was computed using the model of Dodd *et al.* The fractions f_1, f_2 and f_3 smear positive in these age groups were taken from the systematic review and meta-analysis of Kunkel *et al.*. The overall fraction smear positive was then

$$p_1.f_1 + p_2.f_2 + p_3.f_3$$

Propagation of uncertainty

The uncertainty of all distributions, including those characterising the uncertainty in TB prevalence estimates, CDR, proportion of TB that in PLHIV, disease durations and proportions smear-positive were propagated through to give an estimate of ARI variance using the delta method. The validity of this approximation was checked by simulation for a data subset (not shown). The largest contributors to uncertainty in ARI from this procedure were uncertainties in the prevalence estimates and the Styblo ratio.

Gaussian Process calculations

We took the log of ARI to follow a Gaussian process

$$\log(ARI_t) \sim \mathcal{GP}(m(t), k(t, t'))$$

where $m(t) = c_0 + c_1.t$ for the linear trends analysis and simply a constant for the flat trends sensitivity analysis. We assumed vague priors for these coefficients, and used a squared exponential kernel to model the covariance

$$k(t, t') = \sigma_k^2.\exp\left(-\frac{(t-t')^2}{2\ell^2}\right)$$

with normal priors on the hyper-parameters log (σ_k) and log (ℓ), with standard deviations of 100 and means corresponding to 0.5 for the overall kernel scale and 2 years for the smoothing time scale, respectively.

For the observed log ARI values, y_t, we assumed that

$$cov(y_t, y_{t'}) = k(t, t') + \sigma_t^2.\delta_{t,t'}$$

where $1/\sigma_t^2$ specifies the measurement precision, as calculated by propagation of errors for data points derived from prevalence estimates, and using the method of the previous section of data points derived from TST surveys.

Hyper-parameters were set gradient-based optimisation of the posterior, i.e. the sum of the log marginal likelihood (Equation 2.45 of Rasmussen *et al.*) and the log priors specified above. Models were visually assessed for fit to data mid-points and uncertainty.

Modelling LTBI burden given ARI

All M.tb infection

Let λ_t be a sampled ARI through calendar time for a particular country.

$$H_a = \int_0^a da.\lambda_a$$

The cumulative hazard, H_a, of infection for those of age a is

$$H_a = \sum_{i=0}^{a} \lambda_{2015-i}$$

The proportion of this age group that is latently infected is therefore

$$P_a = 1 - \exp(-H_a)$$

Given that in this country the number of people who are age a in 2014 is N_a, the number who are latently infected in each age group L_a is just

$$L_a = P_a N_a = (1 - \exp(-H_a))N_a$$

Now in fact we are only provided with demographic information in 5-year age bins, M_A for a particular age group A. We therefore have

$$L_A = \sum\nolimits_{a \in A} P_a N_a = M_A \times \frac{1}{5} \sum\nolimits_{a \in A} P_a$$

Infection with M.tb for the first time within 2 years

Let $T = 2$ years. The probability of infection for the first time within 2 years is given by

$$P_a^{<T} = \exp(-H_{a-T}) - \exp(-H_a)$$

where we define $H_a = 0$ when $a < 0$.

Infection or re-infection with M.tb within 2 years

The hazard ratio protection α was characterized as

$$\alpha \sim Beta(77.88, 20.70)$$

to match the mean and 95% confidence interval reported in Andrews *et al.* The incidence of infection for a given age is then

$$I_a = \lambda_a(\alpha(1 - \exp(-H_a)) + \exp(-H_a))$$

where λ_a is the force-of-infection experienced by a cohort alive now when they were age a, which integrates to give

$$P_a^{<T} = \alpha(H_a - H_{a-T}) + (1 - \alpha)(e^{-H_{a-T}} - e^{-H_a})$$

where H_a is defined to be 0 when $a < 0$.

Code for calculations can be found at https://github.com/petedodd/LTBIest.

