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TB CARE II

DR|TB TRAINING NETWORK

WHAT'S IN A NUMBER? TWO RECENT REPORTS ESTIMATING CHILDHOOD TB CASES.

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Sentinel Project on pediatric drug resistant tuberculosis

Thursday
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10:00 a.m. EDT
(GMT -5:00)

www.drtbnetwork.org

Two 2014 reports & accompanying commentaries

1. Jenkins HE et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet* 2014 May 3; 383(9928):1572-9.

* Marais BJ. Quantifying the tuberculosis disease burden in children. *Lancet* 2014 May 3; 383(9928):1530-1.

2. Dodd PJ et al. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Global Health* 2014 Aug; 2(8):e453-9.

* Cruz AT, Starke JR. What's in a number? Accurate estimates of childhood tuberculosis. *Lancet Global Health* 2014 Aug; 2(8):e432-3.

How many children get sick with MDR-TB every year?

How many children get sick with ~~MDR-~~TB every year?

Childhood TB is different from adult TB

↑ Extrapulmonary disease

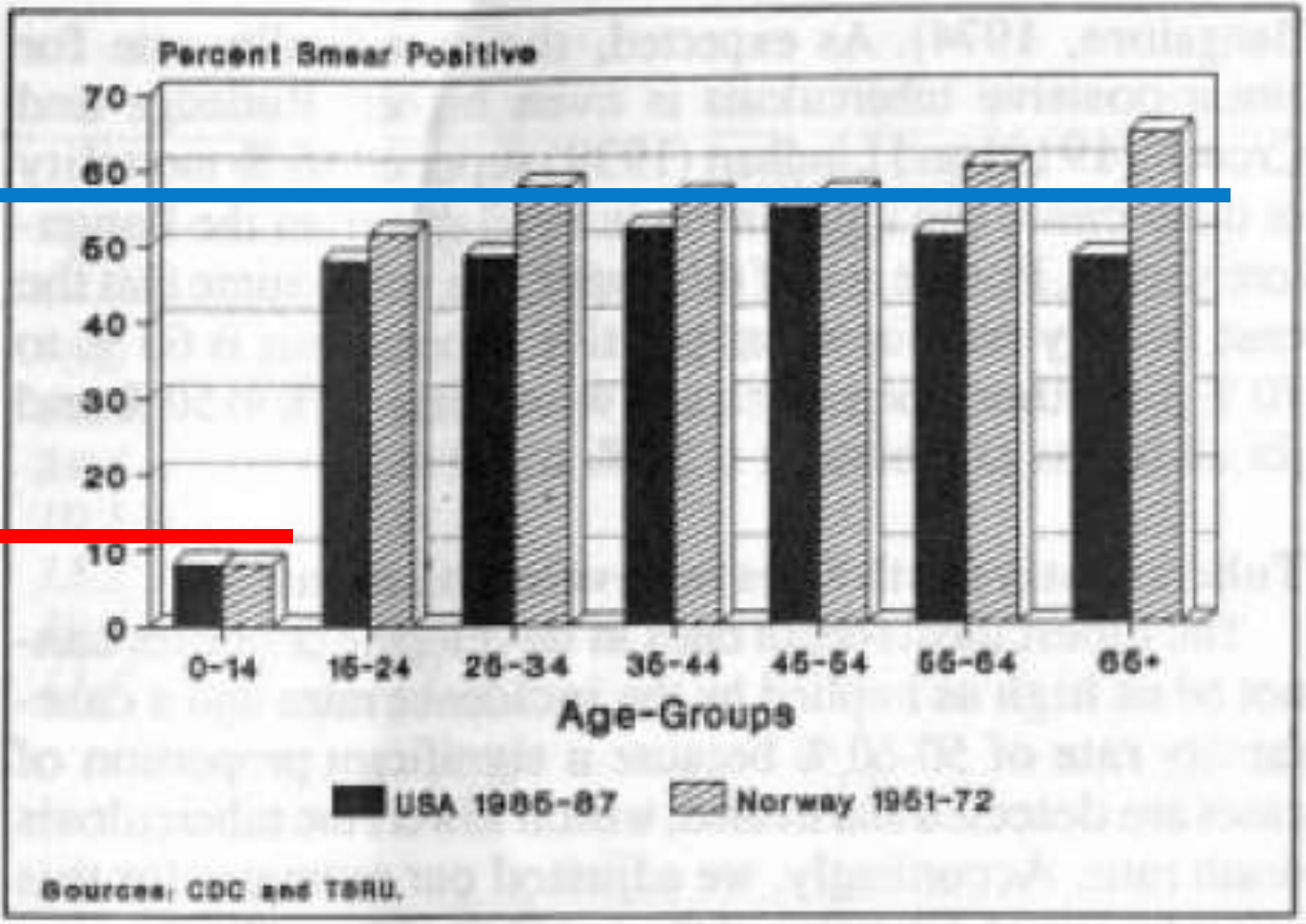
↓ Bacterial burden

↓ Testable sputum

Accounting for under diagnosis with smear microscopy

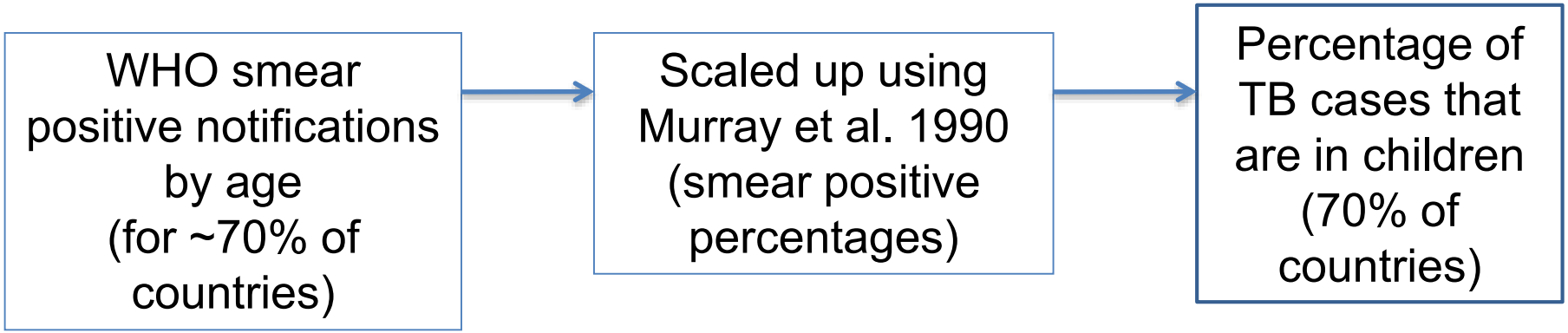
~50-60%

~10%



Murray, Styblo, Rouillon. BIUATLD 1990

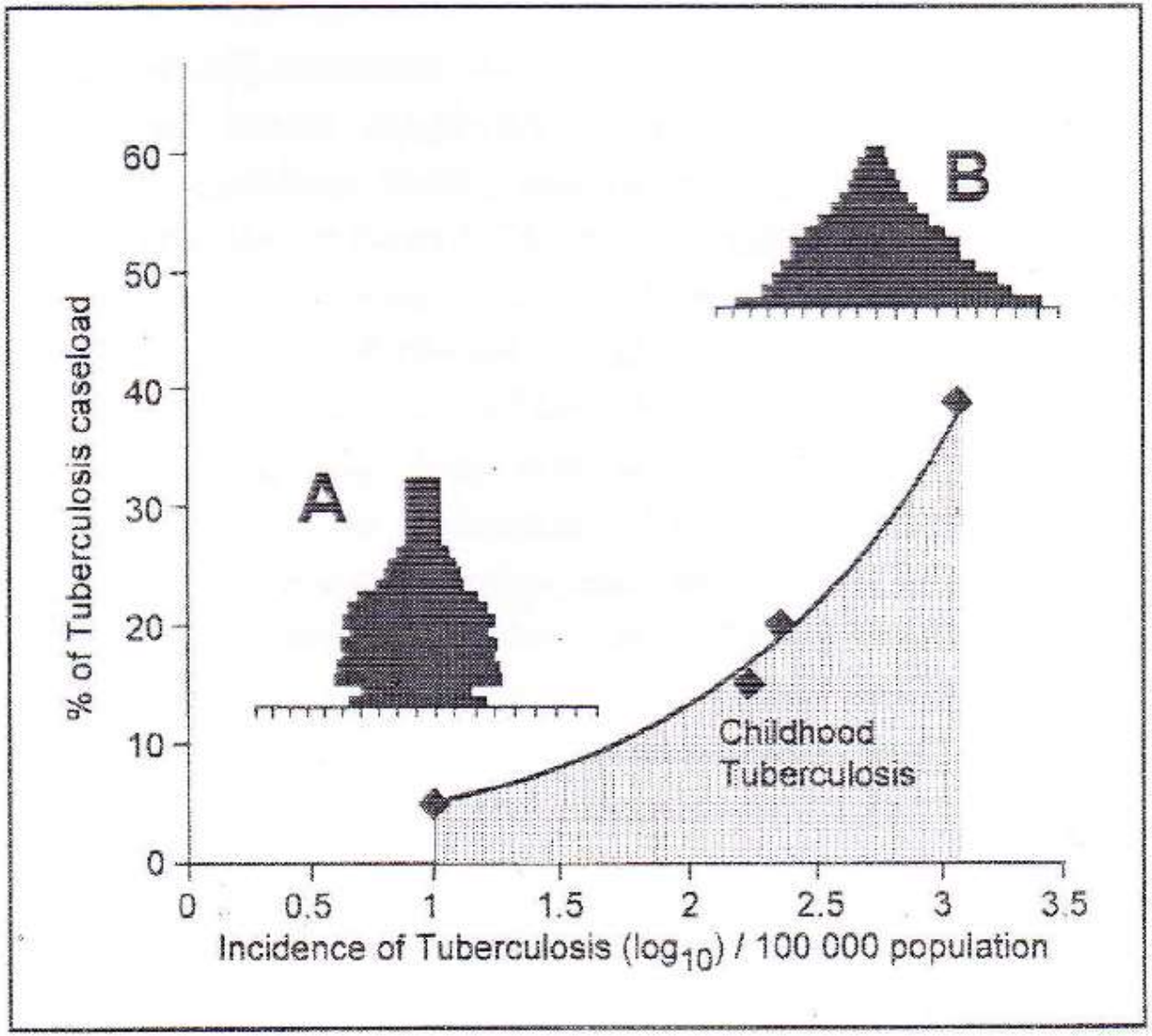
Data inputs and outputs



Can we estimate proportion of all cases that are in children?