Results

Gaussian process regressions for ARI with linear trends

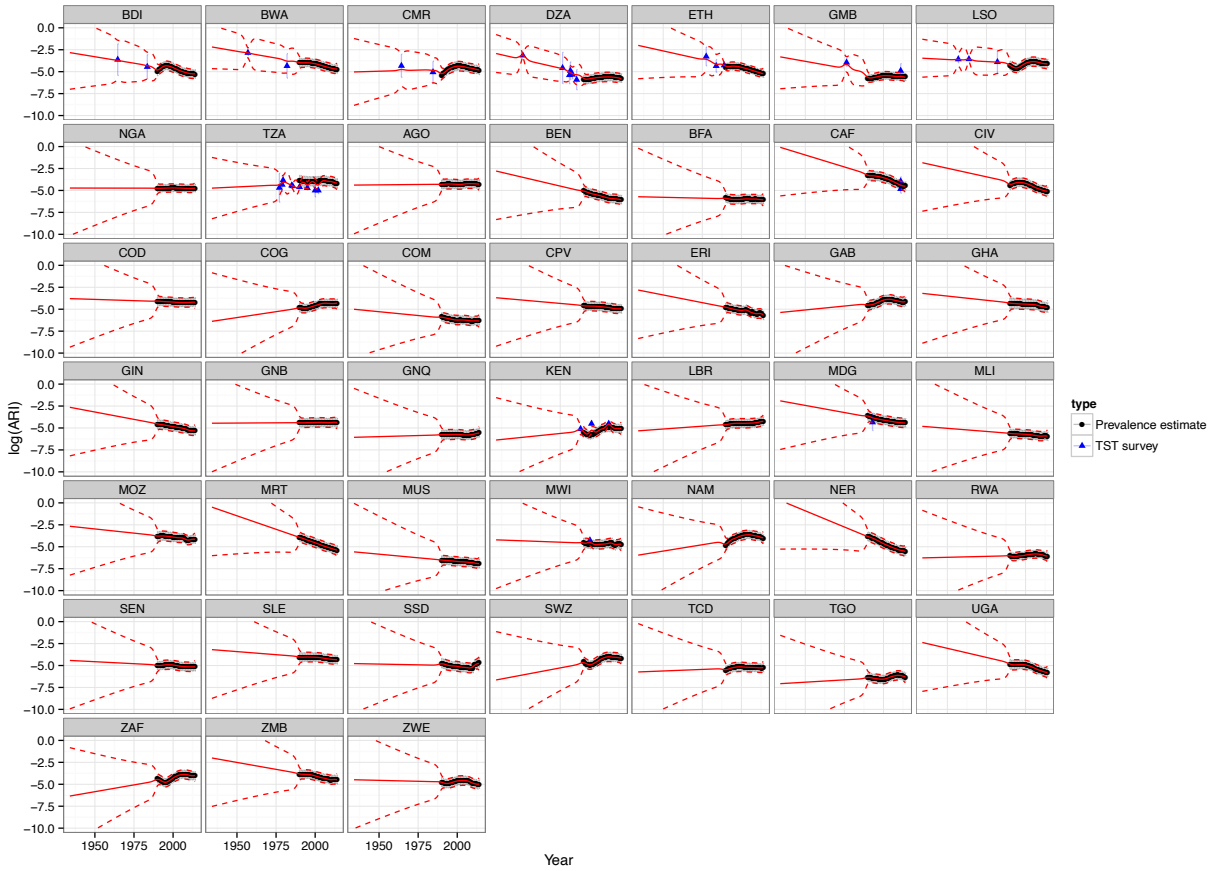

Figure C: WHO AFR region

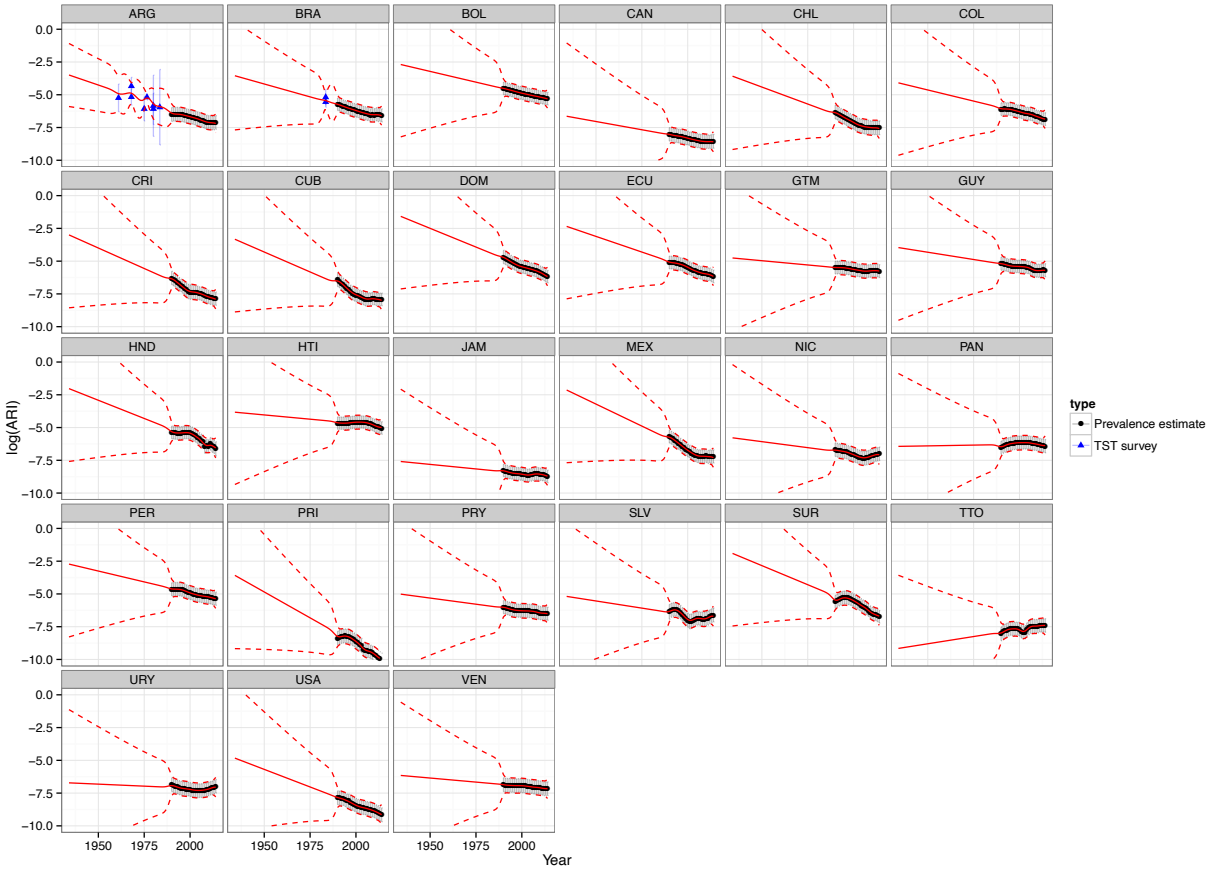

Figure D: WHO AMR region

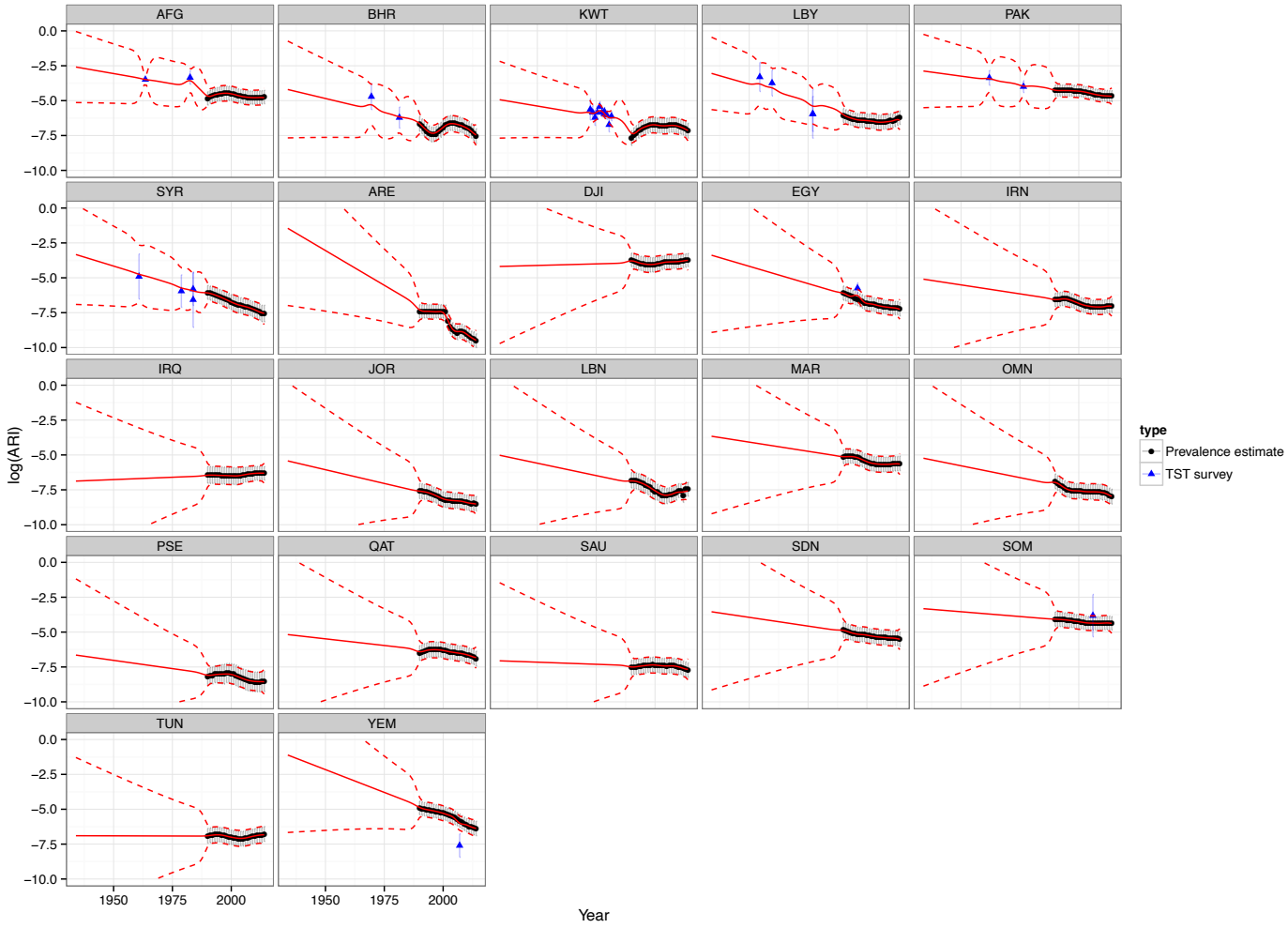

Figure E: WHO EMR region