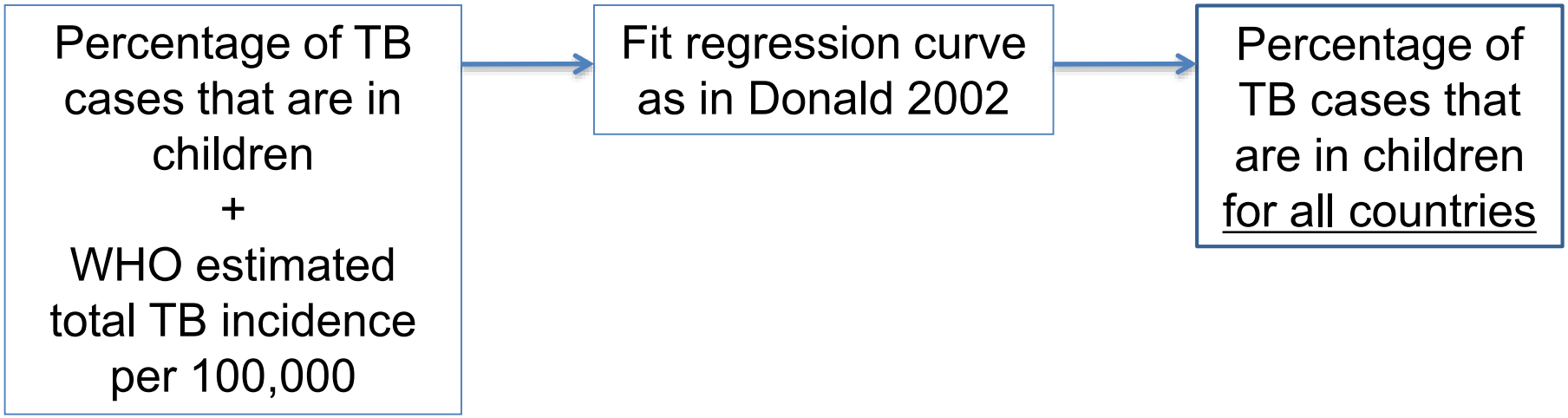
Donald P.
"Childhood TB:
Out of control?"
Curr Opinion
Pulm Med 2002

Figure 1. Percentages of the tuberculosis caseload

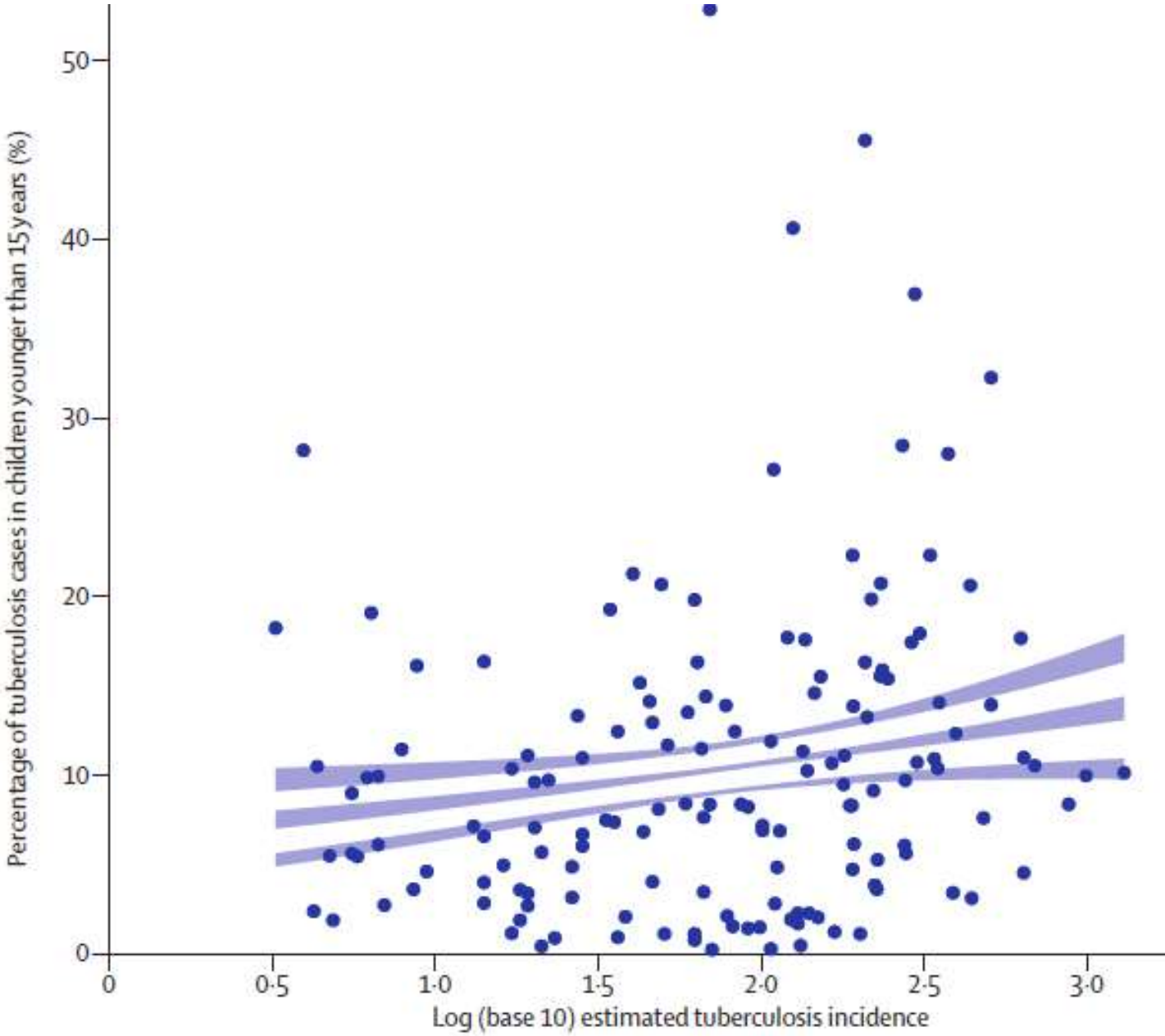


The percentage of the tuberculosis caseload made up by children <15 years of age in relation to the incidence of tuberculosis/100,000 population and the population pyramids typical of an (A) developed and a (B) developing community.

Data inputs and outputs



Logistic regression using our scaled-up TB incidence estimates shows *exponential increase consistent with Donald 2002*



Jenkins et al. Lancet 2014

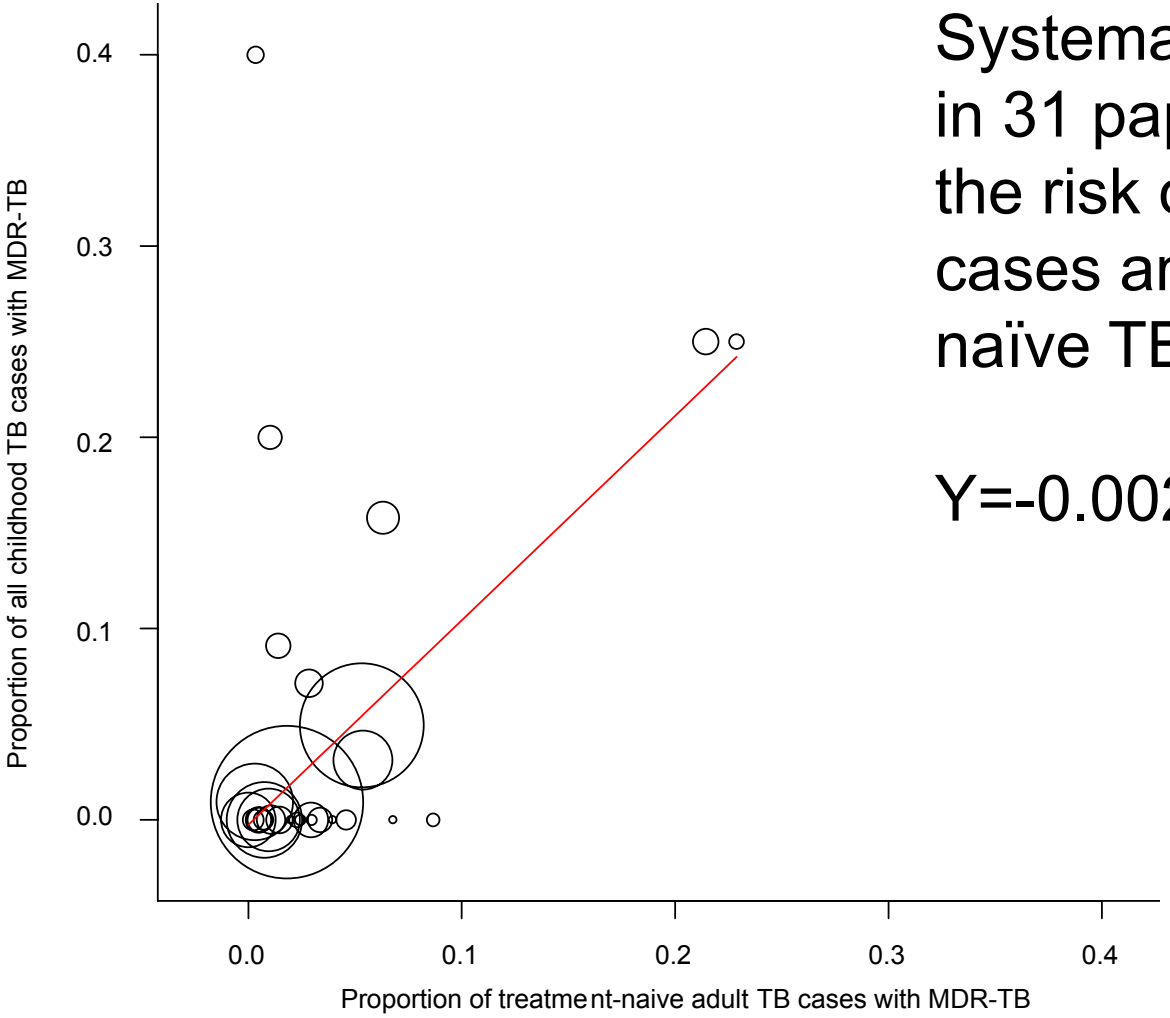
Data inputs and outputs

WHO TB incidence per 100,000 estimates
* UN population numbers
* Percentage of TB cases in children