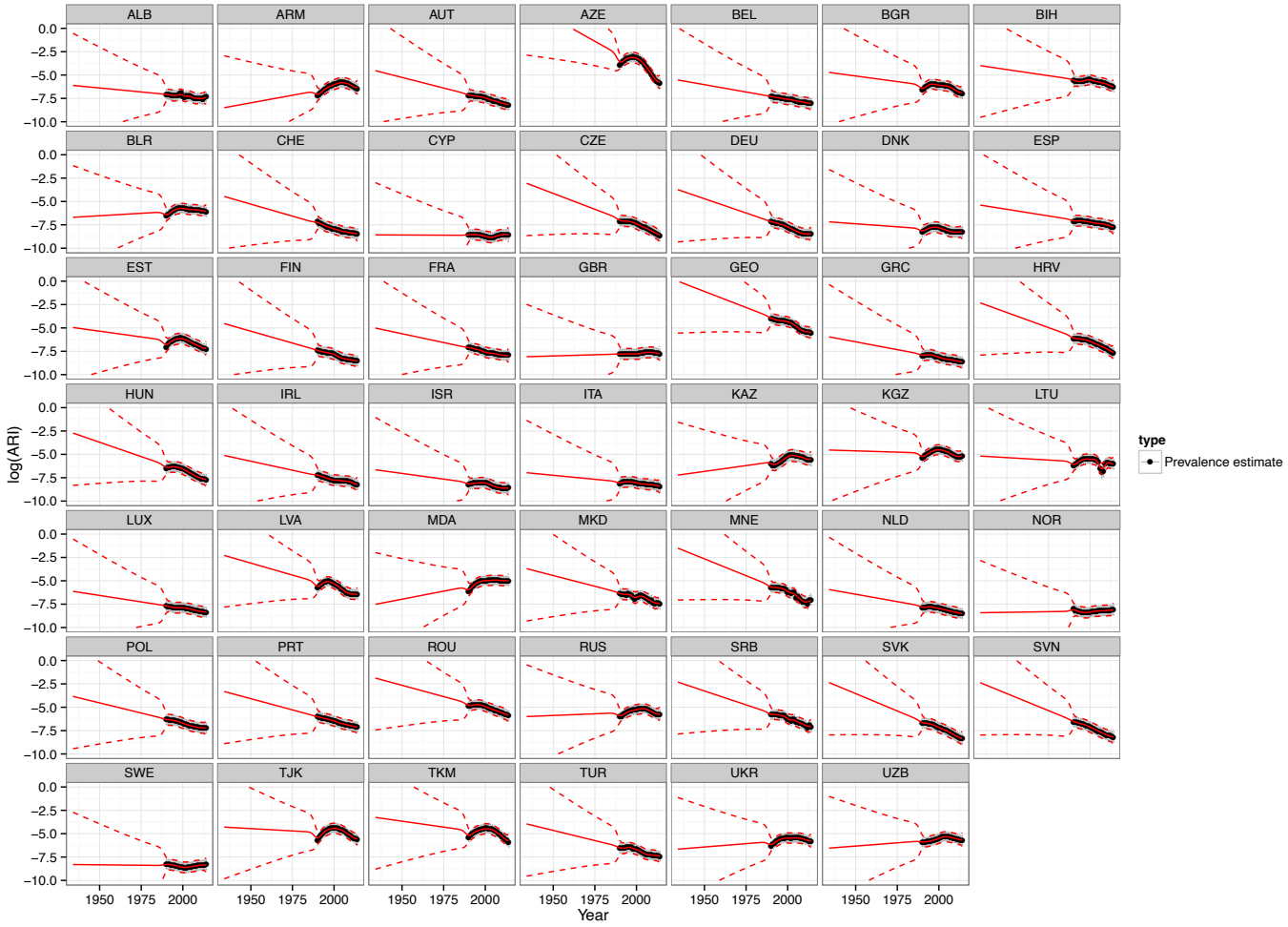

Figure F: WHO EUR region

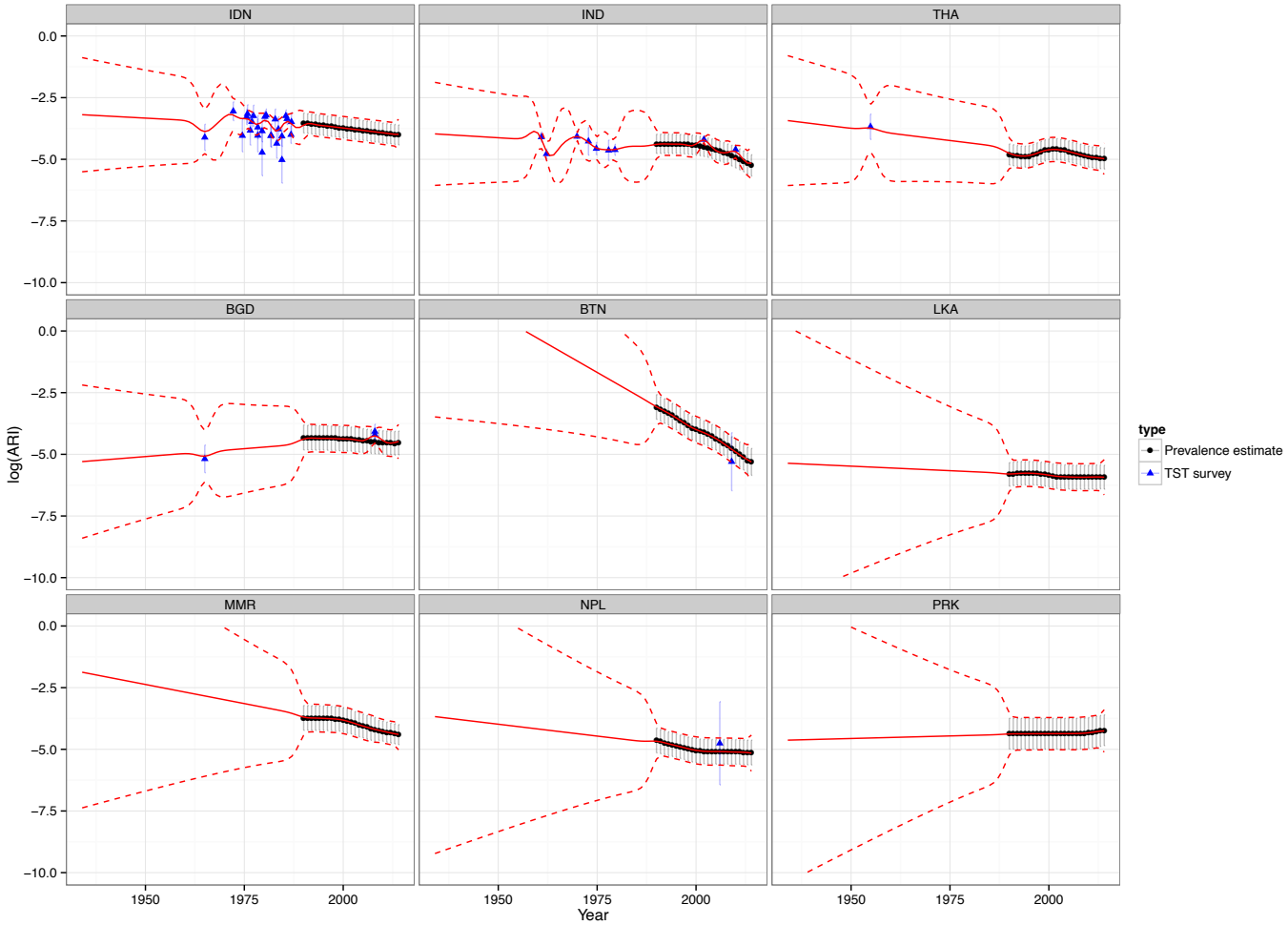

Figure G: WHO SEA region

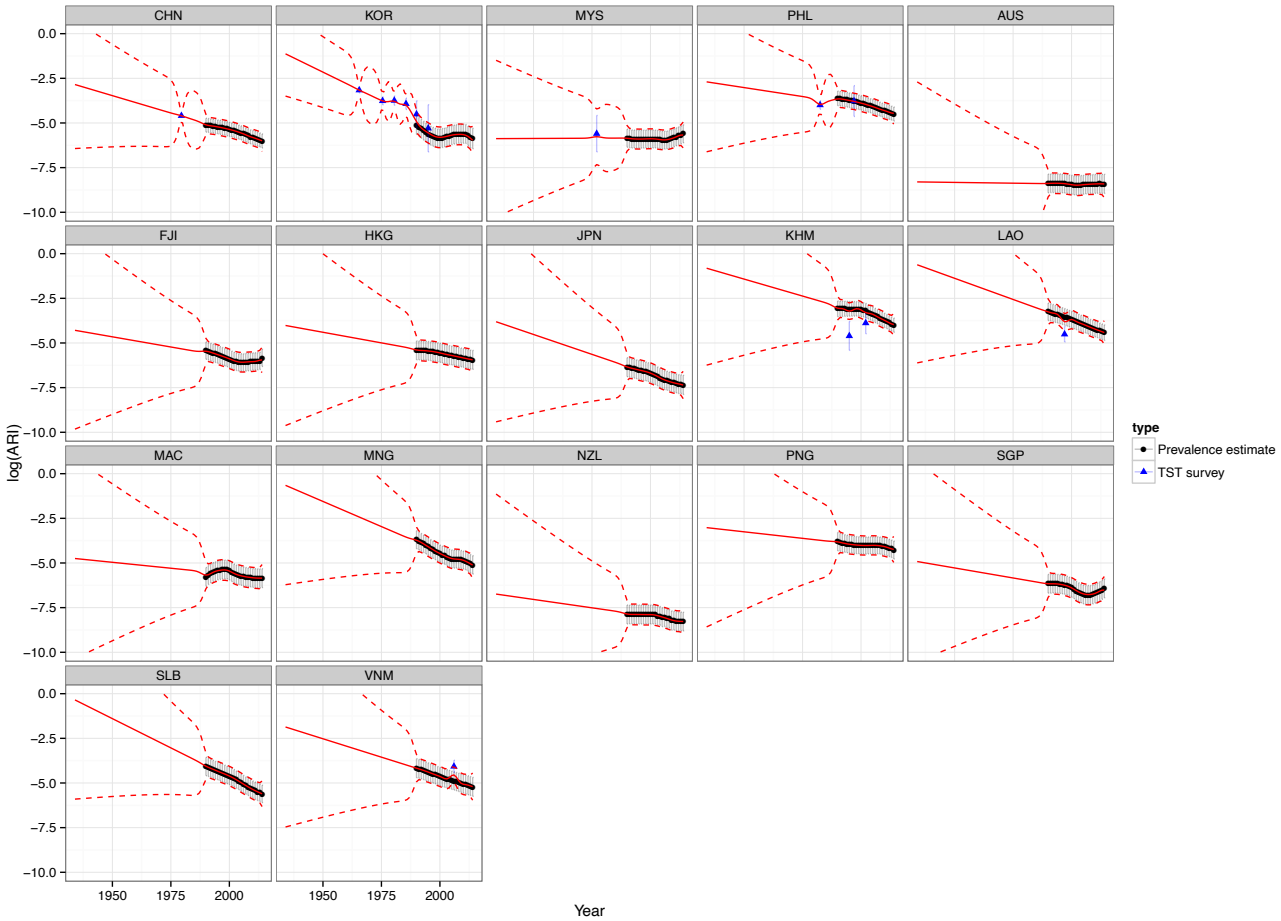

Figure H: WHO WPR region

Top 20 countries by absolute LTBI burden (figure) and country level results (file)

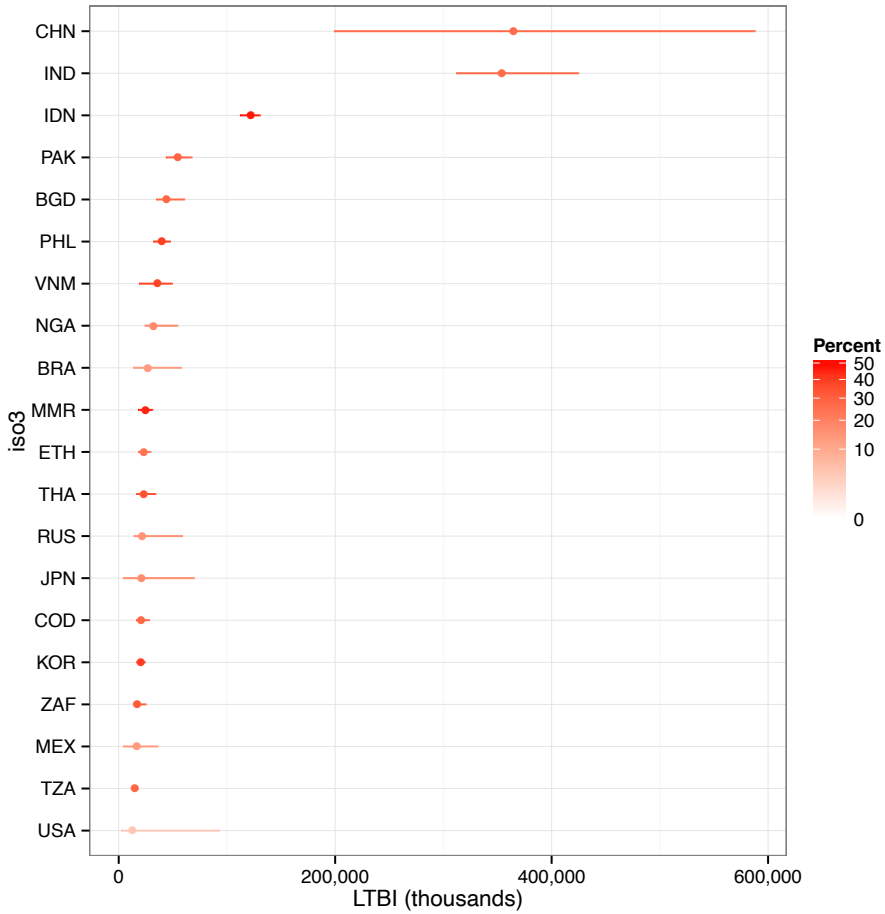

Figure I: Top 20 countries by number of latent *M.tb* infections (color shows percentage prevalence). Country level results can be viewed in the supporting file individual_country_ests.csv

Recent infection and re-infection by age

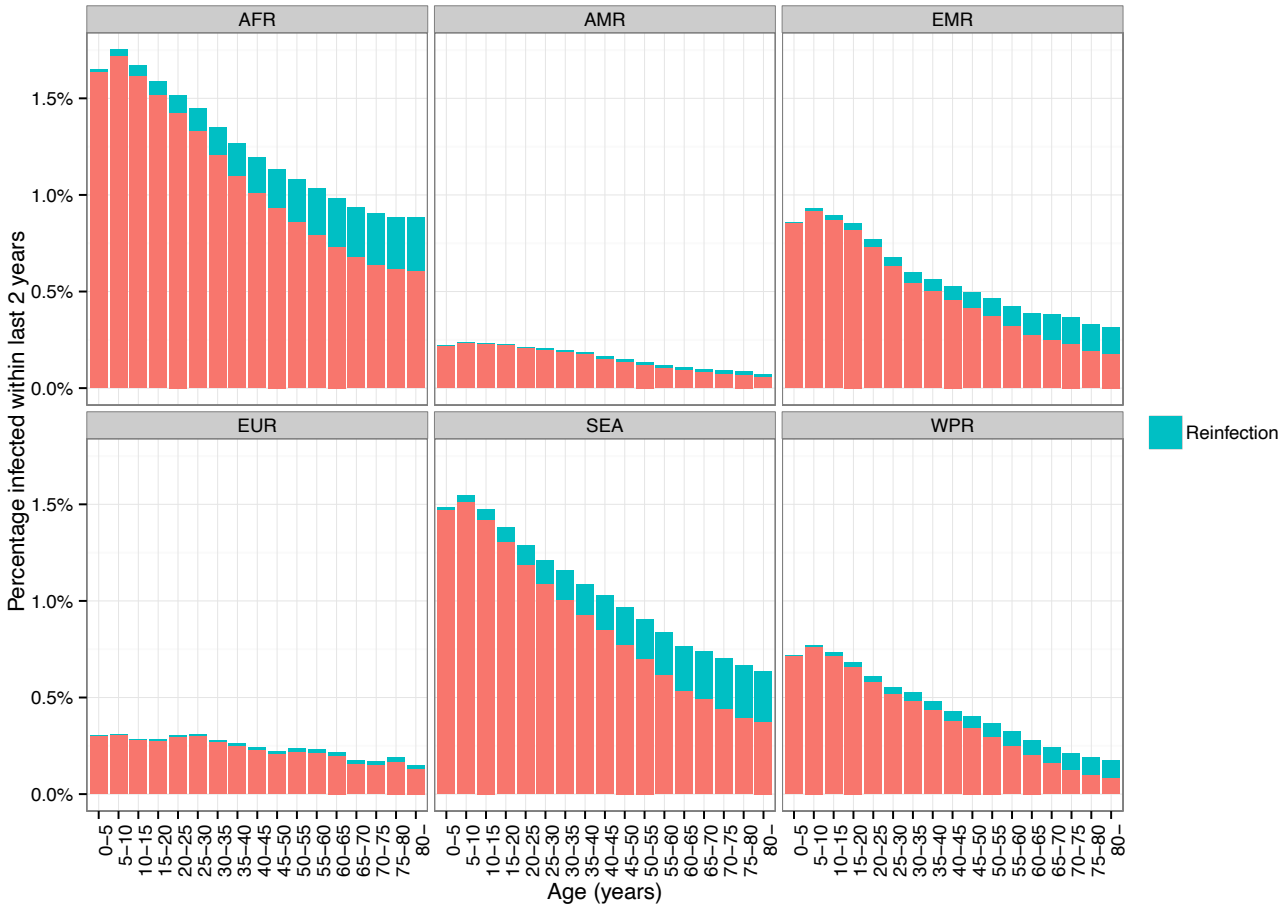

Figure J: Recent infection and re-infection by age under base case assumption around protection from re-infection.