→ Number of incident active childhood TB cases in one year

999,792 (95% CI: 937,877 – 1,055,414) child TB cases

Estimating the risk of MDR-TB in child TB cases

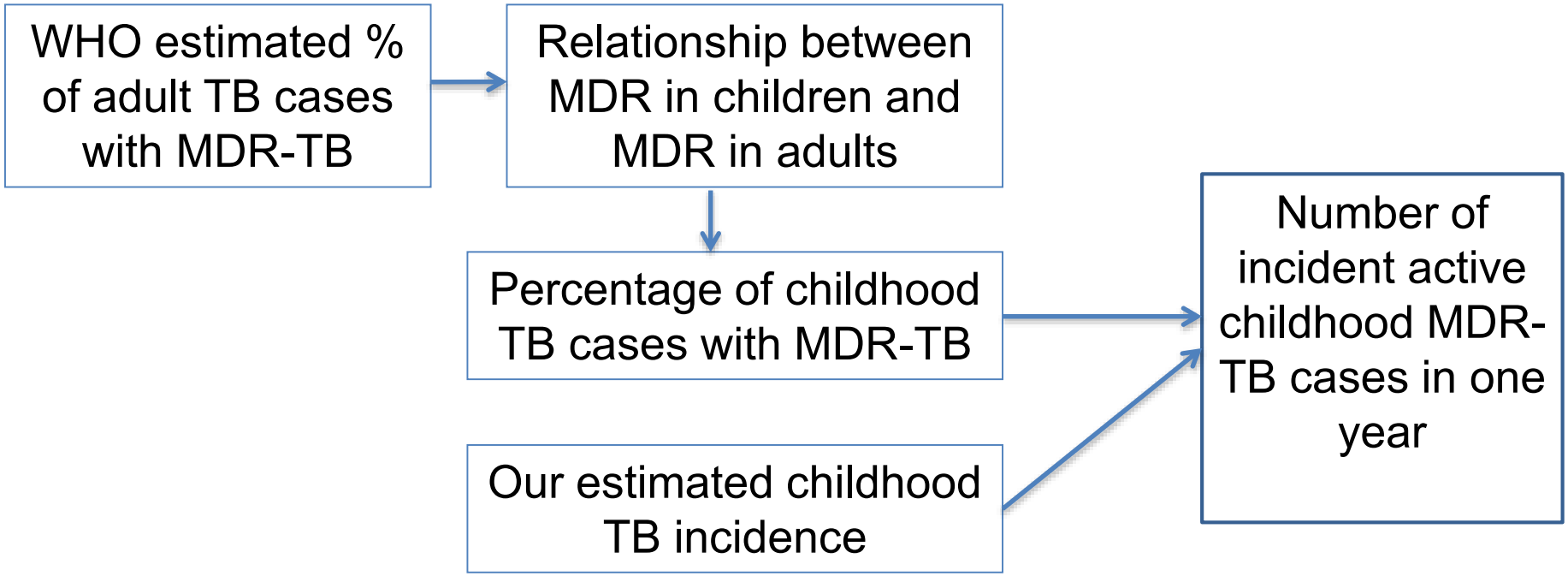


Systematic review resulting in 31 papers quantifying the risk of MDR in child TB cases and adult treatment-naïve TB cases

$Y=-0.00261+1.0691X$

Jenkins et al. Lancet 2014

Data inputs and outputs



31,948 (95% CI: 25,594 – 38,663) childhood MDR-TB cases

What does this mean?

- We now understand the magnitude of the discrepancy better and can better predict resources needed:
  - 3 x annual notified child TB of 349,000
  - 2 x WHO recent global estimates of 540,000
  - Slightly higher that Dodd et al. of ≈ 800,000 (global)
  - reports of MDR-TB in the literature (across 40 years) ~2% of total burden (in one year!)
- Most of this morbidity (and mortality) is preventable
- We need more investment in diagnostics and treatment
- In the meantime we need to use tools available to us (eg. contact tracing, preventive treatment…)

Acknowledgements

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University of Arizona: Carlos Perez-Velez

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Estimating the burden of paediatric tuberculosis through mathematical modelling

Pete Dodd (University of Sheffield)
& James Seddon (Imperial College London)

Thursday, 9 October 2014

Health Economics & Decision Science
School of Health & Related Research
University of Sheffield

Overview

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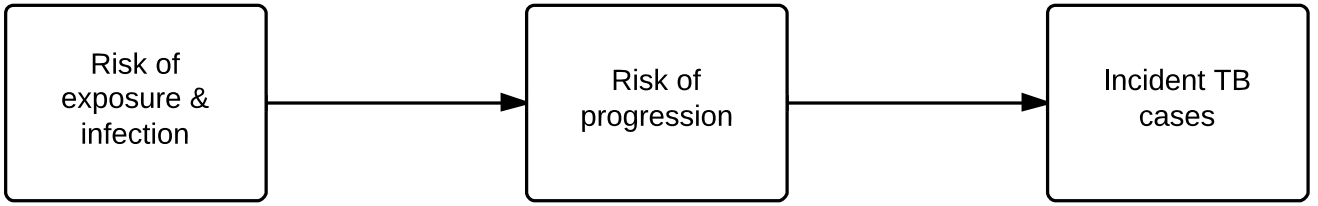
The University Of Sheffield.

Goal:

Circumvent potential shortcomings in paediatric notification data by mathematical modelling starting from adult data. Applied to the 22 HBCs.*



Two modelling steps:

1. Relate adult prevalence to infection risk (2 ways)
2. Model progression from infection to disease

Uncertainty in knowledge of each ingredient must be included.

* *mechanistic* vs. *phenomenological*

Styblo's rules: the model you know

Pete Dodd

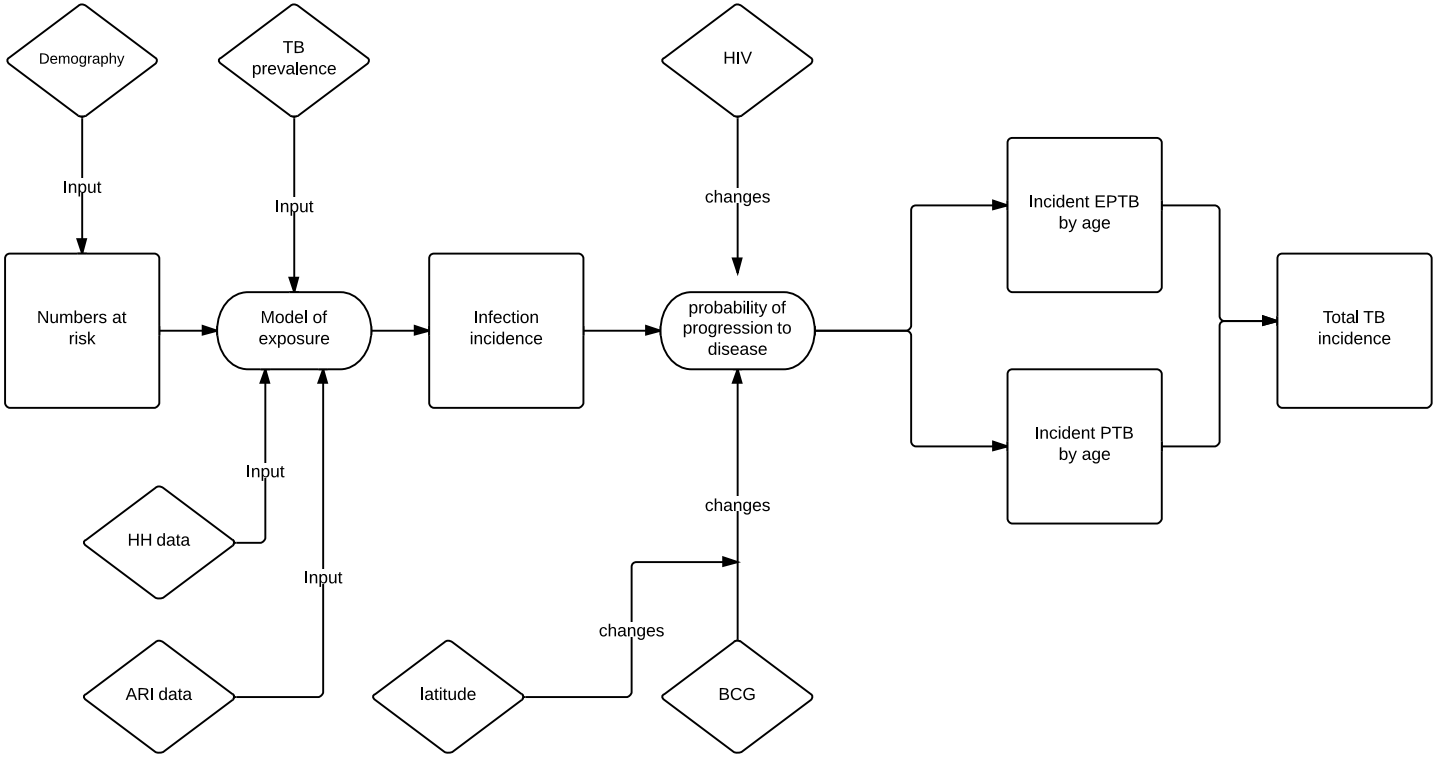
The University Of Sheffield.

Figure: Karel Styblo, 1921-1998: the `father of TB control'

The canonical picture

- deaths : incidence : prevalence
  in ratio
  1 : 2 : 4 for smear positive TB
  I.e. CFR$\approx$ 50% & duration $\approx$ 2 years
- ARI of 1% corresponds with
  smr+ incidence 50/100,00 per year
  $\beta \approx (1\%/\mathrm{y})/(2\mathrm{y} \times 50 \times 10^{-5}/\mathrm{y}) = 10\ \mathrm{y}^{-1}$
- With a 10% lifetime risk of disease, 50%
  of it smear positive
  1 smr+ case$\rightarrow$ 20 infections $\rightarrow$ 2 cases $=$
  1 smr+ case
  I.e. Stable situation, $R_n = 1$

Bird's eye view



Ovals = models; diamonds = data inputs; squares = numbers.