Gaussian process regressions for ARI with flat trends

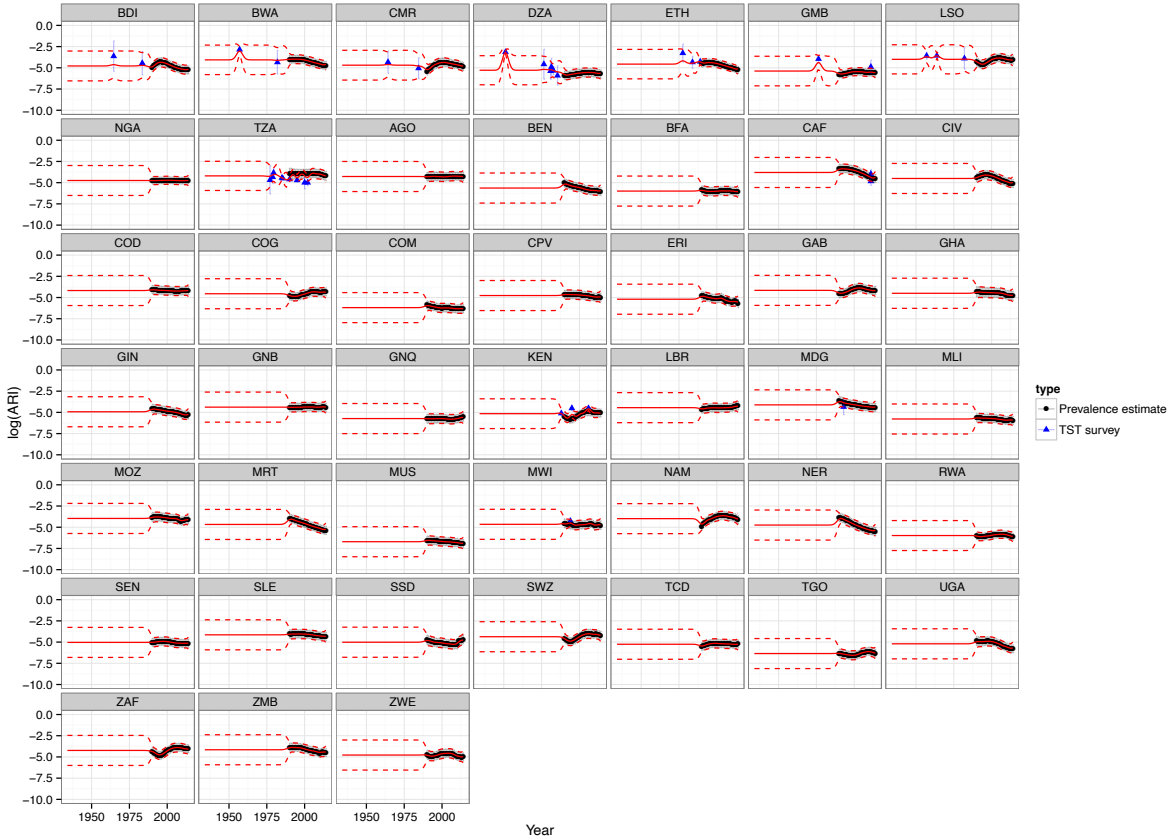

Figure K: WHO AFR region (flat trends)

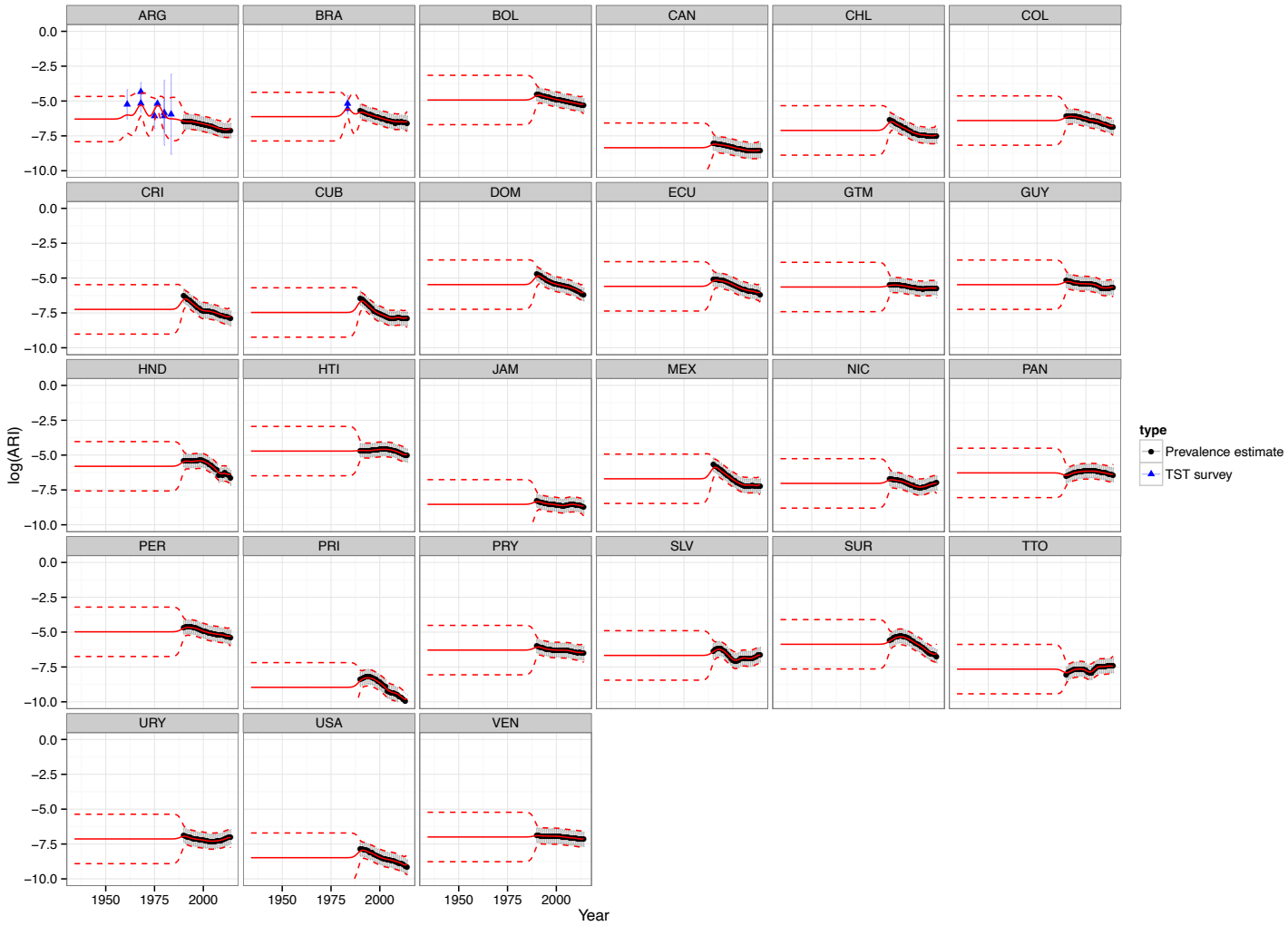

Figure L: WHO AMR region (flat trends)

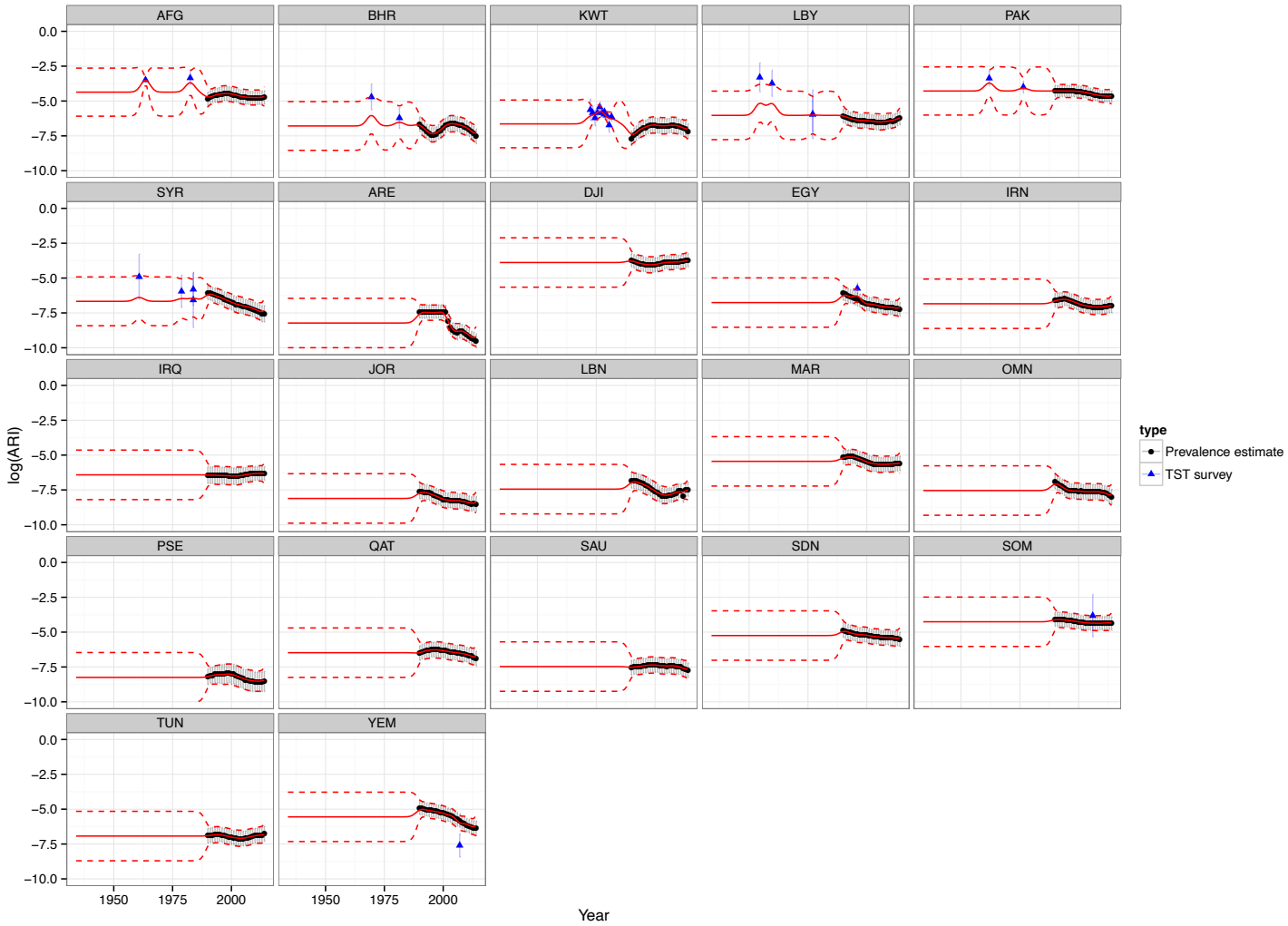

Figure M: WHO EMR region (flat trends)

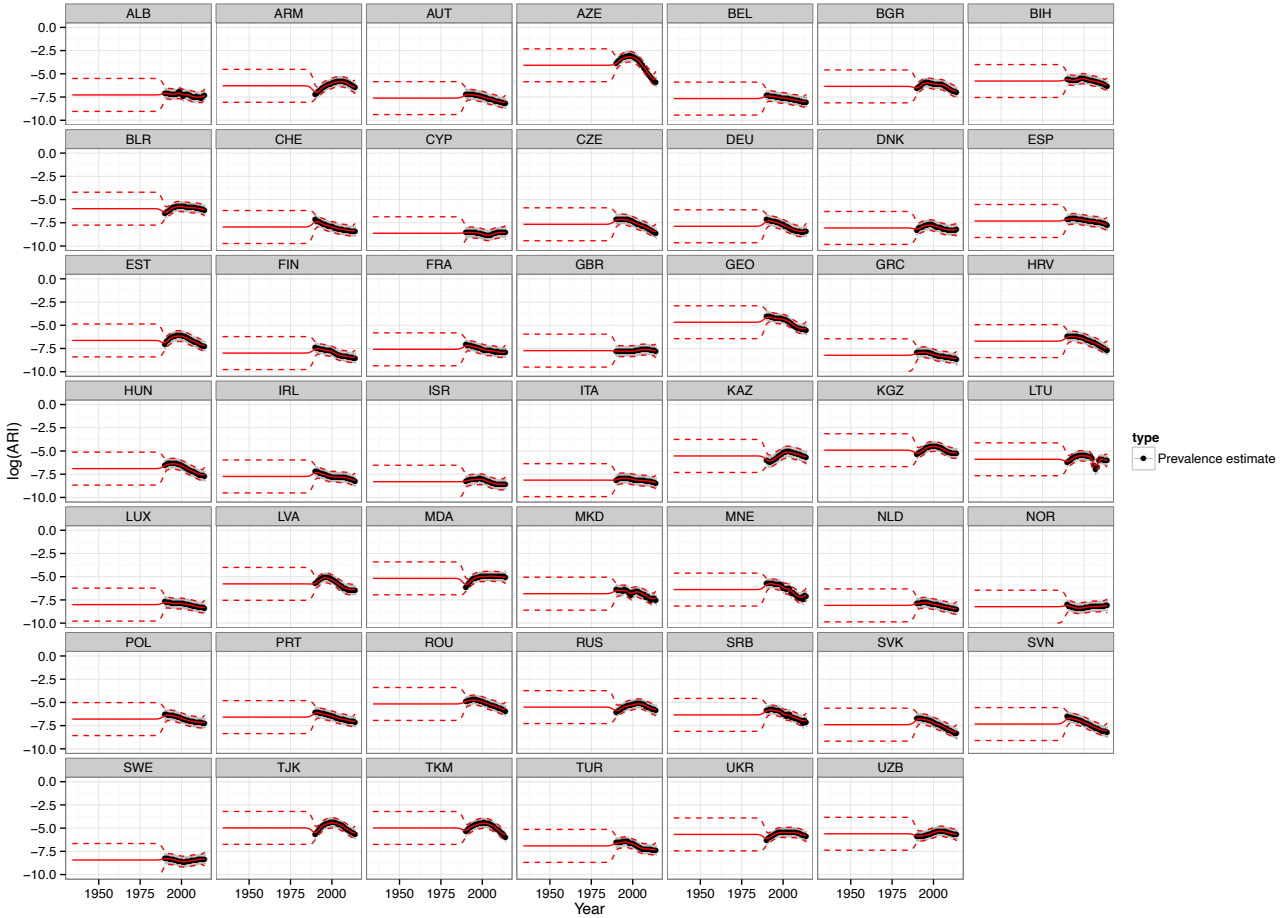

Figure N: WHO EUR region (flat trends)

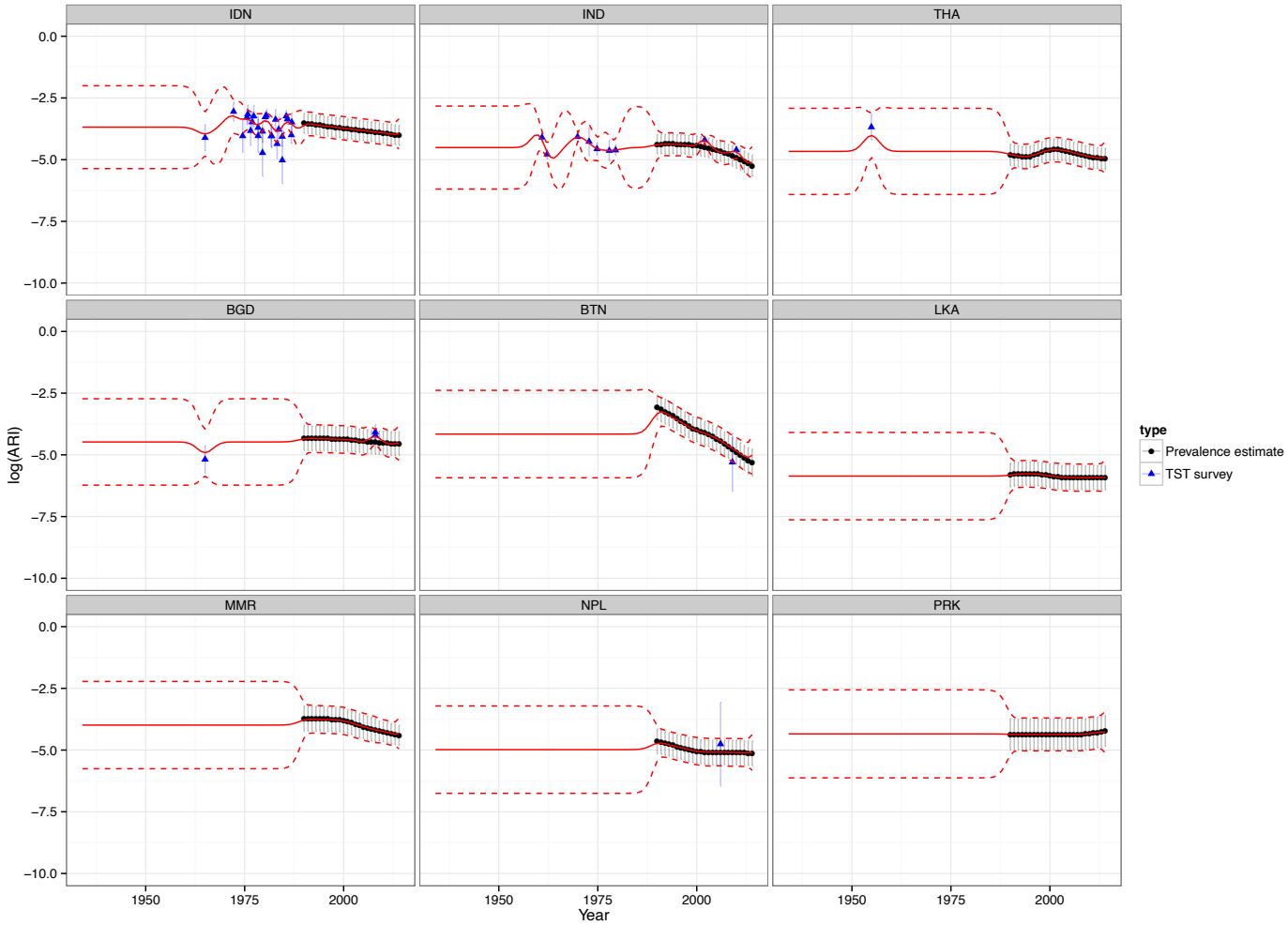

Figure O: WHO SEA region (flat trends)