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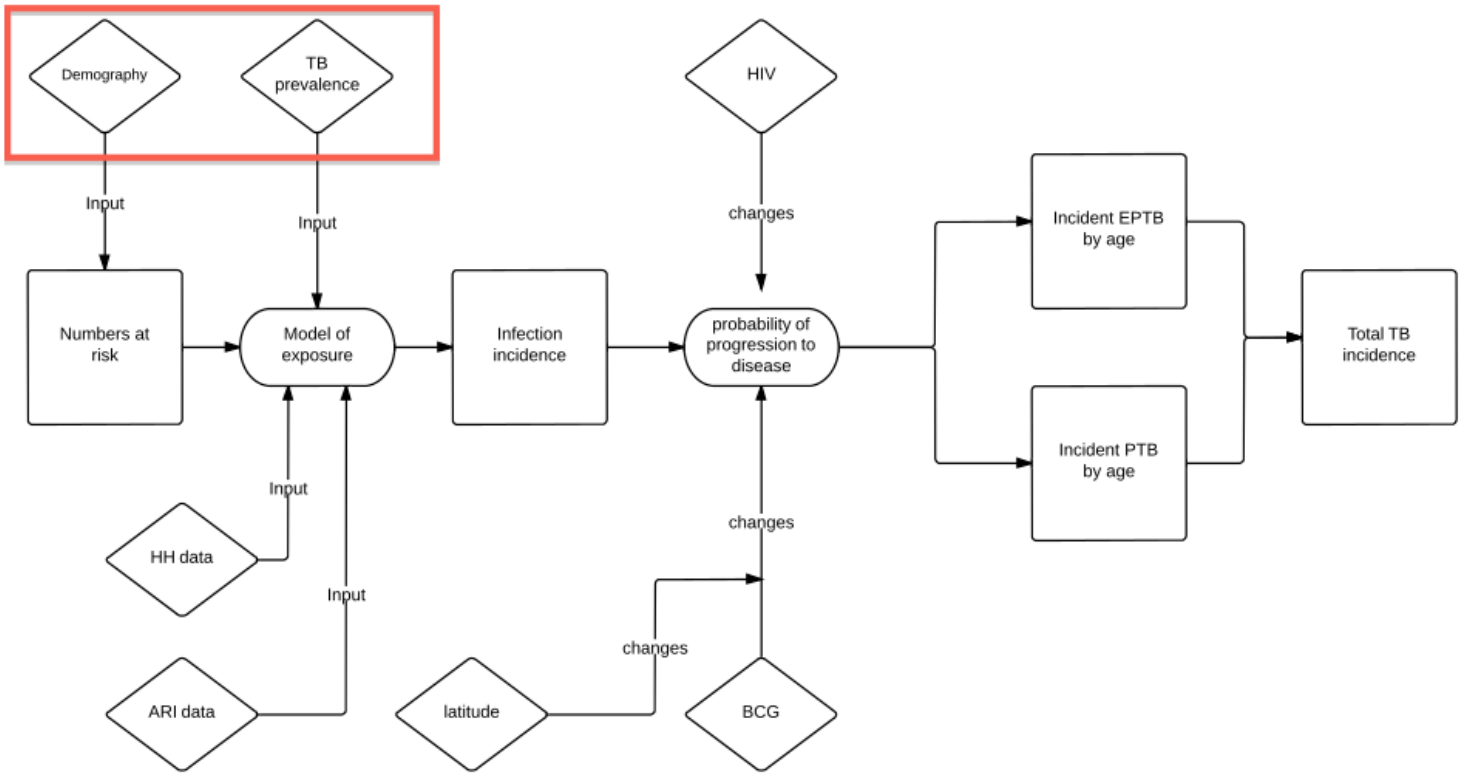
Exposure



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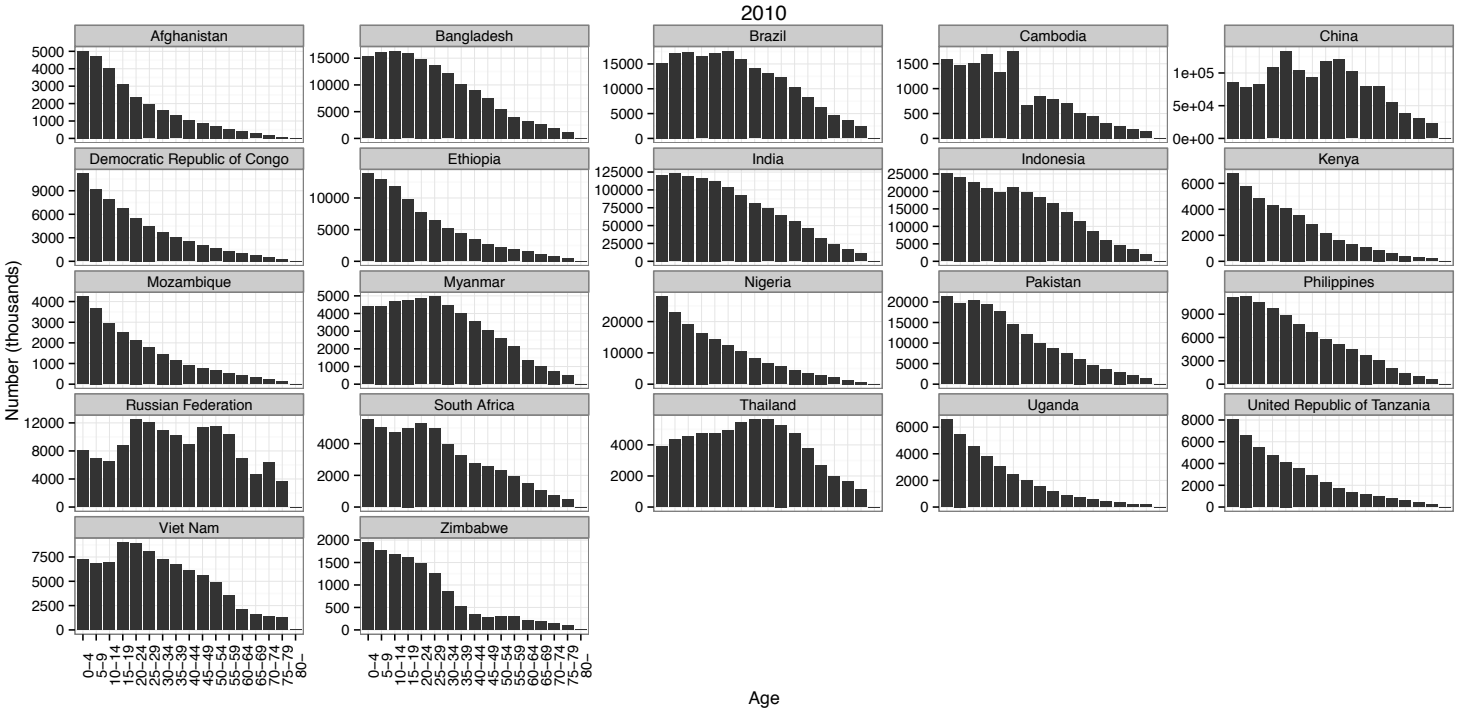
Demography



data: UN ESA

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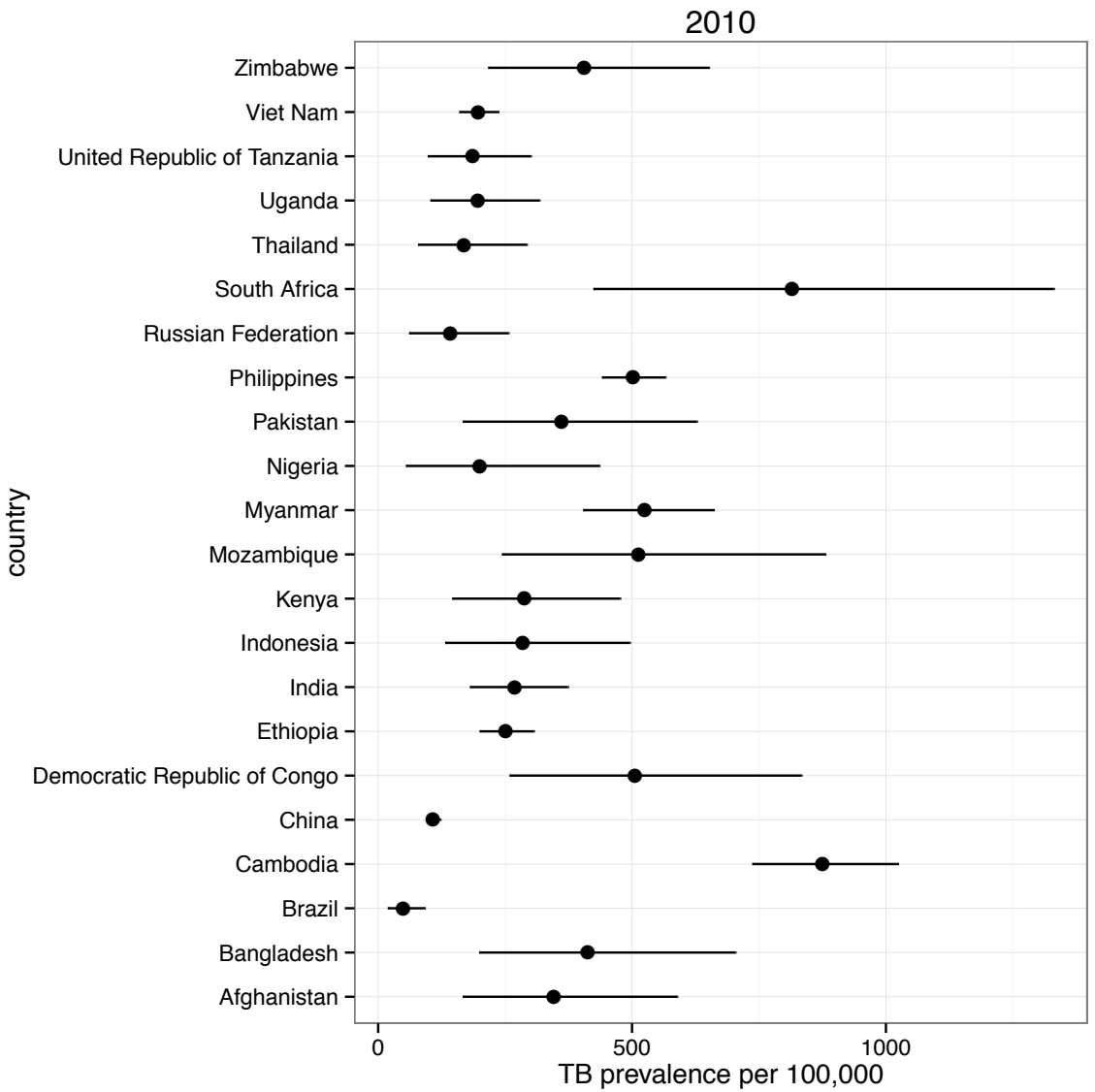
TB prevalence



data: WHO

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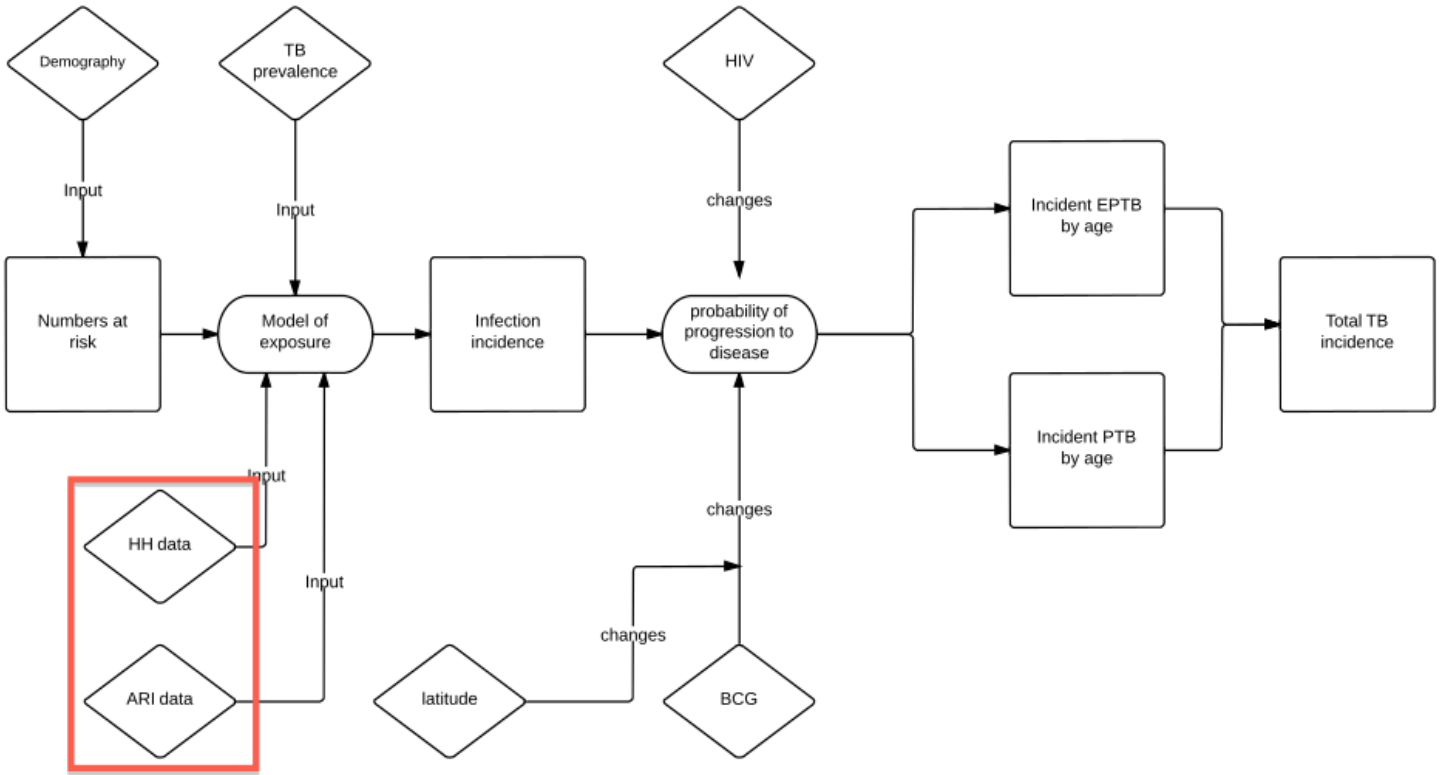
Infection



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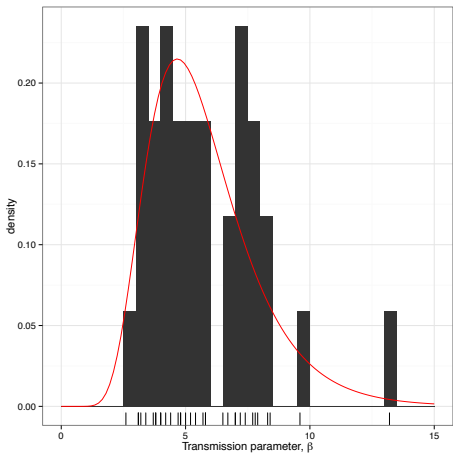
Infection



Two approaches:

1. A model of community infection, via an updated Styblo's rule.
   - data on ARI/prevalence ratios (see left)
2. A household (only) infection model from:
   - detailed data on household make-up
   - data informing risks of household infection

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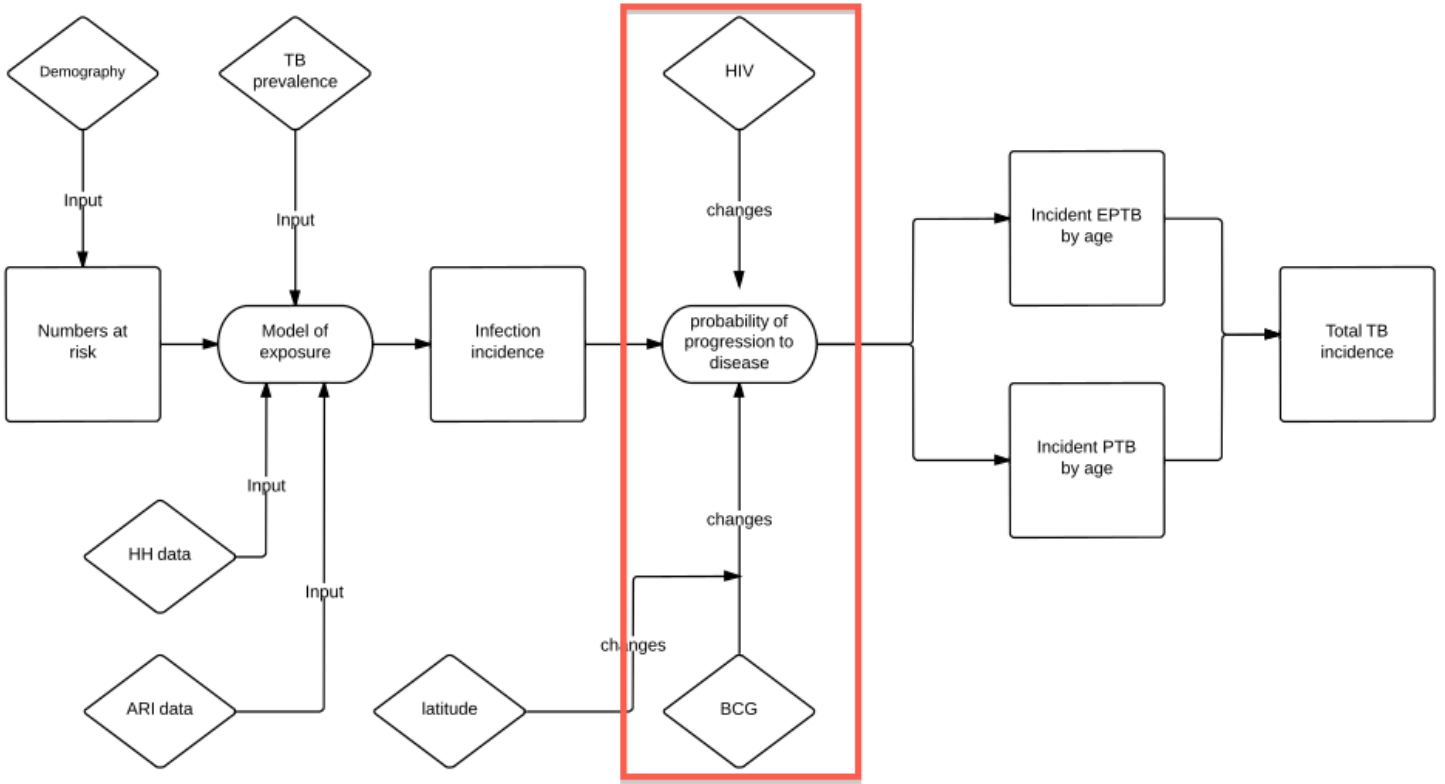
Progression



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Age-dependent progression

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Risks of disease following infection

Separated by 5 age groups and type of disease:

age	quantity	median	LQ	UQ
0	probability of disease	0.500	0.298	0.702
1	probability of disease	0.215	0.108	0.360
2-4	probability of disease	0.016	0.002	0.064
5-9	probability of disease	0.001	0.000	0.013
10-14	probability of disease	0.110	0.043	0.219
0	probability disease is EP	0.255	0.112	0.451
1	probability disease is EP	0.295	0.107	0.557
2-4	probability disease is EP	0.060	0.017	0.145
5-9	probability disease is EP	0.085	0.029	0.183
10-14	probability disease is EP	0.000	0.000	0.008

distributions based on Marais *et al.*, 2004 review of the pre-chemotherapy literature.