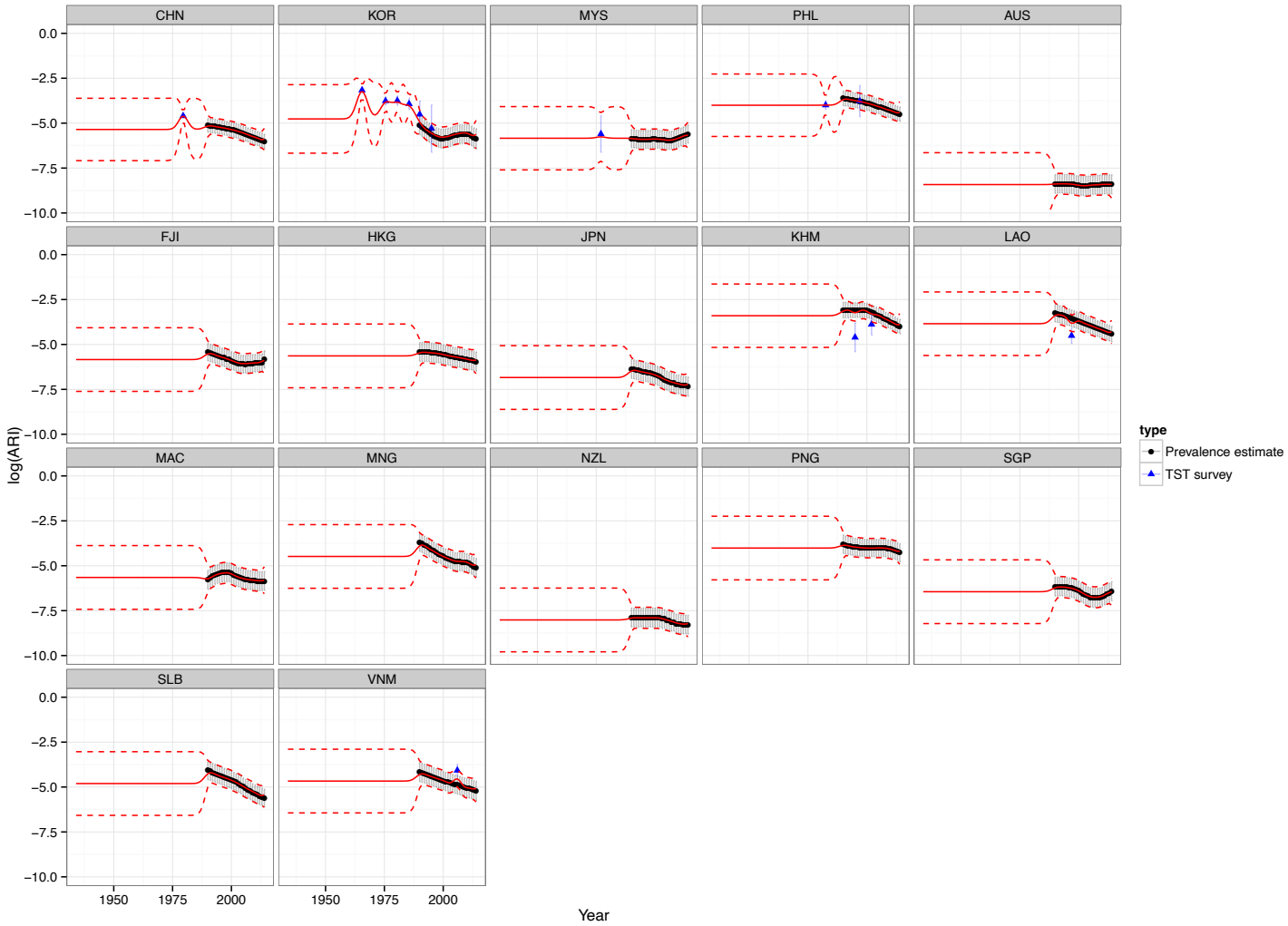

Figure P: WHO WPR region (flat trends)

Supporting tables

Table A: Proportions with LTBI for flat trend sensitivity analysis

	All LTBI		Recent infection prevalence (within 2 years)	
WHO region	**Prevalence (%)**	**Proportion of infections in children <15 years (%)**	**(%)**	**Proportion with INH-R infection (%)**
AFR	20.8 [19.4 - 22.6]	14.4 [13.4 - 15.3]	1.5 [1.3 - 1.8]	7.4 [6.5 - 8.7]
AMR	5.2 [4.5 - 6.2]	5.0 [4.1 - 5.7]	0.2 [0.2 - 0.3]	7.1 [6.1 - 9.0]
SEA	30.3 [27.1 - 35.2]	7.6 [6.6 - 8.5]	1.2 [1.0 - 1.7]	9.6 [8.8 - 10.3]
EMR	13.3 [11.7 - 16.0]	9.8 [8.3 - 11.2]	0.7 [0.6 - 1.0]	13.3 [9.9 - 15.6]
WPR	18.7 [14.8 - 26.8]	3.7 [2.7 - 4.5]	0.6 [0.4 - 0.8]	14.8 [13.9 - 15.7]
EUR	8.2 [7.0 - 10.1]	3.3 [2.7 - 3.8]	0.3 [0.2 - 0.3]	28.7 [23.0 - 44.1]
GLOBAL	**18.5 [17.0 - 20.7]**	**7.4 [6.5 - 7.9]**	**0.8 [0.7 - 1.0]**	**11.0 [10.3 - 12.0]**

Table B: Proportions with LTBI for 50% protection sensitivity analysis

	All LTBI		Recent infection prevalence (within 2 years)	
WHO region	**Prevalence (%)**	**Proportion of infections in children <15 years (%)**	**(%)**	**Proportion with INH-R infection (%)**
AFR	22.4 [20.6 - 24.6]	13.3 [11.8 - 14.6]	1.6 [1.4 - 1.9]	7.4 [6.5 - 8.8]
AMR	11.0 [7.0 - 20.0]	2.3 [1.3 - 3.7]	0.2 [0.2 - 0.2]	7.1 [6.2 - 8.7]
SEA	30.8 [28.3 - 34.8]	7.4 [6.3 - 8.2]	1.4 [1.0 - 1.8]	9.5 [8.7 - 10.4]
EMR	16.3 [13.4 - 20.5]	7.9 [6.0 - 9.4]	0.8 [0.5 - 1.1]	13.2 [10.1 - 15.5]
WPR	27.9 [19.3 - 40.1]	2.4 [1.7 - 3.5]	0.6 [0.4 - 0.8]	14.7 [13.8 - 15.6]
EUR	13.7 [9.8 - 19.8]	2.0 [1.3 - 2.7]	0.3 [0.2 - 0.4]	29.1 [23.9 - 48.1]
GLOBAL	**23.0 [20.4 - 26.4]**	**5.9 [5.1 - 6.7]**	**0.9 [0.7 - 1.0]**	**11.0 [10.2 - 12.0]**

Table C: Numbers (thousands) of infections for flat trend sensitivity analysis

WHO region	All LTBI		Recent infection prevalence (within 2 years)	
	Number (K)	Number (K) of infections in children <15 years	Number (K)	Number (K) with INH-R infection
AFR	200,000 [187,000 - 218,000]	28,700 [26,700 - 31,600]	14,400 [12,500 - 17,000]	1,070 [863 - 1,350]
AMR	51,100 [44,400 - 60,800]	2,550 [2,310 - 2,800]	1,990 [1,580 - 2,520]	143 [105 - 185]
SEA	577,000 [516,000 - 670,000]	43,700 [38,800 - 49,800]	23,400 [18,900 - 32,600]	2,230 [1,730 - 3,180]
EMR	84,800 [74,300 - 102,000]	8,240 [7,220 - 9,520]	4,760 [3,710 - 6,300]	631 [418 - 899]
WPR	344,000 [272,000 - 493,000]	12,700 [11,300 - 14,500]	10,300 [7,960 - 14,200]	1,540 [1,130 - 2,140]
EUR	74,600 [63,300 - 91,500]	2,450 [2,220 - 2,710]	2,360 [1,970 - 3,060]	702 [516 - 1,110]
GLOBAL	**1,340,000 [1,230,000 - 1,500,000]**	**98,600 [93,100 - 106,000]**	**57,700 [51,700 - 68,800]**	**6,390 [5,620 - 7,660]**

Table D: Numbers (thousands) of infections for 50% protection sensitivity analysis