Other factors influencing progression

BCG vaccination

- Greater protection against extrapulmonary disease
- Potential variation in efficacy by latitude

HIV infection

Scant data on the effect of HIV on TB progression in children

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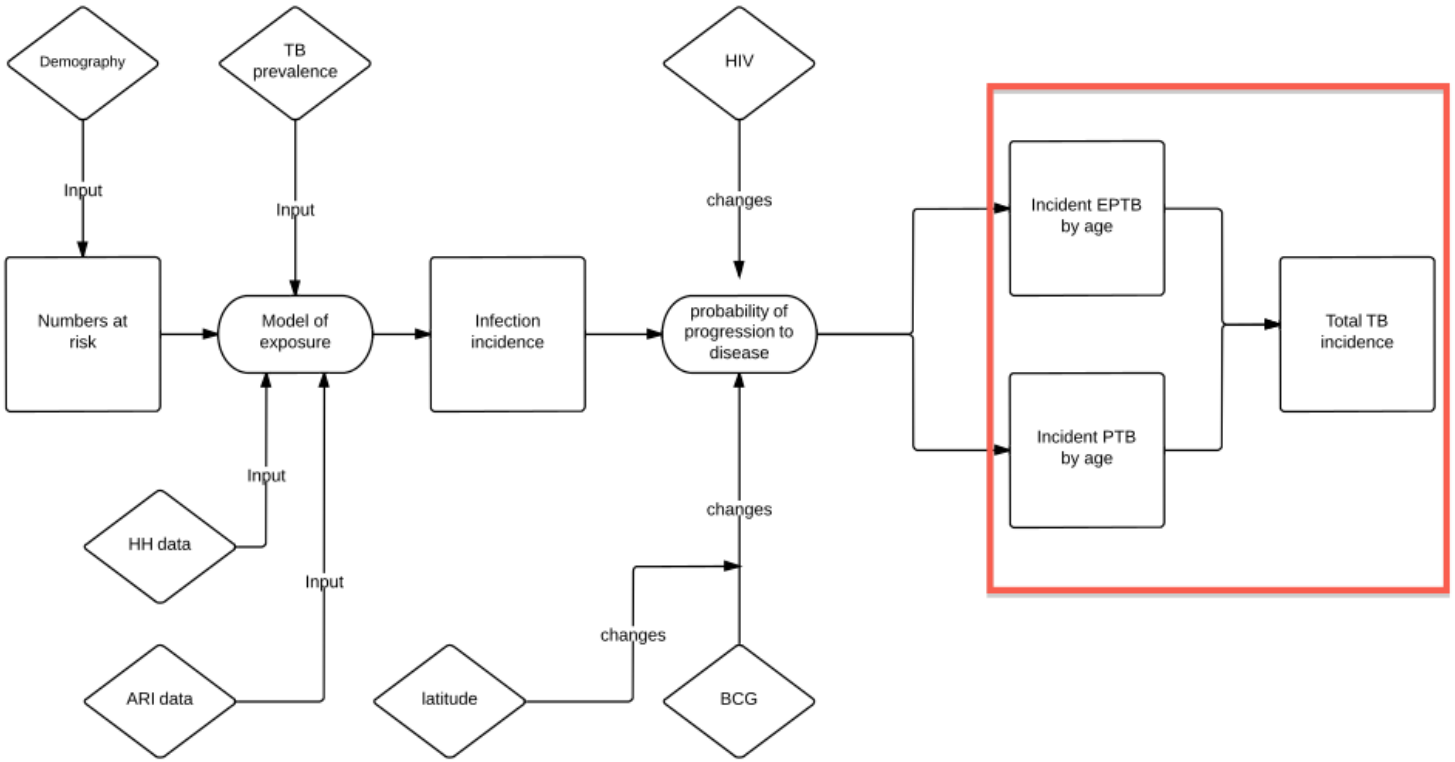
Results



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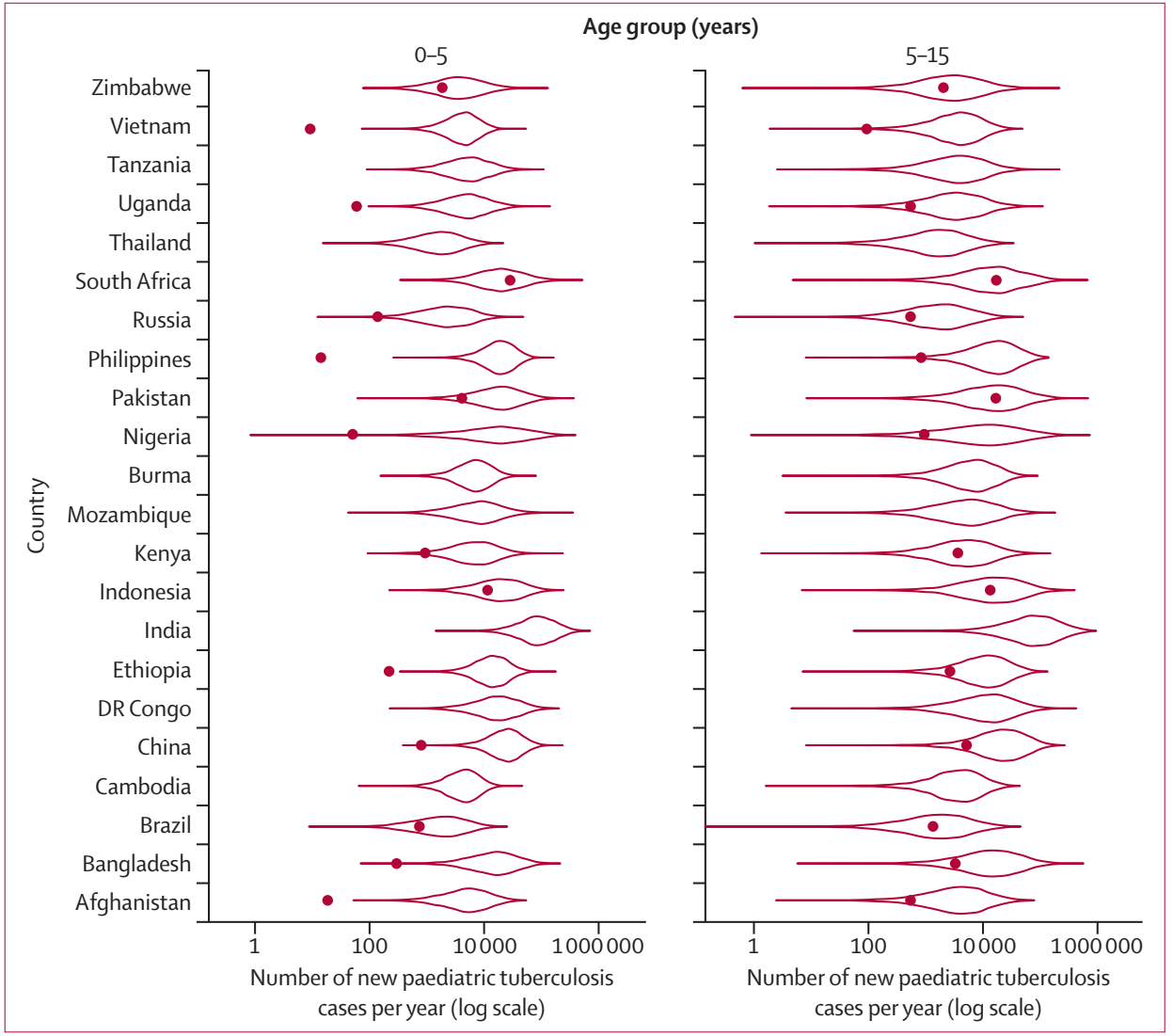
Comparison with notifications



Suggests a CDR of 35% (IQR 23% - 54%)

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Overall Numbers

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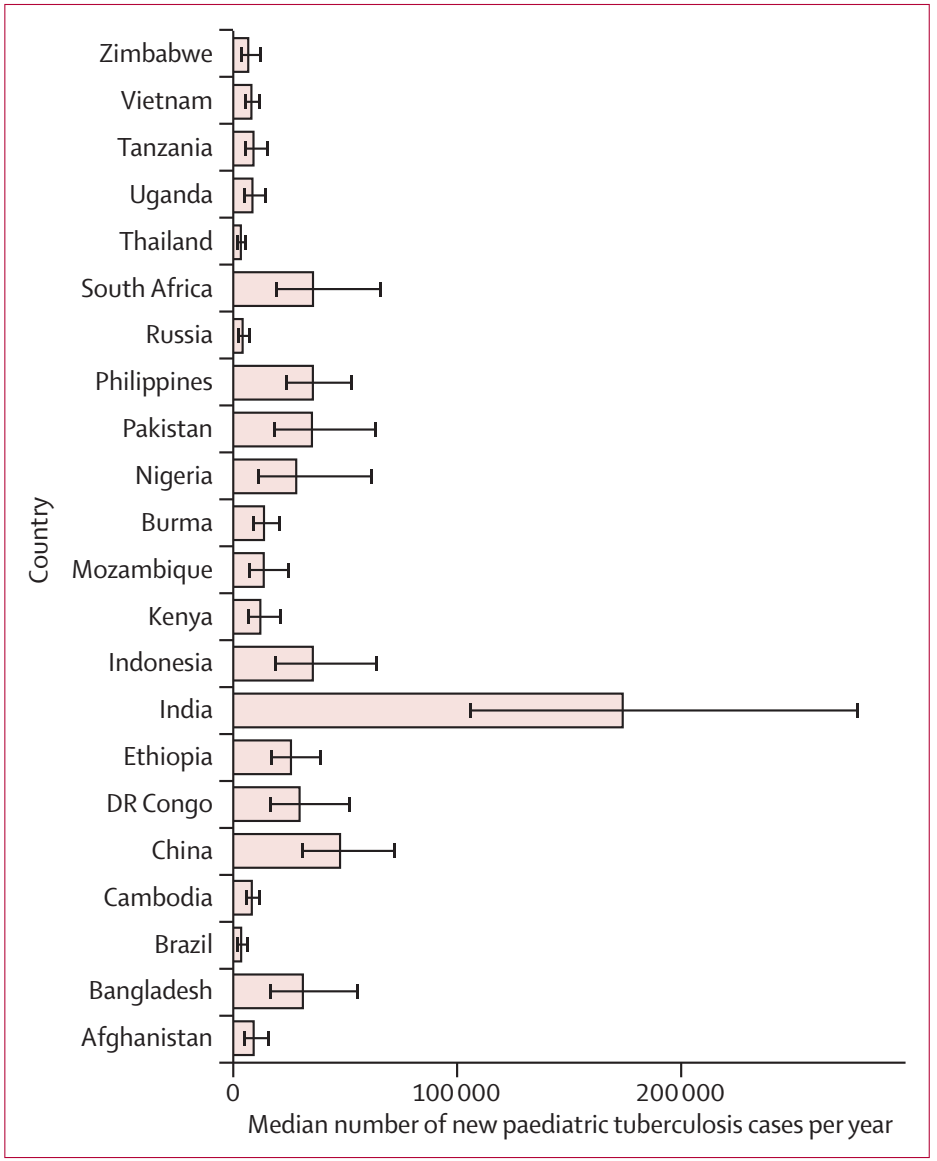
Remember: data from 2010; estimates for 22 HBCs

quantity	median	LQ	UQ
cohabit w/ TB case	15,300,000	13,800,000	17,100,000
incident *M.tb* infections	7,600,000	5,800,000	9,970,000
prevalent *M.tb* infections	53,200,000	41,000,000	69,000,000
incident TB cases	651,000	425,000	983,000

Table: For children (<15 years) the 22 HBCs in 2010.