WHO region	All LTBI		Recent infection prevalence (within 2 years)	
	Number (K)	Number of infections in children <15 years	Number (K)	Number (K) with INH-R infection
AFR	216,000 [198,000 - 237,000]	28,700 [26,700 - 30,800]	15,600 [13,300 - 18,200]	1,160 [943 - 1,410]
AMR	108,000 [68,900 - 196,000]	2,470 [2,240 - 2,710]	1,860 [1,530 - 2,360]	134 [101 - 179]
SEA	587,000 [540,000 - 662,000]	43,300 [38,700 - 48,300]	26,100 [19,300 - 35,200]	2,510 [1,850 - 3,370]
EMR	104,000 [85,200 - 130,000]	8,060 [7,090 - 9,240]	4,940 [3,460 - 6,860]	633 [433 - 891]
WPR	514,000 [356,000 - 739,000]	12,400 [10,900 - 13,800]	10,300 [7,750 - 14,100]	1,520 [1,130 - 2,140]
EUR	124,000 [89,100 - 180,000]	2,430 [2,220 - 2,690]	2,420 [1,980 - 3,300]	712 [516 - 1,260]
GLOBAL	**1,660,000 [1,480,000 - 1,910,000]**	**97,100 [91,700 - 103,000]**	**61,900 [53,400 - 71,300]**	**6,740 [5,820 - 8,030]**

Recent infection and re-infection by age (sensitivity analysis)

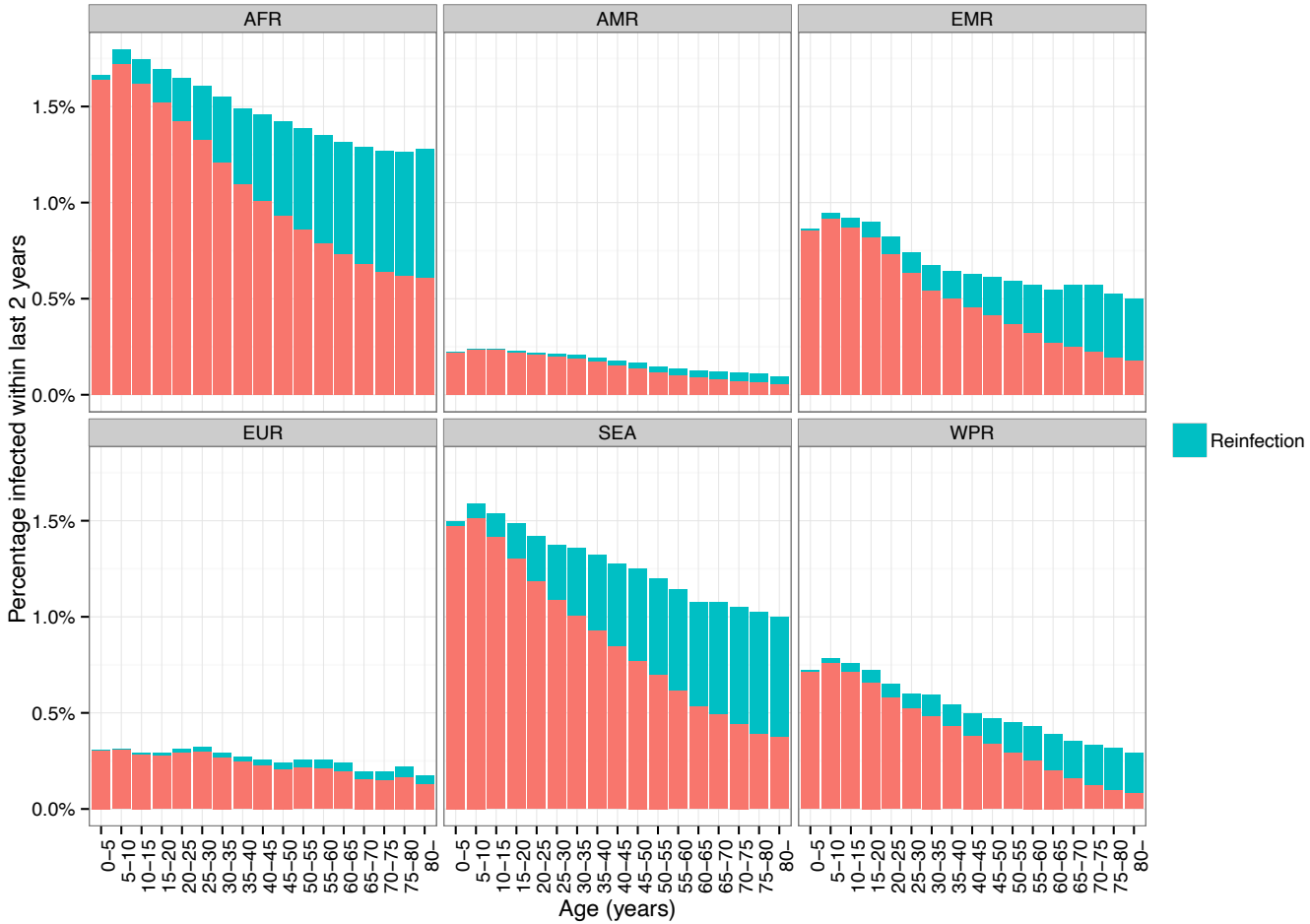

Figure Q: Sensitivity analysis 50% protection against re-infection

Conceptual overview

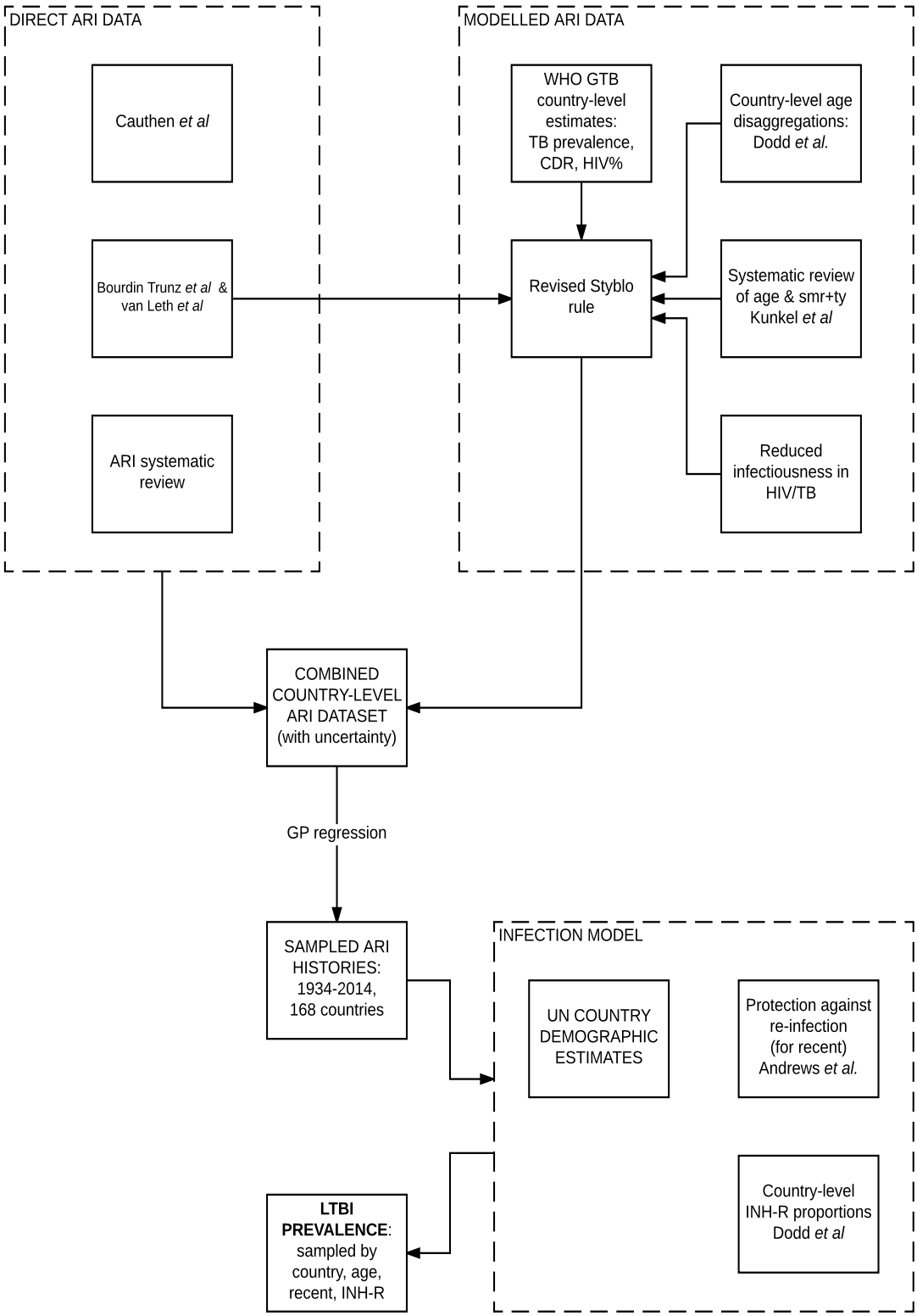

Figure R: Conceptual overview