- large uncertainty
- other model variants ...

By country



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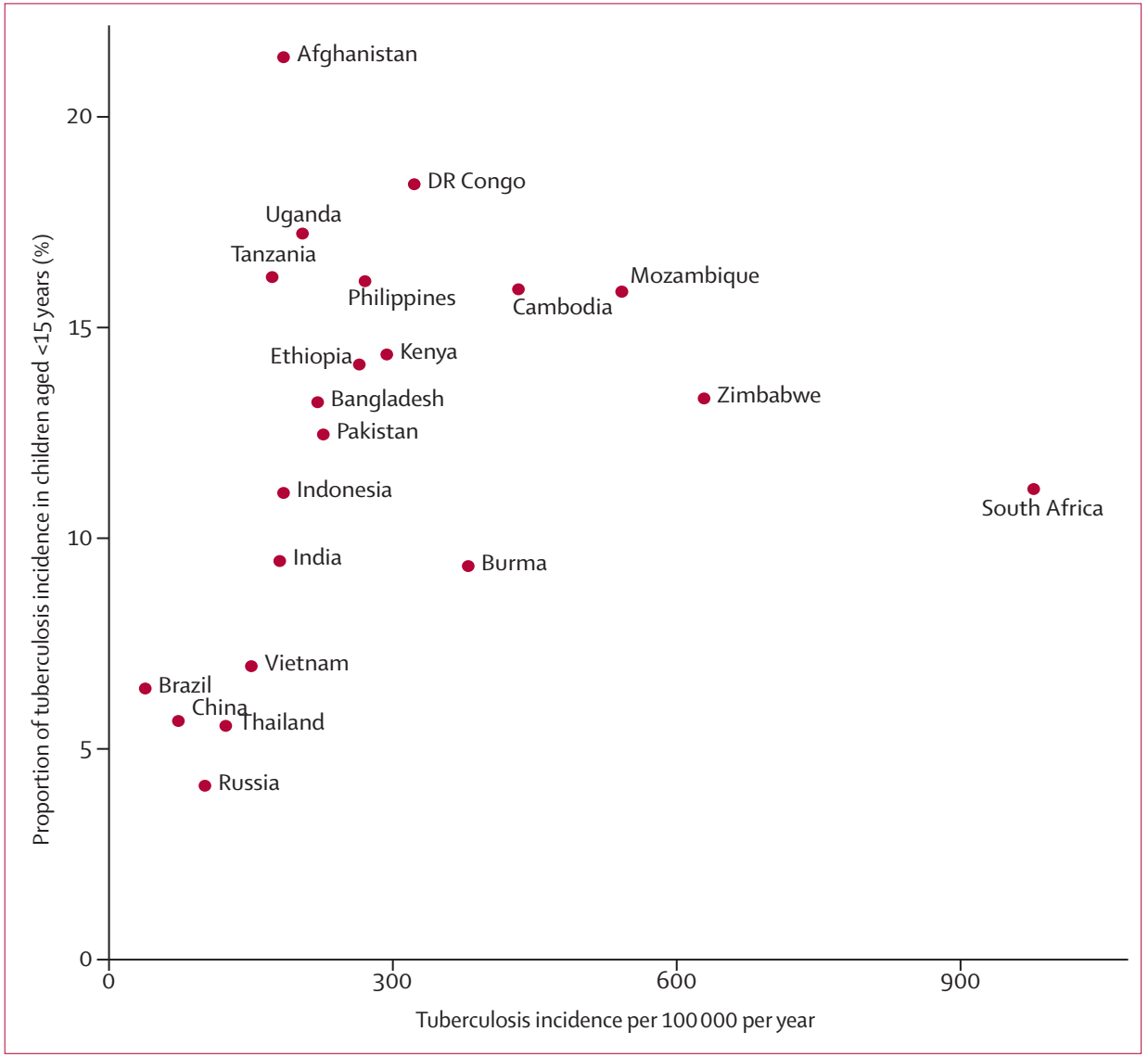
Pattern by incidence



Recall Helen's slide...

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Conclusion

Summary & comments

- We presented a mathematical modelling approach to estimating the burden of paediatric TB starting from adult prevalence data.
- Pros and cons:
  - More assumptions needed ($\rightarrow$ more uncertainty, more frailty).
  - Highlights important areas of relative ignorance
  - A richer set of esimates
  - Can be used to model interventions
- Substantial burden of disease in children, with large numbers targetable for preventive therapy.

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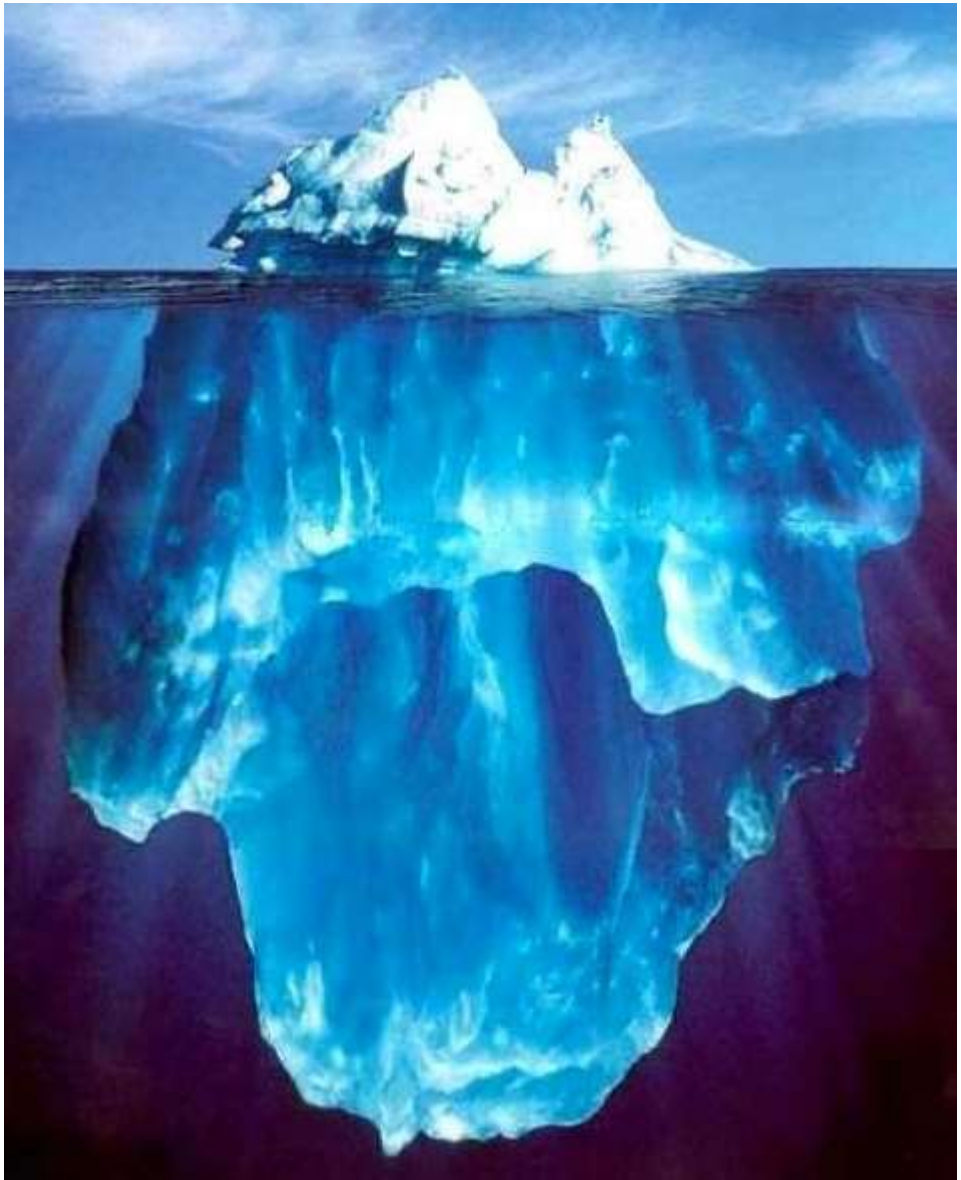
Impact of Global TB Estimates for Clinicians: Measuring the Chasm



Chasms

LTBI

- Not reportable
- 1/3 of global population (?)
- Few recent national-level data
- Data from certain cohorts not generalizable

Disease

- Reportable (but reporting gaps)
- 2012: disaggregated pediatric data
- #s don't correspond to population structure
- Few HIV/TB data in children

MDR-TB

- Reporting obstacles if linked solely to microbiologic confirmation
- Few disaggregated pediatric data
- Diagnostic limitations in HBCs

Clinical impact: how the #s help

- While we knew we were under-reporting disease in children, we had few prior estimates of infection
- Raises awareness of prevention opportunities
- Opportunity to benchmark
  - Impossible to benchmark what's not currently measured
- Allows for estimates of resource allocation

Infection Prevalence

- Prior estimate: 1/3 of global population
  - If accurate, should have many more cases of TB disease
- Not reportable in most settings
- U.S. estimates:
  - Non-generalizable cohorts (e.g., military recruits, nurses)
  - Recent immigrants
  - Single-center studies

Infection Incidence

- Estimated that ½ of lifetime risk of progression to disease is within first 1-2 years of infection
- Better #s:
  - Identify a cohort of children who would benefit most from preventive therapy
  - Allow for potential risk-stratification in resource-limited settings where IPT may not be able to be operationalized across the pediatric age spectrum

MDR-Infection

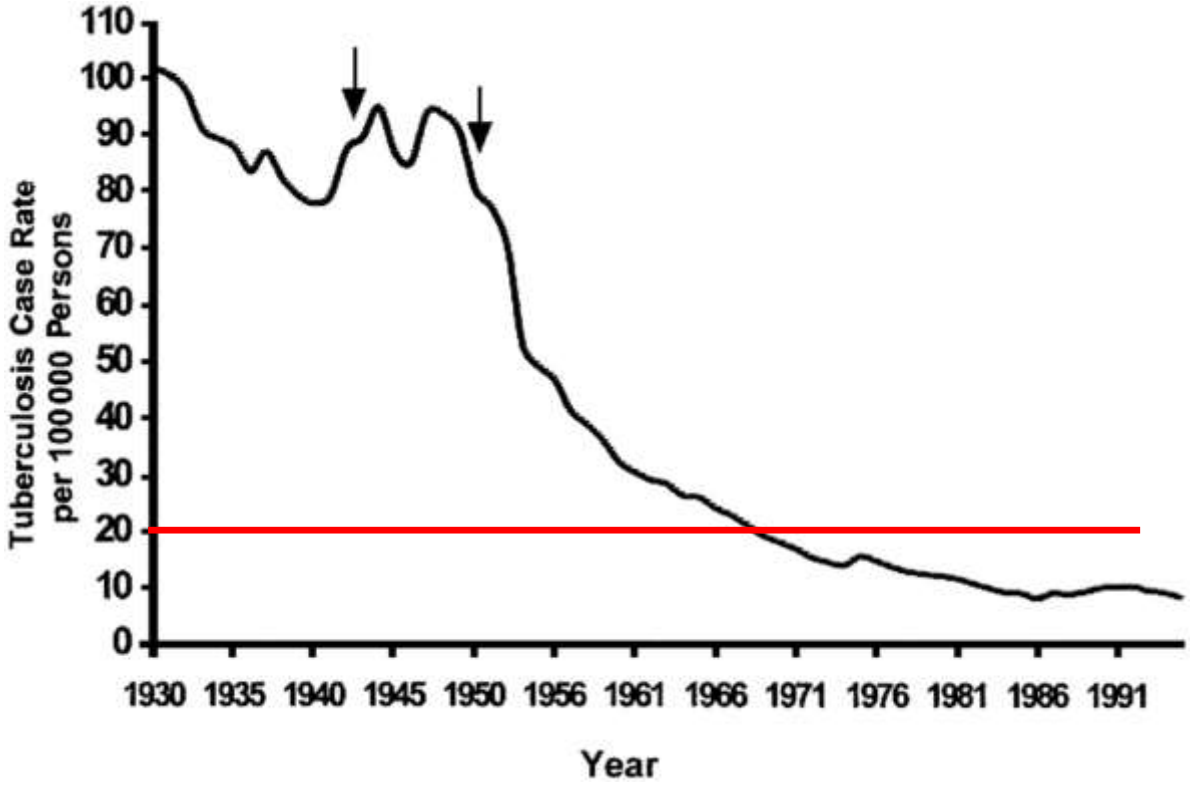
- No current estimates
- Few data on optimal treatment regimens
  - Efficacy
  - Tolerability
- Few children with MDR-TBI treated
  - Heterogeneous regimens preclude comparison
- Could data from Jenkins & Dodd papers be used to model MDR-TBI?
  - Impetus for clinical trials?

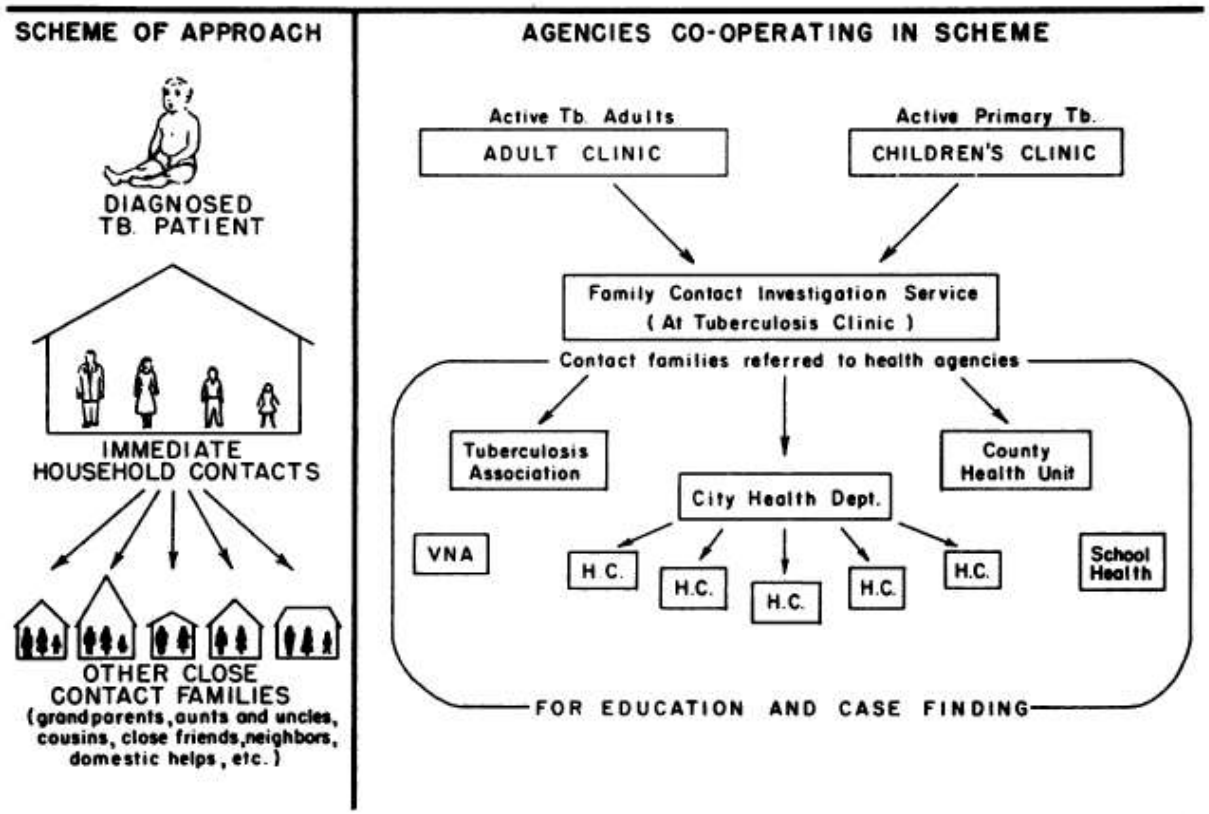
Prevention Opportunities

- Many HBCs may be overwhelmed by disease, which is measurable
- TB infection seems invisible.. until it is not.
- Most data on prevention come from low-incidence nation, where lessons learned may seem to be difficult to generalize across the resource gradient

How did high-incident countries become low-incident countries (pre-HIV)

- Societal infrastructure changes
- Active surveillance
- Emphasizing prevention





KHK Hsu Amer J Publ Health **1963**;53:1761

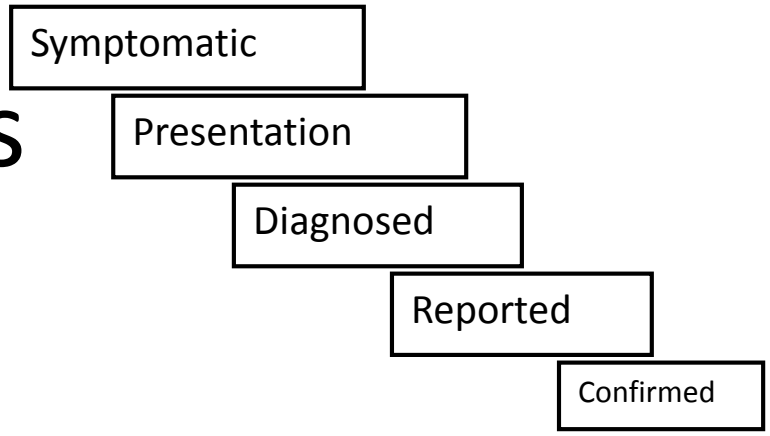
Figure 1—The Scheme for Tuberculosis Contact Investigation

Becerra et al. Lancet **2011**;377:147

Findings 693 households of index patients with MDR tuberculosis were enrolled in the study. In 48 households, the *Mycobacterium tuberculosis* isolate from the index patient was XDR. Of the 4503 household contacts, 117 (2·60%) had active tuberculosis at the time the index patient began MDR tuberculosis treatment—there was no difference in prevalence between XDR and MDR tuberculosis households. During the 4-year follow-up, 242 contacts developed active tuberculosis—the frequency of active tuberculosis was nearly two times higher in contacts of patients with XDR tuberculosis than it was in contacts of patients with MDR tuberculosis (hazard ratio 1·88, 95% CI 1·10–3·21). In the 359 contacts with active tuberculosis, 142 (40%) had had isolates tested for resistance against first-line drugs, of whom 129 (90·9%, 95% CI 85·0–94·6) had MDR tuberculosis.

Interpretation In view of the high risk of disease recorded in household contacts of patients with MDR or XDR tuberculosis, tuberculosis programmes should implement systematic household contact investigations for all patients identified as having MDR or XDR tuberculosis. If shown to have active tuberculosis, these household contacts should be suspected as having MDR tuberculosis until proven otherwise.

Disease Estimates



- ~ 1/3 reported
  - Reporting barriers?
- Even more underestimated in countries reliant upon smear microscopy
- Better #s help quantify unmet needs for diagnosis & treatment
  - Education for clinicians
  - Augmented laboratory support:
    - Sputum induction, gastric aspirates
    - Molecular modalities

TB/HIV in Children

- Even harder to measure than TB in immunocompetent children
- Historically has gone unmeasured
- With current IPT guidelines, most of these children represent preventable cases
- Better #s:
  - Benchmark IPT
  - Trials: minimizing adverse events; shorter-course regimens

MDR-TB Estimates

- Disparities in reporting:
  - Underreporting if no cultures obtained (TB)
  - Over-reporting if no culture obtained (NTM)
- No disaggregated pediatric data
- Better #s:
  - Improved contact tracing
  - Trials: duration of therapy, pharmacokinetic information, # of drugs needed
  - Pediatric-friendly formulations

How to Operationalize?

- Add childhood contacts to TB case card
  - Actually implement IPT for at-risk child contacts
  - Allows for linkages to source case susceptibilities
- Integrate into existing maternal/child health services
  - Venues where children already seeking care
  - Decentralize from national tuberculosis programs

Conclusions

- The estimates may differ; however, they still serve as estimates for something which had been suboptimally measured previously
- Better numbers help us make the case for:
  - Increasing programmatic resources
    - Infection
    - Disease
  - Augmenting pediatric-friendly drug formulations
  - Enabling countries to benchmark what they are currently doing and setting future goals

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